Osteonecrosis of the Jaw (ONJ) Case Registry

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Investigator's Agreement

I have read the attached protocol entitled Osteonecrosis of the Jaw (ONJ) Case Registry, dated **19 July 2018** and agree to abide by all provisions set forth therein.

I agree to comply with the International **Council for** Harmonisation Tripartite Guideline on Good Clinical Practice.

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: Osteonecrosis of the Jaw (ONJ) Case Registry

Study Phase: Post-Marketing Safety Study

Indication: Advanced Cancer

Objectives:

The ONJ case registry is part of the denosumab post-marketing pharmacovigilance program. This ONJ case registry will describe the natural history of positively-adjudicated, newly diagnosed ONJ in subjects with cancer with an observation period of 5 years. Most of these subjects are expected to have received antiresorptive medications such as bisphosphonates or denosumab together with cancer-specific therapies (eg, chemotherapy, steroids, or antiangiogenic agents). It is also possible that the ONJ case registry will include subjects with cancer who developed ONJ without exposure to any antiresorptive medications.

The primary objective of the ONJ case registry is:

- Estimate the rate and describe the time course of resolution of ONJ
  - Resolution: complete coverage of the exposed bone by mucosa in the absence of clinical symptoms
  - Improvement: a decrease in the stage or severity of the lesion
  - Progression: an increase in the stage or severity of the lesion
  - Stable: not resolved, improved, or progressed

The secondary objectives of the ONJ case registry are:

- Describe the clinical features of ONJ including severity and staging at registry enrolment
- Characterize the frequency of risk factors for incident ONJ such as a history of inflammatory dental disease (periodontal and dental abscesses), dentoalveolar procedures, smoking, use of antiangiogenic agents, and duration/dosing regimens of antiresorptive medications prior to the development of ONJ
- Characterize subsequent treatment patterns for ONJ including antimicrobial oral rinses, antibiotics, and surgery
- Characterize treatment patterns of antiresorptive medications subsequent to incident ONJ such as the proportion of subjects who continue to be treated with antiresorptive medications by specific agents and ONJ severity and stage

Exploratory objectives are:

- Explore the relationship between severity and stage of ONJ with the rate and time course of resolution
- Explore what additional prognostic value beyond severity and stage of ONJ is suggested by baseline risk factors for ONJ
- Explore differences in ONJ rate and time course of resolution by antiresorptive medications and patterns of their continuation/discontinuation.

Clinical Hypotheses:

This is an observational registry. The estimation hypothesis is that the rate of resolution of ONJ observed in the registry is similar to that observed in the 3 denosumab phase 3 clinical trials of skeletal-related events (SRE) in subjects with advanced cancer with bone metastases.

Other clinical hypotheses that direct the analysis plan include the following:

- The time course and rate of resolution of ONJ is similar to that observed in the SRE phase 3 trials
- The rate of resolution of ONJ is related to the severity and stage of ONJ
- The rate of resolution of ONJ is inversely related to the presence of oral risk factors that preceded the event.

Study Design:

The ONJ case registry is a case-series prospective follow-up study of positively-adjudicated, newly diagnosed ONJ cases. After obtaining informed consent, subjects with suspected newly diagnosed ONJ will be screened for eligibility, including having an evaluation by the study dental specialist to collect information for adjudication of these cases by an external adjudication committee. Subjects with positively-adjudicated, newly diagnosed ONJ and who meet all other study eligibility criteria will be enrolled in this registry for follow up. These subjects are expected to be receiving antiresorptive medications such as bisphosphonates or denosumab together with cancer-specific therapies (eg, chemotherapy, steroids, or antiangiogenic agents as part of standard cancer treatment). It is also possible that the ONJ case registry will include subjects with cancer who developed ONJ without exposure to any antiresorptive or antiangiogenic medications based on the eligibility criteria in the original study protocol as well as in protocol amendment 1.

ONJ is defined as exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks. ONJ has occurred in the absence of radiotherapy to the jaw or metastatic disease to the jaws, and in the presence of current or previous treatment with antiresorptive medication or antiangiogenic agents.

Baseline data including cancer history and treatment, general medical and dental history and information about the event of ONJ will be collected upon enrollment. Follow-up visits will be conducted by study dental specialists every 3 months ($\pm$1 month) for 2 years, then every 6 months ($\pm$1 month) for 3 years, for a total duration of 5 years or until death, withdrawal of consent, or lost to follow-up, whichever comes first. ONJ clinical features, associated factors, management, and outcome, as well as cancer therapy and outcomes, will be collected prospectively.

Treatment for ONJ may be provided by the subject's dentist or the study dental specialist. Subjects may concurrently participate in other open-label, therapeutic, nontherapeutic, and/or observational clinical trials.

Positively-adjudicated, newly diagnosed ONJ cases in subjects treated with denosumab will be reported to regulatory agencies by Amgen according to local country regulations.

Interim analyses will be conducted annually, commencing in 2014.

Endpoints:

The primary endpoint is the rate and time course of ONJ resolution

Secondary endpoints:

- The clinical features of ONJ, including severity and staging at enrollment
- The frequency of risk factors for incident ONJ
- Therapeutic treatment patterns for ONJ
- Treatment patterns of antiresorptive medications subsequent to incident ONJ

Exploratory Endpoints:

- The relationship between severity and stage of ONJ resolution rate and time course
- The prognostic value of baseline risk factors on ONJ resolution rate and time course
- Differences in ONJ resolution rate and time course by antiresorptive medications and continuation or discontinuation

Sample Size:

Enrollment will continue until at least 300 subjects with positively-adjudicated, newly diagnosed ONJ are enrolled, and approximately 75 subjects exposed to denosumab alone (ie, no treatment with bisphosphonates), are accrued. It is projected that approximately 150 enrolled subjects will have been exposed to denosumab.

Summary of Subject Eligibility Criteria:

Subjects with cancer with Eastern Cooperative Oncology Group (ECOG) ≤ 2, expected survival ≥ 3 months, and newly-diagnosed positively-adjudicated ONJ.

For a full list of eligibility criteria, please refer to Section 4.1 and 4.2.

Procedures:

Subjects receiving routine cancer care at a cancer center who develop suspected ONJ will be screened after they have given written informed consent. Subjects will be evaluated by the study dental specialist to assess the suspected ONJ. ONJ-related medical and dental information (eg, history, staging, appropriate imaging, and treatments) will be collected and submitted to an external adjudication committee. Subjects with positively-adjudicated, newly diagnosed ONJ and who meet all other study eligibility criteria will be enrolled in the registry for detailed follow-up of the ONJ.

Baseline medical and dental history will be obtained.

During follow-up, subjects will attend study visits to be evaluated by a study dental specialist every 3 months ($\pm$1 month) for 2 years, then every 6 months ($\pm$1 month) for 3 years. These study visits may be conducted in addition to or in conjunction with standard-of-care visits. Treatment for ONJ can be provided by the subject's dentist or study dental specialist. Visits with a study oncologist are optional.

Information to be collected at each visit includes historical and current ONJ clinical features, treatment and surgical procedures, and outcomes. Information regarding historical and current cancer treatment, outcomes, and comorbidities will be collected from the treating physician (eg, oncologist, hematologist, or urologist).

It may be necessary for the subject to provide permission to receive and release information from their primary physician, oncologist, and/or dentist to the study site regarding medical and dental history. This permission may need to be updated throughout the study to be able to collect information on an ongoing basis.

For a full description of study procedures, please refer to Section 6.

Statistical Considerations:

Sample size:

Since the resolution rate of ONJ is of particular interest in this study, the confidence interval for the expected resolution rate of ONJ with this sample size has been calculated. Amgen clinical trials suggest that the ONJ resolution rate is approximately 27% in zoledronic acid and 35% in denosumab-treated advanced cancer patients with bone metastases. With a sample size of 300 subjects, the 95% confidence interval (CI) for an expected ONJ resolution rate of 30% is (25, 35)% with a half-width of 5%. The half-width of the 95% confidence interval will be 5% and 6% for an expected ONJ resolution rate of 20% and 40% respectively. The 95% CIs for an expected ONJ resolution rate of 30% in 150 subjects never exposed to denosumab and 75 subjects exposed to denosumab alone are (23, 37)% and (20, 40)% respectively.

Analysis:

The principal analysis for ONJ outcomes will employ the primary analysis set; the full analysis set will be considered supportive. All other analyses will use the full analysis set. The full analysis set-subset is defined as all subjects who are enrolled into the study. The primary analysis set-subset is defined as all subjects in the full analysis set that have at least one follow-up visit, without prior radiation to the jaws. A small number of enrolled subjects received radiation to the maxillofacial area for palliative indications based on the eligibility criteria in the original study protocol as well as in protocol amendment 1. Additionally, a small number of subjects had no

exposure to either antiresorptive medications or antiangiogentic agents prior to ONJ development based on the eligibility criteria in the original study protocol and protocol amendment 1.

The proportion of subjects with ONJ resolved, progressed, improved, or stable will be estimated for all subjects and by antiresorptive treatment history. Large sample normal approximation will be used for the calculation of 95% confidence intervals. If the number of events is low or the number of subjects is small in a group, exact method will be used. As the subjects will be recruited from different cancer centers, sensitivity analysis may be conducted to accommodate potential clustering effect due to center. Kaplan-Meier curves will be produced to graphically describe time to ONJ resolution.

ONJ clinical features, such as time to onset, stage, grade, location, and severity of lesions will be summarized at enrollment.

Baseline subject characteristics, including demographic factors, medical, dental, and medication history, such as history of inflammatory dental disease (periodontal and dental abscesses), dentoalveolar procedures, smoking, use of antiangiogenic agents, and duration/dosing regimens of antiresorptive medications prior to the development of ONJ will be summarized using descriptive statistics. Information on antiresorptive medications, cancer treatment, comorbidities, and concomitant treatments during longitudinal follow-up will also be summarized using descriptive statistics.

Subsequent treatment and management of ONJ, such as antimicrobial oral rinses, antibiotics, surgery, and antiresorptive medications continuation/discontinuation treatment patterns after ONJ diagnosis will be summarized.

The relationship of baseline ONJ clinical features and putative ONJ risk factors, including antiresorptive treatment history, with ONJ resolution rate will be explored using logistic regression and Cox-regression techniques.

Interim analyses will be conducted annually, commencing in 2014. All subjects will be included in the interim analyses. Analyses for the primary and secondary endpoints will be included in the report and the results will be submitted.

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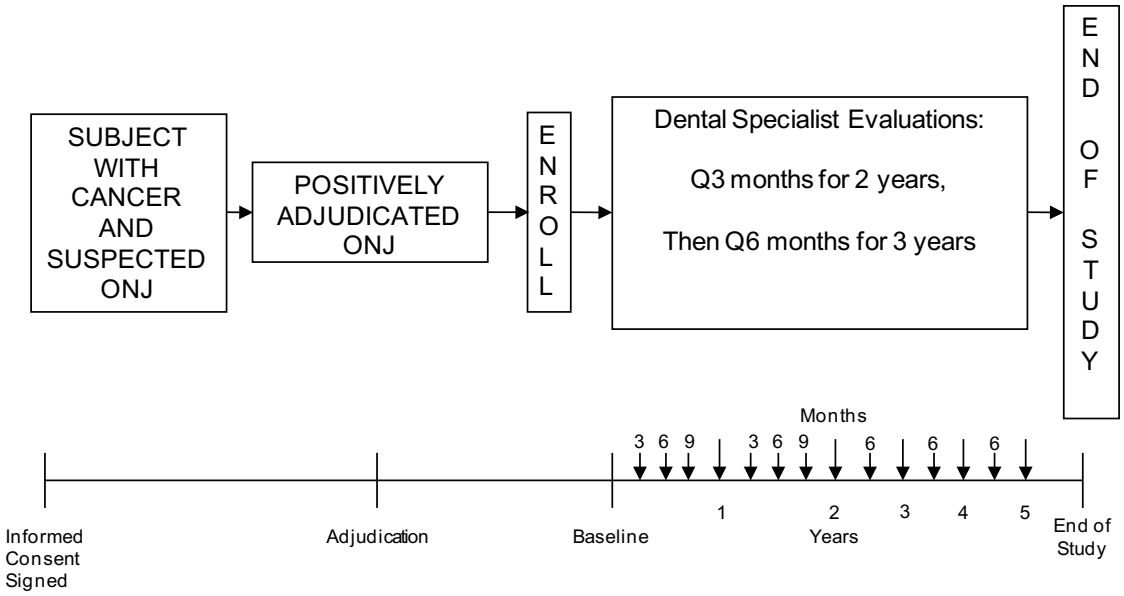
Study Design Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
AAOMS	American Association for Oral and Maxillofacial Surgeons
ADR	**adverse drug reaction**
CI	Confidence interval
CRF	Case report form
eCRF	electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
GCP	Good Clinical Practice
ICH	International **Council for** Harmoni**s**ation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IRB	Institutional review board
ONJ	Osteonecrosis of the jaw: ONJ is defined as exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks. ONJ has occurred in the absence of radiotherapy to the jaw or metastatic disease to the jaws, and in the presence of current or previous treatment with antiresorptive medication or antiangiogenic agents.
SADR	**serious adverse drug reaction**
SEC	Self-evident corrections
Enrollment	Defined as the day the subject is positively-adjudicated for ONJ

TABLE OF CONTENTS

List of Tables

List of Appendices

1. OBJECTIVE

The osteonecrosis of the jaw (ONJ) case registry is part of the denosumab post-marketing pharmacovigilance program. This ONJ case registry will describe the natural history of positively-adjudicated, newly diagnosed ONJ in subjects with cancer with an observation period of 5 years. Most of these subjects are expected to have received antiresorptive medications such as bisphosphonates or denosumab together with cancer-specific therapies (eg, chemotherapy, steroids, or antiangiogenic agents). It is also possible that the ONJ case registry will include subjects with cancer who developed ONJ without exposure to any antiresorptive medications.

The primary objective of the ONJ case registry is:

- Estimate the rate and describe the time course of resolution of ONJ
  - Resolution: complete coverage of the exposed bone by mucosa in the absence of clinical symptoms
  - Improvement: a decrease in the stage or severity of the lesion
  - Progression: an increase in the stage or severity of the lesion
  - Stable: not resolved, improved, or progressed

The secondary objectives of the ONJ case registry are:

- Describe the clinical features of ONJ including severity and staging at registry enrolment
- Characterize the frequency of risk factors for incident ONJ such as a history of inflammatory dental disease (periodontal and dental abscesses), dentoalveolar procedures, smoking, use of antiangiogenic agents, and duration/dosing regimens of antiresorptive medications prior to the development of ONJ
- Characterize subsequent treatment patterns for ONJ including antimicrobial oral rinses, antibiotics, and surgery
- Characterize treatment patterns of antiresorptive medications subsequent to incident ONJ such as the proportion of subjects who continue to be treated with antiresorptive medications by specific agents and ONJ severity and stage

Exploratory objectives are:

- Explore the relationship between severity and stage of ONJ with the rate and time course of resolution
- Explore what additional prognostic value beyond severity and stage of ONJ is suggested by baseline risk factors for ONJ
- Explore differences in ONJ rate and time course of resolution by antiresorptive medications and patterns of their continuation/discontinuation.

2. BACKGROUND AND RATIONALE

2.1 Disease and Rationale

ONJ is defined as exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks. ONJ has occurred in the absence of radiotherapy to the jaw or metastatic disease to the jaws, and in the presence of current or previous treatment with antiresorptive medication or antiangiogenic agents (Ruggiero et al, 2014; Woo et al, 2006, Marx, 2003; Ruggiero et al, 2004).

The pathogenesis of ONJ is likely multifactorial. Consideration of major risk factors associated with ONJ may provide insight into possible pathogenetic mechanisms. Major factors considered to be involved in ONJ development are suppression of bone turnover, local oral trauma, and infection/inflammation.

Although a direct cause and effect relationship has not been established, there is a strong association of ONJ with suppression of bone turnover. The magnitude and duration of pharmacologically mediated suppression of bone turnover appear to significantly affect risk. This is suggested by the observations that incidence of ONJ is increased with cumulative dosing of bisphosphonates (Ruggiero et al, 2009; Cartsos et al, 2008), which results in a marked sustained suppression of bone turnover. Similarly, the longer the duration of antiresorptive medications, the more opportunity for the occurrence of a potentially inciting oral event.

Local factors in the mouth clearly play a role in determining risk. Cancer patients treated with IV bisphosphonates with a history of inflammatory dental disease have an increased incidence of ONJ (Hoff, 2006). Events traumatic to the oral mucosa such as tooth extraction or injury from poorly fitting dentures result in exposure of bone to the microbial flora of the oral cavity and increase the need for bone remodeling.

Because denosumab suppresses bone turnover by inhibiting osteoclast differentiation and activity, its use could be a risk factor for ONJ in certain populations. In clinical trials with denosumab in patients with advanced cancer and bone metastases, all events reported as ONJ or corresponding to a prespecified list of Medical Dictionary for Regulatory Activities (MedDRA) adverse event preferred terms were reviewed and adjudicated by an independent adjudication committee. Based upon the results of 3 phase-3, randomized clinical trials, ONJ occurs with similar frequency during treatment with denosumab as during treatment with zoledronic acid in this setting.

Since the original description of bisphosphonate-related ONJ in 2003 (Marx, 2003) awareness of the condition has increased and medical management has evolved from aggressive surgical intervention initially, to a more conservative, less interventional approach more recently. As the understanding of ONJ management and outcomes is progressing, further evaluation of the natural history of ONJ is warranted. An ONJ case registry is a mechanism from which to obtain data on the clinical features, treatment, and outcomes of ONJ.

2.2 Clinical Hypotheses

This is an observational registry. The estimation hypothesis is that the rate of resolution of ONJ observed in the registry is similar to that observed in the 3 denosumab phase 3 clinical trials of skeletal-related events (SRE) in subjects with advanced cancer with bone metastases.

Other clinical hypotheses that direct the analysis plan include the following:

- The time course and rate of resolution of ONJ is similar to that observed in the SRE phase 3 trials
- The rate of resolution of ONJ is related to the severity and stage of ONJ
- The rate of resolution of ONJ is inversely related to the presence of oral risk factors that preceded the event.

3. METHODS

3.1 Study Design

This is an observational registry of subjects with cancer who have positively-adjudicated, newly diagnosed ONJ. Sites that will conduct this registry will be cancer centers that treat a large volume of patients and utilize antiresorptive medications according to current practice guidelines.

After obtaining informed consent, subjects with suspected newly diagnosed ONJ will be screened for eligibility, including having an evaluation by the study dental specialist to collect additional information for adjudication of these cases by an external adjudication committee. Subjects with positively-adjudicated, newly diagnosed ONJ and who meet all other study eligibility criteria will be enrolled in the registry. These subjects are expected to be receiving antiresorptive medications such as bisphosphonates or denosumab together with cancer-specific therapies (eg, chemotherapy, steroids, or antiangiogenic agents as part of standard cancer treatment). It is also possible that the registry will include subjects with cancer and ONJ without exposure to any antiresorptive

medication based on the eligibility criteria in the original study protocol as well as in protocol amendment 1.

Subjects with a history of ONJ will be included in the registry, with the understanding that subjects with a history of ONJ that will be re-exposed to an antiresorptive medication may be rare and difficult to recruit into the registry.

The external adjudication committee will be comprised of experts in the field of ONJ diagnosis and treatment. An oncologist and an endocrinologist will serve as consultant experts as needed by the adjudicators.

ONJ is defined as exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks. ONJ has occurred in the absence of radiotherapy to the jaw or metastatic disease to the jaws, and in the presence of current or previous treatment with antiresorptive medication or antiangiogenic agents.

Osteoradionecrosis of the jaw associated with the administration of therapeutic doses of radiation to the jaw is a separate clinical entity from osteonecrosis of the jaw associated with use of antiresorptive medications and is excluded in current definitions of ONJ. Therefore, patients who have had radiation treatment to the jaws will be excluded from this registry.

Baseline information will be collected upon enrollment. Follow-up visits will be conducted by a study dental specialist every 3 months (±1 month) for 2 years, then every 6 months (±1 month) for 3 years, for a total duration of 5 years or until death, withdrawal of consent, or lost to follow-up, whichever comes first. Visits with a study oncologist are optional.

Although the median survival in the population most likely to develop ONJ and enroll in this registry (advanced cancer; most with bone metastases requiring antiresorptive therapy) is likely to be less than 3 years, the 5 year duration of follow-up in this study will ensure the adequate description of the natural history of ONJ.

Information regarding ONJ clinical features, associated factors, management, and outcome, as well as cancer therapy and outcomes, will be collected.

Treatment of ONJ may be provided by the subject's dentist or the study dental specialist. Subjects may concurrently participate in other open-label, therapeutic, nontherapeutic, and/or observational clinical trials.

Positively-adjudicated, newly diagnosed ONJ cases in subjects treated with denosumab will be reported to regulatory agencies by Amgen according to local country regulations.

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

Interim analyses will be conducted annually, commencing in 2014.

The study endpoints are defined in Section 9.1.

3.2 Number of Centers

This study will be conducted at approximately 70 sites globally. Additional sites may be added.

Sites that do not enroll subjects within 12 months of site initiation may be terminated.

3.3 Number of Subjects

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

Enrollment will continue until at least 300 subjects with positively-adjudicated, newly diagnosed ONJ are enrolled and approximately 75 subjects treated with denosumab alone (ie, no treatment with bisphosphonates) are accrued. It is projected that approximately 150 enrolled subjects will have been exposed to denosumab.

Refer to Section 9.2 for the rationale for the number of subjects.

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

The estimated study duration for each participant is approximately 5 years.

3.4.2 End of Study

- End of study (end of trial): defined as when **all** subject**s have had the opportunity to** complete the final follow-up assessment**, have died, withdrawn consent, or are lost to follow-up**.
- End of study for individual subject: defined as the last day that protocol-specified procedures (ie, final follow-up assessment) are conducted for an individual subject**, or until death, full consent withdrawal, or are lost to follow-up, whichever occurs first**.

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 such as sex, age, race, screening date, and outcome of the screening process (eg, enrolled into

study, reason for ineligibility [eg, ONJ not positively adjudicated], or declined to participate). The rate of nonparticipation will be monitored during the trial.

Before any study-specific procedure, the appropriate written informed consent will be obtained (see Section 10.1).

4.1 Inclusion Criteria

4.1.1 Adult (≥ 18 years of age) with diagnosis of cancer

4.1.2 Newly diagnosed, positively-adjudicated ONJ

4.1.3 ECOG ≤ 2 and expected survival ≥ 3 months

4.1.4 Willing to provide access to previous and future medical and dental information

4.1.5 Subject or subject's legally acceptable representative has provided written informed consent

4.2 Exclusion Criteria

4.2.1 History of radiation to the jaws administered for the treatment of cancer

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

4.2.3 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 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 and/or recruitment material, if applicable (see Section 10.2). Each subject or legally acceptable representative must personally sign and date the consent form before screening.

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 enrollment.

PPD [redacted]

PPD [redacted].

The enrollment date is defined as the date the subject's ONJ is adjudicated to be positive by the external adjudication committee.

6. STUDY PROCEDURES

6.1 General Study Procedures

The schedule of assessments is provided in Appendix A.

Screening

Subjects with cancer who develop suspected ONJ will be asked to provide written informed consent. Subjects will be evaluated by the study dental specialist to assess the suspected ONJ. ONJ-related medical and dental information (eg, history, staging (Appendix F), appropriate imaging, and treatments) will be collected and submitted to an external adjudication committee. Subjects with positively-adjudicated, newly diagnosed ONJ will be enrolled in the registry for detailed follow-up of the ONJ. Subjects who initially do not meet eligibility criteria (eg, are not positively-adjudicated, or other reason) may be rescreened up to 2 times. Subjects can be enrolled within 6 months of the local diagnosis of suspected ONJ diagnosis and/or subjects to be enrolled within 8 months of first exposed bone. Subjects with ONJ that resolved during this interval may be enrolled pending positive adjudication by the external committee.

It may be necessary for the subject to provide permission to receive and release information from their primary physician, oncologist, and/or dentist to the study site regarding medical and dental history. This permission may need to be updated throughout the study to be able to collect information on an ongoing basis.

Baseline

The following information will be collected upon enrollment (via medical and dental record review):

Medical and Dental History:

- Demographic characteristics
- Current and previous medication use, including antiresorptive medications

- Cancer history and treatments
- Medical history
- Dental history, including treatments and procedures
- ONJ-related medical and dental information (collected at screening)

Follow-up

Subjects will attend study visits to be evaluated by a study dental specialist every 3 months (±1 month) from enrollment for 2 years, then every 6 months (±1 month) for 3 years. These study visits may be conducted in addition to or in conjunction with standard-of-care visits. Treatment for ONJ may be provided by the subject's dentist or study dental specialist. Visits with a study oncologist are optional.

The information to be collected includes, but is not limited to:

ONJ Follow-up:

- Clinical features, including size, stage, grade (Appendix G), location, and duration of each lesion
- Treatment, including medications and surgeries
- Dental procedures performed including extractions
- Outcomes, including resolution, improvement, and progression
  - Resolution: complete coverage of the exposed bone by mucosa in the absence of clinical symptoms
  - Improvement: a decrease in the stage or severity of the lesion
  - Progression: an increase in the stage or severity of the lesion
  - Stable: not resolved, improved, or progressed

Cancer, Medications, and Comorbidity Follow-up: (Information regarding cancer, medications, and comorbidity will be collected from the treating physician [eg, oncologist, hematologist, or urologist]):

- Antiresorptive medication type/s and duration of treatments
- Cancer status and treatments
- Other major medical conditions since last visit: infections, others

Reporting

Each **suspected** ONJ case among denosumab-treated subjects that is adjudicated **to meet prespecified criteria for ONJ** will be **captured in the Amgen Global Safety Database as a serious adverse drug reaction (SADR), as the objective of this study is to characterize the clinical course of ONJ**.

Amgen will submit an aggregated report of key study parameters to regulatory agencies every 6 months for the first 3 years after denosumab becomes commercially available to advanced cancer patients, and then annually through study completion according to the Periodic Safety Update Report (PSUR) submission schedule. Interim analyses will be conducted annually, commencing in 2014. A final study report will be completed at the end of the study and submitted.

7. REMOVAL AND REPLACEMENT OF SUBJECTS

7.1 Removal of Subjects

Subjects have the right to withdraw fully 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 or is unable to continue further study participation; subject data up to withdrawal of consent will be included in the subject's study data. Any subject may withdraw 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 case report forms (CRFs).

Reasons for removal from protocol-specified observation might include:

- withdrawal of consent
- death
- lost to follow-up

7.2 Replacement of Subjects

Subjects will not be replaced.

8. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

This is an observational study. Adverse drug reactions, other safety findings and product complaints, and serious adverse drug reactions reported in **denosumab-exposed** subjects will be collected and reported in this study. **All fatal events for denosumab-exposed subjects will also be collected and reported in this study.** Investigators should also follow appropriate local post-marketing reporting requirements.

8.1 Definitions

8.1.1 Definition of Adverse Events and Adverse Drug Reactions

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, combination product, or medical device whether or not considered related to the product. The definition of an adverse event includes:

- worsening of a pre-existing condition
- events occurring from a medication error or overdose of a product(s), whether accidental or intentional
- events occurring from abuse of a product(s)
- events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)
- any lack or loss of intended effect of the product(s)

An adverse drug reaction is an adverse event that is considered related to the medicinal product.

It is the Investigator's responsibility to evaluate if an event is related to **denosumab** prior to reporting the event to Amgen.

8.1.2 Definition of Serious Adverse Events and Serious Adverse Drug Reactions

For the purposes of this study, a serious adverse event is any adverse event as defined using the criteria above that meets at least one serious criterion per ICH GCP requirements:

- 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, and/or
- other significant medical hazard.

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

Any reaction that does not exactly meet this definition yet, in the investigator's opinion represents a significant hazard, can be assigned the "other significant hazard" regulatory reporting serious criteria.

Additionally, important medical reactions that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

For this study, reporting serious adverse events that are not adverse drug reactions related to the use of **denosumab** is not required **unless the event is fatal and the patient has been exposed to denosumab (see Section 8.2.1)**.

8.1.3 Definition of Other Safety Findings

Other Safety Findings include:

- medication errors, overdose, misuse, or abuse, whether accidental or intentional, involving an Amgen product, regardless of whether associated with an adverse drug reaction or serious adverse drug reaction
- pregnancy and lactation exposure regardless of whether associated with an adverse drug reaction or serious adverse drug reaction
- transmission of infectious agents regardless of whether associated with an adverse drug reaction or serious adverse drug reaction
- reports of uses outside the terms for authorized use of the product including off-label use when associated with an adverse drug reaction or serious adverse drug reaction
- occupational exposure
- any lack or loss of intended effect of the product(s)

8.1.4 Definition of Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device 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 all components distributed with the product(s) such as packaging, product containers, delivery system, labeling, inserts, etc.

Product Complaints may include but are not limited to issues related to:

- appearance (eg, broken, cracks, color, particles, odor)
- labeling (eg, missing, torn, smudged)
- durability (eg, stability issues)
- open packaging
- device damage (eg, prefilled syringe with bent needle)
- inability of customer to understand product labeling
- inability of customer to deliver the product successfully, including partial or incomplete delivery (eg, defective delivery system [syringe])

8.2 Reportable Events and Reporting Timeframes

The investigator is responsible for ensuring that safety events (adverse drug reactions, serious adverse drug reactions, product complaints, and other safety findings) for **denosumab-exposed subjects** observed by the investigator or reported by the subject that occur after signing of the informed consent form through the final study visit are recorded in the subject's medical record and are submitted to Amgen via the applicable Amgen Safety Reporting Form **(Appendix E)**. Table 1 describes the reporting timeframes for reportable events.

Table 1. Reporting Timeframes for Reportable Events

Report Type	Description	Reporting Timeframe
Fatal serious adverse events	**All fatal events (including exempted events that have a fatal outcome)**	**Within 1 business day of investigator's awareness**
SADR and any associated Other Safety Findings	Initial or follow-up reports	Within 1 business day of investigator's awareness
ADR that are not serious and any associated Other Safety Findings	Initial or follow-up reports	Within 1**5 calendar** day**s** of investigator's awareness
Other Safety Findings NOT associated with ADR or SADR	Initial or follow-up reports	Within 1 business day of investigator's awareness
Product complaints	Initial or follow-up reports	Within 1 business day of investigator's awareness
Pregnancy and/or lactation	• Initial or follow-up reports of pregnancies or lactation occurring in females while taking **denosumab** and/or • Initial or follow-up reports of pregnancies occurring in female partners of males taking **denosumab**	Within 1 business day of investigator's awareness

See Appendix E for sample Safety Report Form(s), Appendix B for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix D and Appendix H for sample Pregnancy and Lactation Notification Worksheets. The investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded **i**n study **documentation** where safety data may also be recorded (eg, Adverse Event Summary CRF).

Due to the focused objectives of this post-marketing pharmacovigilance study, it is expected that the study investigators will have limited and incomplete access to non-dental adverse events and serious adverse events, for example, resulting from the subject's advanced cancer or cancer therapy. Furthermore, given the myriad of complications experienced by patients with advanced cancer (eg, with bone and visceral metastases, receiving concurrent chemotherapy) non-medical doctor dental providers may not be trained to properly assess or capture severity, grading, and clinical relevance of medical adverse events related to the subject's oncologic diagnosis.

In addition, the broader safety profile of denosumab is well-known and continues to be studied in Amgen's ongoing clinical trial program and routine pharmacovigilance. As individuals with ONJ were eligible for enrollment regardless of prior bone-targeted agent exposure, only a small portion of enrolled subjects were exposed to denosumab as their only bone-targeted agent. Thus, it is unlikely that this study will contribute to the understanding of the broader safety profile of denosumab.

8.2.1 Protocol Exempt Safety Information

Collection of **adverse** events that are not **considered** related to denosumab **by the investigator** is not required. Denosumab has an established safety profile with extensive post-marketing experience. In this observational study, it is considered appropriate to collect only adverse drug reactions (ie, adverse events considered by the investigator to be related to denosumab) together with product complaints (see Section 8.1.4) and other safety findings (eg, pregnancy, breast feeding, medication errors, overdose; see Section 8.1.3).

If any of the exempted events have a fatal outcome, they should be considered a serious adverse event and must be collected and reported individually within 1 business day of Investigator awareness.

Protocol-exempted events and safety events that are suspected to be related to any medicinal product other than denosumab should be reported to the local authority in line with the local country requirements.

8.2.2 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs/IECs, or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of serious adverse events in accordance with local procedures and statutes.

9. STATISTICAL CONSIDERATIONS

9.1 Study Endpoints, Subsets, and Covariates

9.1.1 Study Endpoints

The primary endpoint is the rate and time course of ONJ resolution

Secondary endpoints:

- The clinical features of ONJ, including severity and staging at enrollment
- The frequency of risk factors for incident ONJ
- Therapeutic treatment patterns for ONJ
- Treatment patterns of antiresorptive medications subsequent to incident ONJ

Exploratory Endpoints:

- The relationship between severity and stage of ONJ resolution rate and time course
- The prognostic value of baseline risk factors on ONJ resolution rate and time course
- Differences in ONJ resolution rate and time course by antiresorptive medications and continuation or discontinuation

9.1.2 Subsets

The principal analysis for ONJ outcomes will employ the primary analysis set; the full analysis set will be considered supportive. All other analyses will use the full analysis set. The full analysis set-subset is defined as all subjects who are enrolled into the study. The primary analysis set-subset is defined as all subjects in the full analysis set that have at least one follow-up visit, without prior radiation to the jaws. A small number of enrolled subjects received radiation to the maxillofacial area for palliative indications based on the eligibility criteria in the original study protocol as well as in protocol amendment 1. Additionally, a small number of subjects had no exposure to either

antiresorptive medications or antiangiogenic agents prior to ONJ development based on the eligibility criteria in the original study protocol and protocol amendment 1.

9.1.3 Covariates

The relationship of the following covariates to the primary endpoints will be explored:

- severity of ONJ
- stage of ONJ
- history of inflammatory dental disease (yes/no)
- dentoalveolar procedures (yes/no)
- smoking (yes/no)
- use of antiangiogenic agent (yes/no)
- antiresorptive treatment history
- antiresorptive treatment continuation/discontinuation pattern subsequent to incident ONJ
- ONJ therapies

9.2 Sample Size Considerations

Enrollment will continue until at least 300 subjects with positively-adjudicated, newly diagnosed ONJ are enrolled and approximately 75 subjects treated with denosumab alone (ie, no treatment with bisphosphonates) are accrued. It is projected that approximately 150 enrolled subjects will have been exposed to denosumab.

The ONJ registry study has three objectives. Resolution is the primary ONJ outcome of interest and the sample size was estimated primarily to estimate this rate. However, the range of resolution rates considered also covers the potential values to address the other two objectives which are clinical features including severity and staging, and treatment patterns, including the proportion of subjects who continue to be treated with antiresorptive medications.

Amgen clinical trials suggest that the ONJ resolution rate is approximately 27% in zoledronic acid and 35% in denosumab-treated advanced cancer patients. A sample size of 300 subjects with positively-adjudicated, newly diagnosed ONJ cases provides estimates of the resolution rate with reasonable precision. With a sample size of 300 subjects, the 95% confidence interval (CI) using large sample normal approximation for an expected ONJ resolution rate of 30% is (25, 35)% with a half-width of 5%. The half-width of the 95% confidence interval will be 5% and 6% for an expected ONJ resolution rate of 20% and 40% respectively. The 95% CIs for an expected ONJ resolution rate of 30% in 150 subjects never exposed to denosumab and 75 subjects

exposed to denosumab alone are (23, 37)% and (20,40)% respectively. Table 2 provides the 95% confidence intervals and their half-widths for various resolution rates and sample sizes. (Values over 0.5 are not presented because the confidence interval for 0.5 is the widest for all possible values for a percentage.)

The coefficient of variation for the scenarios considered in the Sample Size Consideration section are displayed in Table 2 below, where the coefficient of variation is a normalized measure of dispersion of a distribution defined as the ratio of the standard deviation to the mean. A low coefficient of variation indicates less dispersion around the mean and the value of 1 is often used as the rule of thumb threshold for low variability. As the highest coefficient of variation is 0.35 for the scenarios considered, the proposed sample size allows for the objectives to be addressed with sufficient precision.

Table 2. Confidence Intervals for Various Resolution Rates and Sample Sizes

Sample Size	Expected Rate (%)	95% Confidence Interval (%, %)	Half-Width of 95% CI (%)	Coefficient of Variation
300	10	7, 13	3	0.17
300	20	15, 25	5	0.12
300	30	25, 35	5	0.09
300	40	34, 46	6	0.07
300	50	44, 56	6	0.06
150	10	5, 15	5	0.24
150	20	14, 26	6	0.16
150	30	23, 37	7	0.12
150	40	32, 48	8	0.10
150	50	42, 58	8	0.08
75	10	3, 17	7	0.35
75	20	11, 29	9	0.23
75	30	20, 40	10	0.18
75	40	29, 51	11	0.14
75	50	39, 61	11	0.12

9.3 Interim Analysis

Interim analyses will be conducted annually, commencing in 2014. All subjects will be included in the interim analyses. Analyses for the primary and secondary endpoints will be included in the report and the results will be submitted.

9.4 Planned Methods of Analysis

9.4.1 General Approach/Considerations

The objective of this study is to describe the natural history of positively-adjudicated, newly diagnosed ONJ in subjects with cancer. Due to the likelihood of unmeasured confounding factors, no formal comparisons will be conducted.

Continuous parameters will be summarized using descriptive statistics, which includes mean, standard deviation, median, and/or selected percentiles, and the number of non-missing observations. Categorical parameters will be summarized using frequencies and percentages.

Subjects may have missing data points for a variety of reasons. Data may be missing due to subject's early withdrawal from study, a missed visit, or non-evaluability of an endpoint at a particular time point. In general, analyses will be based on available data. Sensitivity analyses may be conducted using different approaches to handle missing data.

9.4.2 Analyses for Primary Endpoint

The ONJ outcome of resolution will be summarized.

For the purpose of these analyses, the definition of resolution is complete coverage of the exposed bone by mucosa in the absence of clinical symptoms

The proportion of subjects with resolved ONJ will be estimated for all subjects and by antiresorptive treatment history. Large sample normal approximation will be used for the calculation of 95% confidence intervals. If the number of events is low or the number of subjects is small in a group, exact method will be used. As the subjects will be recruited from different cancer centers, sensitivity analysis may be conducted to accommodate potential clustering effect due to center. Kaplan-Meier curves will be produced to graphically describe time to ONJ resolution.

9.4.3 Analyses for Secondary Endpoints

The proportion of subjects with ONJ progressed, improved, or stable will be estimated for all subjects and by antiresorptive treatment history. Large sample normal approximation will be used for the calculation of 95% confidence intervals. If the number

of events is low or the number of subjects is small in a group, exact method will be used For the purposes of these analyses, the definitions of these outcomes are:

- Improvement: a decrease in the stage or severity of the lesion
- Progression: an increase in the stage or severity of the lesion
- Stable: not resolved, improved, or progressed

Baseline subject characteristics, including demographic factors, medical, dental, and medication history, such as history of inflammatory dental disease (periodontal and dental abscesses), dentoalveolar procedures, smoking, use of antiangiogenic agents, and duration/dosing regimens of antiresorptive medications prior to the development of ONJ will be summarized using descriptive statistics. Information on antiresorptive medications, cancer treatment, comorbidities, and concomitant treatments during longitudinal follow-up will also be summarized using descriptive statistics.

ONJ clinical features, such as time to onset, stage, grade, location, and severity of lesions will be summarized at enrollment.

Subsequent treatment and management of ONJ, such as antimicrobial oral rinses, antibiotics, surgery, and antiresorptive medications continuation/discontinuation treatment patterns after ONJ diagnosis will be summarized.

9.4.4 Analyses for Exploratory Endpoints

The relationship of baseline ONJ clinical features and putative ONJ risk factors with ONJ resolution rate and time to resolution will be explored using logistic regression and Cox-regression techniques. Univariate analysis will be conducted using covariates listed in Section 9.1.3 to explore the relationship between each individual factor with the ONJ resolution rate and time to resolution. Multivariate regression using a stepwise model selection approach will be fit starting with all covariates with a p-value < 0.05 in the univariate analysis and interaction terms. If an interaction term is kept in the final model, the corresponding main terms will also be kept. Prognostic value of the terms in the final model will be examined and interpreted in proper context.

10. REGULATORY OBLIGATIONS

10.1 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 study manager 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 or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures are conducted. A legally acceptable representative is 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.

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 or a legally acceptable representative 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 or legally acceptable 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 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.

10.2 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.

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 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.

10.3 Subject Confidentiality

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

- 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.
- On Serious Adverse Event forms submitted to Amgen, subjects should be identified by their initials, date of birth, and a subject identification number only.
- Documents that are not for submission to Amgen (eg, signed informed consent forms) should be kept in strict confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the 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.

10.4 Investigator Signatory Obligations

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

The coordinating investigators, identified by Amgen, will either be:

- 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

11. ADMINISTRATIVE AND LEGAL OBLIGATIONS

11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the investigator must be obtained where applicable per local governing law and/or regulations. 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.

11.2 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 to 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

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.

11.3 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 is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the 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 Research & Development Compliance and Audit function (or designees). Inspection of site facilities 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 eCRFs must be maintained and readily available.
- Updates to eCRFs 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 EDC system database for site resolution and closed by Amgen reviewer.
- For early site closures (prior to database lock) **and f**or sites closing after the database lock, the investigator applies an electronic signature in the EDC system. This signature will indicate that the principal investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the eCRF instructions available in the 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, [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

11.4 Language

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local 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.

11.5 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 committee is expected to solicit input and assistance from other investigators and Amgen staff as appropriate. 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 International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, 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, and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy of integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for 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.

11.6 Compensation

Subject will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the Informed Consent.

12. REFERENCES

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13. APPENDICES

Appendix A. Schedule of Assessments

	Screening	Baseline	Follow-up													
Study Assessments	Identified ONJ	Adjudicated Positive ONJ	3 Month	6 Month	9 Month	1 Year	3 Month	6 Month	9 Month	2 Year	6 Month	3 Year	6 Month	4 Year	6 Month	5 Year
Informed consent	x															
Adjudication (± imaging)	x															
Demographics		x														
Medical and dental history and ongoing information		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Cancer history and ongoing information		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Oncologist evaluation (optional)			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dental evaluation			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Safety events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix B. Additional Safety Assessment Information

Adverse Drug Reaction Severity Scoring System

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

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Grade	Amgen Standard Adverse Event Severity Scoring System
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity
4	LIFE-THREATENING: Refers to an event in which the patient was, in the view of the investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe.)
5	FATAL

Appendix C. Classification Eastern Cooperative Oncology Group (ECOG) Performance Scale and Karnofsky Performance Status

ECOG Scale		Performance Status
0	-	Fully active, able to carry out all predisease performance without restriction.
1	-	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, (eg. light housework, office work).
2	-	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	-	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	-	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	-	Dead.

Karnofsky Performance Status

100%	-	Normal; no complaints; no evidence of disease.
90%	-	Able to carry on normal activity; minor signs or symptoms of disease.
80%	-	Normal activity with effort; some signs or symptoms of disease.
70%	-	Cares for self, unable to carry on normal activity or do active work.
60%	-	Requires occasional assistance, but is able to care for most personal needs.
50%	-	Requires considerable assistance and frequent medical care.
40%	-	Severely disabled; hospitalization indicated, although death not imminent.
30%	-	Severely disabled; hospitalization necessary; active support treatment is necessary.
20%	-	Very sick; hospitalization necessary; active support treatment is necessary.
10%	-	Moribund; fatal processes progressing rapidly.
0%	-	Dead.

Karnofsky Score of 100 - 90% corresponds to ECOG 0
Karnofsky Score of 80 - 70% corresponds to ECOG 1
Karnofsky Score of 60 - 50% corresponds to ECOG 2
Karnofsky Score of 40 - 30% corresponds to ECOG 3
Karnofsky Score of 20 - 10% corresponds to ECOG 4
Karnofsky Score of 0% corresponds to ECOG 5

Appendix D. Pregnancy Notification Worksheet

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20101102

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

Appendix E. Sample Safety Reporting Form

Project ID: 20101102	AMGEN	Observational Research Safety Reporting Form	Date of Reporter Awareness:
			Date Reported to Amgen:
	Fax reports to: Amgen Local Office	<<*populate LAO fax here or delete language*>>	

1. Initial: ☐ **Follow-up:** ☐

2. Site Number: **Subject Number:**

3. Indicate event type: *(Please tick all that apply)* ☐ **AE/Other Safety Finding** ☐ **Product Complaint (PC)** ☐ **Adverse Device Effect (ADE)**

4. Contact Details (Vendor/Investigator)			**5. Reporter ID**		
Name	*Phone*	*Fax*	*Name or ID*	*Phone*	*Fax*
Address			*Address*		
City	*State/Province*		*City*	*State/Province*	
Postal Code	*Country*		*Postal Code*	*Country*	

6. HCP Contact Details (if other than reporter)			**7. Patient**			
Name			*Initials (optional)*	*Sex* ☐ F ☐ M	*Age (at time of event)*	*Was consent obtained to follow-up with HCP?* ☐ Yes ☐ No
Country						
Address						
City	*State/Province*	*Postal Code*	*Weight* ☐ lbs ☐ kg	*Height* ☐ in ☐ cm	*Race*	*Is patient also reporter?* ☐ Yes ☐ No
Phone	*Fax*					

8. Medical History (include primary diagnosis)	**9. Suspect Product Information (include dosing details)**				
	Product/Device: _____				
	Indication: _____				
	Start Date day month year	Stop Date day month year	Dose	Route	Frequency

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial Size

10. AE, Other Safety Finding, or PC/ADE information — **HCP ONLY**

Finding (List main event first; one event per line)	Onset Date day month year	Resolved Date (If patient died, list date of death) Cause of Death: (provide autopsy report) day month year	Hospitalization: Hospitalized? ☐ Yes ☐ No; Prolonged Hospitalization? ☐ Yes ☐ No; Admitting dx _____; Date Admitted day month year	Date Discharged day month year	Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/Prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly/birth defect; 06 Other significant medical hazard; 07 Non serious	Action Taken: 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=drug rechallenge (state outcome)	Outcome: 01 Recovered/ Resolved; 02 Recovering/ Resolving; 03 Not recovered/not resolved; 04 Recovered/ resolved with sequelae; 05 Fatal; 06 Unknown	Severity 1=mild 2=moderate 3=severe	Relationship to Product/Device Is there a reasonable possibility that this event may have been caused by the Product/Device? Product	Device
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N

11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	 Yes	Continuing No	 Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Appendix F. ONJ Staging and Grading Criteria

AAOMS ONJ Staging (Adapted from Ruggiero et al, 2014)

Stage	Description
1	Exposed and necrotic bone, or fistulas that probe to bone in patients who are asymptomatic and have no evidence of infection.
2	Exposed and necrotic bone, or fistulas that probes to bone, associated with infection as evidenced by pain and erythema in region of exposed bone with or without purulent drainage .
3	Exposed and necrotic bone, or fistulas that probes to bone, in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, (ie, inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor.

Appendix G. ONJ Lesion Size Grading

(Weitzman et al 2007)

Grade	Size, Diameter [a]
1A	Single lesion < 0.5 cm
1B	Multiple lesions, largest < 0.5 cm
2A	Single lesion 0.5-0.99 cm
2B	Multiple lesions, largest 0.5-0.99 cm
3A	Single lesion 1-2 cm
3B	Multiple lesions, largest 1-2 cm
4A	Single lesion > 2 cm
4B	Multiple lesions, largest > 2 cm

[a] Lesion size measured as the largest diameter

ONJ Severity (CTCAE 4.03)

Osteonecrosis of the Jaw	
Severity Grade	**Description**
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; medical intervention indicated (eg., topical agents); limiting instrumental ADL
3	Severe symptoms; limiting self-care ADL; elective operative intervention indicated
4	Life-threatening consequences; urgent intervention indicated
5	Death

Appendix H. Lactation Notification Worksheet

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: 20101102

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 4

Protocol Title: Osteonecrosis of the Jaw (ONJ) Case Registry

Amgen Protocol Number 20101102

Amendment Date: 19 July 2018

Rationale:

This protocol is being amended to:

- clarify the initial osteonecrosis of the jaw (ONJ) cases for denosumab-treated subjects identified during screening do not need to be reported as serious adverse drug reactions as they are entered into the safety database automatically. Instructions were added that follow-up of these initial ONJ cases must be collected as Amgen upgraded all positive ONJ cases (exposed to denosumab) to be serious and related. Worsening of ONJ does not need to be reported as an adverse drug reaction (ADR; since this will be collected as part of the study objectives); however, all fatal events must be reported.
- align safety reporting language with current observational research protocol template.
- clarify end of study language to account for death of subject, consent withdrawal, and lost to follow-up.
- make administrative and editorial updates.

Description of Changes:

Section: Global

Change: Updated version date from 04 May 2016 to **19 July 2018** throughout the protocol.

Section: Global

Change: Update ICH definition from International Conference on Harmonisation to International **Council for** Harmonisation.

Section: Global

Change: Made editorial updates and corrections throughout the protocol.

Section: Title Page, Key Sponsor Contact

Replace:

PPD

Global Clinical Trial Manager
Amgen Ltd.
Email: PPD
Phone:

With:

PPD

Global Clinical Trial Manager
Amgen Ltd.
Email: PPD
Phone:

Section: Title Page

Add:

Amendment 4 19 July 2018

Section: 3.4.2 End of Study

Replace:

- End of study (end of trial): defined as when the last subject completes the final follow up assessment.
- End of study for individual subject: defined as the last day that protocol-specified procedures (ie, final follow-up assessment) are conducted for an individual subject.

With:

- End of study (end of trial): defined as when **all** subject**s have had the opportunity to** complete the final follow-up assessment**, have died, withdrawn consent, or are lost to follow-up**.
- End of study for individual subject: defined as the last day that protocol-specified procedures (ie, final follow-up assessment) are conducted for an individual subject**, or until death, full consent withdrawal, or are lost to follow-up, whichever occurs first**.

Section: 6.1 General Study Procedures, Reporting, paragraph 1

Replace:

Each ONJ case among denosumab-treated subjects that is adjudicated positive will be reported to the regulatory agencies as a product adverse event per local country regulations for reporting adverse events.

With:

Each **suspected** ONJ case among denosumab-treated subjects that is adjudicated **to meet prespecified criteria for ONJ** will be **captured in the Amgen Global Safety Database as a serious adverse drug reaction (SADR), as the objective of this study is to characterize the clinical course of ONJ**.

Section: 8 Safety Data Collection, Recording, and Reporting

Replace:

Adverse drug reactions, other safety findings and product complaints, and serious adverse drug reactions reported in subjects receiving any Amgen products will be collected and reported in this study.

With:

Adverse drug reactions, other safety findings and product complaints, and serious adverse drug reactions reported in **denosumab-exposed** subjects will be collected and reported in this study. **All fatal events for denosumab-exposed subjects will also be collected and reported in this study.**

Section: 8.1.1 Definition of Adverse Events and Adverse Drug Reactions, paragraph 3

Replace:

It is the Investigator's responsibility to evaluate if an event is related to an Amgen product prior to reporting the event to Amgen.

With:

It is the Investigator's responsibility to evaluate if an event is related to **denosumab** prior to reporting the event to Amgen.

Section: 8.1.2 Definition of Serious Adverse Events and Serious Adverse Drug Reactions, paragraph 5

Replace:

For this study, reporting serious adverse events that are not adverse drug reactions related to the use of an Amgen product is not required.

With:

For this study, reporting serious adverse events that are not adverse drug reactions related to the use of **denosumab** is not required **unless the event is fatal and the patient has been exposed to denosumab (see Section 8.2.1)**.

Section: 8.2 Reportable Events and Reporting Timeframes, paragraph 1

Replace:

The investigator is responsible for ensuring that safety events (adverse drug reactions, serious adverse drug reactions, product complaints, and other safety findings) for Amgen product(s) observed by the investigator or reported by the subject that occur after signing of the informed consent form through the final study visit are recorded in the subject's medical record and are submitted to Amgen via the applicable Amgen Safety Reporting Form.

With:

The investigator is responsible for ensuring that safety events (adverse drug reactions, serious adverse drug reactions, product complaints, and other safety findings) for **denosumab-exposed subjects** observed by the investigator or reported by the subject that occur after signing of the informed consent form through the final study visit are recorded in the subject's medical record and are submitted to Amgen via the applicable Amgen Safety Reporting Form **(Appendix E)**.

Section: 8.2 Reportable Events and Reporting Timeframes, Table 1

Add:

Report Type	Description	Reporting Timeframe
Fatal serious adverse events	**All fatal events (including exempted events that have a fatal outcome)**	**Within 1 business day of investigator's awareness**

Section: 8.2 Reportable Events and Reporting Timeframes, Table 1

Replace:

Report Type	Description	Reporting Timeframe
ADR that are not serious and any associated Other Safety Findings	Initial or follow-up reports	Within 1 business day of investigator's awareness
Pregnancy and/or lactation	• Initial or follow-up reports of pregnancies or lactation occurring in females while taking Amgen product(s) and/or • Initial or follow-up reports of pregnancies occurring in female partners of males taking Amgen product(s)	Within 1 business day of investigator's awareness

With:

Report Type	Description	Reporting Timeframe
ADR that are not serious and any associated Other Safety Findings	Initial or follow-up reports	Within 1**5 calendar** day**s** of investigator's awareness
Pregnancy and/or lactation	• Initial or follow-up reports of pregnancies or lactation occurring in females while taking **denosumab** and/or • Initial or follow-up reports of pregnancies occurring in female partners of males taking **denosumab**	Within 1 business day of investigator's awareness

Section: 8.2 Reportable Events and Reporting Timeframes, paragraph 2

Replace:

If the electronic data capture (EDC) system is unavailable to the site staff to report the adverse event, the information is to be reported to Amgen via a paper Adverse Event Contingency Report Form (Appendix E) within 1 business day of the investigator's awareness. For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

See Appendix B for the Common Terminology Criteria for Adverse Events (CTCAE) severity grading scale that will be used in this study.

The investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on study electronic case report forms (eCRFs) where safety data may also be recorded (eg, Adverse Event Summary CRF).

With:

See Appendix E for sample Safety Report Form(s), Appendix B for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix D and Appendix H for sample Pregnancy and Lactation Notification Worksheets. The investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded **i**n study **documentation** where safety data may also be recorded (eg, Adverse Event Summary CRF).

Section: 8.2 Reportable Events and Reporting Timeframes, paragraph 5

Delete:

~~Amgen will report adverse drug reactions and unlisted serious adverse drug reactions as required to regulatory authorities or other relevant ethical review board in accordance with Pharmacovigilance guidelines and in compliance with local regulations.~~

Section: 8.2.1 Protocol Exempt Safety Information

Add:

Collection of **adverse** events that are not **considered** related to denosumab **by the investigator** is not required. Denosumab has an established safety profile with extensive post-marketing experience. In this observational study, it is considered appropriate to collect only adverse drug reactions (ie, adverse events considered by the investigator to be related to denosumab) together with product complaints (see Section 8.1.4) and other safety findings (eg, pregnancy, breast feeding, medication errors, overdose; see Section 8.1.3).

If any of the exempted events have a fatal outcome, they should be considered a serious adverse event and must be collected and reported individually within 1 business day of Investigator awareness.

Protocol-exempted events and safety events that are suspected to be related to any medicinal product other than denosumab should be reported to the local authority in line with the local country requirements.

Section: 8.2.2 Reporting Pregnancy and Lactation

Delete:

8.2.2 ~~Reporting Pregnancy and Lactation~~

~~Any confirmed pregnancy- or lactation-related case in a female subject with exposure to a marketed Amgen product is required to be reported to Amgen Global Patient Safety. In addition, any confirmed pregnancy case in a female partner of a male subject with exposure to a marketed Amgen product is required to be reported to Amgen Global Patient Safety. Initial information should be recorded on the Pregnancy Notification Worksheet (Appendix D) or the Lactation Notification Worksheet (Appendix H) and reported to Amgen Global Patient Safety within 1 business day of discovery or notification. Amgen Global Patient Safety may contact the investigator regarding additional pregnancy, birth outcome, and infant health information that may be requested.~~

Section: 8.2.2 Safety Reporting Requirement to Regulatory Bodies

Add:

8.2.2 **Safety Reporting Requirement to Regulatory Bodies**

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs/IECs, or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of serious adverse events in accordance with local procedures and statutes.

Section: 11.3 Study Monitoring and Data Collection, paragraph 5, bullet 4

Replace:

- For early site closures (prior to database lock), the principal investigator signs the Investigator Verification Form page for this electronic data capture study. For sites closing after the database lock, the investigator applies an electronic signature in the EDC system.

With:

- For early site closures (prior to database lock) **and f**or sites closing after the database lock, the investigator applies an electronic signature in the EDC system.

Section: Appendix E. Sample Safety Reporting Form

Replace:

Appendix E. Adverse Drug Reaction Report Form

AMGEN Study # 20101102 Denosumab	Electronic Adverse Reaction 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/Study manager/Author 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 ☐F ☐M	Race	If applicable, provide End of Study date

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

3. ADVERSE EVENT

Provide the date the investigator became aware of this information: Day Month Year

Adverse Reaction 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 drug under study	Is event serious?	Previous, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by Amgen drug under study or an Amgen device used to administer the Amgen drug under study? <drug1> <drug2> <drug3> <drug4>	Outcome of Event: Resolved, Not resolved, Fatal, Unknown	Check only if event is related to study procedure (eg, biopsy)
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

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

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

Date Admitted (Day Month Year)	Date Discharged (Day Month Year)

FORM-099346 Page 1 of 3 Version 1.0 Effective Date: 1 February 2016

AMGEN Study # 20101102 Denosumab	**Electronic Adverse Reaction Contingency Report Form** For Restricted Use

Site Number	Subject ID Number

6. Was drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 6

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

8. 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											

8. 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 # 20101102 Denosumab	**Electronic Adverse Reaction 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

FORM-099346 *Version 1.0 Effective Date: 1 February 2016*

Page 3 of 3

With:

Appendix E. **Sample Safety** Report**ing** Form

Project ID: 20101102	AMGEN	**Observational Research Safety Reporting Form**	**Date of Reporter Awareness:**
			Date Reported to Amgen:
	Fax reports to: Amgen Local Office	*<<populate LAO fax here or delete language>>*	

1. Initial: ☐ **Follow-up:** ☐

2. Site Number: **Subject Number:**

3. Indicate event type: *(Please tick all that apply)* ☐ **AE/Other Safety Finding** ☐ **Product Complaint (PC)** ☐ **Adverse Device Effect (ADE)**

4. Contact Details (Vendor/Investigator)			**5. Reporter ID**		
Name	*Phone*	*Fax*	*Name or ID*	*Phone*	*Fax*
Address			*Address*		
City	*State/Province*		*City*	*State/Province*	
Postal Code	*Country*		*Postal Code*	*Country*	

6. HCP Contact Details (if other than reporter)			**7. Patient**			
Name			*Initials (optional)*	*Sex* ☐ F ☐ M	*Age (at time of event)*	*Was consent obtained to follow-up with HCP?* ☐ Yes ☐ No
Country						
Address						
City	*State/Province*	*Postal Code*	*Weight* ☐ lbs ☐ kg	*Height* ☐ in ☐ cm	*Race*	*Is patient also reporter?* ☐ Yes ☐ No
Phone	*Fax*					

8. Medical History (include primary diagnosis) **9. Suspect Product Information (include dosing details)**

Product/Device: _____

Indication: _____

Start Date (day month year)	Stop Date (day month year)	Dose	Route	Frequency

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial Size

10. AE, Other Safety Finding, or PC/ADE information **HCP ONLY**

Finding (List main event first; one event per line)	**Onset Date** (day month year)	**Resolved Date** (If patient died, list date of death) **Cause of Death:** (provide autopsy report) (day month year)	**Hospitalization** Hospitalized? ☐ Yes ☐ No Prolonged Hospitalization? ☐ Yes ☐ No Admitting dx _____ Date Admitted (day month year)	Date Discharged (day month year)	**Serious Criteria** 01 Fatal 02 Immediately life-threatening 03 Required/Prolonged hospitalization 04 Persistent or significant disability /incapacity 05 Congenital anomaly/birth defect 06 Other significant medical hazard 07 Non serious	**Action Taken** 1=none 2=dose reduced 3=dose increased 4=drug withdrawn 5=drug rechallenge (state outcome)	**Outcome** 01 Recovered/ Resolved 02 Recovering/ Resolving 03 Not recovered/not resolved 04 Recovered/ resolved with sequelae 05 Fatal 06 Unknown	**Severity** 1=mild 2=moderate 3=severe	**Relationship to Product/Device** Is there a reasonable possibility that this event may have been caused by the Product/Device? Product	Device
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N

11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	 Yes	Continuing No	 Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).