Document Coversheet

Study Title: A Phase II Multicenter, Single Arm, Open-Label Trial to Evaluate the Efficacy and Safety of Denosumab in Treatment of Post-Allogenic Hematopoietic Stem Cell Transplant Bone Loss

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PROTOCOL TITLE:

A Phase II Multicenter, Single Arm, Open-Label Trial to Evaluate the Efficacy and Safety of Denosumab in Treatment of Post-Allogenic Hematopoietic Stem Cell Transplant Bone Loss

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Confidentiality Statement

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1. OBJECTIVES

1.1 Primary Objective

- To evaluate the efficacy and safety of denosumab therapy for the treatment of bone loss in patients who have received an allogeneic hematopoietic stem cell transplant.

2 BACKGROUND

2.1 Bone Health in Hematopoietic Stem Cell Transplant

Allogeneic Hematopoietic Stem Cell Transplant (HSCT) is a curative treatment of hematologic malignancies but can have varying effects on quality of life due to complications. [1]Amongst survivorship monitoring in these patients bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) scan is commonly monitored due to accelerated bone loss from the effects of previous chemotherapy, the HSCT, and/or administration of steroids. Previous research has shown on average a patient undergoing HSCT can expect to have a decrease in BMD by 3.5% to 8.5% correlating with 7 to 17 years of bone loss with in a 4-month time frame after HSCT. [2]Furthermore, accelerated bone loss exponentially increases the risk of a fracture with 10% to 15% of bone loss correlated to a doubling of the fracture risk regardless of osteopenia/osteoporosis status. This is leading to direct and indirect increases in treatment costs as well as a hindrance to the quality of life of post-HSCT patients. [3]

Currently, bisphosphonate therapy including zoledronic acid infusions have shown benefit in slowing and even reversing the effects of bone loss in HSCT patients but can be associated with adverse effects, including infusion reactions associated with fevers and flu-like symptoms, which can lead to unsubstantiated evaluation and treatment of infection, decreased compliance, and even discontinuation. [4]Denosumab is a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor which is also currently approved for treatment of osteoporosis and is less likely to be associated with the same injection reactions as zoledronic acid (http://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/prolia/prolia_pi.ashx). Currently, there has been minimal data produced on the efficacy and safety of denosumab in HSCT patients. To address this lack of published data, Roswell Park and Cleveland Clinic are proposing a joint phase 2 study to evaluate the utility of denosumab in post-allogeneic HSCT patients.

2.2 Denosumab

Denosumab is a fully human monoclonal antibody with high affinity and specificity to RANK Ligand (RANKL) leading to decreased activation. Denosumab has high specificity to RANKL while being devoid of activity towards other members of the tumor necrosis factor (TNF) family including TNFα, TNFβ, TNF-related apoptosis-inducing ligand (TRAIL), or CD40 ligand. Down regulation of RANKL caused by denosumab decreases bone resorption by indirect inhibition of osteoclast formation, leading to an increase in bone mass and strength.

Currently, denosumab is approved in the United States (US) for treatment of osteoporosis in postmenopausal women as well as men at increased or high risk for fracture, bone loss due to

hormone-ablation therapy in men with prostate cancer as well as women with breast cancer at high risk for fracture.

A detailed discussion of the preclinical pharmacology, pharmacokinetics, and toxicology of denosumab can be found in the Investigator's Brochure.

2.2.1 Mechanism of Action

Denosumab Binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Prolia prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/ RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

2.2.2 Preclinical Pharmacology and Pharmacokinetics

Onset of action: Decreases markers of bone resorption by ~85% within 3 days; maximal reduction observed within 1 month.

Duration: Markers of bone resorption return to baseline within 12 months of discontinuing therapy[2]

Bioavailability: SubQ: 62%

Half-life elimination: ~25 to 28 days

Time to peak: 10 days (range 3 to 21)

Elimination: Clearance may occur via reticuloendothelial system; renal excretion not expected

2.2.3 Toxicology/ Interactions

No preclinical drug-drug interactions were studied using Denosumab.

In ovariectomized monkeys, once-monthly treatment with Denosumab suppressed bone turnover and increased bone mineral density and strength of cancellous and cortical bone at doses 50-fold higher than the recommended human dose of 60 mg administered once every 6 months, based on body weight. Bone tissue was normal with no evidence of mineralization defects, accumulation of osteoid or woven bone.

Adolescent primates treated with Denosumab at doses >10 times higher than the recommended human dose of 60 mg administered once every 6 months, based on mg/ kg, had abnormal growth plates, considered to be consistent with the pharmacological activity of Denosumab.

RANK/ RANKL knockout mice exhibited absence of lymph node formation, as well as an absence of lactation due to inhibition of mammary gland maturation. Neonatal RANK/ RANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. A corroborative study in 2-week-old rats given the RANKL inhibitor also showed reduced bone growth, altered growth plates, and impaired tooth eruption.

2.3 Clinical Studies with Denosumab

2.3.1 Osteoporosis in Postmenopausal Women at High Risk for Fracture

A 3-year, randomized, double-blind, placebo-controlled trial enrolled postmenopausal women with baseline BMD T-scores between -2.5 and -4.0 at either the lumbar spine or total hip:

A total of 7808 woman were enrolled with a mean age of 72 years and either received denosumab 60 mg (n=3902) or placebo (n=3906) every 6 months along with 1000 mg calcium and 400 IU vitamin D daily. The primary efficacy variable was incidence of vertebral fracture after 3 years. The incidence of new vertebral fractures was clinically significant ($P < 0.0001$) between the placebo group (7.2%) compared to the denosumab group (2.3%) over the 3-year period. This produced an absolute risk reduction of 4.8% and a relative risk reduction of 68%. A secondary outcome of the study was incidence of hip fractures which was clinically significant (P=0.04) as well between the placebo group (1.2%) compared to the denosumab group (0.7%) after 3 years. This produced an absolute risk reduction of 0.3% and a relative risk reduction of 40%.

2.3.2 Osteoporosis in Men at High Risk for Fracture

A 1-year, randomized, double-blind, placebo-controlled trial enrolled men with baseline BMD T-scores between -2.0 and -3.5 as well as men with previous fractures with BMD T-scores between -1.0 and -3.5 at the lumbar spine or femoral neck:

A total of 242 men were enrolled with a mean age of 65 years and either received denosumab 60 mg (n=121) or placebo (n=121) every 6 months along with 1000 mg calcium and 400 IU vitamin D daily. The primary efficacy variable was percentage change in the BMD of the lumbar spine, total hip, and femora neck from baseline to 1 year. The treatment differences were 4.8% [(+0.9% placebo, +5.7% denosumab (95% CI 4.0, 5.6), $p< 0.0001$)] at lumbar spine, 2% (+0.3% placebo, +2.4% denosumab) at the hip, and 2.2% (0.0% placebo, +2.1% denosumab) at femoral neck.

2.3.3 Treatment of Bone Loss in Men with Prostate Cancer

A 3-year, randomized, double-blind, placebo-controlled, multinational study:

The trial enrolled men < 70 years of age with baseline BMD T-scores between -1.0 and -4.0 at the lumbar spine, total hip or femoral neck, or had a history of osteoporotic fracture. A total of 1468 men were enrolled with a median age of 76 years (Range: 48 to 97 years) and either received denosumab 60 mg (n=734) or placebo (n=734) every 6 months for a total of 6 doses along with 1000 mg calcium and 400 IU vitamin D daily. The primary efficacy variable was percentage change in the BMD of the lumbar spine from baseline to 2 years. The treatment differences were 6.7% (-1.0% placebo, +5.6% denosumab; (95% CI 6.2, 7.1); $p< 0.0001$)

2.3.4 Treatment of Bone Loss in Women with Breast Cancer

A 2-year, randomized, double-blind, placebo-controlled, multinational study:

The trial enrolled women with baseline BMD T-scores between -1.0 and -2.5 at the lumbar spine, total hip or femoral neck, and had not experienced a fracture after age 25. A total of 252 women were enrolled with a median age of 59 years (Range: 35 to 84 years) and either received denosumab 60 mg (n=127) or placebo (n=125) every 6 months for a total of 4 doses along with 1000 mg calcium and 400 IU vitamin D daily. The primary efficacy variable was percentage change in the

BMD of the lumbar spine from baseline to 1 year. The treatment differences were 5.5% [(-0.7% placebo, +5.5% denosumab, (95% CI 4.8, 6.3); p< 0.0001)].

2.4 Rationale

Fractures due to bone loss in HSCT patients have been shown to have an enormous effect on patient satisfaction and quality of life. Denosumab has been proven to not only decrease the rate of bone loss but also reverse the effects in both cancer patients as well as the general public. This study intends to prove that denosumab is a viable option to prevent HSCT-associated bone loss thus decreasing the risk of fractures in this patient population. This study is intended to evaluate these effects in all patients with any statistically bone loss from the pre-transplant DXA to the post-transplant DXA and/or osteopenia/osteoporosis at any DXA (pre or post-transplant).

3 INCLUSION AND EXCLUSION CRITERIA

3.1 Inclusion Criteria

To be included in this study, participants must meet the following criteria:

1. The patient is ≥ 18 years.
2. The patient has undergone an Allogeneic Hematopoietic Stem Cell Transplant.
3. The patient has completed a base line DXA scan ≤ 6 months prior to transplantation.
4. The patient has completed a post-transplant DXA scan at Day 100 (±30 days) or up to 6 months post transplantation.
5. The patient has completed and passed a dental clearance exam up to 6 months prior to transplant or 6 months after transplant.
6. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
7. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

Refer to **Appendix A** for the ***ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA*** checklist.

3.2 Exclusion Criteria

Participants will be excluded from this study for the following:

1. The patient has a history of a hypersensitivity reaction to denosumab.
2. The patient has a history of osteonecrosis of the jaw.
3. The patient has predisposing risk factors for hypocalcemia including the following:
    a. Hypoparathyroidism
    b. CrCl < 30 mL/min
    c. Dialysis

d. Malabsorption Syndrome

4. The patient has history of any bone fracture ≤ 30 days prior to denosumab therapy.
5. Pregnant or nursing female patients.
6. The patient has clinically significant GVHD leading to hospitalization at the time of denosumab dose per prescriber discretion.
7. The patient has clinically significant infection leading to hospitalization at the time of denosumab dose (excluding hospitalization due to complexity of treatment leading to inability to treat outpatient, i.e., Foscarnet) per prescriber discretion.
8. The patient is unwilling or unable to follow protocol requirements.
9. The patient has any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug including relapsed malignancy.

Refer to **Appendix B** for the ***ELIGIBILITY VERIFICATION FORM: EXCLUSION CRITERIA*** checklist.

3.3 Special Populations

The following special populations are excluded from this study:

- Cognitively impaired adults/adults with impaired decision-making capacity
- Individuals who are not yet adults (infants, children, teenagers)
- Prisoners
- Pregnant women

3.4 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

4 LOCAL AND STUDY-WIDE NUMBER OF SUBJECTS

A target of 114 participants (a maximum of 150 participants and a minimum of 100 evaluable participants) at multiple sites, including Roswell Park, will be enrolled over a 3.6-year period with enrollment to conclude by August 2022.

5 LOCAL AND STUDY-WIDE RECRUITMENT METHODS

Participants will be identified/recruited/screened from patients at the BMT clinic at Roswell Park and participating sites and from multi-disciplinary conference discussion.

6 MULTI-SITE RESEARCH

Two centers will be enrolling in this study in parallel single-center studies. The data will be jointly analyzed from Roswell Park Cancer Institute and the Cleveland Clinic.

This is a multi-site study. It is the responsibility of the lead investigator to ensure that:

- All sites have the most current version of the protocol, consent document, and HIPAA authorization.

- All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).
- All modifications have been communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented.
- All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.
- All local site investigators will conduct the study in accordance with applicable federal regulations and local laws.
- All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Refer to: Instructions for Multi-Site Studies (**Appendix F**) for additional details.

7 STUDY TIMELINES

A maximum of 150 participants, at multiple sites including Roswell Park, will be enrolled. Accrual is expected to take up to 3.6 years with enrollment to conclude by August 2022, with follow-up for 12 months from the start of investigational treatment. We will attempt to enroll 75 patients at Roswell Park and 75 patients at the Cleveland Clinic with a goal of 57 evaluable patients at each site for a total of 114 evaluable patients. In the event that one site reaches that site's expected accrual number goal before the other site's goal is met, the site that has reached the site expected accrual may continue to enroll patients in order to contribute to the overall accrual goal.

Patient's participation in the study will be initiated with enrollment and last for approximately 365 days with completion of "Day 465" DXA Scan.

Patients will be given a maximum of two (2) subcutaneous doses of denosumab 60 mg during the study time frame.

The time frame to enroll all patients will take up to 3.6 calendar years from the initiation of the study with enrollment to conclude by August 2022, and completion of data collection will take 365 days from the final patient enrolled. We estimate preliminary analyses will be completed 2 years after the completion of the study accrual.

8 STUDY ENDPOINTS

8.1 Primary Endpoint(s)

- The primary endpoint will be BMD on "Day 465" DXA Scans (**Appendix E**) in comparison to "Day 100" DXA scans based on the percent change in BMD (g/cm^2) in the Total hip and/or lumbar spine between the two time points. Stabilization of BMD will be defined as a Least Significant Change (LSC) in BMD from "Day 100" DXA to "Day 465" DXA while improvement will be defined as any increase in BMD from "Day 100" DXA to "Day 465" DXA.

8.2 Secondary Endpoints

Secondary endpoints include:

- Percent change in BMD between the pre-HSCT and the Day 465 DXA scans for Total hip and/or lumbar spine (L1-L4)
- Frequency of bone fractures
- Frequency of adverse effects of denosumab (see section 17) including but not limited to the following:
    - Injection/Hypersensitivity related reactions
    - Osteonecrosis of the jaw
    - Graft Versus Host Disease

9 DESIGN

This is a Phase II, multicenter, single-arm, open-label study designed to evaluate the efficacy and safety of denosumab therapy for the treatment of BMD loss in allogeneic HSCT patients. Eligible patients must have been treated with an allogeneic HSCT and at the "Day +100" DXA scan must have decrease in BMD compared to the pre-transplant DXA scan, or have osteopenia, and/or osteoporosis on either the pre-HSCT or Day +100 (up to 6 months) post-HSCT DXA scan.

This is a Phase II multicenter, single-arm, open-label study where all patients who meet inclusion criteria will receive the study drug (denosumab). All patients will be followed for about 1 year after the first dose of denosumab and/or a minimum of 15 months post HSC infusion (Day 0). A total of 150 patients will be accrued. Assuming 80% complete the follow-up period, 114 patients should be evaluable for the primary endpoint. Patients with a Day +100 and Day +465 DXA scans, and who received at least one dose of denosumab, will be considered evaluable for response/efficacy. Response/Efficacy will be based on stabilization and/or improvement of BMD (defined in Section 8.1). Patients who received at least one dose of denosumab will be evaluable for safety.

10 TREATMENT

Reported adverse events (AEs) and potential risks are described in **Section 13**. Appropriate dose modifications are described in **Section 10.2.**

Treatment is intended for an outpatient setting. However, at the investigator's/physician's discretion, the participant may receive treatment as an inpatient, if deemed necessary.

10.1 Dosing and Administration

<u>Denosumab</u>

- Dose: 60 mg prefilled syringe
- Administration Route: Subcutaneous Injection (See **Appendix D**)
    - All subjects will receive one subcutaneous (SC) injection administered in the subject's upper arm, upper thigh, or abdomen by an experienced and qualified staff

member. It is recommended that all subjects be closely observed for approximately 30 minutes after 1st dosing with IP.

- Patients are to be evaluated for hypocalcemia (corrected calcium < 8.4 mg/dL and/or ionized calcium < 1.19 mmol/L) prior to administration (See **Appendix C**) and this should be corrected prior to administration of denosumab.

- Frequency: Every 6 months for a maximum of 2 doses
  - Dose #1: Receive between Day 70 and Day 130
  - Patients should be monitored for a minimum of 30 minutes after their 1st dose due to risk of hypersensitivity reactions
  - Dose #2: Receive between Day 250 and Day 310

10.2 Dose Modifications and Treatment Delays

This medication is commercially available, and all treatment delays should be determined as specified from the treating clinician. There will be no dose modifications based on the product being only commercially available as a prefilled syringe.

(https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125320s181lbl.pdf)

10.3 General Concomitant Medication and Supportive Care

Participants should not be given any concomitant bone strengthening agents including bisphosphonates.

Administration of calcium and vitamin D as necessary to treat or prevent hypocalcemia will be per the physician's discretion.

10.4 Duration of Treatment

Participants may remain on study and receive the two (2) doses of denosumab in the absence of disease progression, unacceptable toxicity or withdrawal from study, inter-current illness that prevents further administration of treatment, participant demonstrates an inability/refusal to comply with medication regime and, participant withdraws from study or as per discretion of the providing clinician.

10.5 Off-Study Treatment

At the discretion of the treating physician, patients may continue to be treated with any available agent once they are off study treatment.

11 PROCEDURES INVOLVED

The study-specific assessments are detailed in this section and outlined in Appendix C: Schedule of Procedures and Observations.

Baseline and/or Screening assessments must be performed within 14 days prior to the first dose of investigational product, unless otherwise indicated. Any results falling outside of the reference

ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed a window of ± 30 days unless otherwise noted.

11.1 Participant Registration

Eligibility of each participant will be established prior to study enrollment.

Informed consent **MUST** be completed prior to receiving any study related procedures.

11.2 Correlative Studies

BMD studies by DXA scan will be performed on patients prior to HSCT as well as Day 100 ± 30 days (up to 6 months) (both as part of BMT standard of care) and Day 465(± 60 days) post HSCT. These studies will include BMD (g/cm^2), T-score (standard deviations), and change from baseline (%).

12 WITHDRAWAL OF SUBJECTS

12.1 Treatment Discontinuation

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Progressive disease (Per Physician Discretion)
- Toxicity: treatment related or unrelated
- Hypersensitivity Reaction
- Osteonecrosis of the Jaw
- Any bone fracture
- Investigator judgment
    - The Investigator may discontinue a participant if, in his/her judgment, it is in the best interest of the participant to do so.
- Noncompliance
- Participant voluntary withdrawal
    - A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.
- Sponsor decision.

13 RISKS TO SUBJECTS

Most common adverse reactions reported for denosumab for the following indications:

- Postmenopausal osteoporosis: Most common adverse reactions (> 5% and more common than placebo) were: back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Pancreatitis has been reported in clinical trials.
- Male osteoporosis: Most common adverse reactions (> 5% and more common than placebo) were: back pain, arthralgia, and nasopharyngitis.
- Bone loss due to hormone ablation for cancer: Most common adverse reactions (≥ 10% and more common than placebo) were: arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials.

14 POTENTIAL BENEFITS TO SUBJECTS

Patients may have stabilization and/or improvement of bone mineral density after administration of denosumab. This may decrease the risk of future adverse events associated with bone loss after transplantation including fractures.

15 DATA AND SPECIMEN BANKING

Not Applicable.

16 MEASUREMENT OF EFFECT

16.1 Bone Density Status

Bone Density Status: "Day 465" DXA scans [(465 days ± 60 days from transplantation (Day 0)] obtained in comparison to Day +100 ± 30 days (up to 6 months from transplantation) DXA scans based on percent change in Bone Mineral Density in both the Total Hip and lumbar spine (L1-L4).

16.2 Other Response Parameters

Patients will also be evaluated based on percentage change in BMD (g/cm^2) from pre-HSCT to Day 465 post-HSCT.

17 SAFETY EVALUATION

17.1 Adverse Events

Only grade 3 or greater adverse events will be captured, with an exception for events of special interest. All grades of events of special interest will be captured and reported to Amgen. Events of special interest include: pregnancy, lactation, fractures, and osteonecrosis of the jaw and infusion reactions (study drug only).

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed.

17.1.1 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

17.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF. However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

17.1.3 Abnormal Laboratory Values

Only clinically significant (Grade 3-5) laboratory abnormalities that do not predate the 1st infusion of the investigational agent, that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated blood potassium level of 7 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

17.1.4 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

17.2 Grading and Reporting Adverse Events

17.2.1 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 5 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 5 of the CTCAE is identified and located at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology and documented according to the grading scales provided in the CTCAE Version 5. The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.
- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

17.3 Reporting Adverse Events

Significant AEs (grade 3-5) which are new and considered probable or definite in relation to the investigational agent that are occurring between the start date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

17.4 Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor is probable or definite in relation to the investigational agent and results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

17.4.1 Reporting Serious Adverse Events

All new SAEs meeting the above definition occurring from the date the participant signs consent for the investigational study until 30 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The Roswell Park SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30-day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs as unexpected and possibly, probably, or definitely related must be reported as an Unanticipated Problem. Please refer to Section 17.7.1 for details on reporting Unanticipated Problems.

17.5 Investigator Reporting: Notifying the Study Sponsor

Investigators MUST report (within 1 business day upon becoming aware), to the sponsor ANY Serious Adverse Events that are considered probable or definite in relation to the investigational agent(s)/intervention.

17.6 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

17.7 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
    - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
    - The characteristics of the participant population being studied.

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized or if in relation to an AE is deemed Serious per Section 17.3.

17.7.1 Reporting Unanticipated Problems:

The Reportable New Information (RNI) Form will be submitted to the CRS Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS QA Office with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems to the IRB in accordance with their local institutional guidelines.

17.8 Amgen Safety Reporting

Amgen Adverse Event Reporting Process:

Safety Data	**Timeframe for submission to Amgen**
Suspected Unexpected Serious Adverse Reactions (SUSARs)	Sent to Amgen at time of regulatory submission
Pregnancy/Lactation	Within 10 calendar days of Sponsor awareness
Annual Safety Report (e.g., EU Clinical Trial Directive [CTD] DSUR, and US IND Annual Report)	Annually
Other Aggregate Analyses (any report containing safety data generated during the course of a study)	Sent to Amgen at time of regulatory submission (e.g., FDA, IRB)
Final (End of Study Report, including): • Reports of unauthorized use of a marketed product	Sent to Amgen at time of regulatory submission (e.g., FDA, IRB) but not later than 1 calendar year of study completion

17.9 FDA Reporting

Roswell Park is not the IND holder and therefore this section is not applicable.

18 DATA MANAGEMENT AND CONFIDENTIALITY

18.1 Data Collection

Full build studies are managed by Roswell Park CRS Data Management for analysis by Roswell Park Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.

Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. CRS Data Management designs the study-specific database and facilitates development by the Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

18.2 Maintenance of Study Documents

Essential documents will be retained per Roswell Park's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with Roswell Park.

18.3 Revisions to the Protocol

Roswell Park may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

18.4 Termination of the Study

It is agreed that, for reasonable cause, either the Roswell Park Investigators or the Sponsor, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, Roswell Park may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

18.5 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

19 STATISTICAL PLAN

The primary objective is to show the effectiveness of denosumab on stabilization and/or improvement of BMD (defined in Section 8.1) in allogeneic HSCT patients who have experienced either BMD loss between baseline (pre-HSCT) and Day +100 (up to 6 months) post-HSCT, or who have osteopenia or osteoporosis at either the pre-BMT or Day+100 (up to 6 months) post-HSCT DXA scan. DXA scans will be obtained at baseline (pre-HSCT), at time of enrollment (Day

+100, (up to 6 months) post- HSCT) and at Day +465 post- HSCT. The primary endpoint will be the slope in bone mineral density (g/cm^2) regressed on time from the time of enrollment to Day 465 post HSCT in both Total Hip and lumbar spine (average of L1-L4).

The primary analysis for both the Total Hip and lumbar spine will consist of a regression model of the percent change from enrollment to Day 465 post HSCT regressed on the enrollment BMD levels, which is a more stable approach to modeling percent change type outcomes in terms of model assumptions. The analysis model will be fit using Ordinary Least Square (OLS) methods. A secondary model will include and expand upon a list of covariates to explore the effects of demographic, disease and treatment characteristics on BMD loss and effectiveness of denosumab using an analysis-of-covariance (ANCOVA) model. Examples of covariates to be tested are age, sex, corticosteroid exposure, and graft-versus-host disease. Given the assumed high degree of correlation between the Total Hip and lumbar spine percent change values, both models will be tested at alpha=0.05 (two-sided). Residual plots and other diagnostic methods will be used to evaluate compliance with model assumptions and goodness of fit.

It is assumed under the null that the historical percent change in BMD from enrollment in the Total Hip is -6.3% and for the lumbar spine is -2.3%, which translates to testing in our regression model about the hypotheses $H_0: \beta_1 = -0.063$ vs $H_a: \beta_1 \neq -0.063$ and $H_0: \beta_1 = -0.023$ vs $H_a: \beta_1 \neq -0.023$ for the Total Hip and lumbar spine, respectively.

19.1 Sample Size Determination

BMD will be reported in g/cm^2. We are setting the sample size target to n=114 evaluable subjects assuming a 20% drop-out rate between enrollment and Day 465 post BMT. Setting power to 0.80 we will be able to detect a regression coefficient for the Total Hip different from $\beta_1 = -0.063$ of -0.050 or larger and we will be able to detect a regression coefficient for the lumber different from $\beta_1 = -0.023$ of -0.016 or larger, respectively, assuming a standard deviation for the Total Hip BMD percent change of 5% and a standard deviation for the lumber BMD percent change of 2.5%.

19.2 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

19.3 Efficacy Analysis

Objective BMD response will be tabulated overall. Only participants who have completed at least one dose of denosumab and both study DXA scans will be evaluable for response.

19.4 Adverse Events

The frequency of toxicities will be tabulated by grade. The frequency of toxicities will also be tabulated. All participants who receive at least one dose of denosumab will be evaluable for toxicity.

19.5 Interim Analysis and Criteria for Early Termination of the Study

No explicit interim analyses are planned for this study.

19.6 Correlative Data Analysis

20 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

The Roswell Park Data and Safety Monitoring Committee will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMC will review the study and will make recommendations that include but not limited to: (a) continuation of the study, (b) modifications to the design, (c) suspension of, or (d) termination of the study.

21 VULNERABLE POPULATIONS

Not Applicable.

22 COMMUNITY-BASED PARTICIPATORY RESEARCH

Not Applicable.

23 SHARING OF RESULTS WITH SUBJECTS

Individual response data is shared with the participant as a part of their clinical care.

24 SETTING

All treatment will be conducted on an outpatient basis at BMT clinic at Roswell Park and the Cleveland Clinic. Potential study participants will be identified and recruited from current BMT clinic patients and from community referral.

25 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

26 RESOURCES AVAILABLE

Not Applicable.

27 PRIOR APPROVALS

Not Applicable.

28 COMPENSATION FOR RESEARCH-RELATED INJURY

If the subject believes they have been injured as a direct result of their participation in this research study, they will be advised to notify the Roswell Park Patient Advocate at (716) 845-1365 or the Study Doctor at (716) 845-8412.

Medical diagnosis and treatment for the injury will be offered, and a determination will be made regarding appropriate billing for the diagnosis and treatment of the injury. A financial counselor

(716-845-3161) will be able to provide an explanation of coverage and to answer questions the subject may have regarding study related billing.

The subject is not prevented from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

29 ECONOMIC BURDEN TO SUBJECTS

The participants will not be subject to any economic burden.

30 CONSENT PROCESS

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given. Consent and enrollment will occur after "Day 100" DXA is completed as this will be the main determination of eligibility of patients.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act (HIPAA) regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

31 PROCESS TO DOCUMENT CONSENT IN WRITING

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator or designee shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form

must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

32 DRUGS OR DEVICES

32.1 Denosumab (Prolia®)

32.2 Active Substance and Source

Denosumab is supplied in a single-use prefilled syringe (PFS) containing 60 mg in a 1 mL solution. Each PFS is intended for single use only.

32.3 Drug Shipment

Denosumab will be provided by Amgen and will be shipped by Amgen to each participating site.

32.4 Preparation for Administration

Denosumab needs to be visually inspected for discoloration or particulate matter as it should be a clear, colorless to pale yellow solution that may contain trace amounts of translucent to white particles. The solution should be discarded if discolored or cloudy or contains foreign particulates.

Prior to administration denosumab may be removed from the refrigerator and brought to room temperature (up to 25°C/77°F) by standing in the original container for 15-30 minutes. Do not warm in any other way.

Please refer to the Pharmacy Guide for additional details.

32.5 Storage and Stability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility and, in accordance with the applicable regulatory requirements.

Store denosumab in a refrigerator at 2°C to 8°C in the original carton: *Do not freeze*.

Prior to administration, denosumab **may** be allowed to reach room temperature (up to 25°C) in the original container. Once removed from the refrigerator, denosumab must not be exposed to temperatures above 25°C and must be used within 24 hours, once at room temperature. If not used within 24 hours, denosumab should be discarded. Protect from direct light and heat. Avoid vigorous shaking of denosumab.

Drug storage temperature will be maintained and recorded, as applicable.

33 REFERENCES

1. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med 2006;354:1813-26.

2. Yao S, Smiley SL, West K, et al. Accelerated bone mineral density loss occurs with similar incidence and severity, but with different risk factors, after autologous versus allogeneic hematopoietic cell transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2010;16:1130-7.

3. Faulkner KG. Bone matters: are density increases necessary to reduce fracture risk? Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2000;15:183-7.

4. Pundole X, Cheema HI, Petitto GS, Lopez-Olivo MA, Suarez-Almazor ME, Lu H. Prevention and treatment of bone loss and fractures in patients undergoing a hematopoietic stem cell transplant: a systematic review and meta-analysis. Bone marrow transplantation 2017;52:663-70.

34 APPENDICES

Appendix A ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA

Participant Name: (Multi-site: use participant initials): _____

Medical Record No.: (Multi-site: use participant IDs): _____

Title: A Phase II, Open-Label, Multicenter Trial to Evaluate the Efficacy and Safety of Denosumab in Treatment of Post-Allogenic Hematopoietic Stem Cell Transplant Bone Loss

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. The patient is ≥ 18 years.	
☐	☐	☐	2. The patient has undergone an Allogeneic Hematopoietic Stem Cell Transplant.	
☐	☐	☐	3. The patient has completed a base line DXA scan ≤ 6 months prior to transplantation.	
☐	☐	☐	4. The patient has completed a post-transplant DXA scan at Day 100 (± 30 days) or up to 6 months post transplantation.	
☐	☐	☐	5. The patient has completed and passed a dental clearance exam up to 6 months prior to transplant or 6 months after transplant.	
☐	☐	☐	6. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.	
☐	☐	☐	7. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____Date: _____

Printed Name of Investigator: _____

Appendix B ELIGIBILITY VERIFICATION FORM: EXCLUSION CRITERIA

Participant Name: (Multi-site: use participant initials): _____

Medical Record No.: (Multi-site: use participant IDs): _____

Title: A Phase II, Open-Label, Multicenter Trial to Evaluate the Efficacy and Safety of Denosumab in Treatment of Post-Allogenic Hematopoietic Stem Cell Transplant Bone Loss

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. The patient has a history of a hypersensitivity reaction to denosumab.	
☐	☐	☐	2. The patient has a history of osteonecrosis of the jaw.	
☐	☐	☐	3. The patient has predisposing risk factors for hypocalcemia including the following: a. Hypoparathyroidism b. CrCl< 30 mL/min c. Dialysis d. Malabsorption Syndrome.	
☐	☐	☐	4. The patient has history of any bone fracture≤ 30 days prior to denosumab therapy.	
☐	☐	☐	5. Pregnant or nursing female participants.	
☐	☐	☐	6. The patient has clinically significant GVHD leading to hospitalization at the time of denosumab dose per prescriber discretion.	
☐	☐	☐	7. The patient has clinically significant infection leading to hospitalization at the time of denosumab dose (excluding hospitalization due to complexity of treatment leading to inability to treat outpatient (i.e. Foscarnet)) per prescriber discretion.	
☐	☐	☐	8. The patient is unwilling or unable to follow protocol requirements.	
☐	☐	☐	9. The patient has any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**
If "NO", do not enroll participant in study.

Investigator Signature: _____ Date: _____

Printed Name of Investigator: _____

Appendix C Schedule of Procedures and Observations

Evaluation	Baseline (Pre-Transplant Evaluation)	Cycle 1-Day 100 (± 30 days)	Cycle 2-Day 280 (± 30 days)	End of Treatment: Day 465(± 60 days)	Follow-Up[2]
Patient Consent		X			
Medical History	X				X
Pre-Existing Conditions	X				
Physical Examination (including vital signs[3])	X				X
Chemistry[4]	X	X[1]	X[1]		
ECOG Performance Status	X				
Dental Clearance[5]	X	X			
DXA Scan	X	X[6]		X	
Denosumab		X	X		
Concomitant[7] Medications		X	X		
Adverse Events		X	X	X	
Off-Study Treatment					X[8]

1. Performed day of treatment prior to denosumab administration to evaluate for hypocalcemia.
2. Follow-up safety evaluations will occur 6 months after discontinuation of study medication for evaluation of vertebral/femoral fractures.
3. Vital signs: temperature, heart rate, respiratory rate, blood pressure, body weight, and height. Height collected at baseline only.
4. Chemistry (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
5. The dental clearance exam is either up to 6 months prior to transplant or 6 months after transplant.
6. The post-transplant DXA scan (Day 100) may be up to 6 months after transplant.

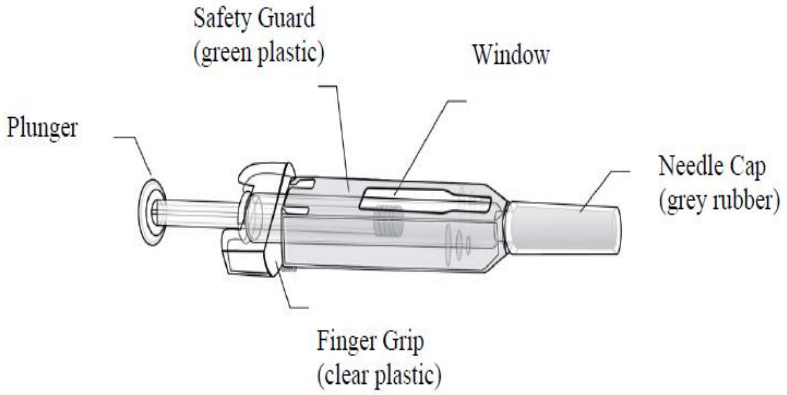
7. Only pertains to vitamin D, calcium (as necessary to treat or prevent hypocalcemia, per physician's' discretion), any other bone strengtheners (if so, which one(s)), or for the treatment of an adverse drug reaction. See Section 10.3.
8. At the discretion of the treating physician, patient may continue to be treated with any available agent once they are off study treatment, when clinically necessary. At the discretion of the treating physician, patient may continue to be treated with any available bone strengthening agent after the end of treatment DXA Scan, as clinically necessary. Subsequent bone strengtheners taken during the follow-up period will be captured as concomitant medications.

Appendix D Prefilled Syringe Instructions

Instructions for Prefilled Syringe with Needle Safety Guard

IMPORTANT: In order to minimize accidental needlesticks, the Prolia single-use prefilled syringe will have a green safety guard; manually activate the safety guard after the injection is given.

DO NOT slide the green safety guard forward over the needle before administering the injection; it will lock in place and prevent injection.

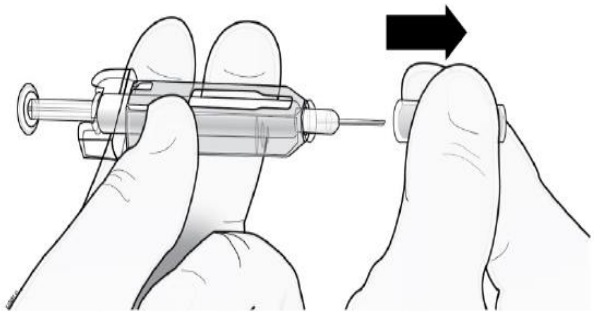


Activate the green safety guard (slide over the needle) after the injection.

The grey needle cap on the single-use prefilled syringe contains dry natural rubber (a derivative of latex); people sensitive to latex should not handle the cap.

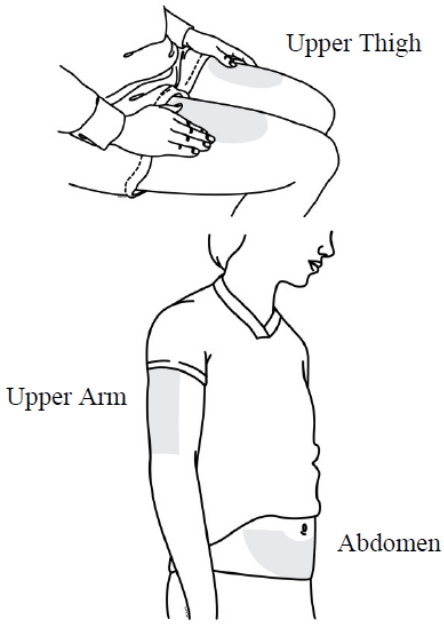
Step 1: Remove Grey Needle Cap

Remove needle cap.

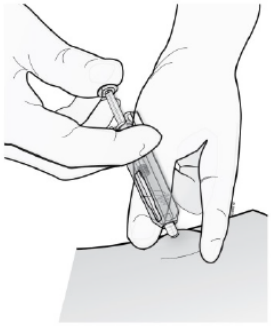


Step 2: Administer Subcutaneous Injection

Choose an injection site. The recommended injection sites for Prolia include: the upper arm OR the upper thigh OR the abdomen.



Insert needle and inject all the liquid subcutaneously. Do not administer into muscle or blood vessel.



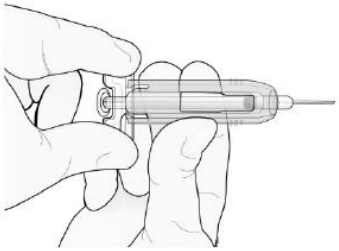
DO NOT put grey needle cap back on needle.

Step 3: Immediately Slide Green Safety Guard Over Needle

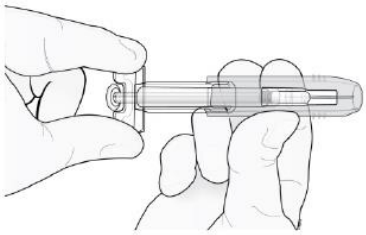
With the *needle pointing away from you…*

Hold the prefilled syringe by the clear plastic finger grip with one hand. Then, with the other hand, grasp the green safety guard by its base and gently slide it towards the needle until the green safety guard locks securely in place and/or you hear a "click." **DO NOT** grip the green safety guard too firmly - it will move easily if you hold and slide it gently.

Hold clear finger grip.



Gently slide green safety guard over needle and lock securely in place. Do not grip green safety guard too firmly when sliding over needle.



Immediately dispose of the syringe and needle cap in the nearest sharps container. **DO NOT** put the needle cap back on the used syringe.

Appendix E X-Ray Bone Densitometer

Intended Use

The X-ray Bone Densitometer (DPX-Bravo, DPX-Duo, DPX-NT, Prodigy, iDXA) supports the following intended uses:

Provides an estimate of bone mineral density at various anatomical sites (Spine, Total Hip, Total Body, and Forearm). These values can then be compared to an Adult reference population at the sole discretion of the physician.

Provides an assessment of relative fracture risk based on the patient's T-score value using the categories of fracture risk defined by the World Health Organization (WHO).

Provides a standardized bone density report using data from each densitometer and physician-generated assessments based on the patient's demographics, which can assist the physician in communicating scan results to the patient and the patient's referring physician

Device Description

Structure

The X-Ray Bone Densitometer is made up of a scan arm, X-ray source assembly, and exam table.

Product Model

DPX Bravo and Duo

The DPX Bravo and Duo models use pencil beam technology with a single-crystal detector and have a compact table design to provide space efficiency (see images below).
The DPX Duo and the DPX Bravo come equipped with a scan arm that swings to the side of the table when not in use when not in use as a densitometer and to facilitate patient loading. X-ray scanning is not possible until the scan arm is locked into the scan position. A handle releases the scan arm interlock and allows operator to move the scan arm for patient loading. Once the patient is loaded on the table, the operator moves the scan arm back to scanning position and the arm locks into scan position.

Measurement/Reporting

Bone Mineral Density (BMD) is measured using Dual-Energy X-Ray Absorptiometry (DEXA).

The bone mineral density of the lumbar spine, L1-L4, and the Total Hip total mean is measured in g/cm2 as well as standard deviations within the young adult population and within the age-matched mean. These are also compared to baseline data as a percentage change.

Appendix F Instructions for Multi-Site Studies

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:
Roswell Park Cancer Institute
CRS Quality Assurance (QA) Network Office
CRSNetworkCoordinators@RoswellPark.org
Elm and Carlton Streets
Buffalo, New York 14263
Telephone:
Monday - Friday; 8: 00 AM to 4: 30 PM EST
716-845-8084
After hours, weekends, and holidays request the Roswell Park Investigator
716-845-2300

2. INFORMED CONSENT

- Informed consent must be obtained by the **site Investigator/designee** from any participants wishing to participate, **prior to any procedures or treatment**.
- An informed consent template is provided by Roswell Park and can be amended to reflect institutional requirements.
- All consent changes **must** be reviewed by Roswell Park CRS QA Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.
- Within 5 business days, notify the Roswell Park CRS QA Network Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. PARTICIPANT REGISTRATION

The participant completes the Gender, Race, and Ethnicity Form and this is placed in the study binder.

Roswell Park does not grant exceptions to eligibility criteria.

Phase 2 Protocol Registration Instructions

The Subject Screening and Enrollment Log must be emailed (CRSNetworkCoordinators@RoswellPark.org) to the Roswell Park CRS QA Network Office within 1 business day of the date the participant is consented. Once the Investigator has determined that eligibility has been met, complete the eligibility check list and email it to the Roswell Park Network QA Coordinator at CRSNetworkCoordinators@RoswellPark.org.

4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this must be reported to the Roswell Park Network, site IRB and any other regulatory authority involved in the study.

- ALL study deviations will be recorded on the **Study Deviation Log**.
- Participants inadvertently enrolled with significant deviation(s) from the study-specified criteria will be removed from the study, at the discretion of the Principle Investigator.

5. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The Roswell Park Network QA Coordinator must be able to read what has been deleted.
- Do **NOT** use white-out, magic marker, scratch-outs.
- Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of Roswell Park to inform the Investigator/ institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to Roswell Park upon written agreement between the Investigator and Roswell Park.

6. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to participants and wasted, lot number, date dispensed, participant ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.
- Study drug supply will only be used in accordance with the IRB approved study.
- Drug accountability forms are protocol and agent specific; they are study source documents and will be used to verify compliance with the study.
- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- Drug accountability forms must be stored with study related documents.
- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
- **NEVER** replace investigational agents with commercial product.
- Do **NOT** "transfer", "borrow" or "replace" supplies between studies.

7. SERIOUS ADVERSE EVENT REPORTING

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the Roswell Park Network QA Coordinator within 1 business day

of being made aware of the SAE. A preliminary written report must follow within 1 business day of the first notification using the following forms:

- Roswell Park SAE Source form
- MedWatch 3500A

For instructions on notifying Amgen Please see **Section 17.8.**

A complete follow-up report must be sent to the Roswell Park Network QA Coordinator when new information becomes available.

8. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 17.7**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify their local **IRB in accordance with their local institutional guidelines**. The site must also notify the Roswell Park Network QA Coordinator within 1 business day of being made aware of the Unanticipated Problem by completing the **Roswell Park Unanticipated Problem Report Form** and emailing it to the Roswell Park Network QA Coordinator.