Title Page

Protocol Title:		Long-term Safety Follow-up of Subjects With Giant Cell Tumor of Bone Treated With Denosumab in Study 20062004
Short Protocol Title:		Long-term Safety Follow-up of Subjects With Giant Cell Tumor of Bone Treated With Denosumab in Study 20062004
Protocol Number:		20140114
Investigational Product:		Denosumab
Trade Name:		XGEVA®
Sponsor	**Name of Sponsor:**	Amgen Inc.
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EudraCT Number:		2017-001758-32
NCT Number:		NCT03301857
Protocol Date:		**Document Version** / **Date** Original / 17 May 2017 Amendment 1 / 15 November 2017 Superseding Amendment 1 / 23 January 2018 **Amendment 2** / **23 August 2018**

Version/Date:	**Data Element Standards Version**	**Date**
	5.0	20 March 2015

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Investigator's Agreement:

I have read the attached protocol entitled Long-term Safety Follow-up of Subjects With Giant Cell Tumor of Bone Treated With Denosumab in Study 20062004, dated **23 August 2018**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Table of Contents

List of Tables

List of Figures

1. Protocol Synopsis

Protocol Title: Long-term Safety Follow-up of Subjects With Giant Cell Tumor of Bone Treated With Denosumab in Study 20062004

Short Protocol Title: Long-term Safety Follow-up of Subjects With Giant Cell Tumor of Bone Treated With Denosumab in Study 20062004

Study Phase: Phase 4

Indication: Giant Cell Tumor of Bone

Rationale

XGEVA® (denosumab) was approved in the United States, Canada, European Union, Australia, and other countries for the treatment of giant cell tumor of bone (GCTB) largely based on results from ongoing Study 20062004. Study 20062004 is an open-label, single-arm trial where subjects with GCTB are treated with denosumab 120 mg every 4 weeks. For subjects with surgically salvageable disease, treatment continued until surgery **for complete resection** and for approximately 6 months post-surgery. For subjects with surgically unsalvageable disease, treatment continued as long as there was investigator-determined clinical benefit. Study 20062004 will continue until all subjects enrolled in the initial phase of the study complete at least 5 years of follow-up on study. Enrollment in the initial phase of Study 20062004 concluded in November 2012; therefore, the study end**ed** in **May 2018**.

Study 20140114 will continue to follow subjects with GCTB who were treated in Study 20062004 for an additional 5 or more years of long-term safety follow-up.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• Evaluate adverse events of interest in subjects with GCTB treated with denosumab in Study 20062004	• Rate of adverse events of interest in subjects with GCTB treated with denosumab in Study 20062004
Secondary	
• Evaluate treatment-emergent adverse events for subjects who are receiving denosumab	• Rate of treatment-emergent adverse events for subjects who are receiving denosumab
• Evaluate serious adverse events for all subjects	• Rate of serious adverse events for all subjects
• Summarize the rate of disease progression or recurrence of GCTB for all subjects	• Rate of disease progression or recurrence of GCTB for all subjects
• Summarize the use of GCTB interventions for all subjects	• Rate of GCTB interventions for all subjects

Hypotheses

This study is descriptive in nature and does not involve testing formal hypotheses.

Overall Design

This prospective study will provide long-term safety follow-up for subjects who complete Study 20062004 and consent to enroll in Study 20140114. The subject's follow-up begins after signing the informed consent form (ICF) and continues through the earliest date of: 5 years after the subject enrolled signs the ICF, death, withdrawal of consent, or lost to follow-up. Study assessments are to be completed every 6 months (± 30 days). **End of study (EOS) visits for all patients will be at 5 years; Cohort A subjects on investigational product will have an EOS visit conducted 30 days following the last dose of investigational product (end of treatment [EOT] visit) if receiving investigational product at the 5 year time point.**

Subjects who are still being treated with denosumab when 20062004 completes can continue receiving open-label denosumab at dose of 120 mg subcutaneously every 4 weeks. Collection of long-term safety information will include the following adverse events of interest: osteonecrosis of the jaw, malignancy (including malignancy in GCTB), atypical femoral fracture, hypocalcemia, hypercalcemia following treatment discontinuation, and pregnancy and lactation (if occurring on treatment or within 5 months of last dose of denosumab). Additionally, all treatment-emergent adverse events and serious adverse events will be collected.

Number of Subjects

The number of subjects in this study will be determined by the number of subjects completing Study 20062004 who are willing to enroll in this study for long-term safety follow-up. It is estimated that this will be approximately 100 to 300 subjects.

Summary of Subject Eligibility Criteria

All subjects from Study 20062004 who agree to participate in this study and sign the ICF will be considered enrolled.

For a full list of eligibility criteria, please refer to Section 6.1 and Section 6.2.

Treatments

For subjects receiving denosumab:

Denosumab will be supplied as a sterile, clear, colorless to slightly yellow, preservative-free liquid, in single-use 3.0 mL glass vials containing a deliverable dose of 1.7 mL. Denosumab will be administered as a subcutaneous (SC) injection 120 mg every 4 weeks. A planned dose may be given up to 7 days before the scheduled visit, as long as there are at least 21 days between doses. If a planned dose is delayed more than 7 calendar days, it will be considered a missed dose and recorded as such on the electronic case report form. **If a subject undergoes retreatment with denosumab, they will receive denosumab as a SC injection 120 mg on days 1, 8, 15, and 28, then every 4 weeks subsequently.**

All subjects receiving denosumab should be adequately supplemented with calcium and vitamin D (at least 500 mg of calcium and 400 IU of vitamin D), except in the case of pre-existing hypercalcemia.

Procedures

Written informed consent must be obtained from all subjects before any study-specific procedures are performed. The following key procedures will occur per the Schedule of Activities (Table 2-1): collection of disease status, GCTB interventions, review of adverse events of interest, serious adverse events, and treatment-emergent adverse events.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1.

Statistical Considerations

The number of subjects in this study will be determined by the number of subjects completing Study 20062004 who are willing to enroll in this study for long-term safety follow-up. It is estimated that this will be approximately 100 to 300 subjects.

Treatment-emergent adverse event will be summarized for all subjects who receive at least 1 dose of denosumab during this study. Serious adverse event and adverse event of interests will be summarized for all subjects who have signed the ICF and enrolled. Exposure-adjusted events of interest will be summarized.

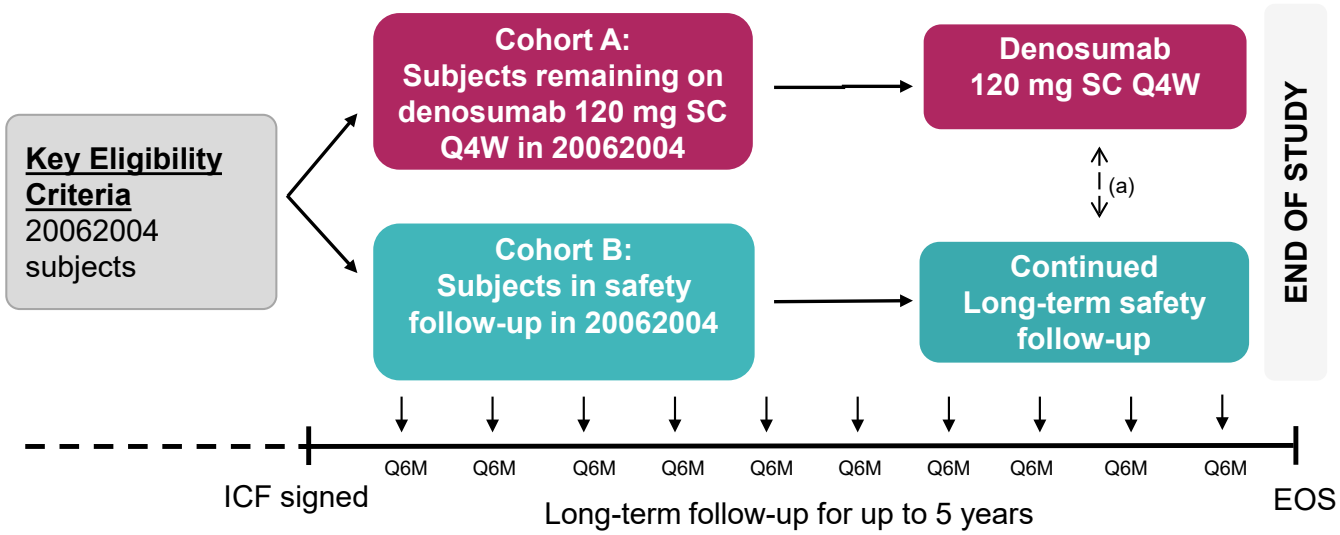
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



EOS = end of study; GCTB = giant cell tumor of bone; ICF = informed consent form; SC = subcutaneous; Q4W = every 4 weeks; Q6M = every 6 months
[a] Subjects in Cohort A who end denosumab for any reason will complete an end-of-treatment visit and move to safety follow-up. Subjects who experience GCTB recurrence in Cohort B are eligible to resume denosumab at investigator's discretion and would then be monitored as per Cohort A requirements. See Section 5.1 for more detail.

2.2 Schedule of Activities

Table 2-1. Schedule of Activities

PROCEDURE	Baseline /Day 1[a]	Long-term Follow-up											
		M6	M12	M18	M24	M30	M36	M42	M48	M54	M60[b]	EOT[c]	End of Study[d]
GENERAL ASSESSMENTS													
Informed consent	X												
Eligibility criteria	X												
Demographics[e]	X												
Medical history[f]	X												
Physical examination[g]	X	X	X	X	X	X	X	X	X	X	X	X	
Disease status and intervention[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
SAFETY ASSESSMENTS[j]													
Adverse events of interest (serious or nonserious)[k, l]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events[m]	X	X	X	X	X	X	X	X	X	X	X	X	X
Product complaints[n]	X	X	X	X	X	X	X	X	X	X	X	X	
Other nonserious adverse events[o]		X	X	X	X	X	X	X	X	X	X	X	
STUDY TREATMENT													
Denosumab administration[p, q, r, s]	←←Subjects will be receiving denosumab 120 mg SC Q4W →→												

eCRF = electronic case report form; EOS = end of study; EOT = end of treatment; GCTB = giant cell tumor of bone; ICF = informed consent form; IP = investigational product; M = months; Q4W = every 4 weeks; Q6M = every 6 months; SC = subcutaneous

[a] Day 1 is defined as the date when the ICF is signed. Baseline safety assessments (below) should include reporting of any events occurring between the end of the 20062004 clinical study and 20140114 enrollment.

[b] Subjects will continue to have in-person clinic visits every 6 months (± 30 days) until the last subject enrolled has had the opportunity to complete 5 years of follow-up, death, withdrawal of consent, or loss to follow-up, whichever comes first.

[c] For subjects in Cohort A only and subjects from Cohort B who resume treatment with denosumab for disease recurrence: EOT in-person clinic visit will occur 30 days **(± 8 days**) after the last dose of denosumab.

[d] End of study will occur when one of the following happens: the last subject enrolled has had the opportunity to complete 5 years of follow-up, death, withdrawal of consent, or loss to follow-up, whichever comes first.

[e] Review the following patient demographics: sex, age, race, and ethnicity.

[f] A complete medical and surgical history will be collected after signing of the ICF.

[g] For subjects in Cohort A only and subjects from Cohort B who resume treatment with denosumab for disease recurrence: physical examination will be performed and will include disease assessment.
[h] Disease status will be clinically accessed by the investigator. GCTB interventions, including surgery, embolization, radiotherapy, and chemotherapy will be collected at each Q6M visit and recorded.
[i] If denosumab treatment is discontinued or interrupted, the calcium and vitamin D supplementation should also be re-evaluated.
[j] Any adverse event leading to study discontinuation (Cohort A and B) must be reported.
[k] The following adverse events of interest will be collected at each Q6M visit and recorded from the signing of the ICF through the EOS visit:
- osteonecrosis of the jaw
- malignancy, including malignancy in GCTB
- atypical femoral fracture
- hypocalcemia
- hypercalcemia following treatment discontinuation
- pregnancy and lactation (if occurred on treatment or within 5 months of last dose of denosumab)

[l] Investigators are advised to include assessment of serum calcium (eg, every 2 to 3 months for approximately 1 year) as clinically indicated following IP treatment discontinuation or interruption.
[m] Serious adverse events will be collected at each Q6M visit and recorded from the signing of the ICF through the EOS visit.
[n] For subjects in Cohort A only and subjects from Cohort B who resume treatment with denosumab for disease recurrence: product complaints as defined in Section 7.1.6 will be collected at each Q6M visit and recorded from signing of the ICF through the EOT visit.
[o] For subjects in Cohort A only and subjects from Cohort B who resume treatment with denosumab for disease recurrence: treatment-emergent adverse events will be collected at each Q6M visit and recorded from the first dose of denosumab through the last EOT visit.
[p] For subjects in Cohort A only and subjects from Cohort B who resume treatment with denosumab for disease recurrence: subjects will receive denosumab 120 mg subcutaneous Q4W until confirmation of disease progression, the subject's decision to discontinue for any reason, or any other reason listed in Section 8.1. The planned dose may be given up to 7 days before the scheduled visit, as long as there are at least 21 days between doses. If a planned dose is delayed more than 7 days, it will be considered a missed dose and recorded as such on the eCRF. For subjects in Cohort A who were receiving denosumab in 20062004, and continue to receive denosumab in this study: denosumab will commence at the next scheduled Q4W visit (with at least 21 days from the last dose of denosumab received in the 20062004 study). Denosumab administration dates will be collected for all subjects receiving denosumab, including Cohort B subjects who resume treatment after disease recurrence. If the subject has discontinued denosumab, stop date and reason for discontinuation will be documented.
[q] All subjects receiving denosumab should be adequately supplemented with calcium and vitamin D (at least 500 mg of calcium and 400 IU of vitamin D), except in the case of pre-existing hypercalcemia.
[r] Retreatment with denosumab is permitted for subjects who demonstrated a previous response to denosumab (eg, in the case of recurrent disease while subject is in the safety follow-up). Eligibility criteria for retreatment are outlined in Section 7.4.1. **Refer to Section 7.1.1 for information on additional doses.**
[s] No study assessments are required during the Q4W dosing visits unless the visits coincide with the timing of the Q6M follow-up study visits.

3. Introduction

3.1 Study Rationale

XGEVA® (denosumab) was approved in the United States, Canada, European Union, Australia, and other countries for the treatment of giant cell tumor of bone (GCTB) largely based on results from ongoing Study 20062004. Study 20062004 is an open-label, single-arm trial where subjects with GCTB are treated with denosumab 120 mg every 4 weeks. For subjects with surgically salvageable disease, treatment continued until surgery **for complete resection** and for approximately 6 months post-surgery. For subjects with surgically unsalvageable disease, treatment continued as long as there was investigator-determined clinical benefit. Study 20062004 will continue until all subjects enrolled in the initial phase of the study complete at least 5 years of follow-up on study. Enrollment in the initial phase of Study 20062004 concluded in November 2012; therefore, the study end**ed** in **May 2018**.

Study 20140114 will continue to follow subjects with GCTB who were treated in Study 20062004 for an additional 5 or more years of long-term safety follow-up.

3.2 Background

3.2.1 Disease

Giant cell tumor of bone is a rare disease characterized clinically by relentlessly expansive osteolytic lesions usually located at the epiphyses of long bones. GCTB has 2 components: a mononuclear stromal cell matrix and dispersed multinuclear giant cells. The mononuclear stromal cells express receptor activator of nuclear factor kappa-B ligand (RANKL); its receptor, RANK, is expressed on the multinuclear giant cells. The RANK/RANKL pathway is an essential mediator of osteoclast function, formation and survival.

3.2.2 Amgen Investigational Product Background: Denosumab

Denosumab, a fully human monoclonal antibody to RANKL, inhibits osteoclast-mediated bone destruction and has been shown to provide therapeutic benefit for patients with GCTB.

A detailed description of the chemistry, pharmacology, efficacy, and safety of denosumab can be found in Denosumab Investigator's Brochure/XGEVA® package insert.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate adverse events of interest in subjects with GCTB treated with denosumab in Study 20062004	• Rate of adverse events of interest in subjects with GCTB treated with denosumab in Study 20062004
Secondary	
• Evaluate treatment-emergent adverse events for subjects who are receiving denosumab	• Rate of treatment-emergent adverse events for subjects who are receiving denosumab
• Evaluate serious adverse events for all subjects	• Rate of serious adverse events for all subjects
• Summarize the rate of disease progression or recurrence of GCTB for all subjects	• Rate of disease progression or recurrence of GCTB for all subjects
• Summarize the use of GCTB interventions for all subjects	• Rate of GCTB interventions for all subjects

4.2 Hypotheses

This study is descriptive in nature and does not involve testing formal hypotheses.

5. Study Design

5.1 Overall Design

This prospective study will provide long-term safety follow-up for subjects who complete Study 20062004 and consent to enroll in Study 20140114. As Study 20062004 nears its end of study (EOS) date, subjects in Study 20062004 will be offered to roll-over into Study 20140114. Study assessments are to be completed every 6 months (± 30 days). The subject's follow-up begins after signing the informed consent form (ICF) and continues through the earliest date of: 5 years after the last subject enrolled signs the ICF, death, withdrawal of consent, or lost to follow-up. Study assessments are detailed in the Table 2-1.

There will be 2 cohorts in this study:

Cohort A: subjects who were receiving denosumab at the conclusion of Study 20062004 can continue receiving denosumab at the current dose and schedule at the investigator's discretion. All subjects should be adequately supplemented with calcium and vitamin D (at least 500 mg of calcium and 400 IU of vitamin D), except in the case of pre-existing hypercalcemia. Follow-up study visits will be performed in clinic every 6 months (± 30 days) while receiving denosumab. Subjects who discontinue denosumab will have

an end of treatment (EOT) in-person clinic visit approximately 30 days **(± 8 days**) after the last dose of denosumab. Thereafter, they will enter the long-term safety follow-up and will be monitored as per Cohort B requirements. In addition to the EOT, all subjects should be monitored for the development of signs and symptoms of hypercalcemia following discontinuation of investigational product (IP). Investigators are advised to include assessment of serum calcium (eg, every 2 to 3 months for approximately 1 year) as clinically indicated following IP treatment discontinuation or interruption. The calcium and vitamin D supplementation following discontinuation of IP should also be re-evaluated. **When investigational product is discontinued, the investigator should evaluate the individual subject's risk for vertebral fragility fractures. Subjects with a high risk for fragility fracture (eg, history of osteoporosis, postmenopausal status, prior fracture history), should be monitored for the development of signs and symptoms of vertebral fractures following discontinuation of denosumab.**

Cohort B: subjects who completed denosumab treatment in 20062004 and were in the safety follow-up at the conclusion of 20062004 will continue in long-term safety follow-up in this study. Follow-up study visits will be done every 6 months (± 30 days) either via telephone or in-person clinic visit. If subjects have completed denosumab treatment less than a year before enrolling in Study 20140114, they should be monitored for development of signs and symptoms of hypercalcemia.

Retreatment with denosumab (120 mg subcutaneous [SC] **on days 1, 8, 15, and 28, then** every 4 weeks **subsequently**) is allowed for subjects who previously demonstrated a response to denosumab and have experienced disease recurrence while in long-term safety follow-up at the investigator's discretion. If more than 12 months have elapsed since the last denosumab therapy, biopsy confirmation of disease for further pathologic evaluation of the recurrence is required. Once denosumab treatment is resumed, the investigator must follow the safety reporting requirements as outlined for Cohort A.

For Cohorts A and B: laboratory assessments are not mandated by the study and will be performed at the investigator's discretion as part of the standard of care or as clinically indicated. Investigators are advised to monitor all subjects for the development of signs and symptoms of hypercalcemia and to consider periodic assessment of serum calcium (eg, every 2 to 3 months for approximately 1 year) as clinically indicated following IP treatment discontinuation or interruption.

At each follow-up study visit, subjects will be assessed (for in-person clinic visit) or asked (for visit via telephone) for signs and symptoms of the following adverse events of interest:

- osteonecrosis of the jaw (ONJ)
- malignancy, including malignancy in GCTB
- atypical femoral fracture (AFF)
- hypocalcemia (assessed per Common Terminology Criteria for Adverse Events [CTCAE] criteria)
- hypercalcemia following treatment discontinuation (assessed by CTCAE criteria)
- pregnancy and lactation (if occurring on treatment or within 5 months of last dose of denosumab)

Specific relevant additional information where available will be requested. Additional information may include, but is not limited to:

- ONJ: dental records; information will be sent for adjudication by independent reviewers
- malignancy, including malignancy in GCTB: pathology reports, tumor slides or blocks, imaging studies, medical/surgical records
- AFF: X-ray or other imaging; medical/surgical records; information will be sent for adjudication by independent reviewers
- hypocalcemia: laboratory reports; medical records
- hypercalcemia following treatment discontinuation: laboratory reports; medical records
- pregnancy and lactation (if occurring on treatment or within 5 months of last dose of denosumab): pregnancy and lactation notification worksheets (Appendix 5).

If the subject has experienced any other serious adverse event (Section 9.2.3.1.1.3) while on study, pertinent information is to be collected and reported. Additionally, all treatment-emergent adverse events will be collected while the subject is receiving denosumab through the EOT visit.

Information regarding GCTB disease status (investigator assessed) and previous or current treatments, including surgery, embolization, radiotherapy, and chemotherapy will be collected at each visit. Embolization, chemotherapy, radiation therapy are permitted in accordance with local guidelines. No investigational agents for GCTB are allowed on study. Use of any unapproved (ie, no marketing authorization has been granted) investigational product or device is not allowed while the subject remains on study.

Denosumab administration dates will be collected for all subjects receiving denosumab, including Cohort B subjects who resume treatment after disease recurrence. If the

subject has discontinued denosumab, stop date and reason for discontinuation must be documented.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

The number of subjects in this study will be determined by the number of subjects completing Study 20062004 who are willing to enroll in this study for long-term safety follow-up. It is estimated that this will be approximately 100 to 300 subjects.

For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

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

5.2.2 Number of Sites

Approximately 25 sites will be enrolling subjects for this study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint, for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed the assessments for 5 years of follow-up.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The EOS date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.

5.3.2 Study Duration for Subjects

The duration of study for each subject is at least 5 years from the date of enrollment (ie, date of signing the ICF).

5.4 Justification for Investigational Product Dose

Subjects in Cohort A will continue denosumab at the same dose and schedule as in the Study 20062004. Denosumab will be dosed at 120 mg SC every 4 weeks.

6. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be provided.

6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject was previously enrolled in Study 20062004.

102 Subject or subject's legally acceptable representative has provided informed consent/assent prior to initiation of any study-specific activities/procedures.

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply.

201 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.

202 Females of childbearing potential on denosumab and not willing to continue to use 1 highly effective method of contraception during treatment and for 5 months after the **EOT**

6.3 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, ICF, and all other subject information and/or recruitment material, if applicable (see Appendix 3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each enrolled subject receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned via Interactive Voice Response System (IVRS). 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, including if a subject is rescreened.

6.4 Screen Failures

Not applicable.

7. Treatments

Study treatment is defined as any investigational product(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 7-1 below.

7.1 Treatment Procedures

7.1.1 Investigational Products

Table 7-1. Study Treatments

	Amgen Investigational Product:[a]
Study Treatment Name	Denosumab (XGEVA)
Dosage Formulation	Denosumab will be supplied as a sterile, clear, colorless to slightly yellow, preservative-free liquid, in single-use 3.0 mL glass vials containing a deliverable dose of 1.7 mL.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	120 mg every 4 weeks
Route of Administration	SC injection
Accountability	Administration dates, doses, and lot number of denosumab are to be recorded on each subject's eCRF(s).
Dosing Instructions	Denosumab is to be administered by a licensed healthcare professional **at a dose of 120 mg SC Q4W with an additional dose of 120 mg SC on days 8 and 15 of treatment for subjects entering retreatment with denosumab (subjects on continuous investigational product from Study 20062004, will not receive an additional dose of 120 mg on days 8 or 15)**. **If the doses on study days 8 and 15 are delayed more than 8 calendar days, it will be considered a missed dose and recorded as such on the eCRF. The next dose is to be given at the next scheduled visit date (based on study day 1). There must be at least 4 days (ie, 96 hours) between the study days 1, 8, and 15 doses (ie, ± 3 days from the scheduled visit date).** The planned dose may be given up to 7 days before the scheduled visit, as long as there are at least 21 days between doses. If a planned dose is delayed more than 7 calendar days, it will be considered a missed dose and recorded as such on the eCRF.

eCRF = electronic case report form; **Q4W = every 4 weeks;** SC = subcutaneous
[a] Denosumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

7.1.2 Non-investigational Products

Non-investigational products will not be used.

7.1.3 Medical Devices

No medical devices are to be used in this study other than those considered to be standard.

Non-investigational medical devices (eg, syringes, sterile needles), 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.

7.1.4 Other Protocol-required Therapies

There are no other protocol-required therapies.

7.1.5 Other Treatment Procedures

Not applicable.

7.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s), or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Any product complaint(s) associated with an investigational product(s), non-investigational product(s), device(s), or combination product(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Concurrent treatment with bisphosphonates is not allowed while the subject is receiving denosumab. Embolization, chemotherapy, and radiation therapy are permitted in accordance with local guidelines. No investigational agents for GCTB are allowed on study. Use of any unapproved (ie, no marketing authorization has been granted) investigational product or device is not allowed while the subject remains on study.

Invasive dental procedures should be avoided when possible and should be recorded in the electronic CRF. Administration of denosumab is recommended to be withheld 30 days prior to any elective invasive oral/dental procedure. Denosumab administration is recommended to remain withheld until documented evidence of complete mucosal healing following any invasive oral/dental procedure. Subjects with ONJ on study may temporarily or permanently discontinue investigational product at investigator discretion. Re-exposure to denosumab may occur if the investigator and sponsor agree subject's safety will not be compromised.

7.2 Method of Treatment Assignment

Not applicable.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dose Modification

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

7.4.1.1 Amgen Investigational Product: Denosumab

There will be no dose adjustments allowed in this study.

Retreatment (restarting denosumab following discontinuation) may be allowed for subjects who demonstrated a response to denosumab and are currently not receiving denosumab treatment (eg, in the case of recurrent disease while subject is in the safety follow-up). Pathological confirmation of GCTB is required prior to retreatment if more than 12 months have elapsed since the last denosumab dose to further evaluate disease recurrence and rule out malignancy. Subjects will not be allowed retreatment if any of the following criteria apply:

- Concurrent bisphosphonate treatment.
- Known or suspected current diagnosis of underlying malignancy including high-grade sarcoma, osteosarcoma, fibrosarcoma, malignant giant cell sarcoma.
- Active dental or jaw condition which requires oral surgery, including tooth extraction.
- Non-healed dental/oral surgery.
- Subject is receiving other investigational agent(s).
- Subject has known sensitivity to denosumab.
- Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 5 months after the last dose of denosumab. (Females of childbearing potential should only be allowed retreatment after a confirmed menstrual period and a negative urine or serum pregnancy test.)

- Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 5 months after the last dose of denosumab.
- 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.
- 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.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of denosumab during the study are provided in the IPIM.

7.6 Treatment Compliance

Not applicable.

7.7 Treatment of Overdose

The effects of overdose of denosumab are not known.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies that were being taken from the EOS visit for 20062004 study through the signing of the ICF for 20140114 should be collected. For prior therapies, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

7.8.2 Concomitant Treatment

All subjects should be adequately supplemented with calcium and vitamin D (at least 500 mg of calcium and 400 IU of vitamin D), except in the case of pre-existing hypercalcemia. Due to differences in regional availability, a dosage form of vitamin D that gives an equivalent of at least 400 IU daily may be given. If denosumab treatment is discontinued or interrupted, the calcium and vitamin D supplementation should also be re-evaluated.

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

For concomitant therapies, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

Concomitant therapies are to be collected from signing of the ICF through the EOS.

8. Discontinuation Criteria

Subjects have the right to withdraw from denosumab treatment, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from denosumab treatment, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving denosumab at any time during the study but continue participation in the study. If this occurs, or if the subject discontinues denosumab treatment for any reason (eg, investigator decision or adverse event [AE]), the investigator is to discuss with the subject the appropriate processes for discontinuation from denosumab, including counseling the subject on signs and symptoms of hypercalcemia, and if clinically indicated, assessment of serum calcium, and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. **When investigational product is discontinued, the investigator should evaluate the individual subject's risk for vertebral fragility fractures. Subjects with a high risk for fragility fracture (eg, history of osteoporosis, postmenopausal status, prior fracture history), should be monitored for the development of signs and symptoms of vertebral fractures following discontinuation of denosumab.** Subjects who have discontinued denosumab should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Appendix 3.

Reasons for removal from denosumab treatment or procedural assessments include any of the following:

- decision by sponsor
- lost to follow-up
- death
- ineligibility determined
- protocol deviation
- noncompliance
- adverse event
- subject request
- disease progression
- pregnancy

8.2 Discontinuation From the Study

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, and must document the subject's decision to withdraw in the subject's medical records.

Refer to the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable.

8.2.2 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

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1).

As protocol waivers or exemptions are not allowed, if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Enrollment

Informed consent must be obtained before completing any assessments detailed in the Schedule of Activities (Table 2-1). If subjects are continuing on denosumab from the Study 20062004 (Cohort A), the informed consent must be signed prior to administration of denosumab in this study.

9.1.2 Treatment Period

Cohort A subjects can continue receiving denosumab at the investigator's discretion. Denosumab will commence at the next scheduled every-4-week visit (with at least 21 days from the last dose of denosumab received in the 20062004 study). Cohort B subjects who enter retreatment only may also receive denosumab at the investigator's discretion. All dosing and follow-up study visits will be scheduled based on the day 1 date defined as the date the ICF is signed. Dosing visits will occur every 4 weeks, per the Schedule of Activities (Table 2-1). Follow-up study visits will be performed in clinic

every 6 months (± 30 days). No safety assessments are required during the every-4-week dosing visits unless the visits coincide with the timing of the follow-up study visit.

9.1.3 End-of-treatment Visit

Cohort A and Cohort B subjects who enter retreatment only: upon discontinuation from denosumab for any reason, an EOT in-person clinic visit will be performed approximately 30 days **(± 8 days**) after the last dose of denosumab.

Thereafter, they will enter the long-term safety follow-up.

In addition to the EOT visit, all subjects stopping denosumab should be monitored for the development of signs and symptoms of hypercalcemia following discontinuation of IP. Investigators are advised to include assessment of serum calcium (eg, every 2 to 3 months for approximately 1 year) as clinically indicated following IP treatment discontinuation or interruption. If denosumab treatment is discontinued or interrupted, the calcium and vitamin D supplementation should also be re-evaluated.

9.1.4 Long-term Safety Follow-up

Cohort B: subjects who completed denosumab treatment in Study 20062004 and were in the safety follow-up at the conclusion of Study 20062004 will continue in long-term safety follow-up in this study. If subjects have completed denosumab treatment less than a year before enrolling in Study 20140114, they should be monitored for the development of signs and symptoms of hypercalcemia with serum calcium assessments as clinically indicated. Study assessments during follow-up study visits in long-term safety follow-up will be completed per the Schedule of Activities (Table 2-1) every 6 months (± 30 days) either via telephone or in-person clinic visit. **An EOS visit should be performed 5 years after signing of the ICF.**

Cohort A and Cohort B subjects who enter retreatment only: subjects will enter long-term safety follow-up after the EOT visit and will be monitored per Cohort B requirements. **Subjects receiving investigational product 5 years after signing of the ICF, should undergo an in-person clinic, combined EOT and EOS visit 30 days following the last dose of investigational product.**

9.1.5 End of Study

End of study will occur when one of the following happens: the last subject enrolled has had the opportunity to complete 5 years of follow-up, death, withdrawal of consent, or lost to follow-up, whichever comes first.

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the Institutional Review Boards/Independent Ethics Committee (IRB/IEC) approved informed consent before any study-specific procedures are performed.

9.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety.

9.2.1.3 Medical History

A complete medical and surgical history will be collected after signing of the ICF. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, GCTB disease specific history must date back to the original diagnosis and reported to the GCTB Details page. The current toxicity grade will be collected for each condition that has not resolved.

9.2.1.4 Physical Examination

For subjects in Cohort A only and subjects from Cohort B who resume treatment with denosumab for disease recurrence: physical examination will be performed. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, GCTB details).

9.2.1.5 Physical Measurements

Not applicable.

9.2.2 Efficacy Assessments

Not applicable.

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Treatment-emergent Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE and is described in Appendix 4.

For Cohort A and Cohort B subjects who enter retreatment only: investigator is responsible for ensuring that all treatment-emergent adverse events observed by the investigator or reported by the subject that occur after the first dose of denosumab through the last EOT visit are reported using the Event CRF.

9.2.3.1.1.2 Adverse Events of Interest

For all subjects (Cohorts A and B): at each visit, subjects will be assessed for signs and symptoms of the following adverse events of interest:

- ONJ
- malignancy, including malignancy in GCTB
- AFF
- hypocalcemia (assessed per CTCAE criteria)
- hypercalcemia following treatment discontinuation (assessed per CTCAE criteria)
- pregnancy and lactation (if occurring on treatment or within 5 months of last dose of denosumab)

If the subject has experienced any adverse events of interest (serious or nonserious) while in study, specific relevant additional information where available will be requested. Additional information may include, but is not limited to:

- ONJ: dental records; information will be sent for adjudication by independent reviewers
- malignancy, including malignancy in GCTB: pathology reports, tumor slides or blocks, imaging studies, medical/surgical records
- AFF: x-ray or other imaging; medical/surgical records; information will be sent for adjudication by independent reviewers
- hypocalcemia: laboratory reports; medical records

- hypercalcemia following treatment discontinuation: laboratory reports; medical records
- pregnancy and lactation (if occurring on treatment or within 5 months of last dose of denosumab): pregnancy and lactation notification worksheets (Appendix 5)

Adverse events of interest will be collected and recorded from the signing of the ICF through the EOS visit.

9.2.3.1.1.3 Serious Adverse Events

For all subjects (Cohorts A and B): 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 EOS visit are reported using the Event CRF.

For all subjects who experienced a treatment gap of more than 30 days between the EOS visit of Study 20062004 and signing the ICF for Study 20140114, all serious adverse events and/or events of interest observed by the investigator or reported by the subject that occurred in that period must be reported using the electronic case report form (eCRF). Events of interest include:

- **ONJ**
- **malignancy, including malignancy in GCTB**
- **AFF**
- **hypocalcemia (assessed per CTCAE criteria)**
- **hypercalcemia following treatment discontinuation (assessed per CTCAE criteria)**
- **pregnancy and lactation (if occurring on treatment or within 5 months of last dose of denosumab)**

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

9.2.3.1.1.4 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the EOS (ie, the protocol-required reporting period). However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after EOS. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported after EOS will be captured within the safety database.

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 4.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of denosumab and until 5 months after the last dose of denosumab.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 5.

9.2.3.1.6 Adjudication Process for Suspected Osteonecrosis of the jaw and Suspected Atypical Femoral Fracture Adverse Events

All subjects with an oral sign or symptom suspicious for ONJ should be examined by a dentist or other qualified oral specialist (eg, oral surgeon). All subjects presenting with new or unusual thigh, hip, or groin pain should be evaluated for a suspected adverse event of AFF.

Adverse events reported as ONJ or AFF as well as adverse events identified by Amgen as potentially representing ONJ or AFF will be reviewed by an independent adjudication panel of experts to determine whether the pre-defined criteria for ONJ or AFF are met. Amgen will request the investigating site to provide all available source documents surrounding that event to be reviewed by the blinded adjudication committee.

9.2.3.2 Vital Signs

Not applicable.

9.2.4 Clinical Laboratory Assessments

Laboratory assessments, both on denosumab and following discontinuation of denosumab are not required and will be performed at the investigator's discretion as part of the standard of care or as clinically indicated. Investigators are advised to include assessments of serum calcium (eg, every 2 to 3 months for approximately 1 year) as clinically indicated following IP treatment discontinuation or interruption (Appendix 2).

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values (Appendix 4). In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

9.2.4.1 Pregnancy Testing

On-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

9.2.5 Other Assessments

9.2.5.1 Giant Cell Tumor of Bone Status Assessments

The following GCTB disease status assessments will be collected:

- disease progression
- disease recurrence
- GCTB interventions, including surgery, embolization, radiotherapy, or chemotherapy

10. Statistical Considerations

10.1 Sample Size Determination

The number of subjects in this study will be determined by the number of subjects completing Study 20062004, and who are willing to enroll in this study for long-term safety follow-up. It is estimated that this will be approximately 100 to 300 subjects.

For the expected sample size of 100 to 300 subjects, the 95% confidence interval (CI) based on exact method for the incidence rate of a particular adverse event is calculated below (Table 10-1). If none of the subjects report a particular adverse event then a true incidence rate of more than 3.6% for 100 subjects and more than 1.2% for 300 subjects is unlikely for that particular adverse event.

Table 10-1. Estimated 95% Confidence Interval for Example Adverse Event of Interest Incidence Rate

Number of Subjects Reporting Adverse Event	Adverse Event Incidence Rate	
	Estimate (%)	95% CI (%)
0/100	0	(0.0, 3.6)
1/100	1	(0.0, 5.4)
5/100	5	(1.6, 11.3)
10/100	10	(4.9, 17.6)
0/200	0	(0.0, 1.8)
2/200	1	(0.1, 3.6)
10/200	5	(2.4, 9.0)
20/200	10	(6.2, 15.0)
0/300	0	(0.0, 1.2)
3/300	1	(0.2, 2.9)
15/300	5	(2.8, 8.1)
30/300	10	(6.8, 14.0)

CI = confidence interval

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

The analysis will be based on the full analysis set which includes all enrolled subjects who have provided informed consent and have a non-missing enrollment date.

10.2.2 Covariates

Not applicable.

10.2.3 Subgroups

Not applicable.

10.2.4 Handling of Missing and Incomplete Data

Subjects may have missing data points for a variety of reasons. In general, data may be missing due to subject's early withdrawal from study, a missed visit, or non-evaluability of an endpoint at a particular point in time. The detailed approach for handling missing data will be included in the statistical analysis plan.

In general, analyses will be based on available data.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses.

10.3.1 Planned Analyses

10.3.1.1 Primary Analysis

Primary analysis will occur upon completion of the study when all subjects have had the opportunity to complete 5 years of follow-up.

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

The statistical analysis in this long-term safety follow-up study will be descriptive in nature and no hypothesis testing will be performed. In general, data summaries will be presented overall. Categorical outcomes will be summarized by the number and percentage of subjects in each category. Continuous outcomes will be summarized by the number of non-missing values, mean, standard deviation, median, lower and upper quartiles and minimum and maximum values. For the incidence, 95% CI will be presented based on an exact method. Kaplan-Meier estimates and their 95% CI will be provided for time to adverse event of interest. The incidence rates (annual and cumulative) of adverse events of interest will be estimated. The incidence of malignancy in GCTB will be compared with the historical control rates based on the published literature.

10.3.2.2 Efficacy Analyses

No formal efficacy analysis is planned for this study.

10.3.2.3 Safety Analyses

10.3.2.3.1 Analyses of Safety Endpoints

Endpoint	Statistical Analysis Methods
Primary	• Rate of adverse events of interest in subjects with GCTB treated with denosumab in Study 20062004
Secondary	• Rate of treatment-emergent adverse events for subjects who are receiving denosumab • Rate of serious adverse events for all subjects • Rate of disease progression or recurrence of GCTB for all subjects • Rate of GCTB interventions for all subjects

10.3.2.3.2 Adverse Events

The incidence of adverse events of interest will be summarized by system organ class and by preferred term per the current Medical Dictionary for Regulatory Activities. The proportion of subjects with adverse events of interest will be estimated for all subjects with 95% CI based on an exact method.

Exposure-adjusted incidence rates will be summarized for adverse events of interest.

For the ONJ, AFF, and malignancy, including malignancy in GCTB events of interest, analyses will be performed by pooling data from Study 20062004 and this study based on all subjects who received at least 1 dose of denosumab. The incidence of malignancy in GCTB will be compared with the historical control rates based on the published literature.

The incidence of treatment-emergent adverse events will be summarized by system organ class and by preferred term per the current Medical Dictionary for Regulatory Activities for subjects who are receiving denosumab. The proportion of subjects with serious adverse events will be estimated.

10.3.2.3.3 Exposure to Investigational Product

Subjects are considered exposed if they received at least 1 dose of denosumab during the study.

Administration dates and doses of denosumab will be collected and cumulative denosumab exposure will be recorded and summarized using descriptive statistics. Similar analysis will be performed for the time period starting from the first denosumab dose in Study 20062004 to the last denosumab dose date (in either Study 20140114 or Study 20062004) plus 28 days, whichever is later.

11. References

Denosumab Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

XGEVA® [package insert]. Thousand Oaks, CA: Amgen, Inc.; March 2016

12. Appendices

Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
AFF	atypical femur fracture
CI	confidence interval
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
EDC	electronic data capture
End of Study (end of trial)	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOS	end of study
EOT	end of treatment
GCP	Good Clinical Practice
GCTB	giant cell tumor of bone
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Interactive Voice Response System (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Boards
ONJ	osteonecrosis of the jaw
RANKL	receptor activator of nuclear factor kappa-B ligand

Abbreviation or Term	Definition/Explanation
SC	subcutaneous
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

Page 2 of 2

Appendix 2. Clinical Laboratory Tests

No laboratory tests are required by this study while subjects are receiving denosumab or following discontinuation of denosumab. Investigators are advised in include assessment of serum calcium (eg, every 2 to 3 months for approximately 1 year) as clinically indicated following IP treatment discontinuation or interruption.

Any laboratory tests performed as standard of care will be performed by the local laboratory.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Appendix 3. Study Governance Considerations

Adjudication Committees

The Osteonecrosis of the Jaw Adjudication Committee and the Atypical Femur Fracture Adjudication Committee will independently adjudicate potential osteonecrosis of the jaw (ONJ) and atypical femur fracture (AFF) events identified in this clinical trial. The respective processes are described in the ONJ and AFF Manuals of Operations.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Boards/Independent Ethics Committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. 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 must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Obtaining annual IRB/IEC approval/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.

- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures.
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the United States Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations.

Recruitment Procedures

This is a roll-over study, and no specific recruitment procedures are required.

Informed Consent Process

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

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, The Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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 unless it is a local requirement. The investigator shall then inform the primary care physician. 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 ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

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 ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

Data Protection/Subject Confidentiality

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

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

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 age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental 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.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to 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; and (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 need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must 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 must qualify for authorship, and all those who qualify are to be listed.

Each author must 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.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An investigator who provided significant contributions to either the design or interpretation of the study
- An investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and

that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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.

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.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research & Development Compliance and Audit 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.

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

Amgen (or designee) will perform Self-Evident Corrections to obvious data errors in the clinical trial database. Self-Evident Corrections will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the electronic data capture (EDC) system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

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

Source Documents

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 provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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. Source documents may also include data captured in the Interactive Voice Response System (IVRS) system (if used, such as subject identification and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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.

- subject files containing completed CRFs, ICFs, 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, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable

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

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the Clinical Trial Agreement. 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.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

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.

Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: an adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from prior results, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • For situations when an adverse event or serious adverse event is due to giant cell tumor of bone, report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer). Note: the term “disease progression” should not be used to describe the disease-related event or adverse event. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:
• **Results in death (fatal)**
• **Immediately life-threatening** The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
• **Requires in-patient hospitalization or prolongation of existing hospitalization** In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
• **Results in persistent or significant disability/incapacity** The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**
- **Other medically important serious event**

Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF).
- 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 (or toxicity defined below)
  - assessment of relatedness to denosumab
  - action taken.
- 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 Event CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Event CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality
• The investigator is obligated to assess the relationship between denosumab and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from denosumab because of a serious adverse event, this information must be submitted to Amgen. • For all deaths, available autopsy reports and relevant medical reports should be provided to Amgen. • New or updated information will be recorded in the originally completed Event CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Event Contingency Report Form (see Figure 12-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see Figure 12-1).

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event.

FORM-056006 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN Study # 20140114 Denosumab	Electronic Serious 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

<<For completion by COM 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. SERIOUS ADVERSE EVENT

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

Serious 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	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 or an Amgen device used to administer the IP? <Device> No / Yes; <Device> No / Yes; <Device> No / Yes; <Device> No / Yes	Outcome of Event 1Resolved 2Not resolved 3Fatal 4Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria:			
	01 Fatal	05 Required/prolonged hospitalization	06 Congenital anomaly / birth defect
	02 Immediately life-threatening	04 Persistent or significant disability /incapacity	08 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

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

		Prior to, or at time of Event: Date of Initial Dose Day Month Year	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/Amgen Device:								
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20140114 Denosumab	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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 # 20140114 Denosumab	Electronic Serious 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 - _____ *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.*	Title	Date

Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for female of childbearing potential are outlined in Section 6.2.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 5 months after the last dose of denosumab.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the Following Categories Are Not Considered Female of Childbearing Potential:

- premenopausal female with 1 of the following:
  - documented hysterectomy;
  - documented bilateral salpingectomy; or
  - documented bilateral oophorectomy.

  Note: site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- premenarchal female
- postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: failure rate of <1% per year when used consistently and correctly.

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device
- intrauterine hormonal-releasing system
- bilateral tubal ligation/occlusion
- vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- periodic abstinence (calendar, symptothermal, post-ovulation methods)
- withdrawal (coitus interruptus)
- spermicides only
- lactational amenorrhoea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking denosumab through 5 months of the last dose of denosumab.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking denosumab through 5 months after the last dose of denosumab. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 5 months after discontinuing denosumab, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking denosumab through 5 months after last dose of denosumab.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking denosumab through 5 months after discontinuing denosumab.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm____/ dd____/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm_____/ dd_____/ yyyy_____ ☐ Unknown

Estimated date of delivery mm_____/ dd_____/ yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm_____/ dd_____/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm_____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Amendment 2

Protocol Title: Long-term Safety Follow up of Subjects With Giant Cell Tumor of Bone Treated With Denosumab in Study 20062004

Amgen Protocol Number (Denosumab) 20140114

NCT Number NCT03301857

EudraCT Number 2017-001758-32

Amendment Date: 23 August 2018

Rationale:

This protocol is being amended to:

- change the interval between last dose of denosumab and the end of treatment (EOT) in-person clinic visit. The current 6 month safety follow-up visit following investigational product discontinuation, is not in line with the historical denosumab clinical trial program. To align with previous standards established in the denosumab clinical program, this visit will be changed to 30 days (± 8) following investigational product discontinuation. This change will not alter the safety or physical or mental integrity of the clinical trial participants, or the scientific value of the trial.
- add detail to denosumab dosing instructions. This is to ensure subjects entering retreatment with denosumab, follow the approved labelled dosing instructions by including additional 120 mg doses on days 8 and 15.
- clarify procedure for reporting serious adverse events and/or events of interest for subjects who experience a treatment gap of more than 30 days between the end of study (EOS) visit of Study 20062004 and signing the informed consent form (ICF) for Study 20140114.
- clarify that Study 20062004 ended in May 2018, as the study was extended by a year.

- clarify that the EOS visit for all subjects will be at 5 years. Cohort A subjects on investigational product will have an EOS visit conducted 30 days following the last dose of investigational product (EOT visit) if receiving investigational product at the 5 year time point.
- clarify that subjects with surgically salvageable disease, treatment continued until surgery for complete resection and for approximately 6 months post-surgery, as aligned to the 20062004 study.
- clarify that investigators will not search publicly available records to ascertain survival status when a subject is lost to follow-up.
- clarify that upon discontinuation, subject's risk for vertebral fragility fractures should be evaluated. This language is being added in order to align language with the core data sheet.
- make editorial, typographical, and formatting changes throughout the document

Description of Changes:

Section: Global

Change:

Version dates updated throughout document from 23 January 2018 to **23 August 2018**.

Section: Global

Change: Made editorial (formatting, typographical, and grammatical) corrections throughout the ICF.

Section: Title Page, Key Sponsor Contact, Name

Replace:

[redacted]

With:

[redacted]

Section: Title Page

Add:

Amendment 2 23 August 2018

Section: 1, Protocol Synopsis, Rationale

Add:

For subjects with surgically salvageable disease, treatment continued until surgery **for complete resection** and for approximately 6 months post-surgery.

Section: 1, Protocol Synopsis, Rationale

Replace:

Enrollment in the initial phase of Study 20062004 concluded in November 2012; therefore, the study is anticipated to end in November 2017.

With:

Enrollment in the initial phase of Study 20062004 concluded in November 2012; therefore, the study end**ed** in **May 2018**.

Section: 1, Protocol Synopsis, Overall Design, Paragraph 1

Delete:

The subject's follow up begins after signing the informed consent form (ICF) and continues through the earliest date of: 5 years after the ~~last~~ subject enrolled signs the ICF, death, withdrawal of consent, or lost to follow up.

Section: 1, Protocol Synopsis, Overall Design, Paragraph 1

Add:

End of study (EOS) visits for all patients will be at 5 years; Cohort A subjects on investigational product will have an EOS visit conducted 30 days following the last dose of investigational product (end of treatment [EOT] visit) if receiving investigational product at the 5 year time point.

Section: 1, Protocol Synopsis, Treatments, Paragraph 1

Add:

If a subject undergoes retreatment with denosumab, they will receive denosumab as a SC injection 120 mg on days 1, 8, 15, and 28, then every 4 weeks subsequently.

Section: 2.2, Table 2-1, Schedule of Activities, Footnote c

Replace:

For subjects in Cohort A only and subjects from Cohort B who resume treatment with denosumab for disease recurrence: EOT in-person clinic visit will occur 6 months (± 30 days) after the last dose of denosumab.

With:

For subjects in Cohort A only and subjects from Cohort B who resume treatment with denosumab for disease recurrence: EOT in-person clinic visit will occur 30 days **(± 8 days**) after the last dose of denosumab.

Section: 2.2, Table 2-1, Schedule of Activities, Footnote r

Add:

Retreatment with denosumab is permitted for subjects who demonstrated a previous response to denosumab (eg, in the case of recurrent disease while subject is in the

safety follow-up). Eligibility criteria for retreatment are outlined in Section 7.4.1. **Refer to Section 7.1.1 for information on additional doses.**

Section: 3.1 Study Rationale, Paragraph 1

Add:

For subjects with surgically salvageable disease, treatment continued until surgery **for complete resection** and for approximately 6 months post-surgery.

Section: 3.1 Study Rationale, Paragraph 1

Replace:

Enrollment in the initial phase of Study 20062004 concluded in November 2012; therefore, the study is anticipated to end in November 2017.

With:

Enrollment in the initial phase of Study 20062004 concluded in November 2012; therefore, the study to end**ed** in **May 2018**.

Section: 5.1 Overall Design, Paragraph 3

Replace:

Subjects who discontinue denosumab will have an end-of-treatment (EOT) in-person clinic visit approximately 6 months (± 30 days) after the last dose of denosumab.

With:

Subjects who discontinue denosumab will have an end of treatment (EOT) in-person clinic visit approximately 30 days **(± 8 days**) after the last dose of denosumab.

Section: 5.1 Overall Design, Paragraph 3

Add:

When investigational product is discontinued, the investigator should evaluate the individual subject's risk for vertebral fragility fractures. Subjects with a high risk for fragility fracture (eg, history of osteoporosis, postmenopausal status, prior fracture history), should be monitored for the development of signs and symptoms of vertebral fractures following discontinuation of denosumab.

Section: 5.1 Overall Design, Paragraph 5

Add:

Retreatment with denosumab (120 mg subcutaneous [SC] **on days 1, 8, 15, and 28, then** every 4 weeks **subsequently**) is allowed for subjects who previously demonstrated a response to denosumab and have experienced disease recurrence while in long-term safety follow-up at the investigator's discretion.

Section: 7.1.1, Table 7-1, Study Treatments, Dosing Instructions

Add:

Study Treatment Name	Amgen Investigational Product:[a] Denosumab (XGEVA)
Dosing Instructions	Denosumab is to be administered by a licensed healthcare professional **at a dose of 120 mg SC Q4W with an additional dose of 120 mg SC on days 8 and 15 of treatment for subjects entering retreatment with denosumab (subjects on continuous investigational product from Study 20062004, will not receive an additional dose of 120 mg on days 8 or 15). If the doses on study days 8 and 15 are delayed more than 8 calendar days, it will be considered a missed dose and recorded as such on the eCRF. The next dose is to be given at the next scheduled visit date (based on study day 1). There must be at least 4 days (ie, 96 hours) between the study days 1, 8, and 15 doses (ie, ± 3 days from the scheduled visit date).** The planned dose may be given up to 7 days before the scheduled visit, as long as there are at least 21 days between doses. If a planned dose is delayed more than 7 calendar days, it will be considered a missed dose and recorded as such on the eCRF.

eCRF = electronic case report form; **Q4W = every 4 weeks;** SC = subcutaneous

Section: 8.1 Discontinuation of Study Treatment, Paragraph 1

Add:

When investigational product is discontinued, the investigator should evaluate the individual subject's risk for vertebral fragility fractures. Subjects with a high risk for fragility fracture (eg, history of osteoporosis, postmenopausal status, prior fracture history), should be monitored for the development of signs and symptoms of vertebral fractures following discontinuation of denosumab.

Section: 8.3 Lost to Follow-up, Paragraph 2, Bullet 4

Delete:

- ~~For subjects who are lost to follow-up, 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.~~

Section: 9.1.3 End-of-treatment Visit

Replace:

Cohort A and Cohort B subjects who enter retreatment only: upon discontinuation from denosumab for any reason, an EOT in-person clinic visit will be performed approximately 6 months (± 30 days) after the last dose of denosumab.

With:

Cohort A and Cohort B subjects who enter retreatment only: upon discontinuation from denosumab for any reason, an EOT in-person clinic visit will be performed approximately 30 days **(± 8 days**) after the last dose of denosumab.

Section: 9.1.4 Long-term Safety Follow-up, Paragraph 1

Add:

An EOS visit should be performed 5 years after signing of the ICF.

Section: 9.1.4 Long-term Safety Follow-up, Paragraph 2

Add:

Subjects receiving investigational product 5 years after signing of the ICF, should undergo an in-person clinic, combined EOT and EOS visit 30 days following the last dose of investigational product.

Section: 9.2.3.1.1.3 Serious Adverse Events

Add:

For all subjects who experienced a treatment gap of more than 30 days between the EOS visit of Study 20062004 and signing the ICF for Study 20140114, all serious adverse events and/or events of interest observed by the investigator or reported by the subject that occurred in that period must be reported using the electronic case report form (eCRF). Events of interest include:

- **ONJ**
- **malignancy, including malignancy in GCTB**
- **AFF**
- **hypocalcemia (assessed per CTCAE criteria)**
- **hypercalcemia following treatment discontinuation (assessed per CTCAE criteria)**
- **pregnancy and lactation (if occurring on treatment or within 5 months of last dose of denosumab)**

Superseding Amendment 1

Protocol Title: Long-term Safety Follow-up of Subjects With Giant Cell Tumor of Bone Treated With Denosumab in Study 20062004

Amgen Protocol Number Denosumab 20140114

NCT Number: NCT03301857

Amendment Date: 23 January 2018

Rationale:

This superseding amendment is being done to clarify inclusion criterion 101. The objective of Study 20140114 is to continue to follow subjects with GCTB who were treated in Study 20062004. A minor language update to inclusion criterion 101 clarifies that 1) to be considered potentially eligible for this study, a subject must have participated in the parent 20062004 study and have completed participation in that study and 2) a subject cannot be concurrently enrolled to Study 20062004 and Study 20140114; which is not clear according to the original protocol inclusion criterion 101.

Amendment 1

Protocol Title: Long-term Safety Follow up of Subjects With Giant Cell Tumor of Bone Treated With Denosumab in Study 20062004

Amgen Protocol Number Denosumab 20140114

NCT Number: NCT03301857

Amendment Date: 15 November 2017

Rationale:

This protocol is being amended to:

- Clarify guidance to investigators about monitoring subjects for hypercalcemia upon discontinuation or interruption of IP
- Add Month 60 to the Schedule of Assessments for clarity
- Make editorial changes and corrections throughout the document