2. SYNOPSIS

Name of Sponsor: Amgen Inc, Thousand Oaks, California

Name of Finished Product: Not applicable

Name of Active Ingredient: Denosumab (AMG 162)

Title of Study: An Open-Label, Multicenter, Phase 2 Safety and Efficacy Study of Denosumab (AMG 162) in Subjects with Recurrent or Unresectable Giant Cell Tumor (GCT) of Bone

Investigators and Study Centers: This study was conducted at 8 study centers: 5 in the United States, 2 in Australia, and 1 in France.

Publications:

Thomas D, Chawla S, Skubitz K, Smith J, Ye Z, Jun S. Effects of denosumab in the treatment of giant cell tumor of bone: Preliminary results from an open-label phase 2 study. Presented at: Connective Tissue Oncology Society 13th Annual Meeting, November 1-3, 2007, Seattle, Washington.

Thomas D, Chawla S, Skubitz K, Staddon A, Henshaw R, Smith J, Ye Z, Sohn W, Jun S. Denosumab in the treatment of giant cell tumor of bone: Preliminary results from an open-label phase 2 study. Presented at: Skeletal Complications of Malignancy V, October 25-27, 2007, Philadelphia, Pensylvania.

Thomas D, Chawla SP, Skubitz K, Staddon AP, Henshaw R, Blay J-Y, Smith J, Ye Z, Roudier M, Jun S. Denosumab treatment of giant cell tumor of bone: Interim analysis of an open-label phase II study. *J Clin Oncol.* 2008;26 (May 20 suppl): abstr 10500.

Study Period:
This clinical study report includes data collected for the treatment period from 10 July 2006 (first subject enrolled) through 07 April 2008 and represents the primary analysis for this study. Data from subjects receiving denosumab after 07 April 2008 and from the 2-year safety follow-up will be reported separately.

Development Phase: 2

Primary Objectives

The primary objective was to evaluate response to treatment of denosumab in subjects with recurrent or unresectable GCT. Response was defined as:

- at least 90% elimination of giant cells relative to baseline, or
- complete elimination of giant cells in cases where giant cells represent < 5% of tumor cells, or
- a lack of progression of the target lesion at week 25 by radiographic measurements in cases where histopathology is not available

Secondary Objectives

The secondary objectives included the following:

- to measure serum trough levels of denosumab
- to evaluate the degree of suppression of bone turnover
- to evaluate the safety profile of denosumab
- to evaluate the incidence of serum antidenosumab antibody formation

Exploratory Objectives

The exploratory objectives included the following:

- [redacted]

Methodology:

This open-label, single-arm, phase-2 study enrolled subjects with histologically confirmed giant cell tumor of bone. All eligible subjects received 120 mg denosumab SC, starting with loading doses on study days 1, 8, 15, and 29 (week 5), followed by dosing every 4 weeks (Q4W) thereafter until complete tumor resection; disease progression; investigator's or Amgen's recommendation for discontinuation; the subject's decision to discontinue; or administration of bisphosphonates, calcitonin, or interferon alfa-2a. End of study is defined as the date of the last dose of denosumab for each subject. During the treatment period, biopsies and radiographic scans were obtained and adverse events, vital signs, and serum and urine samples for clinical laboratory parameters, bone turnover markers, pharmacokinetic analyses, and/or antidenosumab antibody assays were collected. Safety data (ie, adverse events, concomitant medications, and serum samples for antidenosumab antibody assays) will be collected every 6 months for up to 2 years after the last dose of denosumab.

This clinical study report includes data collected for all subjects through the data cut-off date and represents the primary analysis for this study. Data from subjects receiving denosumab after this date and from the 2-year safety follow-up period will be reported separately.

Number of Subjects Planned: Thirty-five subjects were planned for this study.

Number of Subjects Enrolled: Thirty-seven subjects were enrolled

Sex: 20 women, 17 men

Mean (SD, range) Age: 34 (12.3, 19 to 63) years

Ethnicity / Race: white (73% [27 subjects]), Hispanic or Latino (14% [5]), Asian (8% [3]), black (5% [2])

Diagnosis and Main Criteria for Eligibility:
Men and women, ≥ 18 years old, with histologically confirmed GCT of the bone, who have either measurable (defined as ≥ 10 mm in size at the greatest dimension) recurrent GCT confirmed by radiology, or unresectable GCT, were eligible to participate.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:
Denosumab was administered SC at doses of 120 mg Q4W with a loading dose regimen on study days 1, 8, and 15. Denosumab was provided as a sterile, clear, colorless, preservative-free liquid in glass vials. The product formulation was 60 mg denosumab per mL of [redacted] mM sodium acetate and [redacted]% sorbitol at pH [redacted]. A listing of lot numbers and the individual subjects receiving each lot number used in this study is provided in Appendix 18.

Duration of Treatment: The subjects received denosumab treatment until complete tumor resection; disease progression; investigator's or Amgen's recommendation for discontinuation; the subject's decision to discontinue; or administration of bisphosphonates, calcitonin, or interferon alfa-2a.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:
None

Study Endpoints

Primary Endpoint
The primary endpoint was the response rate among evaluable subjects.

Secondary Endpoints
The secondary endpoints included the following:

- Measurements of denosumab trough levels
- Changes in concentrations of bone turnover markers, urinary N-telopeptide corrected for urine creatinine (uNTX/Cr) and serum C-telopeptide (sCTX), compared with baseline
- Overall safety profile of denosumab characterized in terms of the type, frequency, and severity of adverse events; and laboratory abnormalities
- Incidence of serum antidenosumab antibody formation

Statistical Methods:

Frequencies and percentages are provided for all categorical variables. Continuous variables are summarized descriptively using mean, standard deviation (SD), median, and minimum and maximum values.

Efficacy analyses were performed on all evaluable subjects. Evaluable subjects were those who had a baseline histology assessment and a least 1 postdose histology assessment between study weeks 5 and 25 or a baseline radiology assessment and at least 1 postdose radiology assessment between weeks 5 and 25. Evaluable subjects were to be on study for at least 28 days after administration of the first dose of denosumab. The response rates and 95% confidence intervals (95% CI) were provided for all evaluable subjects.

A treatment response was defined for subjects who have tissue samples obtained and measured by histopathology as:

- 90% elimination of giant cells, or
- complete elimination of giant cells in cases where giant cells represent < 5% of tumor cells.

A response was defined for subjects who have only radiographs (histopathology not available) as

- a lack of progression of the target lesion at week 25 by radiographic measurements compared with baseline.

For subjects with both a core biopsy and resected tissue obtained, the sample closest to week 25 was to be used in the analysis.

Safety analyses were performed on all subjects who received at least 1 dose of denosumab. The subject incidence of each adverse event was tabulated by system organ class, preferred term, severity, seriousness, and relationship to treatment. Clinical laboratory parameters and vital signs were summarized using descriptive statistics and/or shift tables. The proportion of subjects developing antidenosumab antibodies was calculated.

Summary statistics of serum concentrations of denosumab were provided for each time point.

Summary of Results:

Subject Disposition:

Thirty-seven subjects enrolled in this study. At the data cutoff, 23 subjects were still receiving denosumab and 14 subjects had discontinued denosumab. Of the subjects who discontinued denosumab, 8 had complete resection and 6 discontinued for other reasons (including adverse events and disease progression).

Efficacy Results:

Of the 35 subjects included in the efficacy analysis set, 86% (95% CI: 69.7, 95.2) had a treatment response as defined in the protocol. Radiographic measurements of changes in longest lesion dimensions were generally consistent with the primary endpoint analysis. The response rate was consistent regardless of age or prior bisphosphonate use. Urinary NTX/Cr and serum CTX were consistently suppressed (approximately 80% below baseline) from week 5 onward. [redacted], and clinical benefit were observed with denosumab treatment.

Pharmacokinetics

Mean and median trough serum denosumab concentrations at the end of the loading dose (Week 5) were approximately 2-fold those following the first dose, indicating that the loading dose regimen increased systemic exposure to target levels as anticipated. Between Weeks 9 and 49, mean and median trough levels varied by less than 22% and 10%, respectively, thus exposures remained stable during the Q4W dosing period. This indicates that denosumab pharmacokinetics did not change with time or upon multiple dosing.

Safety Results:

All 37 enrolled subjects were included in the safety analysis set, and all available safety data up to the data cut-off date was included in the safety analysis and is described in this report. Most subjects (89%) had at least 1 adverse event. Most adverse events reported were mild to moderate in severity. The most common adverse events (reported in > 10% of the subjects) were pain in extremity (19%), back pain (11%), and headache (11%). Ten subjects (27%) had at least 1 adverse event considered by the investigator to be related to denosumab. The most common treatment-related adverse events (reported in ≥ 5% of the subjects) were diarrhea (5%), fatigue (5%), headache (5%), hypocalcemia (5%), and hypophosphatemia (5%).

Serious adverse events were reported for 5 subjects (14%). None of the serious adverse events were considered by the investigator to be related to treatment. The most common serious adverse event was dyspnea (2 subjects [5%]). One subject (3%) died during the study due to disease progression (metastasis to the lung). Three subjects had ≥ 1 serious adverse event of CTCAE grades 3, 4, or 5; these serious adverse events were back pain (grade 3), chest infection (grade 3), dyspnea (grade 3), nausea (grade 3), acute respiratory distress syndrome (grade 4), ankle fracture (grade 4), and metastasis to the lung (grade 5).

Two subjects (8%), including the 1 subject who subsequently died, were withdrawn from study because of adverse events related to disease progression (bone sarcoma and metastasis to the lung). One additional subject discontinued denosumab because of a non-serious adverse event of increased blood human chorionic gonadotropin (hCG). Two subjects (5%) had an adverse event of grade-1 hypocalcemia; both were considered by the investigator to be related to treatment and not serious. No adverse events of osteonecrosis of the jaw or new primary malignancies were reported during this study as of the data cut-off date. Infection events (ie, events coded to the Infections and Infestations system organ class) were reported for 11 subjects (30%); none of these adverse events were considered by the investigator to be related to treatment.

One subject had a serum albumin-corrected calcium concentration of 1.9 mmol/L, which was also reported as an adverse event of hypocalcemia, but was not associated with any other adverse events. No other subjects had serum albumin-corrected calcium concentrations < 2.0 mmol/L. No changes in laboratory parameters or vital signs indicative of a treatment-related effect, other than expected changes in serum calcium and phosphorus, were observed. None of the 31 subjects tested for antidenosumab antibodies were positive for the development of antidenosumab antibodies.

Conclusions:

In conclusion, denosumab demonstrated a favorable benefit-risk profile when administered to subjects with GCT. Denosumab administered to subjects with GCT elicited treatment responses, suppressed bone turnover, and was well tolerated. The results of this study indicate that further evaluation of denosumab treatment in patients with GCT is warranted.

2. SYNOPSIS

Name of Sponsor: Amgen Inc, Thousand Oaks, California

Name of Finished Product: Not applicable

Name of Active Ingredient: Denosumab (AMG 162)

Title of Study: An Open-Label, Multicenter, Phase 2 Safety and Efficacy Study of Denosumab (AMG 162) in Subjects With Recurrent or Unresectable Giant Cell Tumor (GCT) of Bone

Investigator(s) and Study Center(s): This study was conducted at 8 study centers; 5 in the United States, 2 in Australia, and 1 in France. Study centers and principal investigators are listed in Appendix 2.

Publication(s):

Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. Lancet 2010: DOI:10.1016/S1470-2045(10)70010-3.

Thomas D, Chawla S, Skubitz K, Smith J, Ye Z, Jun S. Effects of denosumab in the treatment of giant cell tumor of bone: Preliminary results from an open-label phase 2 study. Presented at: Connective Tissue Oncology Society 13th Annual Meeting, November 1-3, 2007, Seattle, Washington.

Thomas D, Chawla S, Skubitz K, et al. Denosumab in the treatment of giant cell tumor of bone: Preliminary results from an open-label phase 2 study. Presented at: Skeletal Complications of Malignancy V, October 25-27, 2007, Philadelphia, Pennsylvania.

Thomas D, Chawla SP, Skubitz K, et al. Denosumab treatment of giant cell tumor of bone: Interim analysis of an open-label phase II study. J Clin Oncol. 2008;26 (May 20 suppl): abstract 10500.

Roudier MP, Blay J-Y, Chawla S, et al. Denosumab decreases proliferation in giant cell tumor of bone. Presented at: Cancer Induced Bone Disease Annual Meeting. September 2010, Sheffield, England.

Roudier M, Jacobs I, Soriano R, et al. Histologic effects of denosumab on giant cell tumor of the bone. Presented at: Connective Tissue Oncology Society Annual Meeting. November 2009, Miami Beach, Florida.

Roudier M, Jacobs I, Soriano R, et al. Histologic effects of denosumab on giant cell tumor of the bone. Presented at: 3rd International Conference on Osteoimmunology: Interactions of the Immune and Skeletal Systems, June 2010, Santorini, Greece.

Roudier M, Jacobs I, Soriano R, et al. Histologic effects of denosumab on giant cell tumor of the bone. Presented at: Cancer Induced Bone Disease Annual Meeting. November, 2009, Arlington, Virginia.

Study Period: This clinical study report includes additional data after 07 April 2008, the cutoff date for the primary analysis, until the last subject completed the study, 16 November 2010.

Development Phase: 2

Introduction and Objectives:

Giant Cell Tumor (GCT) of bone is a rare, aggressive tumor that presents as an eccentric osteolytic lesion, usually in the epiphysis of long bones, with nearly 50% of cases occurring in the region of the knee (Szendroi et al, 2003; Szendroi, 2004). These tumors typically occur in skeletally mature individuals between the ages of 20 and 50 years, with a male to female ratio of 1:1.5 (Zheng et al, 2001). Surgery is the definitive therapy, with recurrence rates ranging from 10% to 75% (Malawer et al, 2008). Treatment options that can reduce the need for morbid surgical procedures, treat giant cell tumors in patients who cannot have surgery, and improve clinical outcomes are greatly needed for patients with GCT. Currently, no pharmaceutical agents

are approved specifically for the treatment of GCT. Bisphosphonates are under investigation in this population; however, only limited preclinical and clinical data are available and none of these agents are indicated for the use in the treatment of GCT (Cheng et al 2004). Recurrence of GCT is not necessarily fatal; however, further treatment of the recurrent lesions leads to repeated and radical resections (Szendroi, 2004). Patients may undergo amputations or surgery that involves the loss of the affected joints, leading to poor quality of life, continued bone loss, and secondary arthritis. Similarly, unresectable GCT leads to the progression of osteolytic lesions with bone loss, bone pain, and in many cases, death.

Giant cell tumors secrete and are dependent upon RANK ligand (RANKL) for growth (Szendroi et al, 2003; Szendroi, 2004). RANKL is the key mediator of osteoclast differentiation and maturation, and excessive secretion of RANKL causes an imbalance in bone remodeling in favor of bone breakdown (Burgess et al, 1999; Lacey et al, 1998; Yasuda et al, 1998). Excessive RANKL has been implicated in bone diseases associated with increased bone resorption. Denosumab is a fully human monoclonal antibody with a high affinity (K_d 3 x 10^{-12} M). This binding prevents the activation of RANK and inhibits the formation, activation, and survival of osteoclasts, the result of which is a reduction in the number and function of osteoclasts and, consequently, a decrease in bone resorption. Denosumab has a high specificity for RANKL and does not cross-react with other members of the tumor necrosis factor (TNF) family, including TNFα, TNFβ, TNF-related apoptosis-inducing ligand, or CD40 ligand (Elliott et al, 2006).

The primary objective of this study was to evaluate response to treatment with denosumab in subjects with recurrent or unresectable GCT, with response defined as at least 90% elimination of giant cells relative to baseline, complete elimination of giant cells in cases where giant cells represent < 5% of tumor cells, or a lack of progression of the target lesion at week 25 by radiographic measurements in cases where histopathology is not available. The secondary objectives were to measure serum trough levels of denosumab, to evaluate the degree of suppression of bone turnover, to evaluate the safety profile of denosumab, and to evaluate the incidence of serum anti-denosumab antibody formation. These objectives and exploratory objectives were fully described in the primary analysis report, dated 02 April 2009.

This report includes safety data for the entire on-study phase and follow-up phase of the study. No efficacy data are included in this report.

Methodology:

This open-label, single treatment group, phase 2 study enrolled subjects with histologically confirmed giant cell tumor of bone. All eligible subjects received 120 mg denosumab subcutaneously (SC) every 4 weeks (Q4W) starting with study day 1, with additional doses on study days 8 and 15, until complete tumor resection; disease progression; investigator's or Amgen's recommendation for discontinuation; the subject's decision to discontinue; administration of bisphosphonates, calcitonin, or interferon alfa-2a; or rollover to study 20062004. End of study is defined as the date of the last dose of denosumab for each subject. During the treatment period, biopsies and radiographic scans were obtained, adverse events and vital signs were recorded, and serum and urine samples were collected for clinical laboratory parameters, bone turnover markers, pharmacokinetic analyses, and anti-denosumab antibody assays. After the last dose of denosumab, safety data were collected every 6 months for up to 2 years. After 16 November 2010, all subjects on study or in the follow-up were enrolled to Amgen study 20062004.

This clinical study report includes additional data collected after the data cut-off date (07 April 2008) for the primary analysis through to the end of the 2 year safety follow-up period or rollover to study 20062004, whichever occurred first.

Number of Subjects Planned: Thirty-five subjects were planned for this study.

Number of Subjects Enrolled: Thirty-seven subjects were enrolled.

Sex: 20 women, 17 men

Age (mean [SD, range]): 34 (12.3, 19 to 63) years

Ethnicity / Race: white 73% (27 subjects), Hispanic or Latino 14% (5 subjects), Asian 8% (3 subjects), black 5% (2 subjects)

Diagnosis and Main Criteria for Eligibility:
Men and women, ≥ 18 years old, with histologically confirmed GCT of the bone, who had either measurable (defined as ≥ 10 mm in size at the greatest dimension) recurrent GCT confirmed by radiology, or unresectable GCT, were eligible to participate.

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number:
Denosumab was administered SC at doses of 120 mg Q4W starting with study day 1, with additional doses on study days 8 and 15. Denosumab was provided as a sterile, clear, colorless, preservative-free liquid in glass vials. The product formulation was 60 mg denosumab per mL of [redacted] mM sodium acetate and [redacted]% sorbitol at pH [redacted]. A listing of lot numbers and the individual subjects receiving each lot number used in this study is provided in Appendix 6.

Duration of Treatment: The subjects received denosumab treatment until complete tumor resection; disease progression; investigator's or Amgen's recommendation for discontinuation; the subject's decision to discontinue; administration of bisphosphonates, calcitonin, or interferon alfa-2a; or rollover to study 20062004.

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number:
None

Study Endpoints

This report summarizes pharmacokinetic, antibody, histopathology, and safety results for the entire on-study phase and the safety follow-up phase. Results of the primary analysis were reported previously (clinical study report dated 02 April 2009).

Statistical Methods:

Frequencies and percentages are provided for all categorical variables. Continuous variables are summarized descriptively using mean, standard deviation (SD), median, and minimum and maximum values.

Safety analyses were performed on all subjects who received at least 1 dose of denosumab. The subject incidence of each adverse event was tabulated by system organ class, preferred term, severity, seriousness, and relationship to treatment. Clinical laboratory parameters and vital signs were summarized using descriptive statistics and/or shift tables. The proportion of subjects developing antidenosumab antibodies was calculated.

Summary statistics of serum concentrations of denosumab were provided for each time point.

Summary of Results:

Subject Disposition:

Thirty-seven subjects enrolled in this study, and all subjects received at least one dose of denosumab. As of 16 November 2010, all subjects who were in either the on-study phase or the follow-up phase of the study rolled over to study 20062004.

During the on-study phase, 10 of 37 subjects (27%) discontinued the study due to complete resection, 12 subjects (32.4%) discontinued due to rollover to study 20062004, and 15 subjects (40.5%) discontinued for additional reasons: 3 subjects (8.1%) due to disease progression, 2 subjects (5.4%) due to adverse events, 2 subjects (5.4%) due to consent withdrawn, 2 subjects (5.4%) due to noncompliance, 1 subject (2.7%) due to an administrative decision, 1 subject (2.7%) due to a requirement for alternative therapy, and 4 (10.8%) due to other reasons. Ten subjects completed investigational product (IP): 26 subjects discontinued IP, 12 due to rollover to study 20062004, 3 due to disease progression, 1 due to adverse event, and 10 due to other reasons. The end of IP status was unknown for 1 subject due to site closure.

Sixteen subjects (43.2%) did not participate in the safety follow-up phase: 12 (32.4%) were still receiving investigational product and rolled over to study 20062004 and 4 (10.8%) discontinued due to withdrawing consent, noncompliance, or adverse event.

Twenty-one subjects (56.8%) participated in the safety follow-up phase. Two subjects (5.4%) completed the 2-year follow-up phase and 19 subjects (51.4%) discontinued the follow-up phase: 6 (16.2%) due to death, 6 (16.2%) due to rollover to study 20062004, 5 (13.5%) due to lost to follow-up, 1 (2.7%) due to consent withdrawn, and 1 (2.7%) due to patient compliance issues.

Pharmacokinetics Results:

Mean and median trough serum denosumab concentrations at the end of the loading dose (Week 5) were approximately 2 fold greater than those following the first dose, indicating that the loading dose regimen increased systemic exposure to target levels as anticipated. Between Weeks 9 and 49, median trough levels varied by less than 9%; thus exposures remained stable during the Q4W dosing period. This indicates that denosumab pharmacokinetics did not change with time or upon multiple dosing. These results are consistent with the pharmacokinetic analyses reported in the primary analysis report dated 02 April 2009.

Safety Results:

Most subjects had at least 1 adverse event during the on-study phase (89.2%) and during the safety follow-up phase (57.1%). Most adverse events were mild to moderate in severity. The most common adverse events reported during the on-study phase were arthralgia (29.7%), back pain (29.7%), and pain in extremity (24.3%). The most common adverse events during the safety follow-up phase were muscular weakness (14.3%), anemia (9.5%), arthralgia (9.5%), and nausea (9.5%).

Twelve subjects (32.4%) had at least 1 adverse event considered by the investigator to be related to denosumab during the on-study phase, and 1 subject (4.8%) had at least 1 adverse event considered related to denosumab during the follow-up phase. The most common treatment related adverse events (reported in ≥ 5% of the subjects) during the on-study phase were fatigue (10.8%), diarrhea (5.4%), headache (5.4%), and nausea (5.4%).

Serious adverse events were reported for 9 subjects (24.3%) during the on-study phase and for 6 subjects (28.6%) during the safety follow-up phase. None of the serious adverse events during the on-study phase and 1 serious adverse event during the follow-up phase were considered by the investigator to be related to treatment. Dyspnea and nausea were the only serious adverse events that were reported in more than 1 subject. Both dyspnea and nausea were reported in 1 subject each during both the on-study phase and the follow up safety phase.

One subject died due to malignant neoplasm progression that began during the on-study phase, and 5 subjects died during the follow up safety phase, 1 each due to cardiac failure congestive, disease progression, metastases to lung, ventricular tachycardia, and metastasis.

Two subjects (5.4%) discontinued during the on-study phase because of adverse events (1 subject due to metastases to the lung, considered unrelated to treatment, and 1 subject due to osteonecrosis of the jaw, considered related to treatment). During the safety follow-up period, 2 subjects (9.5%) discontinued due to adverse events (1 subject due to disease progression and 1 subject due to metastases to the lung, both considered unrelated to denosumab treatment). A fifth subject discontinued denosumab treatment due to a non-serious event of pathological fracture, but remained in the study for follow-up.

There were no adverse events of hypocalcemia during the on-study phase or during the safety follow-up period. Twenty-one subjects had infection adverse events during the on-study phase and 2 subjects had infection adverse events during the safety follow-up phase. None of these infection adverse events were considered by the investigator to be related to treatment. One adverse event of adjudicated-positive osteonecrosis of the jaw was reported during the on-study phase and was considered related to treatment. No new primary malignancies were reported during the on-study or follow-up phases.

No changes in laboratory parameters were observed other than expected changes in serum calcium and phosphorus. No changes indicative of a treatment-related effect in vital signs were observed. No subject tested had a sample that was positive for anti-denosumab antibodies.

Conclusions:

Denosumab pharmacokinetics did not change with time or multiple dosing.

No subject had samples that were positive for binding antidenosumab antibodies.

On-study samples from subjects treated with denosumab showed a marked reduction in tumor giant cells.

The observed rates of adverse events in this population of subjects with GCT of bone treated with denosumab were consistent with what might be expected in this population in the absence of denosumab treatment. Few serious adverse events were considered related to treatment.