Title: Open-Label Access Protocol of Denosumab for Subjects with Advanced Cancer

Amgen Protocol Number (Denosumab) 20110113

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Investigator's Agreement

I have read the attached protocol entitled "Open-Label Access Protocol of Denosumab for Subjects with Advanced Cancer", dated **22 February 2013**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable FDA regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56 and 312.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- 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 Principal Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: Open-Label Access Protocol of Denosumab for Subjects with Advanced Cancer

Study Phase: 3b

Indication: Treatment of subjects with advanced cancer

Primary Objective: To facilitate the access of denosumab for subjects with advanced cancer who have participated in a denosumab phase 3 study until denosumab is approved and available for sale.

Safety Objective: To further assess the safety of denosumab for subjects who have participated in open label extensions of a denosumab advanced cancer phase 3 study.

Hypotheses: A formal statistical hypothesis will not be tested or estimated.

Study Endpoints: Subject incidence of treatment-emergent adverse events and anti-denosumab antibodies.

Study Design: This is an open-label, single-arm access protocol for subjects with advanced cancer.

Subjects will be offered open-label denosumab at a dose of 120 mg SC Q4W until denosumab is approved and available for sale. Amgen may end this study prior to denosumab being approved and available for sale if another mechanism is identified to provide denosumab to ongoing subjects, or as otherwise stated in Section 12.1 of this protocol.

Severe hypocalcemia can occur in subjects receiving denosumab. Calcium levels should be monitored as part of routine clinical practice. It is strongly recommended that all subjects receive daily supplements of at least 500 mg calcium and at least 400 IU of vitamin D, unless documented hypercalcemia (albumin-adjusted serum calcium > 2.9 mmol/L [11.5 mg/dL] or ionized calcium > 1.5 mmol/L [6.0 mg/dL]) develops on study. 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.

Osteonecrosis of the jaw (ONJ) can occur in subjects receiving denosumab. Subjects should be monitored for ONJ as part of routine clinical practice. Subjects should be instructed to maintain good oral hygiene, and avoid invasive dental procedures, if possible.

Sample Size: The number of subjects will be determined by the number of subjects who qualify for the protocol. It is estimated that up to approximately 400 subjects will participate in this protocol.

Summary of Subject Eligibility Criteria: Adults with advanced cancer and participating in an Amgen denosumab phase 3 study. For a full list of eligibility criteria, please refer to Section 4.1 and 4.2.

Amgen Investigational Product Dosage and Administration: Open-label denosumab at a dose of 120 mg SC Q4W until denosumab is approved and available for sale.

Control Group: None

Procedures: Informed consent must be obtained for all participating subjects. At various times throughout this study adverse events, serious adverse events, and drug accountability will be collected for each subject. A blood sample will be collected after the last dose of denosumab for anti-denosumab antibody testing.

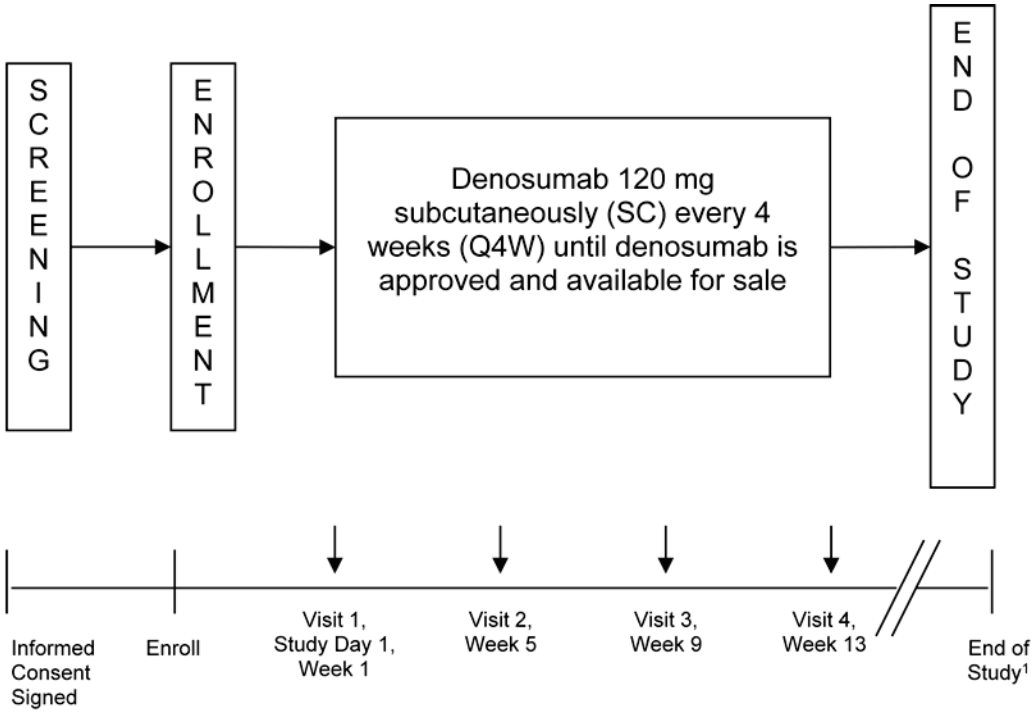
For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and Appendix A.

Statistical Considerations: Adverse events, serious adverse events, deaths, and anti-denosumab antibody status will be summarized.

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

Sponsor: Amgen Inc.

Study Design and Treatment Schema



[1] The end of study for an individual subject is defined as approximately 30 days after the last dose of Denosumab

Study Glossary

Abbreviation/Terminology	Definition
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
GCP	Good Clinical Practice
FDA	Food and Drug Agency
ICH	International Conference on Harmonization
IEC	independent ethics committee
IRB	institutional review board
IV	Intravenous
IVRS	interactive voice response system
MedDRA	Medical Dictionary for Regulatory Activities
mg/dL	Milligrams per deciliter
mmol/L	Millimole per liter
ONJ	Osteonecrosis of the jaw
Q4W	Every 4 weeks
SC	Subcutaneous
SRE	Skeletal Related Events
w/v	Weight per volume
Interactive Voice Response (IVR)	Telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
Source Data	Information from an original record or certified a 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 ID, Randomization ID, and Stratification Value.
study day 1	The first day that protocol-specified investigational product is administered to the subject
end of study for individual subject	Approximately 30 days after the last dose of denosumab
end of study (end of trial)	Defined as when the last subject is assessed or receives an intervention for evaluation in the study

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1. OBJECTIVES

1.1 Primary

To facilitate the access of denosumab for subjects with advanced cancer who have participated in a denosumab phase 3 study until denosumab is approved and available for sale.

1.2 Safety

To further assess the safety of denosumab for subjects who have participated in open label extensions of a denosumab advanced cancer phase 3 study

2. BACKGROUND AND RATIONALE

2.1 Disease

Bone metastases occur in more than 1.5 million patients with cancer worldwide (Coleman and Brown, 2005) and are most commonly implicated in cancers of the prostate, lung, and breast, with incidence rates as high as 75% (Selvaggi and Scagliotti, 2005; Carlin and Andriole, 2000; Coleman, 1997; Viadana et al, 1973). Bone metastases can result in incapacitating clinical sequelae (Coleman, 2006). These complications include debilitating pain that often requires aggressive management with radiation therapy and narcotic analgesics, pathologic fractures that may impair ambulation, surgery to prevent or treat pathologic fractures or manage pain, and spinal cord compressions that can result in numbness or weakness, urinary or fecal incontinence, and paralysis. Furthermore, skeletal complications of bone metastases have been associated with increased mortality (Lage et al, 2008; DePuy et al, 2007).

The underlying pathophysiology of bone metastases, irrespective of primary tumor type and their radiographic appearance, is a locally increased pathologic rate of bone remodeling, including increased osteoclast activity (Roodman, 2004; Yonou et al, 2004). Increased osteoclast activity can be demonstrated on histology (Roudier et al, 2008) and by elevated levels of serum bone resorption markers (Demers et al, 2003). Elevated levels of bone resorption, as measured by increases in bone resorption markers, have been associated with worse prognosis for significant skeletal morbidity (Coleman et al, 2005).

As above, the clinical consequences of increased osteoclastic activity associated with pathological bone remodeling in the setting of bone metastases may lead to fracture, radiation therapy or surgery to bone to alleviate bone pain and/or prevent impending fracture, spinal cord or nerve compression, and hypercalcemia of malignancy. As a

composite, the local irreversible events (fractures, radiation to bone, spinal cord compression or surgery to bone) are defined as Skeletal Related Events (SREs), whereas Hypercalcemia of Malignancy is a systemic and potentially reversible event and is not considered to be a component of SREs.

A key objective in managing the skeletal morbidity associated with bone metastases is to inhibit excessive osteolysis and interrupt the vicious cycle of bone destruction, tumor growth, and further bone destruction, thus preventing or delaying the complications from bone metastases. The pharmacologic armamentarium for this indication is currently comprised of IV bisphosphonates (eg, zoledronic acid, pamidronate), which have been shown to reduce the incidence of SREs in patients with advanced cancer and bone metastases (Kohno et al, 2005; Saad et al, 2002; Rosen et al, 2003; Rosen et al, 2001; Theriault et al, 1999; Berenson et al, 1996; Hortobagyi et al, 1996) and act by reducing bone resorption through inhibition of mature osteoclast activity (Zometa®, 2011 [United States prescribing information]). Suppression of bone resorption and formation markers has been observed following bisphosphonate treatment (Body, 2003). These data, as well as data from nonclinical models (Roodman and Dougall, 2008), suggest that inhibition of osteoclast activity leads to a reduction in cancer-induced bone destruction and support the use of antiresorptives as treatment for bone metastases. Currently, in addition to systemic antitumor therapy, treatment with IV bisphosphonates (eg, zoledronic acid, pamidronate) is recommended for patients with bone metastases (Carlson et al, 2008; Theriault et al, 2006; Warr et al, 2004; Hillner et al, 2003). Of the currently available IV bisphosphonates, zoledronic acid is considered the standard of care, with demonstrated efficacy across tumor types (Kohno et al, 2005; Saad et al, 2002; Rosen et al, 2004; Rosen et al, 2001) and greater potency compared to other bisphosphonates (Gutta and Louis, 2007).

Despite the availability of bisphosphonate treatment, an opportunity exists to improve the management of skeletal complications in patients with bone metastases (Clark et al, 2008; Coleman et al, 2008). A substantial proportion of patients (between approximately 30% to 50%) continue to experience these complications (Rosen et al, 2004; Rosen et al, 2001; Saad et al, 2002), indicating that additional treatment options are warranted. In addition, bisphosphonates are not recommended for use in patients with severe renal impairment because this therapy has been associated with an increased risk of clinically significant deterioration in renal function (Zometa®, 2011 [United States prescribing information]; Aredia®, 2008 [United States

prescribing information]). Renal deterioration is a prevalent condition in patients with advanced cancer, with decreased renal function observed in approximately 50% to 60% of patients with solid tumors, including breast cancer (Launay-Vacher et al, 2008; Kleber et al, 2007). Therefore, minimizing exposure to drugs that may increase the risk of nephrotoxicity, such as bisphosphonates, is an important consideration in the treatment of these patients. Although bisphosphonates have proven to be efficacious inhibitors of bone resorption, it is now clear that their antiresorptive activity resides in their ability to inhibit osteoclast activity (Fleisch, 1998). Denosumab, by virtue of its anti-osteoclastic properties, would be expected to be effective in reducing the occurrence of skeletal-related events in patients with bone lesions from solid tumors or multiple myeloma. Denosumab may also have the potential for use in the pediatric oncology setting.

2.2 Denosumab Background

Perturbations in the balance between bone formation and resorption can lead to generalized osteoporosis (resulting from estrogen deficiency and aging) or local bone lysis (resulting from rheumatoid arthritis and bone metastases). The RANK-RANK ligand (RANKL) system has been identified as an essential mediator of osteoclast formation, function, and survival (Teitelbaum and Ross, 2003). RANKL binds RANK on osteoclasts or osteoclast precursors to stimulate or promote differentiation into osteoclasts and activate mature osteoclasts to resorb bone. Therefore, RANKL is a therapeutic target for diseases associated with increased bone resorption.

Denosumab is a fully human monoclonal IgG2 antibody to RANKL that binds with high affinity (Kd 3 x 10^{-12} M) and specificity to the soluble and cell membrane-bound forms of human RANKL. Denosumab is highly specific because it binds only to RANKL and not to other members of the TNF family, including TNFα, TNFβ, TNF-related apoptosis-inducing ligand (TRAIL), or CD40 ligand (Elliott et al, 2006; Kostenuik et al, 2009). Denosumab binding prevents the activation of RANK and inhibits the formation, activation, and survival of osteoclasts. As a consequence, bone resorption and cancer-induced bone destruction are reduced.

Refer to the investigator's brochure for additional information.

2.3 Rationale

A positive benefit:risk was demonstrated in Amgen study 20050136 (treatment of SREs in advanced breast cancer with bone metastasis) when superiority was demonstrated for both delaying the time to the first on-study Skeletal Related Events (SREs)(fracture,

radiation to bone, surgery to bone, or spinal cord compression) (hazard ratio 0.82, 95 percent CI: 0.71, 0.95), and delaying the time to the first-and-subsequent SREs (hazard ratio 0.77, 95 percent CI: 0.66, 0.89) (Stopeck et al, 2010).

Amgen study 20050103 (treatment of SREs in advanced prostate cancer with bone metastasis) demonstrated superiority for both delaying the time to the first on-study Skeletal Related Events (SREs)(fracture, radiation to bone, surgery to bone, or spinal cord compression) (hazard ratio 0.82, 95 percent CI: 0.71, 0.95), and delaying the time to the first-and-subsequent SREs (hazard ratio 0.82, 95 percent CI: 0.71, 0.94) (Fizazi et al, 2011).

Amgen study 20050147 (delay of bone metastasis-free survival in hormone-refractory [castrate-resistant] prostate cancer] demonstrated that denosumab significantly improved median bone metastasis-free survival by 4.2 months (HR= 0.85, 95 percent CI 0.73-0.98, p=0.03 ie. 15% risk reduction) compared to placebo (primary endpoint), and significantly improved time to first occurrence of bone metastases (secondary endpoint). Overall survival was similar between the denosumab and placebo groups (secondary endpoint) (Amgen Press Release, 2010).

After the above mentioned studies demonstrated a positive benefit:risk, subjects were offered access to denosumab in an open-label extension to the study for either up to 2 or 3 years. As these studies approach the end of the open-label extensions, subjects who are still on-study and receiving benefit from denosumab are not able to get access to denosumab. This study will allow access to denosumab for subjects with advanced cancer who have participated in the Open-label Extension portion of a denosumab phase 3 study and will have access to denosumab until it is approved and available for sale.

2.4 Clinical Hypotheses

A formal statistical hypothesis will not be tested or estimated.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label, single-arm access protocol for subjects with advanced cancer.

Subjects will be offered open-label denosumab at a dose of 120 mg SC Q4W until denosumab is approved and available for sale. Amgen may end this study prior to denosumab being approved and available for sale if another mechanism is identified to

provide denosumab to ongoing subjects, or as otherwise stated in Section 12.1 of this protocol.

Severe hypocalcemia can occur in subjects receiving denosumab. Calcium levels should be monitored as part of routine clinical practice. It is strongly recommended that all subjects receive daily supplements of at least 500 mg calcium and at least 400 IU of vitamin D, unless documented hypercalcemia (albumin-adjusted serum calcium > 2.9 mmol/L [11.5 mg/dL] or ionized calcium > 1.5 mmol/L [6.0 mg/dL]) develops on study. 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.

Osteonecrosis of the jaw (ONJ) can occur in subjects receiving denosumab. Subjects should be monitored for ONJ as part of routine clinical practice. Subjects should be instructed to maintain good oral hygiene, and avoid invasive dental procedures, if possible.

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

3.2 Number of Centers

This access protocol will be available to sites in countries in which Amgen has conducted phase 3 studies with denosumab in oncology. The number of sites in this study will be determined by the number of sites requesting access to denosumab.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

The number of subjects will be determined by the number of subjects who qualify for the protocol. It is estimated that up to approximately 400 subjects will participate in this protocol.

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

The anticipated total duration for a subject enrolling in the study will be until denosumab is approved and available for sale.

It is anticipated that the average treatment duration under this protocol will be approximately 1 year per subject.

3.4.2 End of Study

The end of study for an individual subject will occur approximately 30 days after the last dose of denosumab. The end of the clinical study is defined as the time when the last subject is assessed or receives an intervention for evaluation in the study.

4. SUBJECT ELIGIBILITY

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 procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

4.1.1 Subjects was previously enrolled in a denosumab phase 3 study and participated in the Open-label Extension portion of that study.

4.1.2 Subject or subject's legally acceptable representative has provided informed consent.

4.2 Exclusion Criteria

4.2.1 Subject is of child bearing potential and planning to become pregnant within 7 months after the end of treatment.

4.2.2 Subject is of child bearing potential and is not willing to use, in combination with her partner, two highly effective method of contraception during treatment and for 7 months after the end of treatment

4.2.3 Subject has known sensitivity to any of the products to be administered during dosing.

4.2.4 Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge.

4.2.5 Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures.

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen Inc requires a copy of the site's written Independent Ethics Committee/Institutional Review Board (IEC/IRB) approval of the protocol, informed consent form, and all other subject information if applicable (see Section 11.2). All subjects or legally acceptable representatives must personally sign and date the consent form before any study-specific screening procedures.

All subjects who enter into the screening period for the study (defined as the point at which the subject signs the informed consent) will receive a unique subject identification number before any study procedures are performed. 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 at the time of rescreening or enrollment.

The investigator (or designee) must call the Interactive Voice Response System (IVRS) with the following information to register a subject at the time the informed consent is signed:

- Subject information
- Date of written informed consent

Upon receipt of this information, the IVRS will confirm that the subject has been registered (ie, entered the screening period of the study).

Subjects who meet all inclusion/exclusion criteria will be enrolled into this study. The investigator (or designee) must contact the IVRS with the confirmation of eligibility status to enroll a subject into the study:

On receipt of this information, the IVRS will confirm that the subject has been enrolled.

6. TREATMENT PROCEDURES

Denosumab will be the only investigational product in this study. In addition, subjects are strongly recommended to receive calcium and vitamin D and these medications will be referred to as supplements.

6.1 Denosumab

Denosumab will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

Denosumab will be provided as a sterile, clear, colorless to slightly yellow, practically free from particles, preservative-free liquid in open-label, single-use 3.0-mL vials containing 1.7 mL of 70 mg/mL denosumab, [redacted] mM acetate and [redacted]% (w/v) sorbitol at a pH of [redacted].

To obtain the box number assignment for a scheduled dose, site personnel will call the IVRS. The box number of investigational product is to be recorded on each subject's investigational product administration the Case Report Form (CRF).

Refer to the Investigational Product Instruction Manual for information on the administration of investigational product.

6.1.1 Dosage, Administration, and Schedule

Each subject will receive a 120 mg SC injection of denosumab Q4W until denosumab is approved and available for sale.

Amgen will notify investigators when denosumab is to become available (on a per-country basis) to discuss the timelines for stopping protocol treatment.

6.1.2 Dose-cohort Study Escalation and Stopping Rules

There are no dose escalations or stopping rules in this study.

6.1.3 Dosage Adjustments

There will be no dose adjustments for denosumab.

6.2 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.3.

6.3 Excluded Treatments During Study Period

Bisphosphonates (oral or intravenous [IV]) or commercial denosumab are not to be administered during the study treatment.

6.4 Other Treatment Procedures

Severe hypocalcemia can occur in subjects receiving denosumab. Calcium levels should be monitored as part of routine clinical practice. It is strongly recommended that all subjects receive daily supplements of at least 500 mg calcium and at least 400 IU of vitamin D, unless documented hypercalcemia (albumin-adjusted serum calcium > 2.9 mmol/L [11.5 mg/dL] or ionized calcium > 1.5 mmol/L [6.0 mg/dL]) develops on study. 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.

Osteonecrosis of the jaw (ONJ) can occur in subjects receiving denosumab. Subjects should be monitored for ONJ as part of routine clinical practice. Subjects should be instructed to maintain good oral hygiene, and avoid invasive dental procedures, if possible.

7. STUDY PROCEDURES

Study assessments will be performed only after written informed consent is obtained. The schedule of assessments is provided in Appendix A.

All tests and procedures scheduled for screening must be performed within 35 days before the planned first dose of investigational product (ie, study day 1).

Study visits will occur Q4W (± 8 days). Every effort should be made to keep subjects on the study schedule as planned from study day visit 1.

Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the CRF.

7.1 General Study Procedures

7.2 Adverse Events and Serious Adverse Events

Adverse Events and Serious Adverse Events will be recorded starting at Study Day 1 and will be followed through approximately 30 days after the last dose of denosumab.

7.3 Antibody Testing Procedures

A blood sample at the end of study visit will be collected from all subjects for the measurement of anti-denosumab binding anti-bodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-denosumab antibodies during the study.

Subjects who test positive for neutralizing antibodies to denosumab at the final scheduled study visit will be asked to return for additional follow-up testing. This testing should occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks). More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-denosumab antibody response may also be asked to return for additional follow-up testing.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

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

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and 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. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject appropriate procedures for withdrawal from the study.

Should a subject (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable CRFs.

Reasons for removal from protocol-required product(s) or observation might include:

- withdrawal of full consent
- administrative decision by the investigator or Amgen
- pregnancy in a female subject (report on Pregnancy Notification Worksheet; see Appendix D).
- ineligibility
- significant protocol deviation
- patient noncompliance
- adverse event
- disease progression
- other safety concern by the investigator or Amgen
- death
- lost to follow-up

8.2 Replacement of Subjects

Subjects will not be replaced.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

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

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates the pre-existing medical condition (eg, diabetes, migraine

headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study, and involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

The term “disease progression of the primary tumor” should not be captured as an adverse event (including fatal adverse event). If there are signs and/or symptoms of disease progression (regardless of primary or secondary tumor) that are new or worsened from baseline signs and/or symptoms, these should be reported as adverse event(s). If a new primary malignancy appears, it will be considered an adverse event.

9.1.2 Reporting Procedures for Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after Study Day 1 through approximately 30 days after the last dose of denosumab are reported using the applicable CRF (eg, Adverse Event Summary 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,
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to denosumab, and
- Action taken.

The adverse event toxicity grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The toxicity grading scale used in this study is described in Appendix B.

The investigator must assess whether the adverse event is possibly related to denosumab. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject’s baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not 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) should be recorded as the adverse event.

The investigator's clinical judgment will be used to determine whether a subject should be removed from treatment or from the study due to an adverse event. A subject, or subject's parent/legal guardian, may also voluntarily withdraw from treatment due to an adverse event. If the subject withdraws full consent, the subject should be encouraged to undergo, at a minimum, an end-of-study assessment.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

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

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

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

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

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after Study Day 1 through 30 days after the last dose of denosumab are recorded in the subject's medical record and are submitted to Amgen. The serious adverse event must be submitted to Amgen within **24 hours** of discovery or notification of the event.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is

indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

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

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

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

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

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

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specified product and for 7 months after end of treatment, the pregnancy should be reported to Amgen's global Pregnancy Surveillance Program **within 24 hours of the investigator's knowledge of a pregnancy**. Report pregnancy on the Pregnancy Notification Worksheet (Appendix D). **The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.**

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 7 months after IP discontinuation.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix E).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

Subject incidence of treatment-emergent adverse events and anti-denosumab antibodies.

10.2 Sample Size Considerations

The statistical reporting of the safety outcomes will be entirely descriptive (summary statistics), with no formal statistical hypothesis tested or estimated. The number of subjects will be determined by the number of subjects who qualify for the protocol. It is estimated that up to approximately 400 subjects will participate in this protocol.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

All subjects will receive denosumab.

10.4 Interim Analysis and Early Stopping Guidelines

There will be no interim analysis or early stopping rules.

10.5 Planned Methods of Analysis

10.5.1 General Approach/Considerations

Descriptive statistics provided for categorical outcomes will include the frequency and percentage. Continuous outcomes will include the number of subjects, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum.

Safety data will be summarized for all subjects who received at least 1 dose of investigational product.

10.5.2 Analysis of Key Study Endpoints

10.5.2.1 Treatment-emergent Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The analysis of adverse events will be descriptive. The subject incidence rates of treatment-emergent adverse events will be tabulated by system organ class and preferred term. Additional summary tables will be provided separately for serious adverse events, Common Terminology Criteria for Adverse Events (CTCAE) grade 3, 4, or 5 adverse events, adverse events leading to investigational product discontinuation, and adverse events leading to study withdrawal. Narratives of deaths and serious

adverse events will also be provided. All investigational product related adverse events, serious adverse events, CTCAE grade 3, 4 or 5 adverse events, adverse events leading to investigational product discontinuation, and adverse events leading to study withdrawal will be summarized in the same manner as treatment-emergent adverse events

10.5.2.2 Anti-denosumab Antibodies

The incidence and percentages of subjects who develop anti-denosumab antibodies at any time will be tabulated.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial generic informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template will be communicated by letter from the Amgen to the investigator. The written informed consent document should be prepared in the language(s) of the potential patient population.

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

The acquisition of informed consent should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject.

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

11.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent

form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

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

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

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- On the CRFs or other documents submitted to Amgen, subjects should be identified by a subject identification number only, with a complete and accurate date of birth on the demographics CRF.
- For Serious Adverse Events reported to Amgen, subjects should be identified by their initials, date of birth, and a subject identification number.
- Documents that are not for submission to Amgen (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB 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 named representatives to have access to his/her study-related records, including personal information, without violating the confidentiality of the subject.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator should notify the IEC/IRB 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 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, and by what mechanism, after termination of the trial and before it is available commercially.

12.2 Study Documentation and Archive

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

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

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed CRF, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation, and all correspondence to and from the IEC/IRB and Amgen
- If kept, proof of receipt/delivery sheet, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement (if applicable), and all drug-related correspondence

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

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

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections

Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit—week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. Consult the country-specific requirements for language requirements.

12.5 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several principal 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 should 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), which states:

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

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

12.6 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. Depending on the type of study, and if permitted under applicable regional laws or regulatory guidelines, subjects may be compensated for other inconveniences not associated with study-related injuries (eg, travel costs).

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14. APPENDICES

Appendix A. Schedule of Assessments

Open-Label Treatment (Visits every 4 weeks)									
Study Assessments	Screening (1) ≤ 35 days	Visit 1 D1 (2)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Every Q4W Visits	End of Study Visit (6)
Informed Consent	x								
LABORATORY									
Anti-Denosumab Antibody (3)									x
INVESTIGATIONAL PRODUCT ADMINISTRATION									
Denosumab (SC) (4)		x	x	x	x	x	x	x	n/a
OTHER ASSESSMENTS									
Adverse Event and Serious Adverse Event Collection (5)		x	x	x	x	x	x	x	x

Footnotes for Schedules of Subject Assessments

1	**Screening:** All screening assessments must be completed and results obtained before enrollment into the study.
2	**Study day 1:** The first day that investigational product is administered.
3	**Anti-Denosumab Antibody:** Collect at the end of study visit
4	**Investigational Product Administration:** Denosumab will be administered at dose of 120 mg subcutaneously (SC) every 4 weeks (Q4W)
5	**Adverse Event and Serious Adverse Events:** Adverse event and serious adverse events must be assessed and documented at each clinic visit. Subjects must be followed for serious adverse events for 30 days after the last dose of denosumab.
6	**End of Study Visit:** Will be completed at any point a subject discontinues participation or approximately 30 days after the last dose of denosumab, whichever comes last.

Appendix B. Additional Safety Assessment Information

Adverse Event Toxicity Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following link:

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

Appendix C. Sample Serious Adverse Event Form

AMGEN 20110113 — **Clinical Trial Serious Adverse Event Report Phase 1-4** — *Notify Amgen Within 24 Hours of knowledge of the event* — ☐New ☐Follow-up

SELECT OR TYPE IN A FAX#

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Initials	Date of Birth (Day Month Year)	Sex	Race
			☐F ☐M	

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day ____ Month ____ Year ____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *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	Enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the event may have been caused by IP? **If yes see section 10** No✓ Yes✓	Outcome of Event 01 Resolved 02 Resolving 03 Not resolved 04 Fatal	Check only if event is related to study procedure eg, biopsy

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability /incapacity; **06** Congenital anomaly / birth defect; **07** Other significant medical hazard

4. HOSPITALIZATION

	Date Admitted (Day Month Year)	Date Discharged (Day Month Year)
Was subject hospitalized? ☐No ☐Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld
denosumab ☐✓Open Label						

6. RELEVANT CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Relevant 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✓

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AMGEN 20110113	Clinical Trial Serious Adverse Event Report Phase 1-4 *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

	Site Number	Subject ID Number	

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:

Test / Unit / Date (Day Month Year)											

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

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

Signature of Investigator or Designee	Title	Date

Appendix D. Pregnancy Notification Worksheet

AMGEN Study No.:	Site No.	Subject ID No.	Subject Initials

PREGNANCY NOTIFICATION WORKSHEET

Did subject withdraw from the study? ❑ No 0 ❑ Yes 1

Sex ①	① SEX CODES:
	1 Female subject **0** Male subject partner

Estimated Date of Conception		
Day	Month	Year

Investigational Product Administration Start Date			Investigational Product Administration Stop Date		
Day	Month	Year	Day	Month	Year

Fax to:		
	Date Faxed	
	Day Month Year	

The investigator will be contacted for further information.

Please provide the following information:

Investigator Name:	Telephone: ( )	
Institution:		Site No:
Address:		

Form Completed By: _____ Date: _____

v4 14Apr04sb

Appendix E. Lactation Notification Worksheet

Print Form

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:** _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page 1 of 1

Superseding Original

Protocol Title: Open-Label Access Protocol of Denosumab for Subjects with Advanced Cancer

Amgen Protocol Number denosumab 20110113

Amendment Date: **22 February 2013**

Rationale:

The purpose of this amendment is to clarify the serious adverse event reporting process and timelines and provide a mechanism for reporting of lactation events should they occur in female subjects who are receiving or have received denosumab within 7 months prior.

Summary of changes:

- Clarify that serious adverse events must be reported within 24 hours
- Clarify how serious adverse events reported to Amgen will be reported to regulators and investigators
- Provide lactation notification worksheet in the protocol

Description of Changes (all changes to the protocol are indicated in bolded text):

Section: Key US Sponsor Contact

Replace:

PPD, Clinical Research Study Manager

Thousand Oaks, USA

PPD

With:

PPD, Clinical Research Study Manager

Thousand Oaks, USA

PPD

Section: Key EU Sponsor Contact

Replace:

PPD, Clinical Research Study Manager

Uxbridge, UK

PPD

With:

PPD, Clinical Research Study Manager

Uxbridge, UK

PPD

Section 9.2.2 Reporting Procedures for Serious Adverse Events

Replace:

The serious adverse event must be submitted to Amgen within 1 working day of discovery or notification of the event.

With:

The serious adverse event must be submitted to Amgen within **24 hours** of discovery or notification of the event.

Section 9.2.2 Reporting Procedures for Serious Adverse Events

Add:

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

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

Section 9.2.2 Reporting Procedures for Serious Adverse Events

Replace:

All new information for serious adverse events must be sent to Amgen within 1 working day of receipt.

With:

All new information for serious adverse events must be sent to Amgen within **24 hours** of receipt.

Section 9.2.2 Reporting Procedures for Serious Adverse Events

Delete:

Serious adverse events deemed possibly related to investigational product by the investigator occurring more than 30 days after the last dose of investigational product will be submitted to Amgen within 1 working day of discovery or notification of the event.

Section 9.2.2 Reporting Procedures for Serious Adverse Events

Delete:

Determination of expectedness for Amgen products will be based on the contents of the Investigator's Brochure (Appendices A and/or B when available) for investigational products and the regional prescribing information for products being studied for an approved use. Expectedness assessments will be made for all investigational products (Amgen and non-Amgen) using the appropriate reference safety information per local

regulatory reporting requirements. Suspected unexpected serious adverse reactions reported for subjects receiving a non-Amgen investigational product will be expedited according to local requirements.

Section 9.3 Pregnancy and Lactation Reporting

Replace:

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specified product and for 7 months after end of treatment, the pregnancy should be reported to Amgen's global Pregnancy Surveillance Program. Report pregnancy on the Pregnancy Notification Worksheet (Appendix D).

With:

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specified product and for 7 months after end of treatment, the pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of a pregnancy. Report pregnancy on the Pregnancy Notification Worksheet (Appendix D). **The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.**

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 7 months after IP discontinuation.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix E).

Section: Appendix C Serious Adverse Event Form has been updated

Section: Appendix E Lactation Notification Worksheet has been added