Title: An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Denosumab

Amgen Protocol Number (denosumab) 20062004
EudraCT# 2008-001606-16

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I have read the attached protocol entitled "An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone", dated **15 September 2015**, and agree to abide by all provisions set forth therein.

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

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

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

_____
Signature

_____ _____
Name of Principal Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Study Phase: 2

Indication: Treatment of Giant Cell Tumor of Bone (GCTB)

Primary Objective:

To evaluate the safety profile of denosumab in subjects with GCTB

Secondary Objective(s):

- evaluation of time to disease progression in subjects with unsalvageable GCTB treated with denosumab (cohort 1)
- evaluation of the proportion of subjects who do not require surgery in denosumab treated subjects with salvageable GCTB (cohort 2)
- to evaluate denosumab pharmacokinetics (PK) in adolescent and adult subjects with GCTB (PK subset)

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Hypotheses:

It is anticipated that denosumab, an inhibitor of RANKL, will be a well-tolerated treatment for patients with surgically unsalvageable GCTB disease, and patients with surgically salvageable disease whose planned on-study surgery is associated with severe morbidity.

Study Design:

This is a phase 2, international, multi-center, open-label study in subjects with GCTB, receiving denosumab at a dose of 120 mg subcutaneously (SC) every 4 weeks (Q4W) with a loading dose of 120 mg SC on study days 8 and 15.

There are 3 cohorts in this study:

- Cohort #1: Subjects with surgically unsalvageable disease (eg, sacral, spinal GCTB, or multiple lesions including pulmonary metastases)
- Cohort #2: Subjects with surgically salvageable disease whose planned on-study surgery is associated with severe morbidity (eg, joint resection, limb amputation, or hemipelvectomy)
- Cohort #3: Subjects who are currently participating in Amgen study 20040215 giant cell tumor study who are eligible to enroll

Subjects who are currently receiving denosumab in study 20040215 will receive denosumab at a dose of 120 mg dosing according to their current Q4W schedule and will not receive any loading doses (ie, study day 8 and 15).

For subjects with a complete tumor resection, denosumab treatment continues for 6 doses after pathological confirmation of partial response or complete response. In all other cases, denosumab treatment continues until confirmation of disease progression, investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason, or administration of any of the proscribed therapies.

During the time the study is still open, re-treatment may be allowed for subjects who demonstrated a response to denosumab and are currently not receiving denosumab treatment (eg, in the case of recurrent disease while subject is in the safety follow up phase or subjects that have completed the study and have later experienced disease progression). The re-treatment decision including the use of the loading dose and discontinuation of therapy will be handled on a case-by-case basis; prior authorization from Amgen is required. Subjects must meet all inclusion/exclusion criteria prior to being considered for re-treatment.

To evaluate the long-term safety profile of denosumab, data (treatment plus follow-up) will be collected for all subjects enrolled through November 2012 for a minimum of 60 months, or until death or lost to follow-up, whichever comes first (Section 3.4.2). For subjects enrolled after November 2012 (PK substudy), data (treatment plus follow-up) will be collected until the end of the clinical study (Section 3.4.2).

Subjects who discontinue(d) investigational product will have an End of Treatment visit approximately 4 weeks after the last dose of investigational product. Thereafter, they will complete safety follow-up visits approximately every 6 months (± 1 month) for the first year and every 12 months (± 1 month) thereafter until the end of the clinical study (Section 3.4.2). **During the safety follow-up phase, subjects will be asked about serious adverse events, adverse events of interest, and disease treatments and outcomes (Section 9.2).**

Prior to Amendment 7 IRB/IEC approval, subjects currently in the safety follow-up in study 20040215 will continue on the safety follow-up in this study for up to 2 years after their end of study visit on study 20040215. The total length of safety follow-up on this study for patients enrolling from the safety follow-up phase of Amgen study 20040215 will be 2 years less the time spent in safety follow-up on study 20040215. Upon the approval of Amendment 7, subjects who enrolled in 20062004 from the 20040215 study will also follow the 20062004 schedule, and complete the assessments as described in Appendix A.

Approximately 50 sites will participate.

Primary and Secondary Endpoints:

Primary study endpoints:

Safety profile of denosumab characterized in terms of the type, frequency, and severity of adverse events and laboratory abnormalities for each cohort.

Secondary study endpoints:

- time to disease progression for cohort 1
- proportion of subjects without any surgery at month 6 for cohort 2
- serum denosumab (trough) concentrations (PK subset)

Sample Size:

The number of subjects in this study is determined by the number of GCTB subjects who qualify for the study. It is anticipated that approximately 530 subjects will participate. Prior to Amendment 7, 510 subjects were enrolled. Following Amendment 7, an additional approximately 20 subjects (approximately 10 adolescents and approximately 10 adults) will be enrolled to the PK substudy.

No more than 30 subjects will enroll from the Amgen study 20040215. No adolescents will enroll into cohort 3, since all subjects participating in study 20040215 are adults (≥ 18 years of age).

Summary of Subject Eligibility Criteria:

Inclusion criteria:

- Pathologically confirmed giant cell tumor of bone within 1 year before study enrollment
- Measurable evidence of active disease within 1 year before study enrollment
- Subjects with surgically unsalvageable disease (eg, sacral, spinal GCTB, or multiple lesions including pulmonary metastases) OR subjects whose planned surgery includes joint resection, limb amputation, hemipelvectomy or surgical procedure resulting in severe morbidity
- Karnofsky performance status ≥ 50% (ie, ECOG status 0, 1, or 2)
- Adults or skeletally mature adolescents (ie, radiographic evidence of at least 1 mature long bone [eg, humerus with closed growth epiphyseal plate]) ≥ 12 years of age
- Skeletally mature adolescents must weigh at least 45 kg
- Before any study-specific procedure is performed, the appropriate written informed consent must be obtained

  Inclusion criteria for 20040215 subjects:

- Subjects currently enrolled in study 20040215
- Before any study-specific procedure is performed, the appropriate written informed consent must be obtained

Exclusion criteria:

- Currently receiving other GCTB specific treatment (eg, radiation, chemotherapy, or embolization)
- Concurrent bisphosphonate treatment
- Known or suspected current diagnosis of underlying malignancy including high-grade sarcoma, osteosarcoma, fibrosarcoma, malignant giant cell sarcoma
- Known or suspected current diagnosis of non GCTB giant cell-rich tumors
- Known or suspected current diagnosis of brown cell tumor of bone or Paget's disease
- Known diagnosis of second malignancy within the past 5 years (subjects with definitively treated basal cell carcinoma and cervical carcinoma in situ are permitted)
- Prior history or current evidence of osteonecrosis/osteomyelitis of the jaw
- Active dental or jaw condition which requires oral surgery, including tooth extraction
- Non-healed dental/oral surgery
- Planned invasive dental procedure for the course of the study
- Subject currently is enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s), or subject is receiving other investigational agent(s)
- Subject has known sensitivity to any of the products to be administered during dosing
- Unstable systemic disease including active infection, uncontrolled hypertension, unstable angina, congestive heart failure, or myocardial infarction within 6 months before enrollment
- Subject is pregnant or breast feeding, or planning to become pregnant within **5** months after the end of treatment
- Female subject of child bearing potential is not willing to use **a highly effective** method **of** contraception during treatment and for **5** months after the end of treatment
- Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures

Exclusion criteria for 20040215 subjects:

- Developed sensitivity to mammalian cell derived drug products during the 20040215 study
- Currently receiving any unapproved investigational product other than denosumab
- Subject is pregnant or breast feeding, or planning to become pregnant within **5** months after the end of treatment
- Female subject of child bearing potential is not willing to use **a highly effective** method **of** contraception during treatment and for **5** months after the end of treatment
- Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures

Investigational Product Dosage and Administration:

Denosumab will be supplied in a single use 3.0-mL vial containing 1.7 mL of 70 mg/mL. Each vial contains a sterile, clear, colorless to slightly yellow, practically free from particles, preservative free liquid in open label glass. Denosumab will be administered as a SC injection.

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

Control Group:

None

Procedures:

Study procedures will only be performed after written independent ethics committee / institutional review board (IEC/IRB) approved informed consent is obtained from each subject.

The site will complete an Inclusion/Exclusion Criteria Worksheet for each subject to be enrolled to this study. Once this worksheet is submitted to Amgen and signed as approved, the site will receive a written enrollment confirmation from Amgen allowing the specific subject to enroll in the study. The approval process is required for new enrolling subjects **and subjects considered for retreatment**. Subjects enrolling from Amgen study 20040215 must complete the Inclusion/Exclusion Criteria Worksheet, but do not need to complete the approval process. The site must receive the signed enrollment confirmation form back from Amgen before dosing may begin.

The following procedures will be performed at screening for all subjects (except 20040215 safety follow-up subjects) enrolled to the study: medical history; Karnofsky performance status; physical exam; disease status; pregnancy test for women of childbearing potential; serum collection for anti-denosumab antibody assay (baseline); patient reported outcomes (baseline). Local laboratory values, adverse events, concomitant medications, and treatment procedures will be collected. Subjects enrolled to the PK substudy will also have serum and urine collection for PK and biomarker assessments. **A copy of the standard of care imaging reports obtained within 1 year before enrollment, demonstrating active GCTB must be attached to the subject's medical record**. **H**istopathology reports dated within 1 year before enrollment will also be collected. Subjects from the 20040215 study will not be required to submit screening imaging and histopathology reports upon enrollment into this study. Similar data from procedures performed as standard of care will be **attached to the subject's medical record**. Select historical and select on-study imaging performed as standard of care will be required to be sent to a central imaging vendor for evaluation of disease response.

Statistical Considerations:

The sample size for this study is determined by the number of subjects who qualify for the study. It is anticipated that approximately 530 subjects will participate.

The first and second interim analyses were conducted after 50 and 100 subjects, respectively, had the opportunity to complete 6 months of treatment. The third interim analysis was conducted

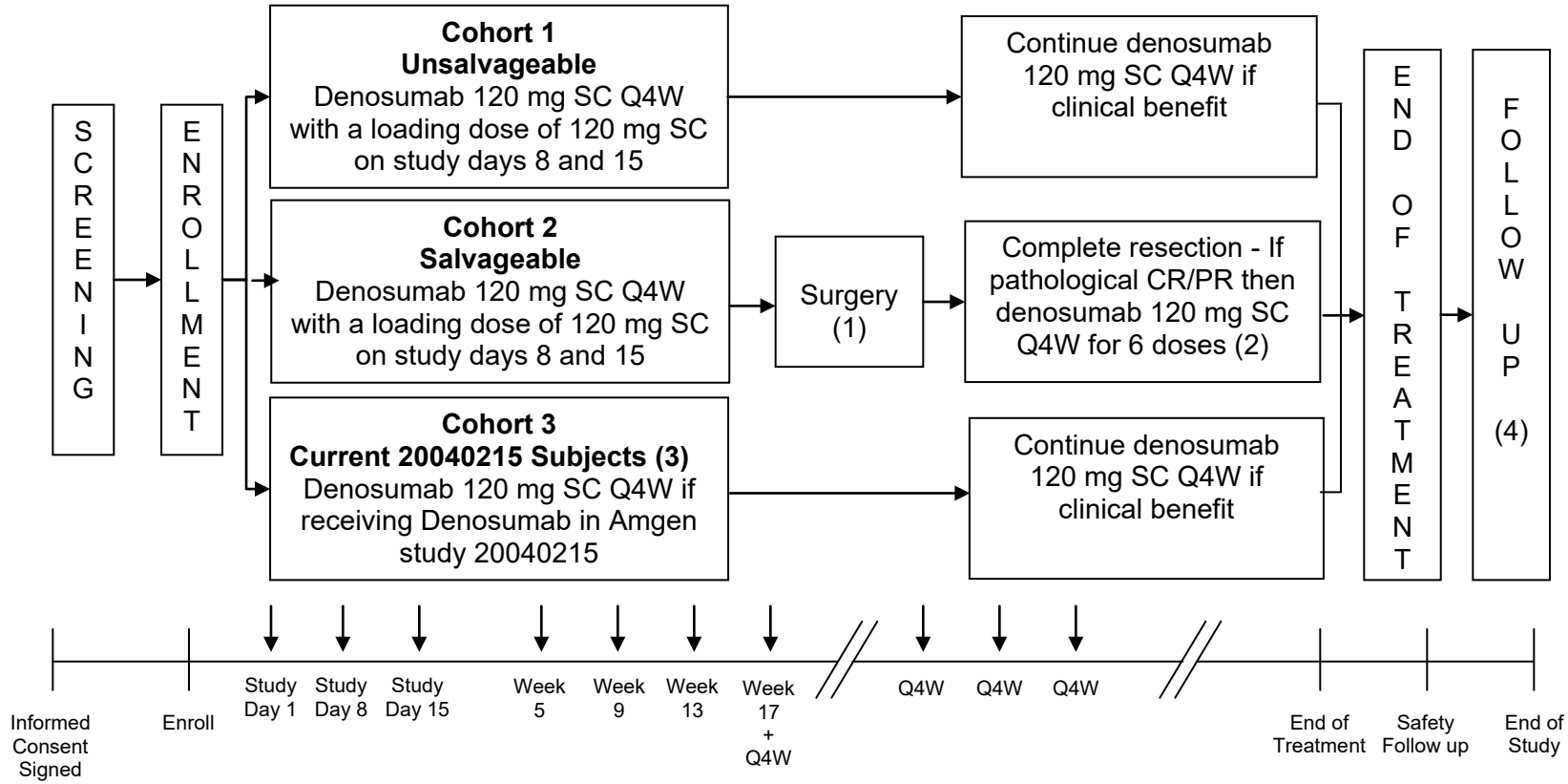
with a data cut-off date of 25 March 2011 and included approximately 286 subjects enrolled. **An unplanned interim analysis was performed in August 2013 in response to a request from the European Medicines Agency that included approximately 507 subjects and a median follow up time of 20.8 months.**

Additional interim analyses may be conducted to monitor the ongoing safety of denosumab or to make decisions regarding the use of denosumab in the treatment of giant cell tumor of bone (GCTB).

Treatment-emergent adverse events, treatment procedures, and anti-denosumab antibodies will be summarized for all subjects who receive at least 1 dose of denosumab.

Sponsor: Amgen Inc.

Study Design and Treatment Schema



1. Surgical resection may occur at any time during the study based on the clinical judgment of the investigator
2. Subjects not achieving a complete resection post surgery may continue to receive denosumab at a dose of 120 mg SC Q4W if clinical benefit is determined
3. Subjects participating in the 20040215 study will enroll and receive denosumab at a dose of 120 mg Q4W (subjects will not receive the day 8 and 15 dose).
4. For all subjects, including the PK substudy, data (treatment plus follow-up) will be collected until the end of the clinical study (Section 3.4.2) which is when subjects enrolled before Amendment 7 will complete a minimum of 60 months on study or otherwise have discontinued. For subjects who discontinue(d) investigational product, safety follow-up visits will be conducted approximately every 6 months (± 1 month) after the End of Treatment visit (approximately 4 weeks after the last dose of investigational product) for the first year, then every 12 months (± 1 month). The final safety follow-up visit will be conducted at the time of the end of the clinical study (Section 3.4.2) (even if this is not approximately 6 or12 months since the previous follow-up visit).

Study Glossary

Abbreviation/Acronym	Definition
BPI-SF	Brief Pain Inventory – Short Form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events (version 3)
CT	Computed tomography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GCTB	Giant cell tumor of bone
IEC/IRB	Independent ethics committee/Institutional review board
IHC	Immunohistochemistry
IPIM	Investigational Product Instruction Manual
IVRS	Interactive Voice Response System
MRI	Magnetic resonance imaging
ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
PET	Positron emission tomography
PET/CT	Positron emission tomography/ Computed tomography
PK	Pharmacokinetic(s)
POR	Proof of Receipt
PR	Partial response
sCTx	Serum C- telopeptide
SC	Subcutaneous
uNTx	Urinary N-telopeptide

Study Term	Definition
Baseline	Closest recorded measurement prior to the administration of denosumab on study day 1
Disease Status (ie, physician's assessment status)	Investigator's subjective opinion of the subject's health status which determines whether subject will enroll, continue treatment, or discontinue the study
Enrollment	Subject is considered enrolled once the screening procedures have been completed and the eligibility criteria worksheet is completed and signed by Amgen.
EOS	End of Study: The end of the clinical study for all subjects will occur when all subjects enrolled through November 2012 (before Amendment 7) have completed at least 60 months on study, or until death or lost to follow-up, whichever comes first. Study enrollment (prior to Amendment 7) concluded in November 2012; therefore the final study visits will be conducted and the study is anticipated to end by approximately November 2017.
EOT	End of Treatment visit: the End of Treatment visit will occur approximately 4 weeks after the last dose of investigational product
Screening period	Begins once written informed consent is signed and ends before administration of investigational product on study day 1, Week 1
Safety Follow-up	Safety Follow Up: Subjects who discontinue(d) investigational product will have an End of Treatment visit approximately 4 weeks after the last dose of investigational product. Thereafter, they will complete safety follow-up visits approximately every 6 months (± 1 month) for the first year and then every 12 months (± 1 month) thereafter until the end of the clinical study (Section 3.4.2). Upon the approval of Amendment 7, subjects who enrolled in 20062004 from the 20040215 study will also follow the 20062004 schedule, and complete the assessments as described in Appendix A. Prior to Amendment 7 IRB/IEC approval, for subjects enrolling from the safety follow-up from study 20040215, subjects will continue on the safety follow-up in this study for up to 2 years after their end of study visit on study 20040215. The total length of safety follow-up on this study for patients enrolling from the safety follow-up phase of Amgen study 20040215 will be 2 years less the time spent in safety follow-up on study 20040215.
Study day 1	Defined as the first day investigational product is administered to the subject

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1. OBJECTIVES

1.1 Primary

To evaluate the safety profile of denosumab in subjects with Giant Cell Tumor of bone (GCTB)

1.2 Secondary

- evaluation of time to disease progression in subjects with unsalvageable GCTB treated with denosumab (cohort 1)
- evaluation of the proportion of subjects who do not require surgery in denosumab treated subjects with salvageable GCTB (cohort 2)
- to evaluate denosumab pharmacokinetics (PK) in adolescent and adult subjects with GCTB (PK subset)

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2. BACKGROUND AND RATIONALE

2.1 Disease

2.1.1 Clinical Presentation of Giant Cell Tumor of Bone

Giant cell tumor of bone is an uncommon benign primary bone tumor with low malignant potential. It occurs more commonly in women than men (1.5:1) (Zheng et al, 2001) and there are approximately 800 newly diagnosed cases of GCTB in the United States each year.

The typical clinical presentation is a painful expansive osteolytic lesion, usually in the epiphyses of long bones, and nearly 50% of cases occur in the region of the knee

(Szendroi et al, 2003; Szendroi, 2004). Giant cell tumor of bone (GCTB) develops after the epiphyseal plates have closed and is most commonly diagnosed during the third decade of life. However, cases occur rarely in skeletally mature adolescents (ie, adolescents who have closed epiphyseal plates).

Symptoms that accompany primary GCTB include localized pain, tenderness, and swelling and the osteolysis may lead to pathologic fractures, decreased joint motion and impaired function. Lesions that originate in the spine may also result in neurological deficits.

Surgery is the definitive therapy for GCTB and about 80% of primary GCTB patients have lesions amenable to surgical resection. Although *en bloc* excisions of the tumor may be curative, they also carry significant morbidity (eg, amputation of a limb, joint resection) and greatly influence quality of life. Curettage procedures with and without bone graft may allow for complete resection of the tumor and preservation of the limb or joint, but the risk for recurrence is greater. Larger GCTB lesions may not be amenable to curettage resections and may result in severe morbid procedures. In addition, lesions in bones of the hand and distal radius have the highest rate of metastasis even with *en bloc* excision. Overall, the risk for recurrence is estimated at 10 to 20 percent after *en bloc* excision and at 40% to 75% (Malawer et al, 2005) after curettage, albeit a less debilitating procedure.

The GCTB lesion has a wide transition zone and poorly defined borders. In order to decrease the risk for recurrence with curettage resections, aggressive adjuvant surgical procedures are usually necessary. These procedures are used to remove normal bone and ensure a wider surgical margin beyond the transition zone. Adjuvant procedures such as cryosurgery, phenol instillation, high-speed burr, reconstitution with cement, and/or radiation therapy have been described. Side effects may include localized bone necrosis, increased risk for fracture, and delayed union of bone. Radiation therapy may be used and carries the risk of malignant induction to the bone.

Prognosis for GCTB is excellent if it does not recur. Recurrent GCTB commonly manifests as localized recurrence, however distant recurrence/metastasis may also occur. The definitive therapy for local recurrences is also surgery. More aggressive surgery for local recurrences carries significant morbidity and patients with local recurrences are at increased risk for subsequent localized and distant recurrences.

Eventually, patients become surgically unsalvageable. For some patients with primary spinal or sacral lesions, there may be no definitive surgical option. In these cases, treatment options are limited. Radiation therapy may control local tumor growth; however, there is a risk for malignant transformation. Systemic therapy with chemotherapy is of limited value and serial embolization of larger lesions may provide symptomatic relief.

2.1.2 Staging and Grading of Giant Cell Tumor of Bone

In general, grades and histologic pattern do not correlate well with prognosis for recurrence or metastasis. The presence of osteoid product in GCTB is not prognostic for recurrence or metastasis. Giant-cell rich osteosarcoma may be difficult to differentiate from benign GCTB. Likewise, the presence of giant cells in osteosarcoma is not prognostic for better outcomes. A grading scale was described; grade I (completely benign), grade II (borderline), and grade III (frankly sarcomatous). Grade I and II have not been correlated with decreased risk for recurrence or metastasis (Malawer et al, 2005).

2.1.3 Pathophysiology of Giant Cell Tumor of Bone (GCTB)

Giant Cell Tumors of bone (GCTB) are highly vascularized, expansile osteolytic lesions with indistinct borders and wide transitional zones. The histological appearance of giant cell tumors includes three distinct cell types; multinucleated osteoclast-like giant cells, spindle-shaped osteoblast-like stromal cells and monocytes (likely precursors of the giant cells). Although the name GCTB implies that the “giant cells” are the neoplastic component, the true neoplastic component remains unknown and controversial. The similarity in appearance of giant cells to normal osteoclasts suggests that the stromal component (spindle-shaped cells) may be the true neoplastic component and that the giant cells are the reactive component (Morgan et al, 2005; Zheng et al, 2001).

In archival samples (n = 33) of primary and recurrent GCTB, RANKL was expressed and detected by immunohistochemistry (IHC) and in situ hybridization. RANKL expression was observed in the stromal component and osteoprotegerin and RANK were expressed on the giant cells. In addition, soluble factors, presumably RANKL, secreted from stromal cells of GCTBs are able to induce osteoclastogenesis from peripheral blood monocytes (Nishimura et al, 2005). Although TGF-b1, MCP-1, TNF IL-1, 6, 11, 17, 18, MCS-F and PTHrP are expressed in the tumor, none of these factors are known to induce osteoclast differentiation. Endothelial cells of normal vessel did not express RANK or RANKL (Roudier et al, CTOS 2006).

2.2 Denosumab Background

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

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

Refer to the latest version of the investigator brochure for additional and updated information on denosumab background, clinical experience, and safety information.

2.2.1 Clinical Experience With Denosumab in Giant Cell Tumor of Bone (GCTB)

The Phase 2 study, Study 20040215, investigat**ed** the potential role for denosumab in the treatment of GCTB. The study test**ed** the hypothesis that denosumab, a RANKL inhibitor, can inhibit the growth and survival of tumor cells in patients with GCTB.

Patients with unresectable or recurrent GCTB were treated with denosumab 120 mg administered SC every four weeks, with additional loading doses on days 8 and 15. This dosing frequency was predicted to attain target serum concentrations of denosumab within the first month of treatment.

The primary endpoint was tumor response, defined as complete or near complete elimination of giant cells or in the absence of histology data, a lack of radiologic progression (single largest dimension < 20% increase by computed tomography [CT] or magnetic resonance imaging [MRI]).

The primary analysis was conducted of 37 subjects (20 female) with a data cut off date of 07 April 2008. Of these 37 subjects, 35 were evaluable for response to treatment. Eighty-six percent (30/35) of subjects had a tumor response: 20 of 20 by histology, and 10 of 15 by radiology. Adverse events (AEs) were reported in 33 of the 37 subjects included in the primary analysis. One death was reported in a subject diagnosed with giant cell sarcoma who developed disease progression (not treatment-related) during the off treatment follow-up period. No treatment-related serious AEs were reported.

2.2.2 Summary of Effects of OPG-Fc Treatment on Tooth Eruption and Long Bone Geometry in Neonate Rats

Genetic ablation of RANKL in knockout mice, and lifelong inhibition of RANKL by OPG in transgenic rats, was associated with deleterious changes in long bone growth, geometry and/or strength (Ominsky et al, 2009; Li et al, 2000; Kong et al, 1999). RANKL knockout mice, but not OPG transgenic rats, also exhibited failure of tooth eruption (Kong et al, 1999). The pharmacologic effects of RANKL inhibition on tooth eruption and on long bone growth, geometry, and strength were therefore evaluated in several nonclinical studies in neonatal rats. RANKL inhibition in neonatal rats via administration of OPG-Fc or RANK-Fc resulted in reduced weight gain, growth plate abnormalities, reduced bone length, increased bone mass and increased structural bone strength parameters. Although material bone strength parameters were on average unchanged, femoral toughness was consistently reduced. Inhibited tooth eruption and impaired root development were also observed with doses of OPG-Fc that effected a dramatic reduction in bone resorption. These effects were partially reversible upon discontinuation of OPG-Fc, however, extrinsic long bone strength was reduced and reduced bone length, femur toughness, and abnormal tooth root development persisted. Overexpression of OPG in OPG-transgenic (OPG-Tg) rats prenatally through to skeletal maturity resulted in a suboptimal long bone phenotype. These data suggest that the use of denosumab in the rapidly growing skeleton carries potential risks from widened growth plates, decreased bone growth, decreased bone toughness, and impaired dentition.

2.3 Rationale

GCTB is a rare disease characterized clinically by expansile osteolytic lesions and histologically by multi-nucleated giant cells that are similar to osteoclasts, the cells that mediate bone destruction. The tumor cells express RANKL and its receptor, RANK. The RANK/RANKL pathway is an essential mediator of osteoclast function, formation and survival. Denosumab, a fully human monoclonal antibody of RANKL, inhibits

osteoclast-mediated bone destruction and may provide therapeutic benefit for patients with giant cell tumor.

For subjects with surgically unsalvageable GCTB, current treatment options are limited and may include treatments (radiation, embolization, chemotherapy) that lead to significant disability, poor quality of life and possibly death. Bisphosphonates are currently under investigation in this subject population; however, only limited preclinical and clinical data are currently available (Cheng et al, 2004).

Study 20040215 was an open-label, phase 2 safety and efficacy study of denosumab in subjects (n = 37) with recurrent or unresectable GCTB. The primary analysis, demonstrated that denosumab has significant biological activity in GCTB based on assessment of histologic or radiologic response. The safety profile of denosumab in this study appeared to be consistent with that observed in other settings.

The potential elimination of osteoclasts by denosumab in subjects with GCTB is expected to inhibit osteolysis and in turn, inhibit the progression of GCTB and potentially improve clinical outcomes for these subjects.

In addition, for patients with surgically salvageable GCTB that require severe morbid procedures, treatment with denosumab may reduce the size of the lesion and improve surgical options to allow limb and joint-sparing procedures.

There have been rare reported cases of GCTB in adolescents. Giant Cell Tumor of Bone (GCTB) usually occurs in skeletally mature adolescents after the epiphyseal plates have closed, and all adolescent subjects enrolled into this study will have radiological confirmation of skeletal maturity. No further long bone growth is anticipated after epiphyseal plates are closed. In the adolescent subset, eruption of adult dentition may not be complete, but in the majority of cases the non-erupted teeth are likely to be limited to non-essential wisdom teeth, which are absent from many adults. There are few treatment options for adolescents with mature skeletons and GCTB. Based on the seriousness of GCTB and the limited treatment options, Amgen believes that this protocol, which includes adolescents with mature skeletons and GCTB, presents greater than minimal risk, but also presents the prospect of direct benefit to the subject.

2.3.1 Selection of Dose

The dose and schedule selected for this study consists of a loading dose regimen of three subcutaneous injections of denosumab 120 mg SC Q4W with a loading dose of 120 mg SC on study days 8 and 15. This dosing regimen is currently being used in the

Amgen study 20040215. Subjects enrolling from study 20040215 will receive denosumab at a dose of 120 mg dosing according to their current Q4W schedule and will not receive any loading doses (ie, study day 8 and 15).

The selection of the dose and schedule of denosumab was based on safety, pharmacokinetic and pharmacodynamic data obtained from the phase 1 and 2 studies described above. Specifically, study 20040113 provided a comprehensive dataset guiding the dose selection for subjects with bone metastases. All the denosumab arms showed biological activity in reducing bone resorption, which was comparable to that seen with the IV bisphosphonate arm. The rate of skeletal-related events in the denosumab arms was similar to that observed in the bisphosphonate arm. Among the denosumab doses and schedules evaluated, the regimen of 120 mg every 4 weeks was associated with maximum reduction of the bone turnover marker uNTX by week 13, the primary endpoint in the study.

Unlike the 30 mg every 4-week dosing, the 120 mg every 4-week schedule avoided low exposures of denosumab (eg, serum levels below 4000 ng/mL) that could potentially translate into reduced efficacy in some subjects based on preliminary population PK/PD modeling of the phase 2 data. Denosumab was found to be safe and well tolerated in all study arms. While no symptomatic hypocalcemia was reported in study 20040113, the 120 mg every 4-week schedule (n = 41) appeared preferable as no grade 2 or higher hypocalcemia was recorded as opposed to 5, grade 2 and one, grade 3 hypocalcemia in the denosumab 180 mg every 4-week treatment group (n = 43).

The subjects on this study have active GCTB with surgically unsalvageable or large GCTB lesions. The goal of denosumab treatment is to reduce or halt the growth of the GCTB lesion and prevent further osteolysis. The pharmacodynamic goal is to quickly attain target serum concentrations of denosumab and maintain a constant level of maximal suppression of osteoclast activity and bone resorption.

Based on the PK model, denosumab 120 mg given subcutaneously every 4 weeks would require 6 to 9 months to achieve steady-state. With the loading doses on day 8 and 15, subjects are expected to achieve steady-state within the first month resulting in exposure levels that were previously tested in phase 2 studies.

In clinical trials denosumab has been administered to adults with a weight as low as 38 kg. Adults weighing as low as 38 kg had a similar adverse event profile as compared to subjects in higher weight ranges. It is anticipated that skeletally mature adolescents

weighing at least 38 kg will have a similar adverse event profile as adults in this lower weight range.

2.4 Hypotheses

It is anticipated that denosumab, an inhibitor of RANKL, will be a well-tolerated treatment for patients with surgically unsalvageable GCTB disease, and patients with surgically salvageable disease whose planned on-study surgery is associated with severe morbidity.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 2, international, multi-center, open-label study in subjects with GCTB, receiving denosumab at a dose of 120 mg SC Q4W with a loading dose of 120 mg SC on study days 8 and 15.

There are 3 cohorts in this study:

- Cohort #1: Subjects with surgically unsalvageable disease (eg, sacral, spinal GCTB, or multiple lesions including pulmonary metastases)
- Cohort #2: Subjects with surgically salvageable disease whose planned on-study surgery is associated with severe morbidity (eg, joint resection, limb amputation, or hemipelvectomy)
- Cohort #3: Subjects who are currently participating in Amgen study 20040215 giant cell tumor study who are eligible to enroll

Subjects who are currently receiving denosumab in study 20040215 will receive denosumab at a dose of 120 mg dosing according to their current Q4W schedule and will not receive any loading doses (ie, study day 8 and 15).

For subjects with a complete tumor resection, denosumab treatment continues for 6 doses after pathological confirmation of partial response (PR) or complete response (CR). In all other cases, denosumab treatment continues until confirmation of disease progression, investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason, or administration of any of the proscribed therapies.

During the time the study is still open**,** re-treatment may be allowed for subjects who demonstrated a response to denosumab and are currently not receiving denosumab treatment (eg, in the case of recurrent disease while subject is in the safety follow up phase or subjects that have completed the study and have later experienced disease progression). The re-treatment decision including the use of the loading dose and

discontinuation of therapy will be handled on a case-by-case basis; prior authorization from Amgen is required. Subjects must meet all inclusion/exclusion criteria prior to being considered for re-treatment.

To evaluate the long-term safety profile of denosumab, data (treatment plus follow-up) will be collected for all subjects enrolled through November 2012 for a minimum of 60 months, or until death or lost to follow-up, whichever comes first (Section 3.4.2). For subjects enrolled after November 2012 (PK substudy), data (treatment plus follow-up) will be collected until the end of the clinical study (Section 3.4.2).

Subjects who discontinue(d) investigational product will have an End of Treatment visit approximately 4 weeks after the last dose of investigational product. Thereafter, they will complete safety follow-up visits approximately every 6 months (± 1 month) for the first year and every 12 months (± 1 month) thereafter until the end of the clinical study (Section 3.4.2).

Prior to Amendment 7 IRB/IEC approval, subjects currently in the safety follow-up in study 20040215 will continue on the safety follow-up in this study for up to 2 years after their end of study visit on study 20040215. The total length of safety follow-up on this study for patients enrolling from the safety follow-up phase of Amgen study 20040215 will be 2 years less the time spent in safety follow-up on study 20040215. Upon the approval of Amendment 7, subjects who enrolled in 20062004 from the 20040215 study will also follow the 20062004 schedule, and complete the assessments as described in Appendix A.

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

The study endpoints are defined in Section 10.2.

3.2 Number of Centers

Approximately 50 sites will participate. Sites that do not enroll at least one subject within 6 months of site initiation may be terminated.

3.3 Number of Subjects

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

The sample size for this study is governed by the number of subjects who qualify for the study. It is anticipated that approximately 530 subjects will participate. Prior to Amendment 7, 510 subjects were enrolled. Following Amendment 7, an additional

approximately 20 subjects (approximately 10 adolescents and approximately 10 adults) will be enrolled to the PK substudy.

No more than 30 subjects will enroll from the Amgen study 20040215. No adolescents will enroll into cohort 3, since all subjects participating in study 20040215 are adults (≥ 18 years of age).

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

For each subject enrolled through November 2012 (before Amendment 7), the total duration of a subject's participation will be at least 60 months including treatment and follow-up, or until death or lost to follow-up, whichever comes first. For subjects enrolled after November 2012 (PK substudy), data (treatment plus follow-up) will be collected until the end of the clinical study (Section 3.4.2).

The total duration of this study from start of enrollment to end of follow-up for the last subject is expected to be approximately 9 years (approximately 4 years of enrollment prior to Amendment 7, and approximately 5 years of treatment and follow-up).

3.4.2 End of Study (EOS)

The end of the clinical **study** for all subjects will occur when all subjects enrolled through November 2012 (before Amendment 7) have completed at least 60 months on study, or until death or lost to follow-up, whichever comes first. Study enrollment (prior to Amendment 7) concluded in November 2012; therefore the final study visits will be conducted and the study is anticipated to end by approximately November 2017.

Subjects enrolled in the PK substudy will complete treatment and/or follow-up at the same time as subjects included prior to Amendment 7.

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 (ie, age, sex, and race), date, and outcome of the screening process (eg, enrolled into study, reason for ineligibility, or refused to participate).

Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 12.1). For adolescents, in addition to written informed consent, the assent of the adolescent also must be obtained if requested by the institutional review board/independent ethics committee.

4.1 Inclusion Criteria

Subjects meeting the following criteria are considered eligible for this study.

4.1.1 Pathologically confirmed giant cell tumor of bone within 1 year before study enrollment

4.1.2 Measurable evidence of active disease within 1 year before study enrollment

4.1.3 Subjects with surgically unsalvageable disease (eg, sacral, spinal GCTB, or multiple lesions including pulmonary metastases) OR subjects whose planned surgery includes joint resection, limb amputation, hemipelvectomy or surgical procedure resulting in severe morbidity

4.1.4 Karnofsky performance status ≥ 50% (ie, ECOG status 0, 1, or 2)

4.1.5 Adults or skeletally mature adolescents (ie, radiographic evidence of at least 1 mature long bone [eg, humerus with closed growth epiphyseal plate]) ≥ 12 years of age

4.1.6 Skeletally mature adolescents must weigh at least 45 kg

4.1.7 Before any study-specific procedure is performed, the appropriate written informed consent must be obtained

Inclusion Criteria for 20040215 subjects:

4.1.8 Subjects currently enrolled in study 20040215

4.1.9 Before any study-specific procedure is performed, the appropriate written informed consent must be obtained

4.2 Exclusion Criteria

4.2.1 Currently receiving other GCTB specific treatment (eg, radiation, chemotherapy, or embolization)

4.2.2 Concurrent bisphosphonate treatment

4.2.3 Known or suspected current diagnosis of underlying malignancy including high-grade sarcoma, osteosarcoma, fibrosarcoma, malignant giant cell sarcoma

4.2.4 Known or suspected current diagnosis of non GCTB giant cell-rich tumors

4.2.5 Known or suspected current diagnosis of brown cell tumor of bone or Paget's disease

4.2.6 Known diagnosis of second malignancy within the past 5 years (subjects with definitively treated basal cell carcinoma and cervical carcinoma in situ are permitted)

4.2.7 Prior history or current evidence of osteonecrosis/osteomyelitis of the jaw

4.2.8 Active dental or jaw condition which requires oral surgery, including tooth extraction

4.2.9 Non-healed dental/oral surgery

4.2.10 Planned invasive dental procedure for the course of the study

4.2.11 Subject currently is enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(ies), or subject is receiving other investigational agent(s)

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

4.2.13 Unstable systemic disease including active infection, uncontrolled hypertension, unstable angina, congestive heart failure, or myocardial infarction within 6 months before enrollment

4.2.14 Subject is pregnant or breast feeding, or planning to become pregnant within **5** months after the end of treatment

4.2.15 Female subject of child bearing potential is not willing to use **a highly effective** method **of** contraception during treatment and for **5** months after the end of treatment

4.2.16 Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures

Exclusion Criteria for 20040215 subjects:

4.2.17 Developed sensitivity to mammalian cell derived drug products during the 20040215 study

4.2.18 Currently receiving any unapproved investigational product other than denosumab

4.2.19 Subject is pregnant or breast feeding, or planning to become pregnant within **5** months after the end of treatment

4.2.20 Female subject of child bearing potential is not willing to use **a highly effective** method **of** contraception during treatment and for **5** months after the end of treatment

4.2.21 Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with 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 12.3).

All subjects who enter into the screening period for the study (defined as the point at which the subject signs the informed consent) will receive a unique subject identification number before any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of rescreening or enrollment. Subjects enrolling from the 20040215 study will receive a new subject identification number for this study.

The subject identification number will consist of 9 digits. The first 3 digits will represent a protocol identifier (ie, 204) and will be identical for all sites. The next 3 digits will represent the site number (ie, 101, 102, 103, etc.) and will be identical for all subjects at a particular site. The last 3 digits will represent the subject identification and will be assigned in sequential order, per site, as subjects are screened (ie, 001, 002, 003, etc.). Therefore, the first subject to enter screening at site 101 will receive the number 204101001; the second subject at this site will receive the number 204101002, etc.

Once the site deems the subject is eligible for enrollment to the study and all screening procedures have been completed, the Eligibility Criteria Worksheet (found in the Regulatory Binder) and a case history of the subject's disease must be completed and faxed to the US or European Sponsor Contact (see cover page for contact information) as appropriate, for approval before the first dose of investigational product can be administered to any subject. The approval process is required for new enrolling subjects **and subjects considered for retreatment**. Subjects enrolling from Amgen study 20040215 must complete the Inclusion/Exclusion Criteria Worksheet, but do not need to complete the approval process. The case history must include the treatment history, including original and translated imaging reports and histopathology reports (specimen source must be clearly identified in the report).

Those subjects who meet the inclusion/exclusion criteria at the Screening visit and who receive an enrollment confirmation from Amgen may be enrolled into the study and begin the treatment period. A subject is considered enrolled into the study once the eligibility criteria worksheet is signed by Amgen.

5.1 Treatment Assignment

As this is an open-label study, all subjects will receive denosumab. Investigational product management will be automatically resupplied to the sites through an interactive voice response system (IVRS).

6. TREATMENT PROCEDURES

Denosumab is considered to be the investigational product in this study; therefore, drug accountability must be obtained on all used and unused denosumab vials. For further details regarding preparation and administration of the investigational product, refer to **the Investigational Product Instruction Manual (IPIM), which is a document external to this protocol**.

6.1 Investigational Product Dosage, Administration, and Schedule

Denosumab is to be administered by a licensed healthcare professional at a dose of 120 mg SC Q4W with a loading dose of 120 mg SC on study days 8 and 15. Subjects enrolling from study 20040215 will receive denosumab at a dose of 120 mg dosing according to their current Q4W schedule and will not receive any loading doses (ie, study day 8 and 15).

6.2 Dose Escalation and Stopping Rules

For loading doses, if the study days 8 and 15 doses are delayed more than 8 calendar days, it will be considered a missed dose and recorded as such on the electronic case report form (eCRF). The next dose is to be given at the next scheduled visit date (based on study day 1). There must be at least 4 days (ie, 96 hours) between the study days 1, 8, and 15 doses (ie, ± 3 days from the scheduled visit date).

For Q4W doses, **the planned dose may be given up to 7 days before the scheduled visit, as long as there are at least 21 days between doses. I**f a planned dose (eg, week 5, week 9, etc.) is delayed more than 7 calendar days, it will be considered a missed dose and recorded as such on the eCRF. The next dose is to be given at the next scheduled visit date (based on study day 1).

For subjects with a complete tumor resection, denosumab treatment continues for 6 doses after pathological confirmation of partial response or complete response. In all other cases, denosumab treatment continues until confirmation of disease progression, investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason, or administration of any of the proscribed therapies. See Section 3.1 for potential re-treatment with denosumab following discontinuation.

Administration of investigational product is recommended to be withheld 30 days prior to any elective invasive oral/ dental procedure. Investigational product administration is recommended to be withheld until documented evidence of complete mucosal healing following any invasive oral/ dental procedure.

Subjects with osteonecrosis of the jaw **(ONJ)** on study may temporarily or permanently discontinue investigational product at investigator discretion. Re-exposure to investigational product may occur if the investigator and sponsor agree subject safety will not be compromised.

The dosing schedule is described by a schema in the protocol synopsis.

6.3 Dosage Adjustments

There will be no dose adjustments allowed in this study.

6.4 Concomitant Therapy (Calcium and Vitamin D Supplements)

All subjects should be adequately supplemented with calcium and Vitamin D (at least 500 mg of calcium and 400 IU of Vitamin D**)**, except in the case of pre-existing hypercalcemia. Due to differences in regional availability, a dosage form of vitamin D that gives an equivalent of at least 400 IU daily may be given.

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.5.

6.5 Proscribed Therapy During Study Period

Concurrent treatment with bisphosphonates is not allowed while the subject is on study. Other active therapy for GCTB including chemotherapy, embolization and radiation therapy are not allowed while the subject is on study (embolization immediately prior to planned definitive surgery [e.g. to improve operative hemostasis] is allowed in accordance with local guidelines). Use of any unapproved (ie, no marketing authorization has been granted) investigational product (other than denosumab) or device is not allowed until after all study assessments are completed.

Invasive dental procedures should be avoided. If a subject undergoes an invasive dental procedure while on study, a clinical decision to continue the subject on investigational product must be documented in the medical chart.

7. STUDY PROCEDURES

It is the responsibility of the investigator to obtain an IEC/IRB-approved, signed, informed consent from all subjects before any protocol-related procedures are performed.

Study visits during the treatment period will occur every 4 weeks until the end of treatment with an additional visit at study days 8 and 15. For those subjects enrolling from the 20040215 study, study visits will continue at every 4 week intervals until the end of treatment. When possible, all assessments/procedures during the treatment phase of study should be obtained within 7 calendar days or less of the specified study visit (except during the loading dose period), relative to study day 1. Every effort should be made to keep subjects on the study schedule as planned from study day 1.

To evaluate the long-term safety profile of denosumab, data (treatment plus follow-up) will be collected for all subjects enrolled through November 2012 for a minimum of 60 months, or until death or lost to follow-up, whichever comes first (Section 3.4.2). For subjects enrolled after November 2012 (PK substudy), data (treatment plus follow-up) will be collected until the end of the clinical study (Section 3.4.2).

Subjects who discontinue(d) investigational product will have an End of Treatment visit approximately 4 weeks after the last dose of investigational product. Thereafter, they will complete safety follow-up visits approximately every 6 months (± 1 month) for the first year and every 12 months (± 1 month) thereafter until the end of the clinical study (Section 3.4.2).

Prior to Amendment 7 IRB/IEC approval, subjects currently in the safety follow-up in study 20040215 will continue on the safety follow-up in this study for up to 2 years after their end of study visit on study 20040215. The total length of safety follow-up on this study for patients enrolling from the safety follow-up phase of Amgen study 20040215 will be 2 years less the time spent in safety follow-up on study 20040215. Upon the approval of Amendment 7, subjects who enrolled in 20062004 from the 20040215 study will also follow the 20062004 schedule, and complete the assessments as described in Appendix A.

All study assessments must be completed before investigational product administration.

Missed visits, procedures that are not performed, and examinations that are not conducted must be reported as such on the eCRFs.

All imaging, histopathology samples and chemistry laboratory samples will be analyzed by the site's local laboratory/institution with the exception of antibody samples.

The schedule of assessments is provided in Appendix A.

7.1 Screening/Baseline

Screening assessments conducted as standard of care may be used as screening data prior to signing of informed consent if conducted within the required screening period. Subjects in Cohort 3 will not be required to submit this screening data upon enrollment into this study. All screening procedures must be completed no more than 28 days before Study Day 1 (day of first dose of investigational product) with the following exceptions:

- Histopathology (reports only): A copy of all standard of care reports obtained within 1 year before enrollment, confirming GCTB of bone must be provided to Amgen.

- Imaging (eg, PET, CT, PET/CT, MRI or X-ray): A copy of the standard of care reports obtained within 1 year before enrollment, demonstrating active GCTB must be provided to Amgen. Select historical imaging performed as standard of care will be required to be sent to a central imaging vendor for evaluation of disease response.
- A negative pregnancy test, for women with reproductive potential, must be documented no more than 7 days before first dose of denosumab (Study Day 1). If a pregnancy test result will be more than 7 days old before first dose of investigational product, the test must be repeated and documented in the eCRF.
- Informed consent may be obtained more than 28 days before Study Day 1.

7.2 Medical History

The subject's medical history will be obtained **≤ 28 days before day 1 of the study** and recorded on the eCRF. **A d**etailed history of all pre-existing conditions must be documented on the eCRF (and in the source documents). **Any illness or medical condition that is ongoing at the time of the subject's first dose of study drug should be noted. Worsening of a pre-existing condition should be reported as an adverse event.**

7.3 Treatment History

Anti-neoplastic treatment, including chemotherapy, radiotherapy, and surgery specifically used to treat the subject's primary and metastatic giant cell tumor of bone will be collected.

7.4 Physical Examination

Each physical examination visit will include assessment of Karnofsky performance status, disease status, vital signs (screening only), height (screening only), and weight (screening only). Refer to Appendix E for Karnofsky performance status criteria.

7.4.1 Oral Examination

A visual examination of the oral cavity (oral examination), including teeth, mucosa, and jaws, will be conducted by the investigator, or designated licensed healthcare professional, at screening (for newly enrolled subjects), to establish baseline oral health conditions, and approximately at least 24 weeks thereafter (approximately every 6 months) to identify and document any new abnormalities or changes in pre-existing conditions. Routine oral examinations should be conducted as part of standard subject management.

Appropriate preventive dentistry should be considered prior to treatment with denosumab.

If any new abnormalities or changes in pre-existing conditions are identified, additional information may be requested.

7.5 Imaging

A copy of imaging reports (eg, PET, CT, PET/CT, MRI, or X-ray) performed as standard of care must be **attached to the subject's medical record**. Select on-study imaging performed as standard of care will be required to be sent to a central imaging vendor for evaluation of disease response.

7.6 Histopathology

A copy of all available pathology reports obtained as standard of care must be **attached to the subject's medical record,** including the surgical report of the GCTB target lesion resection. **The h**istopathology samples and reports may be requested **either during the study or** at end of study **for evaluation of histopathological response to treatment**.

7.7 Laboratory Assessments

7.7.1 Serum Chemistry

At a minimum, calcium, albumin, magnesium, phosphorus, and creatinine will be collected and analyzed at the site's local laboratory. No lab supplies will be provided to sites for these tests.

7.7.2 Pregnancy Test

Urine/serum pregnancy labs will be collected and analyzed at the site's local laboratory. No lab supplies will be provided to sites for these tests.

7.7.3 Pharmacokinetic and Serum C-telopeptide (sCTx) Assessments (Pharmacokinetic Substudy)

Serum samples for serum denosumab concentration levels and sCTx will be obtained on a subset of approximately 20 subjects (approximately 10 adolescent and 10 adult subjects) at baseline (prior to administration of investigational product on study day 1) and on study as outlined in the schedule of assessments (Appendix A). Amgen Inc or its designee will be responsible for analyzing these samples.

7.7.4 Urine Assessments (Pharmacokinetic Substudy)

All urine samples will be collected prior to investigational product administration. Urine samples will be collected for urinary N-telopeptide (uNTx). Urine analytes will include creatinine and raw N-telopeptide (NTx). Amgen Inc or its designee will perform these assays and will measure urine creatinine.

The uNTx will be corrected for urine creatinine by generating a ratio. Using the uNTx as reported in units of nM and urine creatinine in units of mg/dL, the creatinine measurement will be multiplied by 0.0884, and used to generate the corrected ratio. The resulting equation will be: uNTx/Cr (nM BCE/mM) = uNTx/(Cr*0.0884).

Urine will be obtained on a subset of approximately 20 subjects (approximately 10 adolescent and 10 adult subjects) at baseline (prior to administration of investigational product on study day 1) and on study as outlined in the schedule of assessments (Appendix A).

Urine collection instructions

A urine sample will be collected from subjects after the first void and preferably in the morning. It is recommended that urine samples be collected in the clinic, if feasible. If the subject is to collect the urine sample at home, he/she will need to be provided with containers for sample collection and for transporting the sample to the site on the day of collection. Subject instructions will be provided on how and when to collect the sample, recording the time of collection, and storing the sample (refrigerated) until it is brought to the study site for processing.

7.7.5 Anti-denosumab Antibody Assay

Serum for anti-denosumab antibody assay will be collected at baseline and as outlined on the schedule of assessments (Appendix A).

Prior to Amendment 7 IRB/IEC approval, for subjects who were in the safety follow-up of study 20040215 and are enrolling in this study, serum samples for anti-denosumab antibody assay will be collected approximately every 6 months for up to 24 months after the end of study visit in the 20040215 study. Upon the approval of Amendment 7, subjects who enrolled in 20062004 from the 20040215 study will also follow the 20062004 schedule, and complete the assessments as described in Appendix A.

Amgen Inc., or its designee, will be responsible for analyzing serum samples for the assessment of anti-denosumab antibodies. Amgen Biological Sample Management (BSM) will provide a study manual that outlines handling, labeling, and shipping procedures for serum samples. These samples may also be used for future biomarker development testing.

7.8 Sample Storage and Destruction

Any serum or urine samples collected according to the schedule of assessments (Appendix A) can be analyzed for any of the tests outlined in the protocol and for any

tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be no less than single coded prior to being shipped from the site for analysis, or storage. Tracking of samples will be independent of the subject's identification number for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand Giant Cell Tumor of Bone, the dose response and/or prediction of response to denosumab, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of the pharmacokinetic study, biomarker studies, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining serum or urine samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the Investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no

commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

7.9 Patient Reported Outcomes - Brief Pain Inventory - Short Form (BPI-SF)

The BPI-SF is a patient completed questionnaire that has been shown to be a valid measure of pain in cancer (Cleeland CS, 1991). It captures information on the intensity of pain (pain severity) as well as the degree to which pain interferes with function (pain interference). The BPI-SF will be collected prior to each administration of investigational product.

7.10 End of Treatment (EOT) Visit

Each subject will have an **E**nd of **T**reatment visit approximately 4 weeks after their last dose of investigational product. Study procedures are listed in Appendix A.

7.11 Safety Follow-up Phase

Subjects who discontinue(d) investigational product will have an End of Treatment visit approximately 4 weeks after the last dose of investigational product. Thereafter, they will complete safety follow-up visits approximately every 6 months (± 1 month) for the first year and then every 12 months (± 1 month) thereafter until the end of the clinical study (Section 3.4.2). **During the safety follow-up phase, subjects will be asked about serious adverse events, adverse events of interest, and disease treatments and outcomes (Section 9.2).**

Upon the approval of Amendment 7, subjects who enrolled in 20062004 from the 20040215 study will also follow the 20062004 schedule, and complete the assessments as described in Appendix A.

Prior to Amendment 7 IRB/IEC approval, for subjects who were in the safety follow-up on study 20040215 and are enrolling in this study, safety data including SAEs, AEs, concomitant medications, and serum samples for anti-denosumab antibody testing will be collected approximately every 6 months for up to 24 months after the end of study visit in the 20040215 study. Thus, the total length of safety follow-up on this study will be 2 years less the time spent in safety follow-up on Amgen study 20040215.

The safety follow-up visits at 6 and 12 months after the End of Treatment visit must be conducted in the clinic. Thereafter, subjects may be contacted by other methods (eg, telephone) to complete the assessments.

Subjects will be asked to provide information regarding their GCTB status and current treatments. Additionally, subjects will be asked if they have experienced any of the following adverse events of interest:

- **ONJ**
- **Malignancy, including malignancy in GCTB**
- **Atypical femoral fracture**

If the subject has experienced any of the adverse events of interest, specific additional information will be requested/collected as necessary according to each type of event. The additional information will include, but is not limited to:

- **ONJ: dental records; information will be sent for adjudication by independent reviewers (see Section 9.4.1)**
- **Malignancy (including malignancy in GCTB): pathology reports**
- **Atypical femoral fracture: x-ray or other imaging; medical/surgical records. Information will be sent for adjudication by independent reviewers (see Section 9.4.1).**

If the subject has experienced any serious adverse event (Section 9.1.2), information is to be collected and reported (see Section 9.3).

If the subject has been receiving treatment with commercial denosumab (XGEVA), or any other Amgen product as standard of care for GCTB or any other condition, Adverse Drug Reactions related to that product will be collected.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

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

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject the most appropriate way to withdraw to ensure the subject's health.

Withdrawal of partial consent means that the subject does not wish to take investigational product any longer but is still willing to collaborate in providing further data by continuing on study (eg, participate in all subsequent study visits or procedures).

Subjects may decline to continue receiving investigational product at any time during the study. These subjects, as well as those who have stopped receiving investigational product for other reasons (eg, investigator or sponsor concern) should continue the schedule of study observations.

Reasons for removal from investigational product or observation might include:

- withdrawal of consent
- administrative decision by the investigator or Amgen
- pregnancy (report on Pregnancy Notification Worksheet, see Appendix C**)**
- ineligibility
- significant protocol deviation
- subject noncompliance
- adverse event
- disease progression
- administration of bisphosphonates or other proscribed therapies

8.2 Replacement of Subjects

No subjects will be replaced.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definitions

9.1.1 Adverse Events

An adverse event is defined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.” (ICH E6:1.2)

This definition of adverse events is broadened in this study to include any such occurrence (eg, sign, symptom, or diagnosis) or worsening of a pre-existing medical condition from the time that a subject has signed informed consent to the time of enrollment to or initiation of investigational product.

This definition of adverse events also includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, cancer, diabetes, migraine headaches, gout) has increased in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

Interventions for pretreatment conditions (eg, elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered adverse events.

Pregnancy is not considered an adverse event (see Appendix C for reporting any pregnancy).

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

9.1.2 Serious Adverse Events

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

- is fatal
- is 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
- is a congenital anomaly/birth defect
- other significant medical hazard

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility excluding hospitalizations for anticipated protocol-specified procedures (eg, to perform resection on affected limb/region with giant cell tumor) or blood product transfusions, if being administered for cancer-related treatment. However, prolongation of hospitalization or re-admission after the subject has been discharged would be considered a Serious Adverse Event. Elective hospitalizations or routine hospitalizations for standard of care administration are not considered to be serious adverse events.

Any adverse event that does not meet one of the definitions of serious (eg, emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other significant medical hazard” criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

9.2 Reporting Procedures for All Adverse Events

The investigator is responsible for ensuring that all adverse events (as defined in Section 9.1 and as further specified below) **and adverse events of interest (Section 7.11)** observed by the investigator or reported by subjects during screening (excluding cohort 3 subjects), treatment, through the first 6-month safety follow up visit **as well as through the end of safety follow-up phase for adverse events of interest (Section 3.4.2)** are collected and recorded in the subjects' medical records and in designated study documents (ie, eCRF, and, on the serious adverse event report (SAER) form for serious adverse events). These adverse events will include all serious and non serious adverse events (as defined in Sections 9.1.1 and 9.1.2) that occur after the subject has signed the informed consent form.

The following adverse event attributes must be assigned by the investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to investigational product and action taken. Diagnoses or syndromes-rather than signs or symptoms-should be recorded. The investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or eCRFs.

If applicable, the relationship of the adverse event to the investigational product will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the investigational product?" The investigator should respond to this question with either Yes or No.

The severity grading scale used in this study is described in Appendix B.

Medically significant adverse events considered related to the investigational product by the investigator or the sponsor will be followed until resolved or considered stable.

It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

9.3 Serious Adverse Event Reporting Procedures

Serious adverse events will be collected and recorded beginning with the signing of the informed consent through the end of the safety follow up phase.

All serious adverse events must be reported to Amgen within 24 hours of discovery or notification of the event. Initial serious adverse event information and all amendments or additions must be recorded on a Serious Adverse Event Report Form (Appendix D) and faxed to Amgen Global Safety. Relevant medical records should be faxed to Amgen Global Safety as soon as they become available; autopsy reports should be provided for deaths if available.

For all deaths, available autopsy reports and relevant medical reports should be faxed to Amgen Global Safety.

If a subject is permanently withdrawn from the study or safety follow-up because of a serious adverse event, this information must be included in the initial or follow-up Serious Adverse Event Report Form as well as the End of Study or End of Safety Follow-up eCRF.

Amgen will report serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARS) as required to regulatory authorities, investigators/institutions and ethics committees in compliance with all applicable regulatory requirements and ICH GCP Guidelines.

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

9.4 Pregnancy and Lactation Reporting

Throughout denosumab treatment and through **5** months after the last dose of IP, the investigator should counsel subjects who are women of childbearing potential on the risks of pregnancy while receiving denosumab, and discuss methods to decrease the risk of becoming pregnant. It is recommended to document these discussions in the medical records.

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should **report** pregnancies that occur after the last dose of protocol-required therapies through **5** months after the last dose **with the exception of subjects who are receiving a commercial Xgeva in the safety follow-up phase. For those subjects investigators should report pregnancies until the end of the safety follow-up phase.**

For both situation/ scenarios the pregnancy should be reported to Amgen **G**lobal **Patient Safety** within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). **Amgen** will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

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

In addition to reporting a lactation case during the study, investigators should **report** lactation cases that occur after the last dose of protocol-required therapies through **5** months after the last dose. **For those subjects receiving a commercial Xgeva in the safety follow-up phase investigators should report lactation cases until the end of the safety follow-up phase.**

Any lactation case should be reported to Amgen **G**lobal **Patient Safety** within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix G).

9.4.1 Adjudication Process for Suspected Osteonecrosis of the Jaw and Suspected Atypical Femoral Fracture Adverse Events

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

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

committee. If an event is adjudicated positive for ONJ, the investigator will be notified of the adjudication decision.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design

This is a phase 2, international, multi-center, open-label study in subjects with GCTB of bone, receiving denosumab at a dose of 120 mg SC Q4W with a loading dose of 120 mg SC on study days 8 and 15.

There are 3 cohorts in this study:

- Cohort #1: Subjects with surgically unsalvageable disease (eg, sacral, spinal GCTB, or multiple lesions including pulmonary metastases)
- Cohort #2: Subjects with surgically salvageable disease whose planned on-study surgery is associated with severe morbidity (eg, joint resection, limb amputation, or hemipelvectomy)
- Cohort #3: Subjects who are currently participating in Amgen study 20040215 giant cell tumor study who are eligible to enroll

10.2 Study Endpoints, Subsets, and Covariates

10.2.1 Primary Endpoint

The primary endpoint is the safety profile of denosumab characterized in terms of the type, frequency, and severity of adverse events and laboratory abnormalities for each cohort.

10.2.2 Secondary Endpoint

The secondary endpoints include

- time to disease progression for cohort 1
- proportion of subjects without any surgery at month 6 for cohort 2
- serum denosumab (trough) concentrations (PK subset)

CCI

CCI

[redacted]

10.2.4 Subsets

The safety analysis set, for adverse events and lab parameters, includes all enrolled subjects who received at least one dose of denosumab. The efficacy analysis set includes all enrolled subjects who were eligible for the study, and received at least one dose of denosumab. The PRO analysis set includes all subjects in the efficacy analysis set who had at least one PRO assessment. The interim analysis set includes the safety, efficacy, and PRO analysis sets of all enrolled subjects up to the time of the interim analyses.

10.3 Sample Size Considerations

The sample size for this study is determined by the number of GCTB subjects who qualify for the study. The availability of subjects may be limited by the number of patients with this rare tumour who meet the inclusion/exclusion criteria.

For the expected sample size of 530 subjects, the 95% confidence interval (CI) based on EXACT method for the incidence rate of a particular adverse event is calculated below (Table 1). If none of the subjects report a particular adverse event then a true incidence rate of more than 0.8% is unlikely for that particular adverse event.

Table 1. Estimated 95% Confidence Interval for Example Adverse Event Incidence Rates

Number of Subjects Reporting Adverse Event	Adverse Event Incidence Rate	
	Estimate (%)	95% CI (%)
0/530	0	(0.0, 0.7)
5/530	0.9	(0.3, 2.2)
10/530	1.9	(0.9, 3.4)
25/530	4.9	(3.2, 7.1)
75/530	15.1	(12.2, 18.4)
150/530	30	(26.1, 34.1)
250/530	50	(45.7, 54.3)
375/530	75.1	(71.2, 78.7)
500/530	100	(99.3, 1.0)

10.4 Access to Individual Subject Treatment Assignments

All subjects will receive denosumab in this open label study.

10.5 Interim Analysis and Early Stopping Guidelines

The first and second interim analyses were conducted after 50 and 100 subjects, respectively, had the opportunity to complete 6 months of treatment. The third interim analysis was conducted with a data cut-off date of 25 March 2011 and included approximately 286 subjects enrolled. **An unplanned interim analysis was performed in August 2013 in response to a request from the European Medicines Agency that included approximately 507 subjects and a median follow up time of 20.8 months.**

Additional interim analyses may be conducted to monitor the ongoing safety of denosumab or to make decisions regarding the use of denosumab in the treatment of giant cell tumor of bone (GCTB).

10.6 Planned Methods of Analysis

10.6.1 General Approach/Considerations

The statistical analysis in this open-label study will be descriptive in nature and no hypothesis testing will be performed. All the efficacy analyses will be conducted separately in each cohort and for cohorts 1 and 2 combined unless specified otherwise; and the safety analyses will be conducted for all cohorts combined. The analyses will be repeated for the adolescent population as applicable. Categorical data will be presented in the form of number and percentage. Continuous data will be provided with the descriptive statistics (n, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum). The primary analysis will be conducted after all subjects have an opportunity to complete 12 months of treatment.

10.6.2 Analysis of Key Study Endpoints

Adverse Events

The analysis will be based on the combined sets of subjects receiving at least one dose of denosumab. The incidence of adverse events will be summarized by system organ class and by preferred term according to the current MedDRA dictionary. This summary includes all treatment-emergent adverse events recorded from the start of investigational product on this study, or any worsening of adverse events initially experienced before initiation of this study. This summary for adverse events will be performed for the following categories:

- All adverse events
- Investigational product (IP) related adverse events

- CTCAE grade 3, 4, or 5 adverse events
- IP related CTCAE grade 3, 4, or 5 adverse events
- Serious adverse events
- IP related serious adverse events
- Adverse events leading to study discontinuation
- IP related adverse events leading to study discontinuation
- Adverse events leading to investigational product discontinuation
- Fatal events

Pharmacokinetic/ Pharmacodynamic Analyses

Summary statistics for serum concentrations of denosumab will be provided for each timepoint (scheduled visit). Summary statistics for the bone turnover markers, uNTx/Cr and sCTx, and their changes from baseline (absolute and % change) will be provided at scheduled visits. The analysis will be based on adolescent and adult subjects enrolled in the PK substudy receiving at least one dose of denosumab.

Laboratory Parameters

The analysis will be based on the combined sets of subjects receiving at least one dose of denosumab. Summary statistics for lab values and their changes from baseline will be provided at scheduled visits. Laboratory shift tables summarizing the worst changes in Common Terminology Criteria for adverse event (v3.0 or higher) grades between baseline and any study visits during the treatment period will be provided.

Time to Disease Progression, Time to Disease Recurrence, Progression Free Survival, and Time to Surgery

Kaplan-Meier estimates will be graphically displayed. Kaplan-Meier event rates at various time points (eg, month 3, month 6, etc) with 2-sided confidence intervals will be summarized. In addition, Kaplan-Meier estimates of quartiles (median, 25th and 75^{th} percentiles) with 2-sided 95% confidence intervals will be calculated if applicable. Time to disease progression, time to disease recurrence, and progression free survival will be analyzed by cohort and for cohorts 1 and 2 combined. Time to surgery will be analyzed for cohort 2 only.

Proportion of Subjects Without Any Surgery, Proportion of Subjects with Pathologic Response, Proportion of Subjects Without Tumor Post-baseline, Proportion of Subjects Able to Undergo a Less Morbid Surgical Procedure Compared With the Planned Surgical Procedure

Crude estimates with 2-sided exact 95% confidence intervals will be summarized. Proportion of subjects without any surgery, and proportion of subjects able to undergo a less morbid surgical procedure compared with the planned surgical procedure will be reported for cohort 2 only. Proportion of subjects with pathologic response and tumor absence post-baseline will be reported for those subjects with histopathology procedures on study, by cohort, and for cohorts 1 and 2 combined.

Radiology Measurement

Radiology change will be summarized descriptively over time by cohort and for cohorts 1 and 2 combined.

Disease Status

Disease status change will be summarized descriptively over time by cohort and for cohorts 1 and 2 combined.

Change in Pain Score from Baseline

Change in the BPI-SF outcomes scores (worst pain score, pain severity score and pain interference score) from baseline, as well as the recorded BPI-SF outcomes scores will be summarized at each visit using summary statistics.

Kaplan-Meier curves reflecting 1) ≥ 2-point decrease in 'pain at its worst' question from baseline, 2) ≥ 2-point increase in 'pain at its worst' question from baseline, and 3) > 4-point in 'pain at its worst' question (in subjects with baseline ≤ 4 points)**, and 4) strong opioid use** will be developed. These estimates will quantify the time to improvement in pain, the time to worsening of pain, **and the time to strong opioid use,** respectively.

10.6.3 Planned Methods of Analysis for the Safety Follow-up Phase

Safety data including AEs and SAEs from the safety follow-up phase will be summarized using the methods described in Section 10.6.2.

11. INVESTIGATIONAL PRODUCT

11.1 Denosumab

Denosumab will be supplied as a sterile, clear, colorless to slightly yellow, preservative free liquid, in single-use 3.0 mL glass vials containing a deliverable dose of 1.7 mL. The formulation of investigational product is 70 mg denosumab per mL, formulated with C mM sodium acetate and C% sorbitol at a pH of CC.

Investigational product details for denosumab, including labeling, storage, preparation, etc., are provided in the **IPIM**.

The fill lot number of investigational product is to be recorded on each subject's eCRF.

11.2 Compliance in Investigational Product Administration

When investigational product is dispensed for administration to the subject during a study, the investigator or responsible person will determine the level of compliance with the administration of the investigational product. The subject's investigational product compliance (eg, amount administered) will be recorded on the subject's eCRF.

12. REGULATORY OBLIGATIONS

12.1 Informed Consent

An initial generic informed consent and a Pediatric Assent Informed Consent form has been provided to the investigator for preparation of the informed consent document to be used at his or her site. Updates to the template will be communicated by letter from the clinical 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 / subject's parent 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 (with the exception of procedures performed as standard of care) or any investigational product is administered.

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.

If applicable, the investigator is also responsible for asking the subject / subject's parent or legally acceptable representative if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study and recording the subject's preference in the medical chart. If the subject / subject's parent or legally acceptable representative agrees to such notification, the investigator shall inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not agree to such notification, the investigator shall not inform the subject's primary care physician.

The acquisition of informed consent if applicable, the subject's / subject parent's or legally acceptable representative agreement or refusal of his/her notification of the primary care physician, should be documented in the subject's medical records, and the

informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily an investigator). 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 / subject parent's 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.

In this study, obtaining assent from the adolescent and consent from the parents or legally authorized representative, as defined by local law, will apply. An adolescent is defined as a person who has not attained the legal age for consent for treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will take place. The local IEC/IRB will determine the process for obtaining and documenting the assent process for pediatric subjects, but should follow the guidelines established by the Department of Health and Human Services (DHHS) Office of Human Research Protections guidelines, which state an explanation of the procedures involved in the study should be made in a language appropriate to the adolescent's age, experience, maturity and condition.

12.2 Independent Ethics Committee/Institutional Review Board

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

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent and Pediatric Assent form (if appropriate) documents. 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 Global Safety, in accordance with local procedures.

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

12.3 Prestudy Documentation Requirements

The investigator is responsible for forwarding the following documents to Amgen for review before study initiation from Amgen or its designee can occur:

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of approved informed consent form and Pediatric Assent Form (if appropriate)
- Copy of the IEC/IRB approval of the denosumab IB, protocol, consent form, and subject information sheet, if applicable
- Up-to-date curricula vitae of principal investigator and all subinvestigators
- IEC/IRB composition and/or written statement that IEC/IRB is in compliance with regulations
- Laboratory normal ranges and documentation of laboratory certification (or equivalent, if applicable)
- Current subject/investigator indemnity insurance, if applicable
- Signed study contract
- Completed FDA form 1572 (or equivalent)
- Completed Financial Disclosure statements for the principal investigator, all subinvestigators, and their spouses (legal partners) and dependent children

12.4 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the eCRFs or other documents submitted to Amgen subjects should be identified by study subject number only. Documents that are not for submission to Amgen (eg, signed informed consent forms, Pediatric Assent form [if appropriate]) should be kept in strict confidence by the investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

12.5 Investigator Signatory Obligations

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

The coordinating investigator, 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

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 Protocol Amendments and Study Termination

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of Amgen. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent and Pediatric Assent form (if appropriate) documents. 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.

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

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

13.2 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 eCRFs will be included on the Amgen Delegation of Authority Form.

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

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

- Subject files containing completed eCRFs (data disc is provided at study closure) and informed consent forms and Pediatric Assent form (if appropriate)
- Study files containing the subject identification list, protocol with all amendments, investigator's brochure, copies of prestudy documentation (see Section 12.3), and all correspondence to and from the IEC/IRB and Amgen.
- Proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence

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

No study document should be destroyed without prior written agreement between Amgen and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify Amgen in writing of the new responsible person and/or the new location.

13.3 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 subject confidentiality is respected.

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

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 eCRFs, 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 Clinical Quality Assurance Department (or designees). Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories)

and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

All data capture for this study is planned to be electronic, however if necessary data capture may be performed utilizing paper CRFs:

- Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator on the Amgen Delegation of Authority Form. No erasures, correction fluid, or tape may be used.
- Corrections to electronic forms 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 raised in the EDC system for site completion.
- EDC only: The principal investigator signs only the Investigator Verification Form for all EDC studies. The principal investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal investigator inspected or reviewed the data on the eCRFs, the data queries, and the site notifications, and agrees with the content. Paper output of the eCRF is available should the Investigator or the IEC/IRB require hard copy output for review, signature, and storage at the study site.
- Amgen's clinical data management department or designees will correct the database for the following eCRF issues without notification to site staff:
  - misspellings that do not change the meaning of the word (excluding adverse events and medications)
  - location of data recorded on an incorrect eCRF (eg, moving lab data from general comments to the appropriate lab table)
  - date errors that occur into the new year
  - standard time to 24-hour clock
  - temperature unit errors (Fahrenheit vs Centigrade)
  - weight unit errors (pounds vs kilograms) if a baseline weight has been established
  - height unit errors (in. vs cm)
  - administrative data (eg, event names for unscheduled visits or retests)
  - clarifying "other, specify" if data are provided (eg, race, physical exam)
  - if both the end date and a status of continuing is indicated (eg, for adverse events, concomitant medication, hospitalization), the end date will supersede
  - deletion of obvious duplicate data (eg, same results sent twice with the same date but different clinical planned events—week 4 and early termination)

- for adverse events that record action taken code = 01 (none) and any other action code, 01 (none) may be deleted as it is superseded by other existing data
- if equivalent units or terms are recorded instead of the acceptable Amgen standard (eg, cc for mL, SQ for SC route, Not Examined for Not Done), the Amgen units or terms will be used
- if the answer to a YES or NO question is blank or obviously incorrect (eg, Answers to the following questions do not reflect the data that are recorded or missing: Were there any adverse events? Concomitant medications? Hospitalizations?)
- correct eCRF page numbers

13.4 Language

Electronic case report forms (eCRFs) must be completed in English.

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.

13.5 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 Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2005), which states:

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

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

13.6 Compensation

If personal injury occurs as a result of participating in this research study, the subject and/or their insurance provider will be responsible for paying for the treatment. No compensation is available from Amgen, other than that provided by law.

14. REFERENCES

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15. APPENDICES

Appendix A. Schedule of Assessments

	Prior To Day 1 Wk 1		First 4-wk period (days 1 to 28)			Treatment Period: (Weeks)											
Protocol Activities	**≤ 28 days**	**≤ 7 days**	**Day 1**	**Day 8**	**Day 15**	**Day 29 W5**	**W9**	**W13**	**W17**	**W21**	**W25**	**W29**	**W33**	**W37**	**W41**	**W45**	**End of Treatment**
Informed Consent[12]	X																
Medical history	X																
Pathology sample[4]			←←←←←**May be requested either during the study or at end of study for evaluation of histopathological response to treatment**→→→→→→														X
Pathology reports[3]	X		←←←←←**Must be attached to the subject's medical record if performed as standard of care**→→→→→→														X
Imaging reports[5]	X		←←←←←←**Must be attached to the subject's medical record if performed as standard of care**→→→→→→														
Serum chemistries[6,14]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
PE, Karnofsky[7, 14]	X		X			X	X	X	X	X	X	X	X	X	X	X	X
Disease Status[7,14]	X		X			X	X	X	X	X	X	X	X	X	X	X	X
Oral Exam	X		X								X						
Pregnancy test[8, 14]		X	X					X			X			X			X
Antibody assay[10]			X														X
Pharmacokinetics[15]			X	X	X	X	X	X	X		X						
sCTx[15]			X	X	X	X	X	X	X		X						
uNTx[15]			X	X	X	X	X	X	X		X						
Denosumab Administration[1]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient Reported Outcomes[9,13]			X	X	X	X	X	X	X	X	X			X			X
Calcium / Vitamin D			←←←←←←←←←←←← **All subjects should be adequately supplemented with calcium and Vitamin D** →→→→→→														
AE Assessment[11]	X	X	←←←←←←←←←←←←←←←←←←←←Documented throughout the study→→→→→→→→→→→→→→→→→→→→														X
Adverse Events of Interest			←←←←←←←←←←←←←←←←←←←←**Documented throughout the study**→→→→→→→→→→→→→→→→→→→→														**X**
Con Med Review	X	X	←←←←←←←←←←←←←←←←←←←←Documented throughout the study→→→→→→→→→→→→→→→→→→→→														X

Footnote displayed on the last page of the table

Protocol Activities	W49	W53	W57	W61	W65	W69	W73	W77	W81	W85	W89	W93 and Q4W	Additional Tests at W97 and Q12W	End of Treatment	SFU[2] 6 mo	SFU[2] 12 mo	SFU[2] Every 12 mo
Pathology sample[4]	←←←←← **May be requested either during the study or at end of study for evaluation of histopathological response to treatment** →→→→→→→													X			
Pathology reports[3]	←←←←← **Must be attached to the subject's medical record if performed as standard of care** →→→→→→→													X			
Imaging reports[5]	←←←←←←**Must be attached to the subject's medical record if performed as standard of care**→→→→→→→																
Serum chemistries[6,14]	X	X	X	X	X	X	X	X	X	X	X	X		X			
PE, Karnofsky[7, 14]	X	X	X	X	X	X	X	X	X	X	X	X		X	**X**	**X**	
Disease Status[7,14]	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Oral Exam	X						X						Q24W	X	X		
Pregnancy test[8, 14]	X			X			X			X			X	X	X		
Antibody assay[10]														X	X	X	
Denosumab Administration[1]	X	X	X	X	X	X	X	X	X	X	X	X					
Patient Reported Outcomes[9,13]	X			X			X			X			X	X			
Calcium / Vitamin D	←←←←← **Subjects should be adequately supplemented with calcium and Vitamin D** →→→→→→→																
AE Assessment[11]	←←←←←←Documented throughout treatment→→→→→→→													X	X		
Adverse events of interest	←←←←←←**Documented throughout the study**→→→→→→→													**X**	**X**	**X**	**X**
Con Med Review	←←←←←←Documented throughout treatment→→→→→→→													X			

Footnote displayed on the next page of the table

Footnotes:

1. Subjects will continue to receive denosumab until complete tumor resection (if applicable), disease progression physician's or subject's decision, or Amgen's decision to discontinue for any reason, or administration of any of the proscribed therapies listed in Section 6.5. Denosumab 120 mg is given by SC injection as a 1.7 mL injection of denosumab 70 mg/mL.

2. Safety Follow-Up: For all subjects, including the PK substudy, data (treatment plus follow-up) will be collected until the end of the clinical study (Section 3.4.2) which is when subjects enrolled before Amendment 7 will complete a minimum of 60 months on study or otherwise have discontinued. For subjects who discontinue(d) investigational product, safety follow-up visits will be conducted approximately every 6 months (± 1 month) after the End of Treatment visit (approximately 4 weeks after the last dose of investigational product) for the first year, then every 12 months (± 1 month). The final safety follow-up visit will be conducted at the time of the end of the clinical study (Section 3.4.2) (even if this in not approximately 6 or 12 months since the previous follow-up visit). Prior to Amendment 7, for subjects who were in the safety follow-up of study 20040215 and were enrolling in this study, safety data will be collected approximately every 6 months for up to 24 months after the end of study visit in the 20040215 study. Upon the approval of Amendment 7, subjects that enrolled from the 20040215 study will also follow the 20062004 schedule, and complete the assessments as described in Appendix A. The safety follow-up visits at 6 and 12 months after the End of Treatment visit must be conducted in the clinic. Thereafter, subjects may be contacted by other methods (eg telephone) to complete the assessments.

3. Histopathology reports confirming the diagnosis of GCT of bone and demonstrating active disease are to be obtained to determine eligibility at screening (not required for 20040215 subjects). All on-study reports **are to be attached to the subject's medical record** if performed as standard of care except at end of study where this may be requested.

4. Histopathology samples may be requested **during or** at end of study.

5. Imaging report will be required at screening to confirm eligibility (not required for 20040215 subjects). All on-study imaging reports **must be attached to the subject's medical record** if performed as standard of care. Select historical and select on-study imaging performed as standard of care will be required to be sent to a central imaging vendor for evaluation of disease response.

6. Serum chemistries performed by local lab must include serum creatinine, calcium, albumin, magnesium and phosphorus.

7. Physical exam: The screening PE includes medical history, Karnofsky performance status, disease status, blood pressure, respiratory rate, temperature, weight and height. (After the subject has signed the informed consent and the medical history is recorded on the Medical and Surgical History eCRF, any new or worsening conditions should be reported on the Adverse Event eCRF, including any reported during the screening period.) Thereafter, only a disease status and Karnofsky performance status will be collected during the treatment phase of the study **and at 6 and 12 months of** safety follow up.

8. Pregnancy test for women of childbearing potential is to be conducted at screening, on study (approximately every 12 weeks while receiving denosumab treatment) and during safety follow up (only at 6 months after **EoT**). A urine/serum pregnancy test must be done at baseline prior to first dose of denosumab if study day 1 is greater than 7 days from the pregnancy confirmation done at screening.

9. Patient Reported Outcomes (PRO): Consist of BPI-SF. The BPI-SF will be administered prior to each administration of investigational product at baseline, study days 8 and 15, then every 4 weeks (Q4W) from weeks 5 – 25, then every 12 weeks (Q12W) to end of study.

10. Serum for anti- denosumab antibody assay will be collected at baseline and as outlined on the schedule of assessments, including 2 samples during follow up (approximately 6 and 12 months after the end of study visit). Prior to Amendment 7, for subjects who were in the safety follow-up of study 20040215 and are enrolling in this study, serum samples for anti-denosumab antibody assay will be collected approximately every 6 months for up to 24 months after the end of study visit in the 20040215 study. Upon approval of Amendment 7, subjects that enrolled in 20062004 from 20040215 study will also follow the 20062004 schedule, and complete the assessments as described in Appendix A. These samples may also be used for future biomarker development testing

11. Adverse event assessment should be documented and recorded at each visit upon signing informed consent through the first 6 month safety follow-up visit. **Adverse events of interest will be followed through the last safety follow-up visit.** Subjects must be followed for adverse events until all denosumab treatment-related toxicities have resolved.

12. Informed consent may be obtained more than 28 days before Day 1 week 1.

13. Cohort 3 subjects will enroll at their next Q4W visit (based on their 20040215 schedule). Informed consent will be obtained prior to any protocol specific procedures; PROs will be collected at their next Q12W assessment visit.

14. Prior to Amendment 7, for subjects who were in the safety follow-up of study 20040215 and are enrolling in this study, serum chemistries, physical examination, disease status, Karnofsky performance status,and pregnancy testing are not required during the safety follow-up. Upon the approval of Amendment 7, subjects that enrolled in 20062004 from the 20040215 study will also follow the 20062004 schedule, and complete the assessments as directed in Appendix A.

15. Pharmacokinetic Substudy – Approximately 10 adolescent and approximately 10 adult subjects will contribute to the PK substudy. Samples for pharmacokinetic, uNTx, and sCTx analysis on Study Day 1 will be obtained prior to IP administration. Subjects enrolled in the PK substudy will be followed (treatment plus follow-up) until all subjects enrolled before Amendment 7 complete a minimum of 60 months.

Appendix B. Adverse Event Severity Scoring System

The Common Terminology Criteria for Adverse Events (CTCAE, version 3.0) are available at the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

Appendix C. 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: _____

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: _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

Appendix D. Sample SAE Report Form

A 20062004	**Clinical Trial Serious Adverse Event Report – Phase 1–4** ***Notify Amgen Within 24 Hours of knowledge of the event***	❑New ❑Follow-up

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number ( )	Fax Number ( )

2. SUBJECT INFORMATION

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

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

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day_____Month____Year_____

Serious Adverse Event Diagnosis or Syndrome **If diagnosis is unknown, enter Signs / Symptoms** **When Final Diagnosis is known, enter as Adverse Event** *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP	**Enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that the event may have been caused by IP? **If yes see section 10**		**Relationship** Is there a reasonable possibility that the event may have been caused by an Amgen device?			**Outcome of Event** **01** Resolved **02** Resolving **03** Not resolved **04** Fatal	Check only if event is related to study procedure *eg, biopsy*
					No ✓	**Yes ✓**	**No ✓**	**Yes ✓**	**If Yes, what device?**		

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

4. HOSPITALIZATION

	Date Admitted Day Month Year	**Date Discharged** Day Month Year

Was subject hospitalized? ☐No ☐Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product **01** Still being Administered **02** Permanently discontinued **03** Withheld
<<IMP>> ☐✓Blinded ☐✓Open Label						

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

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

Site Number	Subject ID Number

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

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

Date Day Month Year	Test										
	Unit										

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

Date Day Month Year	Additional Tests	Results	Units

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

Signature of Investigator or Designee	Title	Date

Appendix E. Karnofsky Performance Status and Eastern Cooperative Oncology Group (ECOG) Performance Status

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.

ECOG Scale Performance Status

0 - Fully active, able to carry out all pre-disease performance without restriction.
1 - Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, (e.g. 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 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

Oken et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. *Am J Clin Onc*. 5: 649 – 655, 1982.

Appendix F. Sample Brief Pain Inventory - Short Form (BPI-SF)

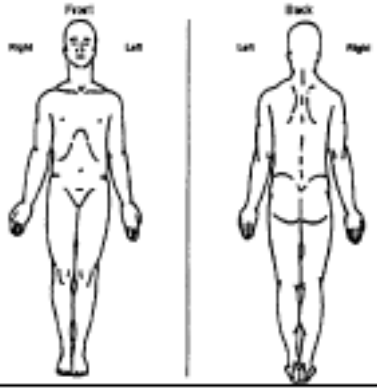
AMGEN Denosumab 20062004 | Site No. | Subject ID No. 204

Date: Day | Month | Year

Day 1 - Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today? 1 Yes 0 No

2. On the diagram, shade the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its **worst** in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its **least** in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the **average**.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have **right now**.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

US-English BPI D1 v0.0 Distribution: White-Amgen; Canary-Investigator 101

AMGEN Denosumab 20062004	Site No.	Subject ID No. 204

Day 1 - Brief Pain Inventory (Short Form)

7. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% No Relief 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

8. Circle the one number that best describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

B. Mood

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

C. Walking Ability

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

D. Normal work (includes both work outside the home and housework)

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

E. Relations with other people

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

F. Sleep

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

G. Enjoyment of life

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely interferes

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Pain Research Group
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US-English BPI D1 v0.0 Distribution: White-Amgen; Cardstock-Investigator 102

Appendix G. 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: _____

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm____ / dd____ / yyyy____

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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

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

Amendment 8

Protocol Title: An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Amgen Protocol Number 20062004

EudraCT# 2008-001606-16

Date:	22 April 2008
Amendment 1:	12 December 2008
Amendment 2:	22 October 2009
Amendment 2 (Superseding)	11 January 2010
Amendment 3:	14 May 2010
Amendment 4:	15 November 2010
Amendment 5:	05 May 2011
Amendment 6:	30 August 2011
Amendment 7:	15 May 2013
Amendment 8:	17 July 2015
Amendment 8 (Superseding):	**15 September 2015**

Rationale:

- Safety follow-up period information was updated and adverse events of interest were listed to align the protocol language with post marketing data collection requirements and to increase compliance with long-term follow-up data requirements.
- Interim analysis 4 was removed as it is not a regulatory requirement and no study report is expected from this interim analysis per regulatory requirements.
- Pharmacy guide is obsolete and has been replaced by IPIM in Amgen protocols.
- Medical history section was updated for clarification and to align with other sections of the protocol.
- The dose escalation and stopping rules section was modified to clarify that the planned dose may be given up to 7 days before the scheduled visit, as long as there are at least 21 days between doses.
- Calcium and Vitamin D information was updated to match Xgeva product information.
- The number of birth control methods and amount of washout time required between the end of treatment and pregnancy or breastfeeding was updated to align with the informed consent and current safety information.
- Pregnancy reporting was changed from the Pregnancy Surveillance Program to Amgen Global Patient Safety as per current Amgen standard.
- Administration, typographical and formatting changes were made throughout the protocol.

Description of Changes (all changes to the Protocol are indicated in bold text):

Section:	All applicable sections and header
Replace:	15 May 2013
With:	**15 September 2015**

Section	Cover page
Replace:	PPD, Clinical Research Study Manager, Amgen Inc. Email : PPD Phone: Fax: PPD
With:	PPD, Clinical Research Study Manager, Amgen Inc. **Email :** PPD Phone: Fax: PPD
Replace:	PPD, Clinical Research Study Manager Amgen Ltd. Email : PPD Phone: Fax: PPD
With:	PPD Clinical Research Study Manager **Amgen Sp.z o.o.** Email : PPD Phone: Fax: PPD
Add:	**Amendment 8 17 July 2015**

Section:	Protocol Synopsis, Study Design Paragraph 7
Add:	**During the safety follow-up phase, subjects will be asked about serious adverse events, adverse events of interest, and disease treatments and outcomes (Section 9.2).**

Section:	Protocol Synopsis, Sample Size
Delete:	and a minimum of 5 subjects will be adolescents

Section:	Protocol Synopsis, Exclusion Criteria
Replace:	• Subject is pregnant or breast feeding, or planning to become pregnant within 7 months after the end of treatment • Female subject of child bearing potential is not willing to use two methods of highly effective contraception during treatment and for 7 months after the end of treatment

With:
- Subject is pregnant or breast feeding, or planning to become pregnant within **5** months after the end of treatment
- Female subject of child bearing potential is not willing to use **a** highly effective method of contraception during treatment and for **5** months after the end of treatment

Section: Protocol Synopsis, Exclusion criteria for 20040215 subjects

Replace:
- Subject is pregnant or breast feeding, or planning to become pregnant within 7 months after the end of treatment
- Female subject of child bearing potential is not willing to use two methods of highly effective contraception during treatment and for 7 months after the end of treatment

With:
- Subject is pregnant or breast feeding, or planning to become pregnant within **5** months after the end of treatment
- Female subject of child bearing potential is not willing to use **a** highly effective method of contraception during treatment and for **5** months after the end of treatment

Section: Protocol Synopsis, Investigational Product Dosage and Administration

Replace: It is strongly recommended that subjects take daily supplementation of at least 500 mg of calcium and 400 IU of vitamin D, except in the case of pre-existing hypercalcemia.

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

Section: Protocol Synopsis, Procedures, paragraph 2

Add: The approval process is required for new enrolling subjects **and subjects considered for retreatment**.

Section: Protocol Synopsis, Procedures, paragraph 3

Add: **A copy of the standard of care imaging reports obtained within 1 year before enrollment, demonstrating active GCTB must be attached to the subject's medical record**.

Delete: Imaging and

Delete: collected throughout the study

Add: Similar data from procedures performed as standard of care will be **attached to the subject's medical record**

Section: Protocol Synopsis, Statistical Considerations, paragraph 2

Delete: An interim analysis will occur when at least 200 subjects have had the opportunity to complete 5 years on study.

Add: **An unplanned interim analysis was performed in August 2013 in response to a request from the European Medicines Agency that included approximately 507 subjects and a median follow up time of 20.8 months.**

Section: Study Glossary

Add: **IPIM Investigational Product Instruction Manual**
ONJ Osteonecrosis of the jaw

Section: Study Term EOS

Delete: trial

Add: study

Section: Study Term EOT

Replace: end of treatment visit

With: **E**nd of **T**reatment visit

Section: Table of Contents, List of Appendices

Delete: Appendix C Pharmacy Guide
Move subsequent appendices up one letter

Section: 2.2.1 Clinical Experience With Denosumab in Giant Cell Tumor of Bone (GCTB)

Replace: Study 20040215 is an ongoing Phase 2 proof of concept study investigating the potential role for denosumab in the treatment of GCTB. The study tests the hypothesis that denosumab, a RANKL inhibitor, can inhibit the growth and survival of tumor cells in patients with GCTB.

With: **The Phase 2 study,** Study 20040215, **investigated** the potential role for denosumab in the treatment of GCTB. The study **tested** the hypothesis that denosumab, a RANKL inhibitor, can inhibit the growth and survival of tumor cells in patients with GCTB.

Section: 3.3 Number of Subjects, paragraph 2

Delete: and a minimum of 5 subjects will be adolescents

Section: 3.4.2 End of Study (EOS), paragraph 1

Replace: trial

With: **study**

Section: 4.2 Exclusion Criteria, 4.2.14 and 4.2.15

Replace:
- Subject is pregnant or breast feeding, or planning to become pregnant within 7 months after the end of treatment
- Female subject of child bearing potential is not willing to use two methods of highly effective contraception during treatment and for 7 months after the end of treatment

With:
- Subject is pregnant or breast feeding, or planning to become pregnant within **5** months after the end of treatment
- Female subject of child bearing potential is not willing to use **a** highly effective method of contraception during treatment and for **5** months after the end of treatment

Section: 4.2 Exclusion Criteria for 20040215 subjects, 4.2.19 and 4.2.20

Replace:
- Subject is pregnant or breast feeding, or planning to become pregnant within 7 months after the end of treatment
- Female subject of child bearing potential is not willing to use two methods of highly effective contraception during treatment and for 7 months after the end of treatment

With:
- Subject is pregnant or breast feeding, or planning to become pregnant within **5** months after the end of treatment
- Female subject of child bearing potential is not willing to use **a** highly effective method of contraception during treatment and for **5** months after the end of treatment

Section: 5. SUBJECT ENROLLMENT, Paragraph 4

Add: The approval process is required for new enrolling subjects **and subjects considered for retreatment**.

Section: 6. TREATMENT PROCEDURES

Replace: For further details regarding preparation and administration of the investigational product, refer to Appendix C (Pharmacy Guide).

With: For further details regarding preparation and administration of the investigational product, refer to **the Investigational Product Instruction Manual (IPIM), which is a document external to this protocol**.

Section:	6.2 Dose Escalation and Stopping Rules, paragraph 2
Replace:	For Q4W doses, if a planned dose (eg, week 5, week 9, etc.) is delayed more than 7 calendar days, it will be considered a missed dose and recorded as such on the eCRF.
With:	For Q4W doses, **the planned dose may be given up to 7 days before the scheduled visit, as long as there are at least 21 days between doses. I**f a planned dose (eg, week 5, week 9, etc.) is delayed more than 7 calendar days, it will be considered a missed dose and recorded as such on the eCRF.
	Paragraph 5
Add:	**(ONJ)**

Section:	6.4 Concomitant Therapy (Calcium and Vitamin D Supplements)
Replace:	It is strongly recommended that subjects take daily supplementation of at least 500 mg of calcium and 400 IU of Vitamin D, except in the case of pre-existing hypercalcemia.
With:	**All subjects should be adequately supplemented with calcium and Vitamin D (**at least 500 mg of calcium and 400 IU of Vitamin D**)**, except in the case of pre-existing hypercalcemia.

Section:	7.2 Medical History
Replace:	The subject's medical history will be obtained prior to enrollment and recorded on the eCRF. Detailed history of all pre-existing conditions must be documented on the eCRF (and in the source documents). All major and minor significant illnesses, surgeries, and conditions that are both historical and present/ongoing at the time of first dose of investigational product will be obtained.
With:	The subject's medical history will be obtained **≤ 28 days before day 1 of the study** and recorded on the eCRF. **A d**etailed history of all pre existing conditions must be documented on the eCRF (and in the source documents). **Any illness or medical condition that is ongoing at the time of the subject's first dose of study drug should be noted. Worsening of a pre-existing condition should be reported as an adverse event.**

Section:	7.4 Physical Examination
Replace:	Refer to Appendix F for Karnofsky performance status criteria.
With:	Refer to Appendix **E** for Karnofsky performance status criteria.

Section:	7.5 Imaging
Replace:	A copy of imaging reports (eg, PET, CT, PET/CT, MRI, or X-ray) performed as standard of care must be provided to Amgen.

With: A copy of imaging reports (eg, PET, CT, PET/CT, MRI, or X-ray) performed as standard of care must be **attached to the subject's medical record**.

Section: 7.6 Histopathology

Replace: A copy of all available pathology reports obtained as standard of care must be provided to Amgen including the surgical report of the GCTB target lesion resection. Histopathology samples and reports may be requested at end of study.

With: A copy of all available pathology reports obtained as standard of care must be **attached to the subject's medical record,** including the surgical report of the GCTB target lesion resection. **The h**istopathology samples and reports may be requested **either during the study or** at end of study **for evaluation of histopathological response to treatment**.

Section: 7.10 End of Treatment (EOT) Visit

Replace: Each subject will have an end of treatment visit approximately 4 weeks after their last dose of investigational product.

With: Each subject will have an **E**nd of **T**reatment visit approximately 4 weeks after their last dose of investigational product.

Section: 7.11 Safety Follow-up Phase

Paragraph 1

Add: **During the safety follow-up phase, subjects will be asked about serious adverse events, adverse events of interest, and disease treatments and outcomes (Section 9.2).**

Paragraph 5

Add: **Subjects will be asked to provide information regarding their GCTB status and current treatments. Additionally, subjects will be asked if they have experienced any of the following adverse events of interest:**

- **ONJ**
- **Malignancy, including malignancy in GCTB**
- **Atypical femoral fracture**

If the subject has experienced any of the adverse events of interest, specific additional information will be requested/collected as necessary according to each type of event. The additional information will include, but is not limited to:

- **ONJ: dental records; information will be sent for adjudication by independent reviewers (see Section 9.4.1)**
- **Malignancy (including malignancy in GCTB): pathology reports**
- **Atypical femoral fracture: x-ray or other imaging; medical/surgical records. Information will be sent for adjudication by independent reviewers (see Section9.4.1).**

If the subject has experienced any serious adverse event (Section 9.1.2), information is to be collected and reported (see Section 9.3).
If the subject has been receiving treatment with commercial denosumab (XGEVA), or any other Amgen product as standard of care for GCTB or any other condition, Adverse Drug Reactions related to that product will be collected.

Section: 8.1 Removal of Subjects, paragraph 4

Replace:
- pregnancy (report on Pregnancy Notification Worksheet, see Appendix D)

With
- pregnancy (report on Pregnancy Notification Worksheet, see **Appendix C**)

Section: 9.1.1 Adverse Events, paragraph 5

Replace: Pregnancy is not considered an adverse event (see Appendix D for reporting any pregnancy).

With: Pregnancy is not considered an adverse event (see **Appendix C** for reporting any pregnancy).

Section: 9.2 Reporting Procedure for All Adverse Events, paragraph 1

Replace: The investigator is responsible for ensuring that all adverse events (as defined in Section 9.1 and as further specified below) observed by the investigator or reported by subjects during the screening (excluding cohort 3 subjects), treatment and through the first 6 month safety follow up visit of the study are collected and recorded in the subjects' medical records and in designated study documents (ie, eCRF, and, on the serious adverse event report (SAER) form for serious adverse events).

With: The investigator is responsible for ensuring that all adverse events (as defined in Section 9.1 and as further specified below) **and adverse events of interest (Section 7.11)** observed by the investigator or reported by subjects during screening (excluding cohort 3 subjects), treatment, through the first 6-month safety follow up visit **as well as through the end of safety follow-up phase for adverse events of interest (Section 3.4.2)** are collected and recorded in the subjects' medical records and in designated study documents (ie, eCRF, and, on the serious adverse event report (SAER) form for serious adverse events).

Section: 9.3 Serious Adverse Event Reporting Procedures, paragraph 2

Replace: Initial serious adverse event information and all amendments or additions must be recorded on a Serious Adverse Event Report Form (Appendix E) and faxed to Amgen Global Safety.

With: Initial serious adverse event information and all amendments or additions must be recorded on a Serious Adverse Event Report Form (**Appendix D**) and faxed to Amgen Global Safety.

Section: 9.4 Pregnancy and Lactation Reporting, Paragraph 1

Replace: Throughout denosumab treatment and through 7 months after the last dose of IP, the investigator should counsel subjects who are women of childbearing potential on the risks of pregnancy while receiving denosumab, and discuss methods to decrease the risk of becoming pregnant.

With: Throughout denosumab treatment and through **5** months after the last dose of IP, the investigator should counsel subjects who are women of childbearing potential on the risks of pregnancy while receiving denosumab, and discuss methods to decrease the risk of becoming pregnant.

Paragraphs 3 and 4

Replace: In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 7 months after the last dose.

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix D). The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

With: In addition to reporting any pregnancies occurring during the study, investigators should **report** pregnancies that occur after the last dose of protocol-required therapies through **5** months after the last dose **with the exception of subjects who are receiving a commercial Xgeva in the safety follow-up phase. For those subjects investigators should report pregnancies until the end of the safety follow-up phase.**

For both situation/ scenarios the pregnancy should be reported to Amgen **G**lobal **Patient Safety** within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix **C**). **Amgen** will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

Paragraphs 6 and 7

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

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

With: In addition to reporting a lactation case during the study, investigators should **report** lactation cases that occur after the last dose of protocol-required therapies through **5** months after the last dose. **For those subjects receiving a commercial Xgeva in the safety follow-up phase, investigators should report lactation cases until the end of the safety follow-up phase.**

Any lactation case should be reported to Amgen **G**lobal **Patient Safety** within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix **G**).

Section: 9.4.1 Adjudication Process for Suspected Osteonecrosis of the Jaw and Suspected Atypical Femoral Fracture Adverse Events, paragraphs 1 and 2

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

Adverse events reported as ONJ or atypical femoral fracture as well as adverse events identified by Amgen as potentially representing ONJ or atypical femoral fracture will be reviewed by an independent adjudication panel of experts to determine whether the pre-defined criteria for ONJ or atypical femoral fracture are met. Amgen will request the investigating site to provide all available source documents surrounding that event to be reviewed by the blinded adjudication committee. If an event is adjudicated positive for ONJ, the investigator will be notified of the adjudication decision.

Section: 10.5 Interim Analysis and Early Stopping Guidelines

Replace: An interim analysis will occur when at least 200 subjects have had the opportunity to complete 5 years on study.

With: **An unplanned interim analysis was performed in August 2013 in response to a request from the European Medicines Agency that included approximately 507 subjects and a median follow up time of 20.8 months.**

Section: 10.6.2 Analysis of Key Study Endpoints

Delete: The analysis of BPI-SF outcomes will employ a piecewise growth curve model (Fairclough et al, 2004). If analgesic use increases over time, the on-study analgesic score will be included as an additional covariate in the analysis.

Replace: **Change in pain score from baseline**

Kaplan-Meier curves reflecting 1) ≥ 2-point decrease in 'pain at its worst' question from baseline, 2) ≥ 2-point increase in 'pain at its worst' question from baseline, and 3) > 4-point in 'pain at its worst' question (in

subjects with baseline ≤ 4 points) will be developed. These estimates will quantify the time to improvement in pain and the time to worsening of pain, respectively.

With: Change in Pain Score from Baseline

Kaplan-Meier curves reflecting 1) ≥ 2-point decrease in 'pain at its worst' question from baseline, 2) ≥ 2-point increase in 'pain at its worst' question from baseline, and 3) > 4-point in 'pain at its worst' question (in subjects with baseline ≤ 4 points)**, and 4) strong opioid use** will be developed. These estimates will quantify the time to improvement in pain, the time to worsening of pain, **and the time to strong opioid use,** respectively.

Section: 11.1 Denosumab, paragraph 1

Replace: Denosumab will be provided as a sterile, clear, colorless to slightly yellow, practically free from particles, preservative-free liquid in open-label, single-use 3.0-mL vials containing 1.7 mL of 70 mg/mL denosumab, [redacted] mM acetate and [redacted]% (w/v) sorbitol, at a pH of [redacted] Investigational product details for denosumab, including labeling, storage, preparation, etc., are provided in the Pharmacy Guide (Appendix C).

With: **Denosumab will be supplied as a sterile, clear, colorless to slightly yellow, preservative free liquid, in single-use 3.0 mL glass vials containing a deliverable dose of 1.7 mL. The formulation of investigational product is 70 mg denosumab per mL, formulated with [redacted] mM sodium acetate and [redacted]% sorbitol at a pH of [redacted].** Investigational product details for denosumab, including labeling, storage, preparation, etc., are provided in the **IPIM**.

Section: 14. REFERENCES

Delete: Fairclough D.L, Gagnon D, and Papadopoulos G. Planning Analyses of Quality-of-Life Studies: A Case Example with Migraine Prophylaxis. *J Biopharm Stat*. 2004;14:31-51

Section: Appendix A, Schedule of Assessments, Pathology sample

Replace: To be submitted if performed as standard of care

With: ←←←←←←**May be requested either during the study or at end of study for evaluation of histopathological response to treatment**→→→→→→→

Section:	Appendix A, Schedule of Assessments, Imaging reports and pathology reports
Replace:	To be submitted if performed as standard of care
With:	**Must be attached to the subject's medical record if performed as standard of care**
Add:	**Adverse events of interest** **←←←←←←←←←←←←Documented throughout the study→→→→→→→→→→→→** **X** in end of treatment box; **X** in SFU 6 mo, SFU 12 mo, and SFU Every 12 mo boxes
Replace:	Calcium / Vitamin D: Strongly recommended to be taken daily
With:	**←←←←←←←←←←←← All subjects should be adequately supplemented with calcium and Vitamin D →→→→→→→**
Section:	Appendix A, PE, Karnofsky
Add:	**X** at 6 and12 month SFU
Section:	Appendix A, footnote 3
Replace:	All on-study reports will be collected if performed as standard of care except at end of study where this may be requested.
With:	All on-study reports **are to be attached to the subject's medical record** if performed as standard of care except at end of study where this may be requested.
Section:	Appendix A, footnote 4
Add:	Histopathology samples may be requested **during or** at end of study.
Section:	Appendix A, footnote 5
Replace:	All on-study imaging reports will be collected if performed as standard of care.
With:	All on-study imaging reports **must be attached to the subject's medical record** if performed as standard of care.
Section:	Appendix A, footnote 7
Add:	Thereafter, only a disease status and Karnofsky performance status will be collected during the treatment phase of the study **and at 6 and 12 months of** safety follow up.

Section:	Appendix A, footnote 8
Replace:	EoS
With:	**EoT**

Section:	Appendix A, footnote 11
Add:	**Adverse events of interest will be followed through the last safety follow-up visit.**

Section:	Appendix C
Replace:	Appendix D. Pregnancy Notification Worksheet
With:	**Appendix C.** Pregnancy Notification Worksheet

Section:	Appendix D
Replace:	Appendix E. Sample SAE Report Form
With:	**Appendix D.** Sample SAE Report Form **New Form**

Section:	Appendices E, F, G
Replace:	Appendix F, G, H in title
With:	Appendix **E, F, G**, respectively

Amendment 8

Protocol Title: An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Amgen Protocol Number 20062004

EudraCT# 2008-001606-16

Date:	22 April 2008
Amendment 1:	12 December 2008
Amendment 2:	22 October 2009
Amendment 2 (Superseding)	11 January 2010
Amendment 3:	14 May 2010
Amendment 4:	15 November 2010
Amendment 5:	05 May 2011
Amendment 6:	30 August 2011
Amendment 7:	15 May 2013
Amendment 8:	**17 July 2015**

Rationale:

- Safety follow-up period information was updated and adverse events of interest were listed to align the protocol language with post marketing data collection requirements and to increase compliance with long-term follow-up data requirements.
- Interim analysis 4 was removed as it is not a regulatory requirement and no study report is expected from this interim analysis per regulatory requirements.
- Pharmacy guide is obsolete and has been replaced by IPIM in Amgen protocols.
- Medical history section was updated for clarification and to align with other sections of the protocol.
- The dose escalation and stopping rules section was modified to clarify that the planned dose may be given up to 7 days before the scheduled visit, as long as there are at least 21 days between doses.
- Calcium and Vitamin D information was updated to match Xgeva product information.
- The number of birth control methods and amount of washout time required between the end of treatment and pregnancy or breastfeeding was updated to align with the informed consent and current safety information.
- Pregnancy reporting was changed from the Pregnancy Surveillance Program to Amgen Global Patient Safety as per current Amgen standard.
- Administration, typographical and formatting changes were made throughout the protocol.

Amendment 7: Rationale and Summary of Amendment Changes

An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Amgen Protocol Number 20062004

EudraCT 2008-001606-16

15 May 2013

Summary of Changes:

The primary reason for the amendment is to include pharmacokinetic analyses for an additional approximately 20 subjects, approximately 10 adolescents and 10 adults. Additionally, the end of the clinical trial is defined as when subjects enrolled through November 2012 (before Amendment 7) complete a minimum of 60 months on study, or until death or lost to follow-up, whichever comes first. Safety follow-up visits are described.

Additional changes include the following:

- Added objectives, endpoints, sample collection, and analyses consistent with the pharmacokinetic subset
- Clarified that subjects who rolled over from 20040215 will follow the 20062004 schedule under Amendment 7
- Clarified the End of Treatment visit and Safety Follow-up visits
- Added oral examinations for all subjects, and provided additional guidance regarding IP dosing and oral/dental procedures
- Clarified safety reporting timelines
- Added updated pregnancy and lactation reporting section, with additional instructions regarding counseling women of childbearing potential on the risks of pregnancy while receiving denosumab and discussing methods to decrease the risk
- Removed references to and sections pertaining to Daiichi Sankyo Co Ltd and Japanese sites, as there are no Japanese sites in this trial.
- Typographic and formatting errors, redundancies, and inconsistencies were corrected

Amendment 6: Rationale and Summary of Amendment Changes

An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Amgen Protocol Number 20062004

EudraCT 2008-001606-16

IND # BB-9838

30 August 2011

Rationale:

The primary reason for this amendment is to increase the sample size from approximately 375 subjects enrolled to approximately 500 subjects enrolled. This sample size will allow additional subjects to be enrolled onto this study allowing greater safety data to be collected in this subject population.

Additional changes include the following:

- Typographic and formatting errors, redundancies, and inconsistencies were corrected

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

Section: Global

Change: Add "Protocol Amendment 6 – 30 August 2011"

Section: Title Page:

Replace:

Key EU Sponsor Contact:	PPD, Clinical Research Study Manager, Global Study Management Amgen Ltd. Phone: PPD Fax: PPD

With:

Key EU Sponsor Contact:	PPD, Clinical Research Study Manager, Global Study Management Amgen Ltd. Phone: PPD Fax: PPD

Amendment 5: Rationale and Summary of Amendment Changes
An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Amgen Protocol Number 20062004

EudraCT 2008-001606-16

IND # BB-9838

05 May 2011

Rationale:

The primary reason for this amendment is to modify the exclusion criteria for contraception to include two methods of highly effective contraception during treatment and for 7 months after the end of treatment.

Additionally, historical and on-study imaging performed as standard of care will be requested to be sent to a central imaging vendor for evaluation of disease response.

Additional changes include the following:

- The criteria for a subject to receive re-treatment has been clarified
- The frequency of interim analyses has been modified
- Typographic and formatting errors, redundancies, and inconsistencies were corrected

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

Section: Global

Change: Add “Protocol Amendment 5 – 05 May 2011”

Amendment 4: Rationale and Summary of Amendment Changes

An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Amgen Protocol Number 20062004

EudraCT 2008-001606-16

IND # BB-9838

15 November 2010

Rationale:

The primary reason for this amendment is to increase the sample size from 250 subjects to 375 subjects. This sample size will allow additional subject to be enrolled onto this study allowing greater safety data to be collected in this subject population.

Additional changes include the following:

- The secondary Objectives have been clarified
- The analysis of safety data from the safety follow-up has been clarified in section 10.6.3
- Typographic and formatting errors, redundancies, and inconsistencies were corrected

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

Section: Global

Change: Add “Protocol Amendment 4 – 15 November 2010

Section: Global

Change: change references to “long-term” follow-up to “safety” follow-up

Section: Synopsis; Secondary Objectives:

Replace:

- evaluation of the proportion of subjects who do not require surgery in denosumab treated subjects with salvageable GCTB who would have otherwise required en bloc excision (cohort 2)

With:

- evaluation of the proportion of subjects who do not require surgery in denosumab treated subjects with salvageable GCTB (cohort 2)

Amendment 3: Rationale and Summary of Amendment Changes

An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Amgen Protocol Number 20062004

EudraCT 2008-001606-16

IND # BB-9838

14 May 2010

Rationale:

The primary reason for this amendment is to allow subjects from Amgen Study 20040215 to enroll in this study.

Additional changes include the following:

- Background section on denosumab was changed to refer to the most current version of the Investigator's Brochure

CCI [redacted]

- Typographic and formatting errors, redundancies, and inconsistencies were corrected

Amendment 2: Rationale and Summary of Amendment Changes

An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Amgen Protocol Number 20062004
EudraCT 2008-001606-16
IND # BB-9838

11 January 2010

Rationale:

The primary reason for this amendment is to increase the sample size from approximately 100 subjects enrolled to approximately 250 subjects enrolled. This sample size will allow additional subject to be enrolled onto this study allowing greater safety data to be collected in this subject population.

Additional changes include the following:

- Clarification of secondary objective and endpoint to include subjects who do not require any surgery
- Addition of exploratory endpoints
- An eligibility criteria excluding women of child-bearing potential who are evidently pregnant or breast feeding has been added
- Addition of interim analyses corresponding with the increased sample size
- The schema, glossary, and schedule of assessments have been updated to reflect changes in the protocol
- Other minor changes and typographical errors have been corrected throughout and highlighted in bold text

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

Pages: Global

Change: Add “Protocol Amendment 2 – Superseding Date: 11 January 2010 to each header

Pages: Global

Change: Case report form or CRF to **eCRF**

Pages: Global

Change: IRB to **IEC/IRB**

Amendment 1

Protocol Title:

An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Amgen Protocol Number 20062004
EudraCT 2008-001606-16
IND # BB-9838

Amendment 1 Date: **12 December 2008**

Rationale:

The primary reason for this amendment is to include skeletally mature adolescents (ie, adolescents who have closed epiphyseal plates) into this study. There have been rare reported cases of GCT of bone in adolescents. Giant Cell Tumor of bone usually occurs in skeletally mature adolescents after the epiphyseal plates have closed, and all adolescent subjects enrolled into this study will have radiological confirmation of skeletal maturity. No further long bone growth is anticipated after epiphyseal plates are closed. There are few treatment options for adolescents with mature skeletons and GCT of bone. Based on the seriousness of GCT and the limited treatment options, Amgen believes that this protocol, which includes adolescents with mature skeletons and GCT of bone, presents greater than minimal risk, but also presents the prospect of direct benefit to the subject

Additional changes include the following:

- The sample size has been clarified to include approximately 100 subjects enrolled and the supporting sample size calculations
- An eligibility criteria excluding women of child-bearing potential who are evidently pregnant or breast feeding has been added
- Extension of follow-up visit to up to 12 months from 6 months
- Other minor changes and typographical errors have been corrected throughout

Printed copy is not official record.