Title: Bone Histomorphometry of the Proximal Femur in Denosumab-treated Subjects Undergoing Total Hip Replacement

AMG 162 Denosumab

Amgen Protocol Number (AMG 162/Denosumab) 20140259

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Investigator's Agreement

I have read the attached protocol entitled Bone Histomorphometry of the Proximal Femur in Denosumab-treated Subjects Undergoing Total Hip Replacement, dated **03 October** 201**6**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

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Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

Title: Bone Histomorphometry of the Proximal Femur in Denosumab-treated Subjects Undergoing Total Hip Replacement

Study Phase: 4

Indication: Postmenopausal Osteoporosis

Primary Objective: The primary objective of this study is to determine the incidence of modeling-based bone formation in the femoral neck of subjects who have received denosumab and are undergoing total hip replacement (THR).

Secondary Objective(s): The secondary objective of this study is to describe the bone formation parameters of the femoral neck in subjects undergoing THR.

Exploratory Objective(s):

The exploratory objectives of the study include:

- To determine the extent of modeling- and remodeling-based bone formation based on morphology of the underlying cement line (smooth = modeling; scalloped = remodeling) as a percentage of bone surface.
- Comparison of histomorphometric parameters of bone formation in the femoral neck of subjects enrolled in this study with those in historical controls.

Hypotheses: A formal hypothesis will not be tested in this study.

Primary Endpoint: Subject incidence of fluorochrome labeling in the cancellous, periosteal **or** endocortical surfaces of the femoral neck indicative of MBF (ie, associated with smooth underlying cement lines).

Secondary Endpoint(s): The secondary endpoints are modeling-based bone formation parameters and remodeling-based bone formation parameters in the cancellous, periosteal, or endocortical regions of the femoral neck.

Exploratory Endpoint(s):

- extent of fluorochrome-labeled bone surface with underlying smooth or scalloped cement lines as a percentage of total bone surface
- histomorphometric parameters of bone formation in the femoral neck

Study Design: This study will enroll approximately 15 subjects who are undergoing elective THR and have taken at least **2** doses of denosumab 60 mg **subcutaneously** prior to hip replacement surgery.

Sample Size: approximately 15 subjects

Summary of Subject Eligibility Criteria:

Subjects will meet the following major inclusion criteria before enrollment:

- ambulatory postmenopausal women and men with osteoporosis
- planning to undergo elective THR due to osteoarthritis of the hip
- received at least **2** doses of denosumab 60 mg subcutaneously prior to the scheduled THR
- provide signed informed consent

Subjects meeting any of the following criteria are not eligible for participating:

- Received treatment for osteoporosis other than denosumab in one year prior to THR
- Subjects with history of any of the following conditions are excluded from this study:
  - Current, uncontrolled hypo- or hyperthyroidism (subjects who have controlled hypo- or hyperthyroidism may be eligible, provided that they have been on a stable therapy for at least 3 months [per subject report]).
  - Current, hypo- or hyperparathyroidism
  - Osteomalacia
  - Paget's disease of bone
  - Other bone diseases which affect bone metabolism (eg, osteopetrosis, osteogenesis imperfecta)
  - Severe chronic kidney disease (CKD), defined as CKD stage 4 or greater
- Malignancy within the last 5 years (except cervical carcinoma in situ or basal cell carcinoma)
- Self-reported alcohol or drug abuse within the previous 12 months
- Known sensitivity to any of the products to be administered (eg, tetracycline, demeclocycline) during the study
- Any disorder that compromises ability to give truly informed consent for participation in this study

For a full list of eligibility criteria, please refer to Section 4.1 through Section 4.1.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: This study involves no administration of investigational product.

Non-Amgen Non-investigational Product Dosage and Administration: Non Amgen non-investigational product(s) tetracycline and demeclocycline will be used in this study. Both tetracycline and demeclocycline will be self-administered orally. During cycle 1, tetracycline will be administered at either 250 mg four times a day or 500 mg twice a day for 3 days. During cycle 2, demeclocycline will be administered at either 150 mg four times a day or 300 mg twice a day for 3 days.

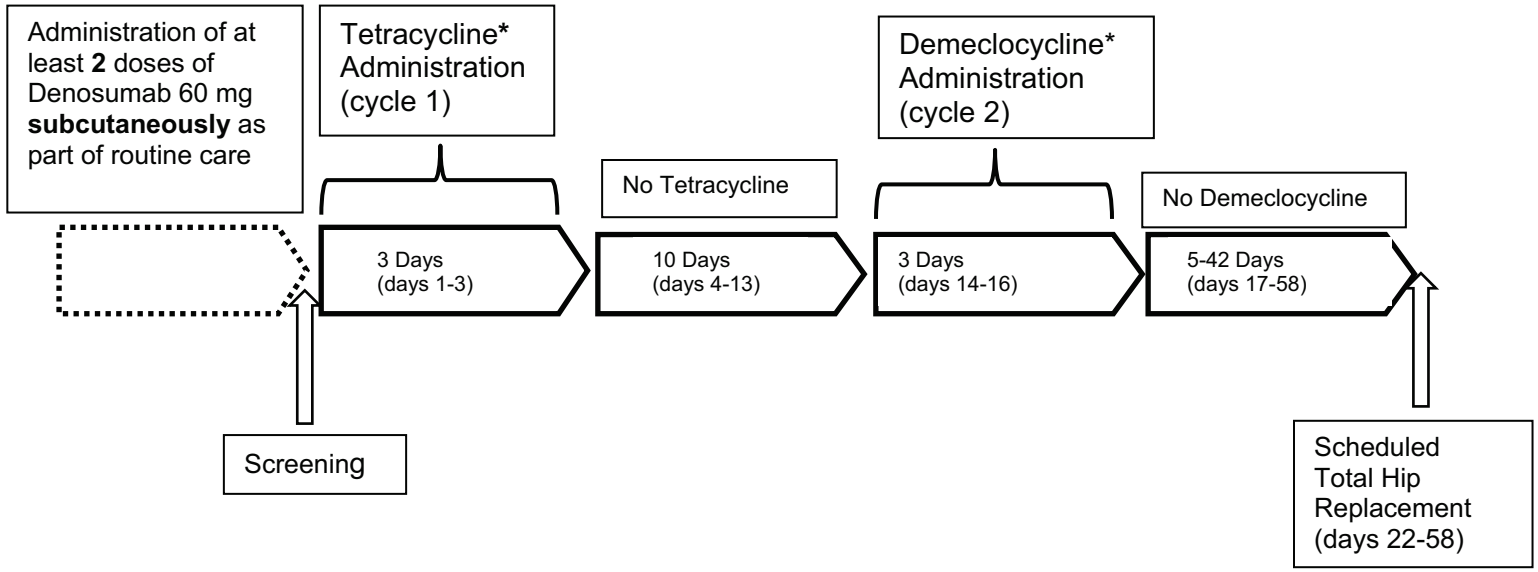
If tetracycline or demeclocycline are not available, other tetracycline derivatives may be used.

Please refer to section 6.1 for additional information.

Procedures: Appropriate written informed consent will be obtained from all subjects prior to enrollment. All subjects will receive tetracycline on 3 consecutive days during cycle 1, administered on days 1-3, and 3 consecutive days of demeclocycline during cycle 2 administered days 14-16. THR surgery will be performed at least 5 days and no greater than 42 days after the last dose of demeclocycline or other tetracycline derivative is received in cycle 2 (ie, between days 22 and 58 on study) to acquire the fragment of femoral bone. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 1).

Statistical Considerations: Analyses will be performed on all enrolled subjects who have available bone tissue samples. All summaries will be descriptive. For a full description of statistical analysis methods, please refer to Section 10.

Study Design and Treatment Schema



* If tetracycline or demeclocycline are not available, other tetracycline derivatives may be used

Study Glossary

Abbreviation or Term	Definition/Explanation
BMD	bone mineral density
CRF	case report form
EDC	electronic data capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint (s).
End of Study (end of trial)	defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
ICF	informed consent form
IRB/IEC	institutional review board/independent ethics committee
MBF	modeling-based bone formation
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6)]. Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol required therapies is/are administered to the subject
THR	total hip replacement

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1. OBJECTIVES

1.1 Primary

The primary objective of this study is to determine the incidence of modeling-based bone formation in the femoral neck of subjects who have received denosumab and are undergoing total hip replacement (THR).

1.2 Secondary

The secondary objective of this study is to describe the bone formation parameters of the femoral bone in subjects undergoing THR.

1.3 Exploratory

The exploratory objectives of the study include:

- To determine the extent of modeling- and remodeling-based formation based on morphology of the underlying cement line (smooth = modeling; scalloped = remodeling) as a percentage of bone surface
- Comparison of histomorphometric parameters of bone formation in the femoral neck of subjects enrolled in this study with those in historical controls

2. BACKGROUND AND RATIONALE

2.1 Disease

Osteoporosis (OP) is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2000). An estimated 30 million women aged 50 or older in the United States have or are at risk for osteoporosis, and this number is expected to increase to approximately 41 million in the year 2020 (National Osteoporosis Foundation, 2010). Osteoporosis and the clinical fractures associated with the disease have significant consequences on human health, quality of life, and represent a major burden to society.

2.2 Denosumab 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 oteoprotegerin (OPG). Denosumab is approved for use in many countries as a treatment for bone loss conditions, including postmenopausal osteoporosis, osteoporosis in men, and bone loss associated with the use of hormone ablation therapies in men with prostate cancer and women with breast cancer. In postmenopausal women with osteoporosis, 3-year data from the randomized, double-blind, placebo-controlled, phase 3 study (20030216) demonstrated

that denosumab treatment reduced the incidence of new vertebral fractures, nonvertebral fractures and hip fractures when compared with placebo (Cummings et al, 2009).

2.3 Rationale

Denosumab administration is associated with continued increases in bone mineral density (BMD) and low fracture incidence through 8 years in the phase 3 pivotal fracture study extension (Study 20060289, FREEDOM Extension) (Ferrari et al, 2014; Papapoulos et al, 2013). Persistently low bone turnover markers and limited iliac crest tetracycline labeling has been observed. It has been hypothesized that, with persistently low bone remodeling, these BMD increases may result from a remodeling-independent mechanism that accrues bone matrix. The fluorochrome labeling pattern in proximal femoral sections from ovariectomized (OVX) cynomolgus monkeys (cynos) treated with denosumab for 16 months demonstrates evidence of modeling-based bone formation (Ominsky et al, 2014). These data provided the first histological evidence of a potential mechanism responsible for the clinical observations of continued BMD increases and low fracture rates with long-term denosumab administration in the FREEDOM Extension.

The current study is being conducted to detect the presence of and validate the preclinical findings of modeling-based bone formation in human subjects. Data obtained on the types of bone formation (modeling- and or remodeling-based) in subjects treated with denosumab will be described. In addition, these data may be compared in an exploratory manner with those from historical controls not treated with denosumab.

2.4 Clinical Hypotheses

A formal hypothesis will not be tested in this **study**.

3. EXPERIMENTAL PLAN

3.1 Study Design

This phase 4 study will enroll approximately 15 subjects who previously received denosumab and are undergoing elective THR due to underlying osteoarthritis.

The study will consist of a screening visit followed by 1 cycle of tetracycline dosing and 1 cycle of demeclocycline. Each cycle will be 3 days in duration, with cycle 2 beginning approximately 10 days after the receipt of the last dose of tetracycline in cycle 1. If tetracycline or demeclocycline are not available, other tetracycline derivatives may be used. The surgery for THR will be at least 5 and no greater than 42 days after the last dose of demeclocycline received in cycle 2 (ie, from days 22 to 58). The fragment of the

femur will be obtained during the THR procedure. There are no visits after THR surgery procedure. The total duration of the study for each subject therefore is expected to be approximately 2 months including the screening visit.

Transverse sections of the femoral neck specimen will be obtained, then fixed and then embedded. The endocortical, periosteal, and cancellous regions will be evaluated in the stained sections for any pathological findings and evidence of modeling-based and remodeling-based bone accretion. Variables of histomorphometry will be measured to assess structural and dynamic parameters, including mineralizing surface, mineral apposition rate, bone formation rate, eroded surface, and activation frequency. Modeling-based (evidenced by smooth cement line) and remodeling-based (evidenced by a scalloped cement line) bone formation units will be described separately.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

The study is planned to be conducted at one investigative site located in in the United States of America. Additional sites or regions may be added as deemed necessary.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Approximately 15 subjects will be enrolled in the study.

3.4 Replacement of Subjects

Subjects who are withdrawn or removed from the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The duration of participation in the study for each subject is expected to last up to approximately 2 months.

3.5.2 End of Study

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis.

End of Study: the same as primary completion, ie, the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis.

4. SUBJECT ELIGIBILITY

Ambulatory postmenopausal women and men with osteoarthritis of the hip, who meet the inclusion/exclusion criteria, will be eligible to participate in the study.

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (age, sex, race), date, and outcome of the screening process (eg, enrolled into study, reason for ineligibility, or refused to participate)

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

101 Subject has provided informed consent/assent prior to initiation of any study-specific activities/procedures

102 Ambulatory postmenopausal women and men with osteoporosis

103 Scheduled to undergo elective THR due to osteoarthritis of the hip

104 Received at least **2** doses of denosumab 60 mg subcutaneously

105 Last dose of denosumab within 6 months of scheduled THR

4.1.2 Exclusion Criteria

201 Received treatment for osteoporosis other than denosumab in one year prior to THR

202 Subjects with current diagnosis of any of the following conditions are excluded

- Current, uncontrolled hypo- or hyperthyroidism (subjects who have controlled hypo- or hyperthyroidism may be eligible, provided that they have been on a stable therapy for at least 3 months [per subject report])
- Current, hypo- or hyperparathyroidism
- Osteomalacia
- Paget's disease of bone
- Other bone diseases which affect bone metabolism (eg, osteopetrosis, osteogenesis imperfecta)
- Severe chronic kidney disease (CKD), defined as CKD stage 4 or greater

203 Malignancy within the last 5 years (except cervical carcinoma in situ or basal cell carcinoma)

204 Self-reported alcohol or drug abuse within the previous 12 months

205 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s)

206 Other investigational procedures while participating in this study are excluded

207 Subject has known sensitivity to any of the products to be administered (eg, tetracycline, demeclocycline) during study

208 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge

209 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2). Subjects must personally sign and date the informed consent form before commencement of study-specific activites/procedures.

A subject is considered enrolled when they have signed the informed consent. The investigator is to document this date in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who signs the ICF receives a unique subject identification number before any study-related activites/procedures are performed. The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment.

5.1 Treatment Assignment

No investigational product will be administered.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s) and/or Medical Device(s)

This study will enroll approximately 15 subjects who previously received at least **2** doses of denosumab and are undergoing THR due to underlying osteoarthritis. No investigational product will be administered as part of this study. Standard bone labeling procedures with tetracycline, demeclocycline, or other tetracycline derivative will be performed prior to the prescheduled THR.

6.1.1 Non-Amgen Non-investigational Product(s)

Non-Amgen non-investigational products tetracycline and demeclocycline will be used as fluorochrome labels that incorporate into bone in this study. If tetracycline or demeclocycline are not available, other tetracycline derivatives may be used.

6.1.1.1 Dosage, Administration, and Schedule

Two cycles of treatment will be administered approximately 10 days apart. Treatment during cycle 1 consists of a total oral dose of 1000 mg of tetracycline daily for a total of 3 days. Following a 10-day break, the second cycle of treatment will begin. Treatment during cycle 2 consists of a total oral dose of 600 mg of demeclocycline daily for 3 days. THR surgery will be performed at least 5 and no greater than 42 days after the last dose of demeclocycline received during cycle 2.

6.1.1.1.1 Cycle 1 (Study Days 1-3)

Either the 250 mg or the 500 mg preparation of tetracycline may be used. All doses should be administered orally, with water, on an empty stomach. The total daily dose of tetracycline to be administered is 1000 mg.

When the 250 mg preparation is used, a single dose may be taken four times a day according to the following recommended administration schedule:

- 1-2 hours before breakfast
- 2 hours after breakfast
- 2 hours after lunch
- 2 hours after dinner

If tolerated, 2 tablets of the 250 mg preparation may be taken twice a day according to the following recommended administration schedule:

- 1-2 hours before breakfast
- 2 hours after dinner

When the 500 mg preparation is used, a single dose should be taken twice a day according to the following recommended administration schedule:

- 1-2 hours before breakfast
- 2 hours after dinner

If a dose is missed, it should be taken as soon as possible, or with the next scheduled dose.

6.1.1.1.2 Cycle 2 (Study Days 14-16)

Either the 150 mg or the 300 mg preparation of demeclocycline may be used. All doses should be administered orally, with water, on an empty stomach. The total daily dose of demeclocycline to be administered is 600 mg.

When the 150 mg preparation is used, a single dose may be taken four times a day according to the following recommended administration schedule:

- 1-2 hours before breakfast
- 2 hours after breakfast
- 2 hours after lunch
- 2 hours after dinner

If tolerated, 2 tablets of the 150 mg preparation may be taken twice a day according to the following recommended administration schedule:

- 1-2 hours before breakfast
- 2 hours after dinner

When the 300 mg preparation is used, a single dose should be taken twice a day according to the following recommended administration schedule:

- 1-2 hours before breakfast
- 2 hours after dinner

If a dose is missed, it should be taken as soon as possible, or with the next scheduled dose.

6.1.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

No dosing adjustments for tetracycline, demeclocycline, or other tetracycline derivatives will be permitted.

6.2 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.5. Concomitant therapies are to be collected from the time of signing informed consent through the end of the study. Information regarding the use of osteoporosis medications during the 3 years prior to enrollment will be collected.

Absorption of tetracycline and demeclocycline are impaired by antacids containing aluminum, calcium, or magnesium, and by iron- containing preparations. Foods and

some dairy products also interfere with absorption. As described above, oral forms of tetracycline and demeclocycline should be given at least 1 hour before or 2 hours after meals. Dietary calcium supplements should be avoided on the days that tetracycline and demeclocycline are taken.

6.3 Other Treatment Procedures

Subjects entering this study are prescheduled to undergo elective THR due to osteoarthritis. Surgery is to be performed according to local standard of care.

6.4 Medical Devices

Medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.5 Excluded Treatments and/or Procedures During Study Period

Medications listed below will be proscribed during the study, as these medications are known or suspected to affect bone metabolism:

- intravenous bisphosphonates
- oral bisphosphonates
- teriparatide or any PTH analogs
- selective estrogen receptor modulators (SERMs)
- calcitonin
- tibolone
- cinacalcet
- any investigational treatment for bone loss

Dietary calcium supplements should be avoided on the days that tetracycline**,** demeclocycline, or other tetracycline derivatives are taken.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 1. Schedule of Assessments

	Eligibility Assessments	**Treatment Period**						
	Screening/**Enrollment**[1]	**Fluorochrome** Labeling Procedure						Scheduled THR Surgery
Study Day		1[2]	2[2]	3	**14**[2]	**15**[2]	**16**[2]	**22** to **58**[3]
GENERAL & SAFETY ASSESSMENTS								
Informed consent	X							
Demographic data	X							
Medical History	X							
Historical BMD[4]	X							
Osteoporosis Medication History	X[5]							
Concomitant Medications	X							X
Adverse events				Continuously				X
Serious Adverse events	X			Continuously				X
Physical examination	X							X
Weight	X							
Height	X							
BONE LABELING ASSESSMENTS								
Self administration of tetracycline[2]		X	X	X				
Self administration of demeclocycline[2]					X	X	X	
Acquisition of proximal femur fragment during total hip replacement surgery								X

[1] Screening and enrollment occur once the subject has signed the informed consent
[2] Study day 1 is the date that the first dose of tetracycline, demeclocycline or other tetracycline derivative is administered in cycle 1 even though the subject may not need to come into the clinic (eg, no study visit). Tetracycline and demeclocycline are self administered. If tetracycline or demeclocycline are not available, other tetracycline derivatives may be used
[3] Total hip replacement surgery should be at least 5 and no greater than 42 days following the last demeclocycline labeling dose.
[4] Only historic bone mineral density values of the lumbar spine, total hip or femoral neck acquired within 2 years of screening will be collected.
[5] Information regarding the use of osteoporosis medications during the 3 years prior to enrollment will be collected at screening.

7.2 General Study Procedures

Study assessments and procedures will be performed only after written informed consent is obtained. During the study, every effort should be made to keep subjects on the study schedule of procedures. Tests and procedures will be performed as per the schedule provided in Section 7.1.

7.2.1 Study Visit Definitions

The screening and enrollment dates are defined as the date the ICF is signed.

Study day 1 is defined as the day the first dose of tetracycline or tetracycline derivative is administered. All on-study (after study day 1) days are to be calculated from the study day 1 visit.

7.2.2 Screening/Enrollment

The following procedures are to be completed during the screening**/enrollment visit** at time points designated in the Schedule of Assessments (Table 1):

- confirmation that the Informed Consent Form has been signed
- demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with study outcomes
- physical examination as per standard of care (including height, weight and medical/surgical history)
- serious adverse event reporting
- documentation of osteoporosis medication use during the 3 years prior to enrollment
- documentation of concomitant medications
- historical BMD collection (as available over 24 months prior to THR)

7.2.3 Treatment Period

Tetracycline and demeclocycline are to be self-administered as described in section 6.1.1.1 at the times designated in the Schedule of Assessments (Table 1).

Adverse events and serious adverse events that occur during the treatment period are to be reported per the procedures outlined in Section 9.

7.2.4 THR Surgery/End of Study

At least 5 and no greater than 42 days following the last dose of demeclocycline, the subject will undergo prescheduled elective THR surgery.

The following procedures are to be completed at this study visit, as designated in the Schedule of Assessments. The following procedures must be completed before THR surgery is commenced.

- physical examination as per standard of care, as recorded in preoperative medical history
- adverse event reporting
- serious adverse event reporting
- documentation of concomitant medications

The following procedures will be completed after THR surgery is commenced.

- Acquisition of proximal femur fragment

The acquisition of the proximal femur fragment will represent the end of the study.

7.2.5 Bone Histomorphometry

At the central bone histomorphometry facility, femoral neck bone samples will be prepared according to standard procedures for bone histology and bone histomorphometry. Histomorphometric analysis will assess structural and dynamic parameters, including mineralizing surface, mineral apposition rate, bone formation rate, **eroding surface,** and activation frequency. The bone formation parameters will be divided into modeling bone formation (MBF) and remodeling-based formation activity, depending on the morphology of the cement lines underlying the **fluorochrome** labels at individual bone forming units. If the cement line is scalloped, the formation unit and its accompanying fluorochrome labels will be designated as remodeling-based formation. If the cement line is smooth, the formation unit and its accompanying tetracycline label will be designated as MBF (Lindsay et al, 2006). Additional structural and remodeling parameters may be evaluated as deemed appropriate.

Refer to the bone histomorphometry methods, a document external to this protocol, for additional information regarding the collection and management of bone samples.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the

appropriate processes for discontinuation from other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 1) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

8.3 Reasons for Removal From Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, hypersensitivity reaction to tetracycline, demeclocycline, or other tetracycline derivative)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study

- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Reporting of Adverse Events

9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through the end of study are reported using the applicable CRF (eg, Adverse Event Summary).

The investigator must assign the following adverse event attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- dates of onset and resolution (if resolved),
- severity,
- assessment of relatedness to protocol-required therapies, and
- action taken.

The adverse event grading scale used will be the Amgen Standard Adverse Event Grading Scale. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the protocol-required therapies. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by protocol-required therapy?

If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Adverse Event Summary CRF.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through end of study are recorded in the subject's medical record and are

submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable CRF.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet /electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable CRF (eg, Adverse Event Summary CRF).

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Primary Endpoint

The primary endpoint is subject incidence of fluorochrome labeling in the cancellous, periosteal, **or** endocortical surfaces of the femoral neck indicative of MBF (ie, associated with smooth underlying cement lines).

10.1.2 Secondary Endpoints

The secondary endpoints are modeling-based bone formation parameters and remodeling-based bone formation parameters in the cancellous, periosteal, or endocortical regions of the femoral neck.

10.1.3 Exploratory Endpoints

The exploratory endpoints to be evaluated in this study are

- extent of fluorochrome-labeled bone surface with smooth or scalloped underlying cement lines as a percentage of total bone surface
- histomorphometric parameters of bone formation in **the** femoral neck

10.1.4 Safety Endpoints

The safety endpoint is subject incidence of adverse events reported during the study.

10.1.5 Primary Analysis Sets

The primary analysis set includes all enrolled subjects who have an evaluable biopsy for fluorochrome labeling.

10.1.6 Safety Analysis Sets

The safety analysis subset includes all enrolled subjects who have received at least one dose of tetracycline**,** demeclocycline, or other tetracycline derivative.

10.1.7 Covariates and Subgroups

No covariate analysis is planned.

10.2 Sample Size Considerations

Approximately 15 subjects who are scheduled to undergo an elective THR procedure and have received at least **2** doses of denosumab will be enrolled in this study. This sample size is typical for studies investigating bone biopsies to evaluate bone histomorphometry variables. The actual sample size, however, will be largely determined (and limited) by the availability of qualified subjects due to the eligibility criteria of the study as well as nature of the study procedures.

10.3 Planned Analyses

10.3.1 Interim Analyses

No interim analysis is planned.

10.3.2 Primary Analysis

The primary analysis of the study will be performed when all enrolled subjects have had the opportunity to complete the study procedures.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

No formal hypothesis will be tested in this study. All analyses will be descriptive in nature. Bone biopsy data from all enrolled subjects may be informally compared with a historical control group as an exploratory analysis.

Frequencies and percentages will be presented for all categorical variables. Continuous variables will be summarized descriptively using mean, standard deviation, minimum, maximum, median, and other selected percentiles.

10.4.2 Primary Endpoint

Number and percentage of subjects with **fluorochrome** labeling present in the cancellous or periosteal, or endocortical surfaces of the femoral neck indicative of MBF will be provided.

10.4.3 Secondary Endpoint(s)

The actual values of the dynamic parameters associated with modeling-based bone formation parameters and remodeling-based bone formation parameters will be summarized descriptively in the cancellous, periosteal, or endocortical regions of the femoral neck.

10.4.4 Exploratory Endpoint(s)

Extent of fluorochrome-labeled bone surface with smooth or scalloped underlying cement line expressed as a percentage of total bone surface will be summarized. Mean,

standard deviation, minimum, maximum and median will be provided. Histomorphometric parameters of bone formation in the femoral neck of subjects enrolled in this study may be informally compared with a historical control group as exploratory analysis.

10.4.5 Safety Endpoints

The number and percentage of subjects experiencing adverse events and serious adverse events at least once during the period from enrollment (subject incidence) will be tabulated by system organ class and preferred term. Incidence of adverse events and serious adverse events related to tetracycline, demeclocycline, or other tetracycline derivatives will also be summarized.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original

signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data). The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- subject files containing completed CRFs, informed consent forms, and subject identification list
- study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- non-investigational product(s) and or medical device(s) documentation, as applicable.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen clinical monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The clinical monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the **study** and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 1), the investigator can search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

To coordinate dissemination of data from this study, the investigator will solicit input and assistance from Amgen staff as appropriate.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

13. REFERENCES

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

Grade	Amgen Standard Adverse Event Grading Scale
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity

Appendix B. Sample Serious Adverse Event Report Form

AMGEN Study # 20140259 denosumab	Electronic Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

[If the protocol provides instructions to submit certain types of events ONLY to Amgen Safety and not to the Clinical Trial Database, state that reason below and remove these instructions. If no protocol-specific reasons, remove these instructions and the following bullet.]

Protocol specific reason(s):

☐ *<<Note protocol instruction/reason here and change text from italics to standard.>>*

<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year_____

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP/drug under study	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study? <Rdoxx> No ✓ / Yes ✓ (×4)	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

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AMGEN
Study # 20140259
denosumab

Electronic Adverse Event Contingency Report Form

For Restricted Use

Site Number	Subject ID Number

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
<<IP/Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Test / Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

AMGEN Study # 20140259 denosumab	Electronic Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee -	Title	Date
_____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*		

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Amendment 2

Protocol Title: Bone Histomorphometry of the Proximal Femur in Denosumab-treated Subjects Undergoing Total Hip Replacement

Amgen Protocol Number AMG 162 (Denosumab) 20140259

Amendment Date: 03 October 2016

Rationale:

Enrollment has been challenging with the current dosing administration inclusion criteria. Decreasing the inclusion criteria that the patient must have received at least 3 doses of denosumab 60 mg subcutaneously over 18 months to 2 doses of denosumab 60 mg subcutaneously will improve enrollment by doubling the recruitment pool. The scientific advisors for the study have confirmed that the dose administration change will not affect the ability to observe the endpoint.

Description of Changes:

Section: Global

Change:

Minor corrections throughout (eg, correcting typographical and formatting errors)

Section: Global

Replace:

6 April 2015

With:

03 October 2016

Section: Title Page

Add:

Amendment 2: 03 October 2016

Section: Title Page

Replace:

PPD
One Amgen Center Drive
Thousand Oaks, CA 91320, USA
PPD

With:

PPD
One Amgen Center Drive
Thousand Oaks, CA 91320, USA
PPD

Section: Synopsis, Study Design

Replace:

This study will enroll approximately 15 subjects who are undergoing elective THR and have taken at least 3 doses of denosumab 60 mg within 18 months prior to hip replacement surgery.

With:

This study will enroll approximately 15 subjects who are undergoing elective THR and have taken at least **2** doses of denosumab 60 mg **subcutaneously** prior to hip replacement surgery.

Section: Synopsis, Summary of Subject Eligibility Criteria

Replace:

- received at least 3 doses of denosumab 60 mg subcutaneously over 18 months prior to the scheduled THR

With:

- received at least **2** doses of denosumab 60 mg subcutaneously prior to the scheduled THR

Section: Study Design and Treatment Schema

Replace:

Administration of at least 3 doses of Denosumab 60 mg every 6 months (within 18 months) as part of routine care

With:

Administration of at least **2** doses of Denosumab 60 mg **subcutaneously** as part of routine care

Section: 4.1.1 Inclusion Criteria

Replace:

104 Received at least 3 doses of denosumab 60 mg subcutaneously over 18 months

With:

104 Received at least **2** doses of denosumab 60 mg subcutaneously

Section: 6.1 Classification of Product(s) and/or Medical Device(s)

Replace:

This study will enroll approximately 15 subjects who previously received at least 3 doses of denosumab in the 18 months prior and are undergoing THR due to underlying osteoarthritis.

With:

This study will enroll approximately 15 subjects who previously received at least **2** doses of denosumab and are undergoing THR due to underlying osteoarthritis.

Section: 10.2 Sample Size Considerations

Replace:

Approximately 15 subjects who are scheduled to undergo an elective THR procedure and have received at least 3 doses of denosumab over the previous 18 months will be enrolled in this study.

With:

Approximately 15 subjects who are scheduled to undergo an elective THR procedure and have received at least **2** doses of denosumab will be enrolled in this study.

Amendment 1

Protocol Title: Bone Histomorphometry of the Proximal Femur in Denosumab-treated Subjects Undergoing Total Hip Replacement

Amgen Protocol Number AMG 162/Denosumab 20140259

Amendment Date: 6 April 2015

Rationale:

The purpose of this amendment was to update the treatment procedures to improve the ability to identify modeling based bone formation during the trial. Updates have also been made to exclusion criteria to address comments received from the Institutional Review Board (IRB) overseeing the trial.

Minor administrative changes and clarifications have also been incorporated.