Title:	DENOSUMAB DISCONTINUATION AND SWITCHING IN GLUCOCORTICOID-INDUCED OSTEOPOROSIS: A PILOT STUDY
NCT number:	NCT04177940
Version date:	31MAR2026

DENOSUMAB DISCONTINUATION AND SWITCHING IN GLUCOCORTICOID-INDUCED OSTEOPOROSIS: A PILOT STUDY

Version 4.3; 260331

Summary of Changes:

Protocol	Affected Section(s)	Summary of Revisions Made	Rationale
Version 4.3, 260331	Section 6.1- Primary outcome	Updated the primary outcome description	Primary outcome description was incorrectly documented in the protocol.
Version 4.2; 201005	Summary Page, 6, 7, 8, Table 1, Figure 1	Updated site list to include University of Verona and NoordWest Ziekenhuisgroep (NWZ), updated visit naming conventions, and updated inclusion/exclusion criteria	Addition to 2 new sites and removal of Vrije University. Updated visit names to limit confusion/easier to follow, time since most recent dose of denosumab, and clarified timing of screening DXA
Version 4.1; 200507	Summary page	Updated name to ReumaClinic	Typo

Version 4; 200421	Table1. Schedule of visits and evaluations	Updated HR-pQCT location to ReumaClinic	Updated procedure location to match previous update
Version 3; 200327	2,8,12,14,15	Updated investigational sites	Updated Maastricht University to Reumaclinic, Genk, Belgium.

1 Contents

2 Summary

Title: Denosumab discontinuation and switching in glucocorticoid-induced osteoporosis: a pilot study
Duration: 4 years
Study Site(s): University of Alabama at Birmingham (US), ReumaClinic (Belgium),University of Verona (Italy), and NoordWest Ziekenhuisgroep (NWZ) (Netherlands)
Approximate number of participants: 45
Investigators: Kenneth G. Saag MD, MSc, Gary Cutter PhD, Maria I. Danila, MD, MSc, MSPH, Piet Geusens MD, Willem Lems MD, Davide Gatti, MD, Giovanni Adami, MD, and Henry G. Raterman, MD.
Methodology: Open-label randomized multicenter pilot trial to evaluate the efficacy of different bisphosphonate strategies to attenuate the rebound effect of bone turnover markers after denosumab discontinuation in glucocorticoid-induced osteoporosis.

List Abbreviations, Tables, and Figures

Abbreviations :

AE	Adverse Event
ALN	Alendronate
BMD	Bone Mineral Density
CBC	Complete Blood Count
CC	Coordinating Center
CFR	Code of Federal Regulation
CMP	Complete Metabolic Profile
CRF	Case Report Form
CTX	Sum C-Terminal Telopeptide
DHHS	Department of Health and Human Services
DXA	Dual Energy X-ray Absorptiometry
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GIOP	Glucocorticoid-induced Osteoporosis
HR-pQCT	High Resolution peripheral Quantitative Computed Tomography
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LVA	Lateral Vertebral Assessment
OHRP	Office of Human Research Protections
OPG	Osteoprotegerin
ONJ	Osteonecrosis of the Jaw
PHI	Personal Health Information
PI	Principal Investigator
P1NP	Procollagen type 1 Amino-terminal Propeptide
PFS	Pre-filled Syringe
PTH	Parathyroid Hormone
OHRP	Office of Human Research Protections
RANKL	Receptor Activator Of Nuclear Factor Kappa-B Ligand
SAS	Statistical Analysis System
SC	Subcutaneous
SOP	Standard Operating Procedure
SAE	Serious Adverse Event
SUSARs	Suspected Unexpected Serious Adverse Reaction
USDA	United States Department of Agriculture

Tables:

Figures:

Zol	Zoledronic Acid	

3 Background

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). Denosumab-induced decrease in bone breakdown is rapidly reversed after discontinuation.[1] A rapid rebound of bone turnover markers (e.g. Serum C-Terminal Telopeptide (CTX) and Procollagen type 1 Amino-terminal Propeptide (P1NP)) after denosumab discontinuation may lead to an increased risk of vertebral fractures.[2] It is less certain if this is a concern in the setting of glucocorticoid-induced osteoporosis (GIOP), where the exposure to denosumab may be less acute but where shorter courses of glucocorticoids may lead to limited denosumab exposure.[3,4] In a previous study, 6-months after discontinuation of denosumab, serum CTX increased by +63% and P1NP by +47% compared to baseline (before the initiation of denosumab).[1] In the same study, denosumab discontinuation was associated with a decrease of lumbar spine and total hip bone mineral density (BMD) as early as 1 year since the last denosumab dose.[1] In addition, it has been suggested that the decrease of BMD after denosumab discontinuation may not be related to previous treatment duration in some studies but not in others including a small sample of patients who received denosumab along with glucocorticoids for rheumatoid arthritis management.[5-7]

4 Rationale for the Study

While prompt anti-resorptive treatment after denosumab discontinuation has been recommended,[8] recently published studies created a controversy around the timing and route of bisphosphonate administration following denosumab discontinuation in post-menopausal osteoporosis. In such patients, alendronate, an oral bisphosphonate administered weekly, did not stop bone loss and did not prevent the development of vertebral fractures.[9] A potent intravenous (IV) bisphosphonate (i.e., zoledronic acid) administered immediately after denosumab discontinuation was found to only partly mitigate the rebound in bone turnover.[10,11] In another small observational study, delayed administration of zoledronic acid (approximately 3-months after the cessation of denosumab activity) was found to be more efficacious in preventing bone loss.[12] We will test the hypothesis that an increase in bone turnover markers (e.g. CTX and P1NP) in patients currently taking chronic glucocorticoids will be attenuated more in those who switch from denosumab to "late" zoledronic acid (9 months after last denosumab dose) compared to participants randomized to "early" zoledronic acid (6 months after last denosumab dose) or weekly alendronate (6 months after last denosumab dose).

5 Research Strategy

5.1 Study Design

This is an open-label, randomized, parallel-group pilot clinical trial in which Denosumab users will be assigned in a 1:1:1 allocation to one the following groups:

- Switch from Denosumab 60 mg administered subcutaneously (SC) to weekly oral alendronate (70 mg; started 6 months after last denosumab dose)

OR

- Switch from Denosumab 60 mg administered subcutaneously (SC) to one “early” zoledronic acid infusion (5 mg; 6 months after last denosumab dose)

OR

- Switch from Denosumab 60 mg administered subcutaneously (SC) to one “late” zoledronic acid infusion (5 mg; 9 months after last denosumab dose)

Participants will be advised to maintain adequate calcium and vitamin D intake per United States Department of Agriculture (USDA) and Department of Health and Human Services (DHHS) guidelines. All individuals will need ≥ 12 months of previous denosumab treatment (minimum of 2 doses) prior to switching to assigned randomization arm. The minimum number of doses (n = 2) is based on published data that the rebound in BMD might be less pronounced in patients receiving very limited denosumab.[1,13] According to a systematic review of patients with multiple vertebral fractures following denosumab cessation, those with ≤2 years of denosumab treatment had fewer fractures compared with those with >2 years.[14] Therefore, the maximum number of prior doses (n = 4) is based on higher incidence of rebound loss of BMD, more rapid turnover, and

potentially greater vertebral fractures after discontinuation of denosumab in patients who received more extensive treatment. Thus, we will limit our trial to a more restricted use of denosumab duration (2-4 doses) to maintain greater homogeneity, given the somewhat smaller planned sample size. Users of denosumab will be sorted into two groups:

- Prevalent users: Defined as individuals with a minimum of one previous dose of denosumab, and up to 4 previous doses of denosumab (maximum). Prevalent users with one previous dose will receive a second dose of denosumab before proceeding to assigned randomization arm. Therefore, randomization will occur 2 weeks after screening visit if they had already 2-4 denusomab doses.

- New denosumab users: Defined as individuals who have not previously received denosumab. New users will receive two doses of denosumab before proceeding to assigned randomization arm. Among those participants that are denosumab naïve or that require additional denusomab doses, randomization will occur 6 months after their second denusomab dose has been provided and thus 12 months after the first dose.

- Because all denosumab users will be screened for enrollment in the study, some subjects screened will not be randomized if they do not meet the requirement of denusomab minimum doses.

Note: If participants have had previous denosumab doses greater than 8 months ago, they are considered new users

5.2 Rationale for Study Design

- **Open-label design**: The pilot nature of this study does not allow for a double-blind design, but given that the primary outcome is a serological measurement (which will be determined by the laboratory blinded to exposure category) this open-label design is unlikely to introduce significant bias.
- **Need for active comparator:** The primary aim of this study is to define an effective exit strategy for denosumab users with GIOP. It has been shown that a prompt anti-resorptive treatment is needed after denosumab discontinuation, thus the use of placebo would not be ethical.
- **Study duration**: Total study duration is 48 months; participants will be enrolled for a minimum of 12 months (prevalent users) or 24 months (new denosumab users) to evaluate changes in bone turnover after denosumab discontinuation and switching to one of three study arms. The primary outcome will be assessed 6 months after switching to assigned study arm.
- **Use of zoledronic acid (ZOL) as intervention**: A study of 67 post-menopausal women with osteoporosis found that treatment with ZOL 5 mg maintained bone turnover markers in the premenopausal range and prevented bone loss in women previously treated with ODN.

6 Outcomes

6.1 Primary Outcome

The primary outcome is the absolute difference in the log-transformed CTX values between randomization (V4) and 6 months after randomization (V6).

6.2 Secondary Outcomes

- Change in the log-transformed CTX between 6 months (V6) and 12 months (V7)
- Percentage change in the log-transformed CTX 12 months (V7) post randomization
- P1NP absolute change (µg/mL) 6 months (V6) post randomization
- P1NP percent change (µg/mL) 12 months (V7) post randomization

- BMD at spine absolute and percent change (g/cm^2) 12 months (V7) post randomization
- BMD at total-hip absolute and percent change (g/cm^2) 12 months (V7) post randomization
- BMD at femoral neck absolute and percent change (g/cm^2) 12 months (V7) post randomization

6.3 Safety Outcomes
Adverse events will be reported as safety outcomes.

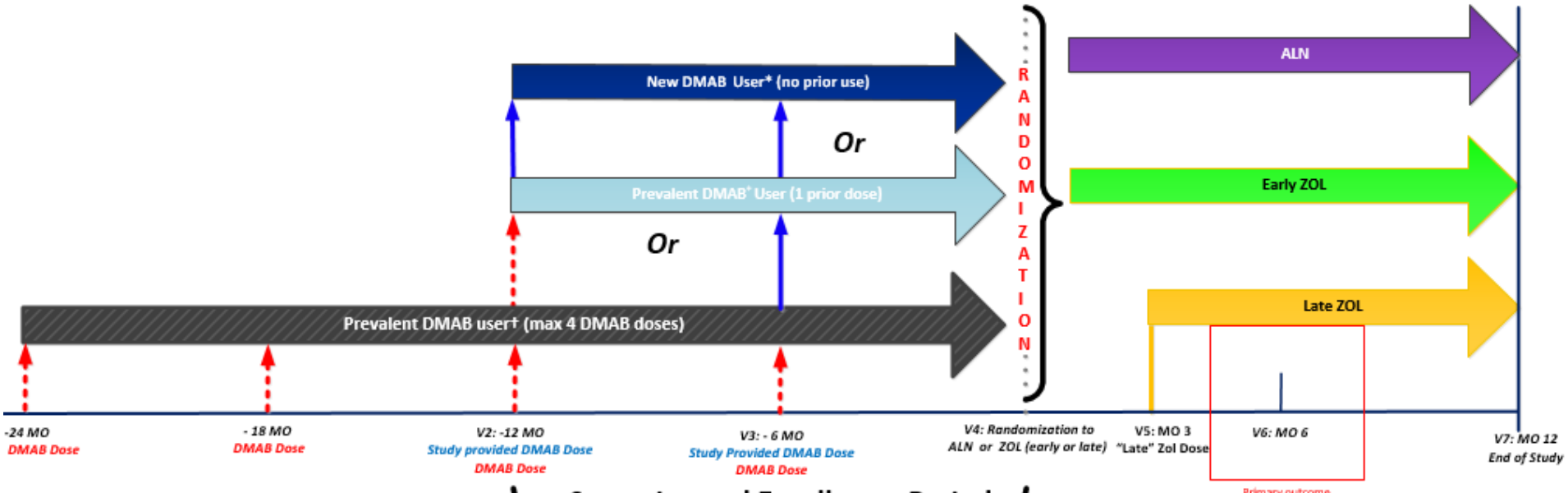
6.4 Exploratory Outcomes
- Fracture outcomes (e.g. vertebral and non-vertebral) as adverse event report
- Serial lateral vertebral assessment (LVA) changes 12 months (V7) post randomization
- High-resolution peripheral quantitative computed tomography (HR-pQCT) parameters changes 6 (V63), 12 months (V74) post randomization
- Micro-indentation parameters changes 6 (V6), 12 months (V7) post randomization

7 Patient Population

7.1 Inclusion Criteria
- Women and men, age 18 years or older and able to provide informed consent (IC)
- ≥ 3 months of glucocorticoid use at ≥ 7.5 mg /day (prednisone equivalent dose) and anticipated to remain on glucocorticoids for at least six months
- A baseline BMD T-score of ≤ -1.0 at the lumbar spine, total hip, or femoral neck (prior to denosumab use if prevalent user)
    - Previous doses of densosumab (for prevalent users) must be continuous and not separated by interval greater than 8 months. If interval between densoumab doses is greater than 8 months, the participant is considered a new user.

7.2 Exclusion Criteria
- Patients with fewer than three lumbar vertebrae that could be evaluated on dual energy x-ray absorptiometry (DXA)
- No past IV bisphosphonates. Oral bisphosphonates must not have been taken in the past 2 months and for no more than 2 cumulative months of use in the past year (e.g. 8 total weekly doses of alendronate maximum)
- Greater than 24 months (>4 injections) of prior treatment with denosumab
- Women of childbearing potential, who are not currently using birth control, are pregnant, planning to become pregnant, or are breastfeeding. For women of childbearing potential: refusal to use 2 highly effective forms of contraception and to continue this practice for 7 months after last injection of study medication*
- 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)]†

Figure 1. Denosumab (DMAB) Discontinuation and Switching in Glucocorticoid-induced osteoporosis (GIOP)



*Randomization for new users at 6 month following 2nd DMAB injection (minimum number of doses)

† Randomization for prevalent users will occur following the 2nd (minimum), 3rd or 4th (maximum) DMAB injection

= Clinician provided DMAB dose(s) (prior to study enrollment)

= Study Provided DMAB dose

= Switch to ALN

= Switch to Early ZOL

= Switch to Late ZOL

1° outcome: Δ CTX @ 6 months post randomization;
2° outcomes: Δ BTMs at 12 months post randomization, Δ BMD @ 12 months post randomization
ALN= alendronate; DMAB= denosumab; ZOL= zoledronic acid
S=screening visit (2 weeks prior to first study provided dose of denosumab or randomization)
V= subsequent study visit

7.1 Exclusion Criteria Continuted

- Hypercalcemia >10% above upper limit of normal (ULN)
- Elevated transaminases or total bilirubin ≥ 2.0 x 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 or localized squamous cell carcinoma of the skin)
- Hypocalcemia <10% below lower limit of normal (LLN)
- Estimated glomerular filtration rate < 30 mL/minute/1.73 m^2
- Intolerance to calcium supplements, vitamin D supplements
- Contraindication to, or poorly tolerant of denosumab therapy (including hypersensitivity to the drug)
- Contraindication to, or poorly tolerant of zoledronic therapy (including hypersensitivity to the drug)
- Contraindication to, or poorly tolerant of alendronate (including hypersensitivity to the drug and sever gastrointestinance intolerance to oral bisphsphonates)
- Recipient of an investigational drug within 4 weeks prior to study drug administration
- Not a good candidate for study participation in opinion of investigator[$]

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

*Denosumab is contraindicated for use in pregnant women because it may cause harm to a fetus. Animal studies at doses 25-fold higher than the recommended human dose have shown increased fetal loss during gestation, stillbirths, and postnatal mortality, and absent lymph nodes. There are no controlled data in human pregnancy, and insufficient data to inform any drug-associated risks for adverse developmental outcomes. No information is available on the clinical use of this drug during breastfeeding. Premenopausal women will have a pregnancy test before the study starts and again throughout the study.

$ If at the time of randomization the site PI deems the participant is no longer a suitable candidate for the study they will be discontinued.

8 Study Procedures and Assessments

All study visits and procedures will be performed in facilities at the University of Alabama at Birmingham-UAB (US), ReumaClinic (Belgium), University of Verona (Italy), and NWZ (Netherlands)

If participants suspect that they may have become pregnant during the study, the study coordinator will contact the study principal investigator (PI) immediately and the PI or Study Coordinator will instruct the participant to stop taking all study medication. If it is confirmed that the participant is pregnant, they will be withdrawn from the study. The study PI will schedule a follow-up visit and may choose to follow the outcome of the pregnancy. If it is discovered that participants are breastfeeding, they are not eligible to participate in the study and their participation will be discontinued immediately.

8.1 Screening Visit (V1, 2 weeks prior to the first denosumab dose or to randomization among prevalent users who have received 2-4 prior doses of denosumab)

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:

- IC
- Review inclusion/exclusion criteria
- Review of current and/or past treatment with denosumab 60 mg – determination whether the subject is an new denosumab user (defined above) or a prevalent denosumab user (defined above)
- Medical history
  - Assess osteoporosis history and past fragility fractures history
  - Current medication review
  - Medication history (including use of: prescription medications (e.g. other osteoporosis medications))

    - Dietary supplement/vitamin use
- Full physical exam includes, but is not limited to
    - Vital signs/Weight/Height
    - Dermatological
    - Chest and cardiac
    - Abdominal
    - Musculoskeletal and nervous system examinations
- Screening visit laboratory
    - Complete blood count (CBC) with differential
    - Comprehensive metabolic panel (CMP)
    - Calcium
    - Vitamin D
    - Phosphorus
    - Intact Parathyroid Hormone (PTH)
    - Bone turnover (serum CTX & P1NP)
    - Serum pregnancy test in non-postmenopausal women‡
    - Serum banking
- DXA at lumbar spine, total-hip and femoral neck

At the conclusion of visit, participants should be advised to maintain adequate calcium and vitamin D intake per USDA and DHHS guidelines.

‡Postmenopausal 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 (e.g. 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 2 (V2) [for new denosumab users]

New denosumab users will be required to receive 12 months of denosumab before randomization (switching). New denosumab users with zero prior denosumab use will report 2 weeks after the screening visit and signing of the ICF to:

- Updated medical history and review of concomitant medications
- Obtain and record vital signs, including pulse rate, sitting blood pressure, and body temperature
- Targeted physical exam includes, but is not limited to
    - Dermatological
    - Chest and cardiac
    - Abdominal
    - Musculoskeletal and nervous system examinations
    - Weight/Height
- Laboratory
    - CBC with differential
    - Calcium
- Administer denosumab 60 mg SC
- Assessment of Adverse Events (AEs) (potentially attributable to denosumab but not study strategy)

At the conclusion of visit, participants should be advised to maintain adequate calcium and vitamin D intake per USDA and DHHS guidelines.

8.3 Visit 3 (V3) [for individuals with one prior dose of denosumab and new denosumab users seen at V2]

Participants with one prior denosumab dose will report within 6 months after the screening visit for a second and participants with no prior denosumab use (determined at screening) will report 6 months after Visit 2 to:

- Updated medical history and review of concomitant medications
- Obtain and record vital signs, including pulse rate, sitting blood pressure, and body temperature
- Targeted Physical exam includes, but is not limited to
    - Dermatological
    - Chest and cardiac
    - Abdominal
    - Musculoskeletal and nervous system examinations
    - Weight/Height
- Laboratory
    - CBC with differential
    - Calcium
    - Urine pregnancy test
- Administer denosumab 60 mg SC
- Assessment of Adverse Events (AEs) (potentially attributable to denosumab but not study strategy)

At the conclusion of visit, participants should be advised to maintain adequate calcium and vitamin D intake per USDA and DHHS guidelines.

8.4 Visit 4 (V4) Randomization visit

The randomization visit will occur within 2 weeks from the screening visit and signing of the ICF for prevalent denosumab users. The randomization visit will occur 12 months after screening visit for new denosumab users. During the randomization visit patients will be randomized across study arms. During the randomization visit, markers for the study primary and secondary outcomes will be assessed, as well as Bone Mineral Density (BMD) at the lumbar spine, total hip and femoral neck, Lateral Vertebral Assessment (LVA), HR-pQCT, micro-indentation (at one study site), and additional data collection needed for safety monitoring.

- Updated medical history and review of concomitant medications
- Obtain and record vital signs, including pulse rate, sitting blood pressure, and body temperature
- Targeted physical exam includes, but is not limited to
    - Dermatological
    - Chest and cardiac
    - Abdominal
    - Musculoskeletal and nervous system examinations
    - Weight/Height
- Laboratory
    - CBC with differential
    - CMP
    - Calcium
    - Vitamin D
    - Bone Turnover (serum CTX and serum P1NP)
    - Serum banking
    - Urine pregnancy
- DXA at lumbar spine, total-hip and femoral neck
- LVA
- HR-pQCT
- Micro-indentation (participants enrolled at UAB)
- Administer “early” zoledronic acid in patients randomized to this treatment arm
- Dispense alendronate to patients randomized to this treatment arm
- Assessment of Adverse Events (AEs) (potentially attributable to denosumab but not study strategy)

At the conclusion of visit, participants should be advised to maintain adequate calcium and vitamin D intake per USDA and DHHS guidelines.

8.5 Visit 5 (V5) (3 months post-randomization)

All participants will report 3 months following the randomization visit (V4) to:

- Updated medical history and review of concomitant medications
- Obtain and record vital signs, including pulse rate, sitting blood pressure, and body temperature
- Targeted Physical exam includes, but is not limited to
    - Dermatological
    - Chest and cardiac
    - Abdominal
    - Musculoskeletal and nervous system examinations
    - Weight/Height
- Laboratory
    - CBC with differential
    - CMP
    - Calcium
    - Vitamin D
    - Bone Turnover (serum CTX and serum P1NP)
    - Serum banking
    - Urine pregnancy
- DXA at lumbar spine, total-hip and femoral neck
- LVA
- Dispense alendronate to patients randomized to this treatment arm
- Administer “late” zoledronic acid in patients randomized to this treatment arm
- Assessment of AEs

Advise participants to maintain adequate calcium and vitamin D intake per USDA and DHHS guidelines.

8.6 Visit 6 (V6) (6 months post-randomization)

Participants will report 3 months following Visit 5 to:

- Updated medical history and review of concomitant medications
- Obtain and record vital signs, including pulse rate, sitting blood pressure, and body temperature
- Targeted Physical exam includes, but is not limited to
    - Dermatological
    - Chest and cardiac
    - Abdominal
    - Musculoskeletal and nervous system examinations
    - Weight/Height
- Laboratory
    - CBC with differential
    - CMP
    - Calcium
    - Vitamin D
    - Bone Turnover (serum CTX and serum P1NP)
    - Serum banking
    - Urine pregnancy
- DXA at lumbar spine, total-hip and femoral neck
- LVA

- HR-pQCT
- Micro-indentation (participants enrolled at UAB)
- Dispense alendronate to patients randomized to this treatment arm
- Assessment of AEs

Advise participants to maintain adequate calcium and vitamin D intake per USDA and DHHS guidelines.

8.7 Visit 7 (V7) (End of Study Visit; 12 months post-randomization)

Participants will report 6 months following Visit 6:

- Updated medical history and review of concomitant medications
- Obtain and record vital signs, including pulse rate, sitting blood pressure, and body temperature
- Targeted Physical exam includes, but is not limited to
    - Dermatological
    - Chest and cardiac
    - Abdominal
    - Musculoskeletal and nervous system examinations
    - Weight/Height
- Laboratory
    - CBC with differential
    - CMP
    - Calcium
    - Vitamin D
    - Bone Turnover (serum CTX and serum P1NP)
    - Serum banking
    - Urine pregnancy
- DXA at lumbar spine, total-hip and femoral neck
- LVA
- HR-pQCT
- Micro-indentation (participants enrolled at UAB)
- Assessment of AEs

Advise participants to maintain adequate calcium and vitamin D intake per USDA and DHHS guidelines.

8.8 Post-study assessment

All patients will be referred to their primary care physician or rheumatologist/endocrinologist at the completion of the study. Based on physician estimation of fracture risk (including, but not limited to, the last visit CTX value and ongoing glucocorticoid treatment), individuals will continue an out-of-study an anti-resorptive medication.

9 Informed Consent (IC) Procedures

The IC process will be carried out by one of the study investigators in conjunction with the study coordinator/research assistant involved at the screening visit. During the screening visit, the study participant (at a minimum) will review the ICF and the research study coordinator obtaining consent will explain each section. 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 participation is strictly voluntary and that he/she may withdraw from the study at any time, and 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 and that treatment will not be compromised if an individual does 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 ICF. 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 in the study binder and an additional copy of the consent form will also be given to the participant.

The ICF contains at a minimum the following:

- Disclosure of relevant information to prospective participants about the research
- 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 to any of the study procedures that may affect the participant, the ICF will be revised and submitted for approval to the Institutional Review Board (IRB). All 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. Based on current EU guidelines the longer archive is only required for "trials in which the clinical trial data are used to support a marketing authorization (including Paediatric Use Marketing Authorisations under Regulation 1901/2006), Directive 2003/63/EC (amending Directive 2001/83/EC)". This pilot study is not being conducted to support a label change.

10 Study Medications

10.1 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 2-year data from the randomized, double blind, active controlled, phase III trial demonstrated that denosumab treatment was effective in the treatment and prevention of glucocorticoid-induced osteoporosis when compared with risedronate.[15,16] In the United States and Canada, denosumab has approvals for indications including the treatment of glucocorticoid-induced osteoporosis. In the European Union, denosumab has been approved for the treatment of glucocorticoid-induced osteoporosis.

10.1.1 Packaging and Labeling of Clinical Supplies

Denosumab will be manufactured and provided to the investigational pharmacies at the University of Alabama at Birmingham (UAB), ReumaClinic, University of Verona, and NWZ by Amgen Inc. Dispensation of denosumab will be handled by the investigational pharmacies at the UAB, ReumaClinic, Vrije University, University of Verona and NWZ. Received denosumab will be annotated with the approved IRB protocol number(s).

Table1. Schedule of visits and evaluations

Visit description / Study procedures	Screening (V1) **	**V2 New users with zero prior denosumab doses**	**V31 Prevalent users with a single (1) prior denosumab dose and "new users" returning for second dose**	V4 Baseline/ Randomization	V5	V6	V7
		-12 mo	**-6 mo**	0	3 mo	6 mo	12 mo
Informed consent	X						
Inclusion/exclusion criteria	X						
Review of current and/or past treatment with denosumab	X						
Medical history	X						
Updated medical history and concomitant medications		**X**	**X**	X	X	X	X
Vital signs	X	**X**	**X**	X	X	X	X
Physical examination (PE)	X						
Targeted PE		**X**	**X**	X	X	X	X
Laboratory							
CBC with diff	X	**X**	**X**	X	X	X	X
CMP	X			X	X	X	X
Calcium	X	**X**	**X**	X	X	X	X
Vitamin D	X						
Intact PTH	X						
Bone Turnover (serum CTX and P1NP)	X			X	X	X	X
Serum banking	X			X	X	X	X
Pregnancy test §	X		**X**	X	X	X	X
DXA lumbar spine/total-hip/femoral neck	X			X	X	X	X
LVA				X	X	X	X
HR-pQCT (ReumaClinic)				X		X	X
Micro-indentation (UAB)				X		X	X
Administer denosumab 60mg SC		**X**	**X**				
Dispense oral alendronate				X	X	X	
Administer "early" zoledronic acid				X			
Administer "late" zoledronic acid					X		
Assess AEs		**X**	**X**	X	X	X	X

CMP = Complete metabolic profile, CBC with diff = Complete blood count with Differentiation, PTH = Parathyroid hormone, *Includes sitting blood pressure, heart rate, respiratory rate, and body temperature; § for non-postmenopausal women defined in section 7.

** 2 weeks prior to the first DMAB dose for new users or to randomization among prevalent users who have received 2-4 prior doses of denosumab

10.1.2 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 destroyed by participating sites, and documentation of destruction will be entered into the study database. All drug supply returns will be made to the study drug packaging and shipment vendor specified in the list of external facilities and personnel.

10.1.3 Denosumab Preparation and Administration

Denosumab will be presented as a pre-filled syringe (PFS) of 60 mg. All new denosumab users will receive denosumab through a SC route of administration. Denosumab will not be administered intravenously, intramuscularly, or intradermal. Authorized site personnel will administer all SC injections. 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.

10.2 Zoledronic acid

Participants who will be randomized in the “early’’ or ‘’late’’ zoledronic acid arm will receive one infusion of Zoledronic acid 5 mg. The data from the randomized, double blind, placebo controlled, phase III trial demonstrated that zoledronic acid treatment was effective in the prevention and treatment of glucocorticoid-induced osteoporosis when compared with risedronate. [17] In the United States, the European Union, and Canada, zoledronic acid has approvals for indications including the treatment of glucocorticoid-induced osteoporosis.

10.2.1 Packaging and Labeling of Clinical Supplies

Zoledronic acid will be purchased and labeled by the investigational pharmacy at University of Alabama at Birmingham. Dispensation of study drug will be handled by the investigational pharmacies at the UAB, ReumaClinic, University of Verona and NWZ. Study drug labeling will be annotated with the approved IRB protocol number(s).

10.2.2 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 and UAB, 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 zoledronic acid will be destroyed by participating sites, and documentation of destruction will be entered into the study database. All drug supply

returns will be made to the study drug packaging and shipment vendor specified in the list of external facilities and personnel.

10.2.3 Zoledronic Acid Preparation and Administration

Zoledronic acid will be presented as a sterile solution in bottles for intravenous infusion. One bottle with 100 mL solution contains 5.330 mg of zoledronic acid monohydrate, equivalent to 5 mg zoledronic acid on an anhydrous basis. All subjects randomized to “early” or “late” zoledronic acid arms will receive zoledronic acid through a IV route of administration. Zoledronic acid will not be administered subcutaneously, intramuscularly, or intradermal. Authorized site personnel will administer all IV infusions. Zoledronic acid infusion will be administered following the procedures indicated in the drug label. Following administration participants will be observed for 1 hour for any AEs.

10.3 Alendronate

Participants who are randomized to the alendronate arm will receive oral alendronate (70 mg) for 12 months (52 pills total). The data from the randomized, double-blind, placebo-controlled, phase III trial demonstrated that alendronate treatment was effective in the prevention and treatment of glucocorticoid-induced osteoporosis when compared with placebo.[18] In the United States, the European Union, and Canada, alendronate has approvals for indications including the treatment of glucocorticoid-induced osteoporosis.

10.3.1 Packaging and Labeling of Clinical Supplies

Alendronate will be purchased by the investigational pharmacy at the University of Alabama at Birmingham (Chris Chapleau, PHarmD; 205-975-0376). Labeling of study drug will be handled by the investigational pharmacy at University of Alabama at Birmingham. Study drug labeling will be annotated with the approved IRB protocol number(s). Dispensation of study drug will be handled by the investigational pharmacies at the UAB, ReumaClinic, University of Verona and NWZ. Study drug labeling will be annotated with the approved IRB protocol number(s).

10.3.2 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 pill case 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 alendronate will be destroyed by participating sites, and documentation of destruction will be entered into the study database. All drug supply returns will be made to the study drug packaging and shipment vendor specified in the list of external facilities and personnel.

10.3.3 Alendronate Preparation and Administration

Alendronate will be presented as tablets for oral administration contain 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 70 mg of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. All subjects randomized to alendronate arm will receive oral alendronate. All OS administration will be self-administered by patients randomized in the alendronate arm. Individuals will be instructed to assume alendronate orally following the procedures indicated in the drug label.

10.4 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).

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

- Risedronate (Actonel, Atelvia)
- Ibandronate (Boniva, Bonviva)
- Pamidronate (Aredia)
- Teriparatide (Forteo, Forsteo)
- Abaloparatide (Tymlos)
- Raloxifene (Evista)
- Estrogen or estroprogestinic treatment (Premarin, Prempro, Prefest, Ativella, Femhrt, Climara, Menostar, Vivelle)
- Denosumab 120 mg (Xgeva)

11 Statistical Considerations

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, larger clinical trials using other funding mechanisms.

11.1 Sample Size Justification

The sample size is based on feasibility needs to estimate the change in bone turnover marker (serum CTX) using alendronate, "early" zoledronic acid, and "late" zoledronic acid across the three switching arms at 6 months post-randomization. The study is descriptive in nature as a Phase II feasibility study, but based on data provided by Amgen Inc. from the Denosumab Adherence Preference and Satisfaction (DAPS) study. As can be seen from Table 2 below, the range of percent changes on CTX from the DAPS study ranges from -78.65% to 815.38% with the median a positive 11.5%. We chose the log of the change in serum CTX as the comparison because it greatly reduces the skewness and appears to show the most normally distributed assessments of change facilitating comparisons of mean or median treatment effects in the simplest and least distorted manner and because of the normality will enable the most efficient summary of the results using a parametric confidence interval in this small feasibility study. We will compare the log of the absolute difference in CTX calculated as CTX at 6 months post-randomization visit – CTX at randomization visit, equivalent to percent change, at the individual level for estimating the overall mean percent changes amongst individuals in each of the 3 switching groups. Based on data kindly provided by Amgen Inc. from the DAPS study, the mean change using the metric above was 0.11 with a standard deviation of 0.80 based on 59 participants in the alendronate arm. A sample size of 15 subjects per group produces a two-sided 95% confidence interval with a distance from the mean paired difference to the limits that is equal to 0.405 when the estimated standard deviation of the paired differences is 0.80 for characterizing the change within any one of the treatment groups. Group sample sizes of 15 produce a two-sided 95% confidence interval using a normal-distribution based on the pairwise differences between the three groups. The distance from the difference in mean log of the changes from randomization to 6 months post randomization is equal 0.573 for any pair of the switching groups when the estimated standard deviations are 0.80 in the alendronate arm. Given this is a feasibility study, we have not adjusted the Type I error level in these planned confidence intervals of the differences between the switching arms, although it is known that adjusted intervals for the 3 pairwise estimates would be at 98.3% confidence level if we used a Bonferonni Correction will be slightly wider, 0.697, but probably will not alter the decisions about future studies and thus, were not incorporated.

Table 2. Descriptive statistics for CTX data from the DAPS study used for sample size calculation

Variable	N	Mean	Std Dev	Minimum	Lower Quartile	Median	Upper Quartile	Maximum
% Change	59	53.79	146.28	-78.65	-35.00	11.50	103.31	815.38
*Diff in log(CTX)**	*59*	*0.11*	*0.80*	*-1.54*	*-0.43*	*0.11*	*0.71*	*2.21*
Cube root of % change	59	1.14	4.02	-4.28	-3.27	2.26	4.69	9.34
AUC	59	1.16	0.56	0.38	0.77	0.96	1.52	3.06
AUC baseline adjusted**	59	0.10	0.52	-1.12	-0.14	0.04	0.36	1.60

N: number of subjects with non-missing data
*: calculated as log(CTX at 18M) – log(CTX at 12M) at individual level.
**: with rectangle of baseline subtracted.

11.2 Data Management

Dr. Gary Cutter of the UAB School of Public Health will oversee all data management and analysis for the proposed study. Dr. Cutter and the study team at UAB will ensure that the data collected and analyzed for this study are of the highest quality possible and will be accomplished in part by having thorough edit checks as close to collection in time as possible, and updated as needed to guarantee high quality data through quality control and quality assurance. Edit checks will be reviewed by the statisticians, program manager, as well as other team members on an ongoing basis to evaluate whether any checks need to be added or any existing checks need to be modified. All data will be entered into the REDCap electronic Data Entry System (Nashville, TN) for seamless data management and auditing across the study sites. All analyses will be conducted using Statistical Analysis System (SAS; Cary, NC) Version 9.4 or higher or R-routines for specialty programs as needed.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the REDCap electronic Data Entry System. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

11.3 Statistical Analyses

Intervention groups will be compared on baseline characteristics and will include the following.

- Inclusion and Exclusion Criteria
- Demographics (e.g. race, age) and Baseline Characteristics
- Medical History
- Disease History (e.g. duration of disease)
- Medication History (e.g. previous doses of DMAB)
- Laboratory Values (e.g. serum CTX/P1NP)

Demographics will be summarized using descriptive statistics, by treatment group and site.

The analysis population will be the intent to treat population for analysis for both primary and secondary outcomes will include all randomized participants who received at least one dose of study medication (alendronate or zoledronic acid) during treatment period. While the sample size was evaluated using pairwise differences and normal distribution derived confidence intervals, the primary analysis will be conducted using all available data at 3 months (visit2) and 6 months (visit 3) post-randomization for the primary endpoint for log change in CTX in a repeated measures model that has treatment group as a fixed effect and participants as random effects to estimate the confidence intervals. This will assume that any individuals not completing the study who have a 3 month observation are missing at random, but will allow the use of the maximum number of participants and their observations. While statistical significance of the differences can be tested using these models, we do not propose hypothesis testing, but confidence intervals and effect size comparisons.

Sensitivity analyses will be conducted using imputation of the missing observations from the same treatment groups using 5 replicates and averaging the missing results. These two (ITT and imputed results) will be compared to the results of a completers analysis for the descriptive summarization.

Secondary endpoints will be similarly evaluated. CTX absolute and percent change (ng/mL; log transformed) 6 (visit 3) and 12 months post-randomization (visit 7) and P1NP absolute and percent change (µg/mL) 6, 12 months post randomization will utilized the mixed effects models. BMD at spine absolute and percent change (g/cm^2) 12 months post randomization; BMD at total-hip absolute and percent change (g/cm^2) 12 months post randomization; BMD at femoral neck absolute and percent change (g/cm^2) 12 months post randomization will be examined using the dependent variable as the BMD parameters, adjusted for baseline with comparisons of treatment groups. We will explore subgroup differences in outcomes between new and prevalent denosumab users, and descriptive analyses comparing the two sets of changes will be produced.

11.3 Interim Analyses

Not applicable

12 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 6 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. The safety officer may recommend at any point that the study be stopped if the risk-benefit assessment for continuance is deemed unfavorable.

Safety will be summarized by occurrence and per participant over the study descriptively, although no safety issues are expected.

12.1 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

12.2 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. The Safety Officer or the PI may call an emergency meeting at any time 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.

12.3 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.

12.4 Meeting Materials

The study staff, typically the statistician, will prepare report templates 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.

12.5 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 Serious Adverse Event (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.

The Safety Officer will prepare a formal report containing the recommendations for continuation or modifications of the study. 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, ReumaClinic, , University of Verona, and NWZ ethics committees.

12.6 Confidentiality

All materials, discussions, and proceedings of the Safety Officer are completely confidential. Meetings are expected to maintain confidentiality. A summary report of the Safety Officers recommendation will be provided to the IRB and Amgen annually.

13 Adverse Events (AE)

Definitions below incorporate guidelines provided by the Office of Human Research Protections (OHRP) of the DHHS and describes 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 zoledronic acid or alendronate. 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 zoledronic acid or alendronate 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]).

13.1 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 Principal 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 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

13.2 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. Suspected SUSARs will be reported to the IRB within 48 hours of the principal investigator becoming aware of the event, and to Amgen at the same time as the regulatory submission (w/in 15 days).

13.3 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.[19]

Table 3. Safety Data Reporting Timeline

Safety Data	**Timeframe for Submission to Amgen**
Suspected Unexpected Serious Adverse Reaction (SUSARs)	At time of regulatory submission (within 15 days)
Pregnancy/Lactation	Within 10 calendar days of investigator becoming aware
Annual Safety Report	At time of submission to any body governing or regulating research conduct (e.g., SO, IRB, etc)
Other Aggregate Analyses (any report containing safety data generated during the course of a study)	At time of submission to any body governing or regulating research conduct (e.g., IRB, etc)
End of Study Report*	At time of submission to any body governing or regulating research conduct (eg, RA, IRB, etc) but not later than 1 calendar year of study completion

*Specific requirements are to be outlined in the Research Agreement

13.3.1 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

13.3.2 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.

13.3.3 Severe AE

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

13.4 Adverse Event (AE) Classifications

13.4.1 Expected AE

The expected adverse effects of denosumab, zoledronic acid or alendronate could be found in the drug Investigator's Brochure. AEs will be collected as described in section 8.

13.4.2 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.

13.4.3 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).

13.4.4 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.

13.4.5 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.

13.5 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).

13.5.1 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

13.5.2 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

13.5.3 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

14 Investigational Study Sites

- University of Alabama at Birmingham; Birmingham, AL, United States
- ReumaClinic; Genk, Belgium
- University of Verona; Verona, Italy
- NoordWest Ziekenhuisgroep (NWZ); Alkmaar, Netherlands

Approximately 15 participants will be enrolled from each study site.

14.1 Site Recruitment

Investigational study sites will be three 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.

14.2 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

14.3 Site Monitoring

Since this is a three-site study, sites will be monitored by the PIs at each respective site (University of Alabama at Birmingham, ReumaClinic, University of Verona and NWZ) 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. University of Alabama at Birmingham, ReumaClinic,, University of Verona and NWZ will monitor recruitment utilizing automated reports generated from the study database. University of Alabama at Birmingham, ReumaClinic, University of Verona and NWZ 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.

15 Institutional Review Board (IRB)

The study will be conducted under the auspices of the IRBs at University of Alabama at Birmingham, ReumaClinic,, University of Verona and NWZ. 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.

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.

16 Administrative Procedures

16.1 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 UAB 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

16.2 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 ICH GCP[20]; 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.

16.3 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). This requirement also extends to Sub-Investigators.

16.4 Confidentiality and Privacy

Participant confidentiality and privacy will be strictly held in trust by the participating investigators, their staff, and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. All research activities will be conducted in as private a setting as possible.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the REDCap electronic Data Entry System. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be archived at UAB. Study participants will be informed that their identifiable information may be reviewed by health regulators.

16.5 Study Reports

Annually, the study team will provide to Amgen copies of all reports related to study safety. These including annual safety reports filed with the IRB, FDA reports (if required), reports to/from the Safety Officer. In addition, within 1 calendar year of study completion the study team will provide to Amgen an End of Study Report that will detail study findings and aggregate analyses.

16.6 Publication of results

It is mandatory that the first publication will be based on data from all three 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.

16.7 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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