FDA ODAC Briefing Document

February 8, 2012

BLA 125320/28
Denosumab (Xgeva™)
Amgen Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions on the determination of whether denosumab has demonstrated a clinically meaningful effect with a favorable risk-benefit profile in men with castrate resistant prostate cancer at high risk of bone metastasis. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

1 EXECUTIVE SUMMARY 2
2 BACKGROUND 4
2.1 Non-Metastatic Castration-Resistant Prostate Cancer: Incidence and Treatment Approaches Employed in the Community 6
2.2 September 14, 2011 Oncology Drugs Advisory Committee Meeting 7
2.3 Primary Issues Related to this Application 7
3 OVERVIEW OF STUDY 20050147 9
3.1 Study Design 9
3.2 Summary Results (Efficacy) 10
3.3 Summary Results (Safety) 13
4 SUMMARY 15
5 APPENDIX: FDA ANALYSES (K-M CURVES) 17
6 REFERENCES 20

Table of Tables

Table 1 Demographics 10
Table 2 Baseline Characteristics 11
Table 3 Trial 20050147: Efficacy Results 12
Table 4 PFS Analysis 13
Table 5 PRO BPI-SF: Worsening Pain Summary Results 13
Table 6 Trial 20050147: Overall Safety 15
Table 7 Trial 20050147: Treatment Emergent Adverse Events (all Grades)* 15

Table of Figures

Figure 1 Kaplan-Meier Curve for BMFS 17
Figure 2 Kaplan-Meier Curve for Time to 1st Bone Metastasis 18
Figure 3 Kaplan-Meier Curve for Overall Survival 19
Figure 4 Kaplan-Meier Curve for PFS 20

1 EXECUTIVE SUMMARY

Amgen, Inc. submitted an efficacy supplement to the Biologics License Application (BLA) for Xgeva (denosumab), STN BL 125320/28, to support the following proposed indication: "Xgeva is indicated for the treatment of men with castrate-resistant prostate cancer at high risk of developing bone metastases. Xgeva prolongs bone metastasis-free survival by reducing the risk of developing bone metastases."

This sBLA is primarily supported by the results of Study 20050147, a randomized, double-blind, placebo-controlled trial in 1,432 men with castrate-resistant prostate cancer (CRPC) considered at high risk for bone metastases. Importantly, patients were not required to have no evidence of disease (NED). Patients with locally progressive disease

were eligible, as were patients with metastases to any lymph node. In Study 20050147, a total of 55% of patients received no prior local treatment for prostate cancer.

FDA met with Amgen regarding Study 20050147 (as well as two other studies that constituted the majority of the discussion during the meeting) on September 20, 2005. During the meeting, FDA stated that the overall study design was acceptable; however, FDA stated that *overall survival, patterns of metastases, and the development of symptomatic metastases will be important review issues.* The study was not conducted under a Special Protocol Assessment (SPA) agreement.

Eligibility criteria required that patients meet at least one of two criteria (PSA level ≥ 8 ng/mL or PSA doubling time ≤ 10 months) to be considered at high risk for development of bone metastasis. Patients were randomized to receive 120 mg Xgeva subcutaneously every 4 weeks or placebo subcutaneously every 4 weeks. This dose and schedule is the same as that approved for denosumab for the prevention of skeletal related events (SREs) in patients with solid tumors metastatic to bone. The primary endpoint was bone metastasis-free survival (BMFS) and secondary endpoints were time to first bone metastasis and overall survival.

The final analysis of Study 20050147 demonstrated a median BMFS of 29.5 months (95% CI: 25.4, 33.3) for the denosumab arm and 25.2 months (95% CI: 22.2, 29.5) for the placebo arm, with a hazard ratio of 0.85 (95% CI: 0.73, 0.98; p = 0.028). The median time to first bone metastasis was 33.2 months (95% CI: 29.0, 37.3) for the denosumab arm and 29.5 months (95% CI: 22.4, 33.1) for the placebo arm, with a hazard ratio of 0.84 (95% CI: 0.71, 0.98; p = 0.032). Median survival was 43.9 months (95% CI: 40.1, NE) for the denosumab arm and 44.8 months (95% CI: 40.0, NE) for placebo, with a hazard ratio of 1.01 (95% CI: 0.85, 1.20; p = 0.91).

Treatment with denosumab did not result in an improvement in overall survival or progression-free survival. A *post-hoc* exploratory analysis of time to symptomatic bone metastasis, which may be considered a more relevant measure of clinical benefit in this setting, is of limited value due to missing data since most patients were not followed until they experienced the first symptomatic metastasis. Exploratory endpoints included patient-reported outcomes, changes in pain intensity, and health-related-quality-of-life (HRQOL); analyses of these endpoints demonstrated results that were either similar between treatment arms or were inconclusive (i.e., different analyses provided contradictory results).

The overall per-patient incidence of osteonecrosis of the jaw (ONJ) in the denosumab group of approximately 5% is an important risk-benefit consideration in patients with few if any cancer-related symptoms at baseline. The incidence of ONJ among denosumab-treated patients was higher and duration of exposure longer than observed in trials supporting the approved indication of prevention of SREs in patients with solid tumors metastatic to bone. Furthermore, the cumulative risk of ONJ for a patient who would

receive denosumab across the continuum of prostate cancer disease states (as defined by the existing indications in addition to that which is currently proposed) is unknown.

FDA requests that the ODAC discuss whether clinical benefit has been demonstrated in this application and to provide their determination on the balance of benefit versus risks. Study 20050147 was a well conducted, double-blind, placebo-controlled trial. Though the study met the pre-specified primary endpoint, with a statistically significant prolongation in BMFS, it is unclear whether an improvement in median BMFS by 4.2 months alone in patients with CRPC at high risk for bone metastases is an adequate measure of clinical benefit. Also unclear is whether the magnitude of the BMFS improvement is meaningful when considered in the context *that denosumab is approved as Xgeva for the prevention of skeletal related events in patients with solid tumors metastatic to bone.* In other words, does early treatment (in the CRPC setting) add to the benefit provided to patients when denosumab is administered in the metastatic setting (i.e., preventing SREs in patients with solid tumors metastatic to bone)? The editorial (Logothetis, 2011) in the Lancet regarding Study 20050147 independently raised the same issues regarding whether to administer denosumab as a preventive drug for bone metastases versus treating at the time of the development of an osseous metastasis. Based on the results of the study, the editorial stated that "the reported findings support its use as an alternative to zoledronic acid, but do not support its broad use as a preventive agent for bone metastases in prostate cancer."

2 BACKGROUND

Denosumab is a monoclonal human IgG2 antibody that binds to human RANKL. The RANK/RANKL (receptor activator for nuclear factor κ B ligand) pathway is involved in the formation, function, and survival of osteoclasts, which are responsible for bone resorption.

FDA approved denosumab under the proprietary name Xgeva (STN 125320/7) on November 18, 2010 for the prevention of skeletal-related events in patients with solid tumors metastatic to bone (including prostate cancer). Prior to this action, FDA approved denosumab under the proprietary name Prolia (STN 125320/0) on June 1, 2010 for the treatment of postmenopausal women with osteoporosis at high risk for fracture. Prolia is also *specifically* approved as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer (STN 125320/6 approved on September 16, 2011).

The recommended dose and schedule of Xgeva is 120 mg every four weeks. The recommended dose and schedule of Prolia is 60 mg every six months. Likely, based on the higher dose intensity, denosumab when administered in accordance with Xgeva labeling confers a higher risk of osteonecrosis of the jaw and of hypocalcemia. In this application, Amgen proposes that denosumab (under the proprietary name Xgeva) be indicated for the treatment of men with castrate-resistant prostate cancer (CRPC) at high risk of developing bone metastases.

Amgen met with FDA for a pre-Phase 3 meeting on September 20, 2005 to discuss the design of three proposed randomized double-blind trials:

- 20050103: "A Randomized, Double Blind, Double Dummy, Multicenter Study of Denosumab Compared with Zoledronic Acid in the Treatment of Bone Metastases in Men with Hormone Refractory Prostate Cancer"
- 20050136 "A Randomized, Double Blind, Double Dummy, Multicenter Study of Denosumab Compared with Zoledronic Acid in the Treatment of Bone Metastases in Advanced Breast Cancer"
- 20050147 "A Randomized, Double Blind, Placebo Controlled, Multicenter Phase 3 Study of Denosumab on Prolonging Bone Metastases-Free Survival in Men with Hormone Refractory Prostate Cancer"

The majority of Amgen's questions to the Agency during the meeting referred to Trials 20050103 and 20050136; these trials provided the data supporting the approved indication for prevention of skeletal-related events. One question posed during this meeting referred to Trial 20050147: "Does the Agency agree that the proposed study and statistical approach is sufficient to obtain an indication for the prolongation on bone metastasis free survival in patients with hormone refractory prostate cancer at high risk for developing bone metastases?"

In response, the Agency stated the following:

- The study design is acceptable. *Overall survival, patterns of metastases, and the development of symptomatic metastases will be important review issues.*
- Results from 20040138 and 20050103 should be consistent with findings in the proposed trial.
- FDA suggests that the clinical protocols provide a detailed description of the approach assessment of new lesions on bone scan; the protocols should specify the hierarchy of studies (X-ray then CT/MRI if non-diagnostic) that will be used to "confirm" the presence of metastatic disease seen on bone scan.
- Given the complex eligibility and stratification factors, FDA requests a description of the proposed plans to monitor study sites for adherence to entry criteria and accuracy of stratification factors in randomization of eligible patients.

Amgen stated during the meeting that timely availability of a CT/MRI may be difficult at some non-U.S. sites and proposed a repeat X-ray instead. Amgen predicted that 20% or fewer events would be confirmed by X-ray in lieu of a CT or MRI. FDA stated such an approach may be acceptable; however FDA urged Amgen to select sites with CT/MRI capabilities.

Amgen subsequently met with the Agency for a Type B pre-BLA meeting on April 5, 2011 to discuss the results of Trial 20050147 and the content of a planned efficacy

supplement supported primarily by this trial. During the meeting, FDA stated that the proposed data from Trial 20050147 supported by Trials 20050103 and 20040138 (a Prolia trial) are adequate to support a sBLA submission; however, FDA stated that the risk-benefit profile of denosumab in the proposed disease setting will be a review issue. FDA informed Amgen that the Agency may request input regarding risk-benefit decisions from an advisory committee.

2.1 Non-Metastatic Castration-Resistant Prostate Cancer: Incidence and Treatment Approaches Employed in the Community

In the United States, approximately 220,000 men are diagnosed with prostate cancer each year. Since the development of serum prostate specific antigen (PSA) testing, most U.S. men are found to have localized prostate cancer at the time of diagnosis. Approximately 15-40% of men will go on to have recurrent disease following an attempt at curative therapy, with the initial presentation of recurrence most frequently evidenced by an increase in serum PSA in the absence of metastases (Pound et al., 1999; Makarov et al., 2008; Donovan et al., 2008).

The PSA-only recurrence of prostate cancer may last for many years in some patients before metastases become clinically evident or are detected with radiographic scans used in routine clinical practice. Because of age, long lag-time, and co-morbid conditions, not all men with PSA-only recurrence develop radiographically-detectable metastatic prostate cancer prior to their death from other causes. In observational studies, patients with PSA-only recurrence of prostate cancer after radical prostatectomy can experience a median time from PSA recurrence to metastasis of 8-10 years (Pound et al., 1999; Antonarakis et al., 2011). Nevertheless, some men are at higher risk for more rapid progression to overt metastases and this interval may be predicted by prognostic factors such as tumor Gleason score, PSA doubling time, and time from surgery to biochemical recurrence.

Practice patterns for treatment of PSA-only recurrence of prostate cancer can vary across the U.S. and may depend upon the perceived risk of future metastases and patient choice regarding benefits of androgen deprivation therapy compared to the side effects of treatment. Active surveillance is an accepted option for some low-risk patients or those with significant co-morbidities. For patients with PSA-only recurrence and prognostic factors or laboratory findings suggestive of more aggressive disease, treatment options employed in the medical community include local salvage therapy (if appropriate) and androgen deprivation therapy (ADT). While most patients exhibit an initial decrease in PSA following ADT, the duration of this effect varies and the majority of patients experience recurrent, sustained increases in PSA despite castrate levels of testosterone. This clinical state of progression despite medical or surgical castration has been termed castration-resistant prostate cancer (CRPC).

Non-metastatic CRPC (NM-CRPC) refers to a disease setting characterized by recurrent PSA increases in the absence of radiographic or clinical evidence of metastases despite castrate-levels of testosterone. Data from the placebo-control arm of a randomized clinical trial terminated early suggested that patients with NM-CRPC have an estimated

median bone metastasis free survival of 30 months and that at 2 years, 33% of patients had developed at least one bone metastasis while 21% had died (Smith et al., 2005). Given the aforementioned prolonged natural history in non-metastatic prostate cancer patients, prolonged treatment of NM-CRPC must take into account an agent's toxicity.

2.2 September 14, 2011 Oncology Drugs Advisory Committee Meeting

The Oncologic Drugs Advisory Committee (ODAC) convened on September 14, 2011 to discuss issues related to the development of drugs for the treatment of patients with non-metastatic castration-resistant prostate cancer (CRPC). Review staff asked the committee to provide advice regarding appropriate trial designs, specific populations, and endpoints for drugs intended to be administered as a treatment for non-metastatic CRPC. The Agency did not ask the committee to provide advice on specific drug development programs or pending applications.

During the meeting, AC members expressed differing opinions on what constituted clinical benefit for patients with NM-CRPC and who should be enrolled on clinical trials. Some members felt that overall survival (OS) was the appropriate endpoint. However, other members felt that either progression free survival (PFS) or bone metastases free survival (BMFS) would be appropriate endpoints to represent benefit due to issues regarding feasibility of the OS endpoint or because metastases in prostate cancer patients can cause symptoms. Nevertheless, some AC members who indicated acceptance of these endpoints stated that the effect should be of sufficient magnitude to represent benefit (e.g., some members expressed that the effect should be greater than 6 months improvement, and other members suggested that the effect should be at least one year).

2.3 Primary Issues Related to this Application

The primary issues related to this application include the following:

1. Does improvement in bone metastasis free survival (BMFS) represent either a direct clinical benefit or a surrogate for clinical benefit?

The use of an improvement in BMFS as the basis for drug approval or new labeling claims for treatment of patients with CRPC would constitute a new regulatory precedent for demonstration of clinical benefit or surrogates for benefit in this disease setting. In this application, Amgen discussed the potential relevance of this endpoint in predicting clinical benefit, stating that bone metastases are often a sentinel metastatic event in the natural history of men with CRPC and that bone metastases can result in serious complications (e.g., SREs and pain) and an increased risk of death.

Available data with denosumab do not support a conclusion that BMFS is a surrogate endpoint for OS based on the following:

- Absence of denosumab treatment effect on OS in two large trials conducted in men with prostate cancer [a total of 501 OS events in Trial 20050147 and a total of 935 total OS events in Trial 20050103 (versus zoledronic acid in men with skeletal metastases)];

- Absence of denosumab treatment effects on PFS in the same two trials; and
- No improvement in PSA over time versus placebo in Trial 20050147.

The second potential argument for the use of BMFS as a surrogate endpoint in this setting is that preventing metastases to the bone could result in the prevention of skeletal morbidity. Ultimately, an application with BMFS as a primary endpoint would be strengthened by findings that also demonstrate an improvement in the time to SREs or a substantial improvement in quality of life (especially related to clinically relevant pain scores).

2. Can bone metastasis free survival, at the magnitude demonstrated in this clinical trial, be considered an endpoint that represents a clinical benefit or a surrogate for clinical benefit in the context of the currently approved indications for denosumab?

As previously stated, FDA approved Xgeva for the prevention of skeletal related events (SREs) in patients with solid tumors metastatic to bone (including prostate cancer). In patients with metastatic prostate cancer (Trial 20050103), Xgeva delayed the time to first on-study SRE by a median of 3.6 months compared to zoledronic acid [time to first on-study SRE HR = 0.82 (95% CI: 0.71, 0.95)]. What cannot be answered by the results of Trial 20050147 is whether the administration of denosumab *prior* to the development of osseous metastases would add to the clinical benefit *already* established for denosumab in patients with metastatic disease (i.e., prevention of SREs). Such a question could only be answered by comparing the clinical benefits of a treatment approach of continuous denosumab (i.e., from the onset of PSA-recurrence on ADT until the first SRE) administered to patients with CRPC at high risk for bone metastases with the benefits of denosumab administered only after an osseous metastasis is identified (currently approved indication). In such a trial, the proper endpoint would be an endpoint designed to assess a meaningful clinical benefit (e.g., prevention of SREs). If denosumab administered to patients with CRPC (at high risk for bone metastases) does not add to the benefit observed in patients who have metastatic disease, then patients will only be exposed to the increased risks of the drug (i.e., ONJ).

3. If BMFS can be considered a meaningful benefit, is the magnitude of BMFS observed in Trial 20050147 sufficient to conclude a favorable risk-benefit profile when denosumab is administered to patients with CRPC at high risk for bone metastases.

The magnitude of BMFS observed in Trial 20050147 expressed through the hazard ratio of 0.85 (95% CI: 0.73, 0.98) and the improvement in median BMFS of 4.2 months compared to placebo is a smaller treatment effect than that proposed by some members of the September 2011 ODAC as sufficient evidence of benefit for a drug intended to treat patients with NM-CRPC. Additionally, this treatment effect must be taken into context with an approximate 5% per-patient incidence rate of osteonecrosis of the jaw (i.e., ~ 1 in 20 patients experienced ONJ). This ONJ rate may differ for patients exposed to denosumab outside the context of a clinical trial. Additionally, because denosumab is

approved for patients with skeletal metastases to prevent SREs, the risk of ONJ may increase even further with continued exposure to denosumab after metastatic progression.

3 OVERVIEW OF STUDY 20050147

3.1 Study Design

Study 20050147 was a randomized (1:1), double-blind, placebo-controlled, multicenter study that compared the effects of denosumab versus placebo on prolonging bone metastasis-free survival in men with CRPC at high risk for bone metastasis. Patients who met either criterion (PSA level ≥ 8 ng/mL or PSA doubling time ≤ 10 months) were considered at high risk for development of bone metastasis. Eligibility criteria also included the following:

- No prior or current evidence of radiographically-detectable bone metastases;
- Serum testosterone levels less than 50 ng/mL;
- Bilateral orchidectomy at least 6 months prior to randomization or continuous androgen-deprivation therapy with a GnRH agonist (ADT) or antagonist for at least 6 months prior to randomization;
- Three rising consecutive PSA values (each at least 2 weeks apart);
- No current or prior IV bisphosphonate; and
- No current or prior oral bisphosphonate administered for ≥ 3 years continuously. Patients could have received oral bisphosphonates for more than 3 months but less than 3 years if the subject underwent a one year washout period before randomization.

The study randomized patients to receive 120 mg Xgeva subcutaneously every 4 weeks or placebo subcutaneously every 4 weeks. Randomization was stratified based on PSA criteria [PSA level ≥ 8 ng/mL *and* PSA doubling time ≤ 10 months (yes/no)] and previous or current chemotherapy for prostate cancer (yes/no).

The primary endpoint was bone metastasis-free survival (BMFS), defined as time to first occurrence of bone metastasis or death from any cause, and secondary endpoints (tested sequentially if the previous endpoint was statistically significant) were time to first bone metastasis (symptomatic or asymptomatic) and overall survival. Exploratory endpoints included changes in patient-reported outcomes (PRO), proportion of patients developing symptomatic bone metastasis, prostate cancer progression at any site, and PFS (the later two endpoints were added in an October 30, 2009 amendment to the protocol). PRO assessments were collected every 8 weeks, though the primary analyses of PRO data were conducted on data collected through week 65 only.

Amgen described the following analysis phases of Trial 20050147 in the application:

- Primary blinded treatment phase: this phase was planned to continue until the total number of events for the primary efficacy analysis had been reached (planned 660 events)
- Extended blinded treatment phase: patients continued to receive blinded investigational product until the primary safety and efficacy analyses were completed
- Open-label extended treatment phase: after the results were analyzed, patients (in both arms) were offered open-label denosumab until they developed bone metastases, until denosumab became commercially available in this setting, or for up to three years.

Absence of bone metastasis at baseline and the incidence of metastasis during the study were confirmed by a blinded central radiology reading facility. Protocol-specified baseline imaging for detection of bone metastasis included bone scan and skeletal survey. On study, bone scans were performed every 16 weeks to detect bone metastases. If the central reader identified any change on bone scan, the protocol required that an X-ray, CT, or MRI scan of the area in question to be obtained [prior to Amendment #1 (June 8, 2007), an X-ray was to initially be ordered after an abnormal bone scan followed by a CT or MRI if the X-ray was inconclusive]. If only an X-ray was obtained and the results of the X-ray were inconclusive, the protocol required additional imaging with CT or MRI of the affected area. Upon central confirmation of bone metastasis, patients were withdrawn from treatment and entered a follow-up phase of the study. Follow-up survival data was collected every 6 months for up to 3 years after the last dose of blinded investigational product.

3.2 Summary Results (Efficacy)

Demographic and baseline characteristics in the intent-to-treat (ITT) population were balanced between treatment arms (refer to Tables 1 and 2). The median age was 74 years, 84.5% of patients were White, 48% had both a PSA level ≥ 8 ng/mL *and* a PSA doubling time ≤ 10 months, and 8% received previous or current chemotherapy for prostate cancer. As previously stated, patients with locally progressive disease were eligible, as were patients with metastases to any lymph node. A total of 12.6% of patients across both arms were considered to have current lymphatic metastases.

Table 1 Demographics

	Denosumab N (%)	**Placebo** N (%)
Randomized	716	716
Race		
White	606 (84.6)	604 (84.4)
Non-White	108 (15.4)	112 (15.6)
Black	41 (5.7)	35 (4.9)
Age		
< 65	118 (16.5)	116 (16.2)
≥ 65	598 (83.5)	600 (83.8)

	Denosumab N (%)	Placebo N (%)
Region		
Europe	299 (41.8)	309 (43.2)
Latin America	92 (12.8)	111 (15.5)
North American	228 (31.8)	237 (33.1)

Table 2 shows that most patients were ECOG 0 at baseline. Not shown in the table is that 55% of patients received no prior local treatment for prostate cancer. A total of 28.4% received radiotherapy, 7.1% surgery, and 9.5% both surgery and radiotherapy as local therapy. A total of 2% of patients in the denosumab group and 1.3% in the placebo group received prior oral bisphosphonate drugs. The most common drugs administered as on-study anti-neoplastic therapy included bicalutamide, leuprorelin acetate, and goserelin. A total of 11% of patients received docetaxel across both arms (10.3% for placebo and 12.2% for denosumab).

Table 2 Baseline Characteristics

	Denosumab N (%)	Placebo N (%)
ECOG Status at Baseline		
0	505 (70.5)	514 (71.8)
1	210 (29.3)	199 (27.8)
2	1 (0.1)	3 (0.4)
Stratum: PSA ≥ 8 ng/mL & Doubling time ≤ 10 Months*		
No	370 (51.7)	370 (51.7)
Yes	346 (48.3)	346 (48.3)
Stratum: Prior/Current Chemo*		
No	661 (92.3)	661 (92.3)
Yes	55 (7.7)	55 (7.7)

*Stratification per randomization

Efficacy results are shown in the following tables and in the Kaplan-Meier curves that are presented in the Appendix of this document. The median number of doses administered (primary analysis phase) was 20 for Xgeva and 19 for placebo. Overall, efficacy results were consistent across subgroups. As shown in Table 3 and Figure 1 below, Study 20050147 showed a statistically significant improvement in BMFS in the denosumab arm, with a hazard ratio of 0.85 (95% CI: 0.73, 0.98) corresponding to a median difference of 4.2 months. The primary issue of this ODAC is whether BMFS of this magnitude represents clinical benefit, especially in context with the toxicities of therapy and the benefit already observed in patients diagnosed with bone metastases.

Amgen reported that fewer subjects in the denosumab arm developed symptomatic bone metastases compared to the placebo group [9.6% (n=69) versus 13.4% (n=96)]; however, the vast majority of patients initially experienced asymptomatic bony metastases. The Agency does not agree that Amgen's analyses of time to first symptomatic metastasis and time to multiple metastases can be supportive of the overall results because these

analyses were ad hoc exploratory analyses, and patients did not undergo systematic assessments for these endpoints after experiencing an initial (asymptomatic) BMFS event.

Overall survival was similar between treatment arms with a hazard ratio of 1.01 (95% CI: 0.85, 1.20; p = 0.91), with 251 events in the denosumab arm and 250 with placebo (also see Figure 3 below).

This lack of an improvement on OS was also demonstrated in Study 20050103. As described above, Study 20050103 was a large randomized study (n=1,901) that evaluated Xgeva (same dose and schedule) versus zoledronic acid in patients with skeletal metastases from prostate cancer. The primary endpoint was time to first on-study SRE and the study (in-part) supported the approval of Xgeva for the prevention of skeletal-related events in patients with bone metastases from solid tumors. In Study 20050103, the HR for OS was 1.03 (95% CI: 0.91, 1.17; p= 0.651). A total of 935 of 1,901 (49%) patients experienced a fatal event in the 103 trial. Note that Study 20050103 was not powered to detect non-inferiority for an effect on OS; however, the CI shows that a large favorable effect (compared to zoledronic acid) is unlikely.

Table 3 Trial 20050147: Efficacy Results

	Denosumab N = 716	**Placebo** N = 716
Primary Analysis - BMFS		
Number of Events (%)	335 (46.8)	370 (51.7)
Median (95% CI)*	29.5 (25.4, 33.3)	25.2 (22.2, 29.5)
p-value	0.028	
HR (95% CI)	0.85 (0.73, 0.98)	
Secondary Analysis - Time to 1st Bone Metastasis		
Number of Events (%)	286 (39.9)	319 (44.6)
Median (95% CI)*	33.2 (29.0, 37.3)	29.5 (22.4, 33.1)
p-value	0.032	
HR (95% CI)	0.84 (0.71, 0.98)	
Secondary Analysis - OS		
Number of Events (%)	251 (35.1)	250 (34.9)
Median (95% CI)*	43.9 (40.1, NE)	44.9 (40.0, NE)
p-value	0.91	
HR (95% CI)	1.01 (0.85, 1.20)	

*in months

The effect on PFS (an exploratory endpoint added in the October 30, 2009 amendment) was not statistically significant, as shown in Table 4 and Figure 4 in the Appendix. The

lack of an effect on PFS was also observed in Study 20050103 (SRE study versus zoledronic acid).

Table 4 PFS Analysis

	Denosumab N = 716	**Placebo** N = 716
Number of Events (%)	419 (58.5)	437 (61.0)
Median in months (95% CI)	21.7 (8.5, NE)	19.3 (7.7, 39.9)
p-value	0.10*	
HR (95% CI)	0.90 (0.78, 1.02)*	

*FDA analysis differs slightly from Amgen's analysis (p value of 0.093)

Patient reported outcomes (PRO) (BPI-SF) analyses (adjusted using a Cox proportional hazards model) are included in the following table. Of note, the application contained primary analyses of PRO endpoints through the week 65 study visit. Additionally, the pain response (progression) definition did not account for analgesic use. FDA's analysis of the PRO data confirmed that insufficient evidence exits to substantiate a benefit regarding PROs following the administration of denosumab based on the lack of complete information (i.e., patients were not all followed through events) and because contradictory results were reported that depended on the analysis conducted (e.g., adjusted versus non-adjusted).

Table 5 PRO BPI-SF: Worsening Pain Summary Results

Endpoint	**Denosumab vs. Placebo Hazard Ratio**	
	HR (95% CI)	**p-value (unadjusted)**
Time to moderate or severe worst pain (worst pain score > 4 points; all patients at baseline)	1.12 (0.96, 1.30)	0.1642
Time to moderate or severe worst pain (worst pain score > 4 points; patients with mild or no pain at baseline)	1.03 (0.85, 1.24)	0.7677

3.3 Summary Results (Safety)

Key safety concerns with Xgeva included in the Warnings and Precautions section of the existing product labeling involve the risks of osteonecrosis of the jaw (ONJ) and hypocalcemia. One additional concern regarding this bone-targeted drug is whether denosumab may shift the pattern of metastases to non-bony areas. An exploratory analysis showed that a higher number of patients developed an extra-osseous progression event in the denosumab arm (184 versus 156, including lymph node progression); however, denosumab-treated patients were undergoing disease related follow-up for a longer period of time (due to longer BMFS).

Severe hypocalcemia (corrected serum calcium less than 7 mg/dL or less than 1.75 mmol/L) occurred in 1.3% of patients treated with Xgeva and 0% of patients receiving placebo. The incidence observed in the denosumab group was lower than that observed in Study 20050103, the prostate cancer trial which served (in part) as a basis for the existing Xgeva (SRE) indication.

Osteonecrosis, or avascular necrosis of the jaw (ONJ) is a pathological process associated with pain, swelling, exposed bone, local infection, and pathologic fracture of the jaw. Risk factors for developing ONJ include treatment with denosumab, bisphosphonates, duration of bisphosphonate exposure, cancer and anti-cancer therapy, dental extractions, dental implants, poorly fitting dentures, glucocorticoids, smoking, and pre-existing dental disease. The mechanism by which ONJ develops is not well understood. ONJ presents as exposed necrotic bone typically involving the maxilla or mandible. It is not known whether ONJ is the primary process that becomes secondarily infected or if ONJ represents primary osteomyelitis that becomes exacerbated.

The definition of ONJ used by the Amgen (a lesion occurring in the oral cavity as an area of exposed alveolar or palatal bone where gingival or alveolar mucosa is normally found, associated with non-healing after appropriate care by 8 weeks in a patient without prior history of radiation to the head, face, or mouth; the lesion can be asymptomatic, or oral/orofacial fistulas suspicious for underlying ONJ can be present) was accurate and consistent with the medical literature.

In order to identify all ONJ events in Study 20050147, adverse events considered possible manifestations of ONJ were identified using pre-specified search criteria and sent for adjudication by a panel of independent experts blinded to treatment group, who used predefined criteria for establishing a diagnosis of ONJ. Reported adverse events were identified by searches of the safety databases using a predefined list of MedDRA search terms and via clinical review of oral examination case report forms and the verbatim terms used to report adverse events. Oral examinations were conducted for each patient every 6 months during the treatment phase of the study.

Including follow-up of patients through the extended blinded treatment phase, the overall incidence of ONJ confirmed by the adjudication committee was 5.4% in denosumab-treated patients [4.6% (33 patients) in denosumab-treated patients compared to no events in patients receiving placebo during the primary analysis phase]. The overall incidence of ONJ was higher than that observed with denosumab treatment in Study 20050103 (the randomized trial that evaluated denosumab versus zoledronic acid for the prevention of SREs); and the median duration of exposure was longer for Study 20050147 as compared to Study 20050103 (19.3 months vs. 11.9 months, respectively). Median time to onset of ONJ was 21 months.

An assessment of patients through the cut-off date for the primary efficacy analysis showed that 30% of patients with ONJ events (10 patients) required no surgical treatment; 21 (64%) required limited surgical procedures (debridement, sequestrectomy,

and curettage) and 2 required bone resection. One patient suffered cardiac arrest, seizures, and post-cardiac arrest coma related to complications of lower jaw osteomyelitis/ONJ.

The increased risk of ONJ observed in Study 20050147 compared to 20050103 is concerning given the context that denosumab is approved for patients with prostate cancer metastatic to bone. These results suggest the possibility that the risk of ONJ increases with increasing exposure to denosumab as Xgeva, and that continued long-term exposure may increase the ONJ rate to a level that off-sets the risk-benefit profile for the SRE indication in patients with prostate cancer. Indeed, the 120-day safety update to the sBLA reported an additional 6 patients with ONJ events out of 100 patients who received denosumab (in the denosumab arm) in the open-label extension phase of Study 20050147.

The incidence rates of adverse events other than ONJ and hypocalcemia, including other serious adverse events, fatal adverse events, and Grade 3-5 adverse events were similar between treatment groups.

Table 6 Trial 20050147: Overall Safety

Adverse Events	Denosumab n=720 (%)	Placebo n=705 (%)
All AEs	676 (94)	655 (93)
Serious	329 (46)	323 (46)
Fatal	73 (10)	67 (10)
Grade 3-5	381 (53)	353 (50)

Table 7 Trial 20050147: Treatment Emergent Adverse Events (all Grades)*

	Denosumab n=720 (%)	Placebo n=705 (%)
Back pain	23	22
Arthralgia	17	16
UTI	15	14
Peripheral edema	15	13
Urinary retention	14	11
Fatigue	14	11
Anemia	13	11

* reported in > 10% of patients, with at least 1% greater incidence in denosumab-treated patients

4 SUMMARY

Study 20050147 met its pre-specified primary objective, with a statistically significant prolongation in BMFS. However, it is unclear whether an improvement in BMFS alone in patients with CRPC at high risk for bone metastases is an adequate measure of clinical benefit in support of new labeling claims for a new patient population. Furthermore, it is unclear whether the magnitude of the BMFS improvement in Study 20050147 (increase in median BFMS of 4.2 months) is clinically meaningful. Treatment with denosumab did

not result in an improvement in overall survival, and the effect on PFS (an exploratory endpoint) favoring the denosumab arm did not reach statistical significance. Analysis of time to symptomatic bone metastasis, which may be considered a more relevant measure of clinical benefit in this setting, was not pre-specified (and most patients were not followed until a symptomatic event to constitute a meaningful analysis). Finally, exploratory endpoints included assessments of patient-reported outcomes, and changes in pain and health-related-quality-of-life were similar (or contradictory) between treatment arms.

The risk-benefit ratio of denosumab must take into account the overall toxicity of denosumab and the context in which denosumab is approved for patients with prostate cancer metastatic to bone. The overall incidence of ONJ in the denosumab group of more than 5% is an important consideration in a population with non-metastatic prostate cancer. The overall incidence of ONJ in the denosumab group was higher and duration of exposure longer than in the trials on which the current prostate cancer indications for denosumab are based, and the cumulative risk of ONJ for a patient who would receive denosumab across the continuum of prostate cancer disease states (as defined by the existing indications in addition to that which is currently proposed) is unknown. An additional unresolved safety issue is whether this bone targeted agent could shift the pattern of metastatic disease to non-bony sites.

5 APPENDIX: FDA ANALYSES (K-M CURVES)

Figure 1 Kaplan-Meier Curve for BMFS

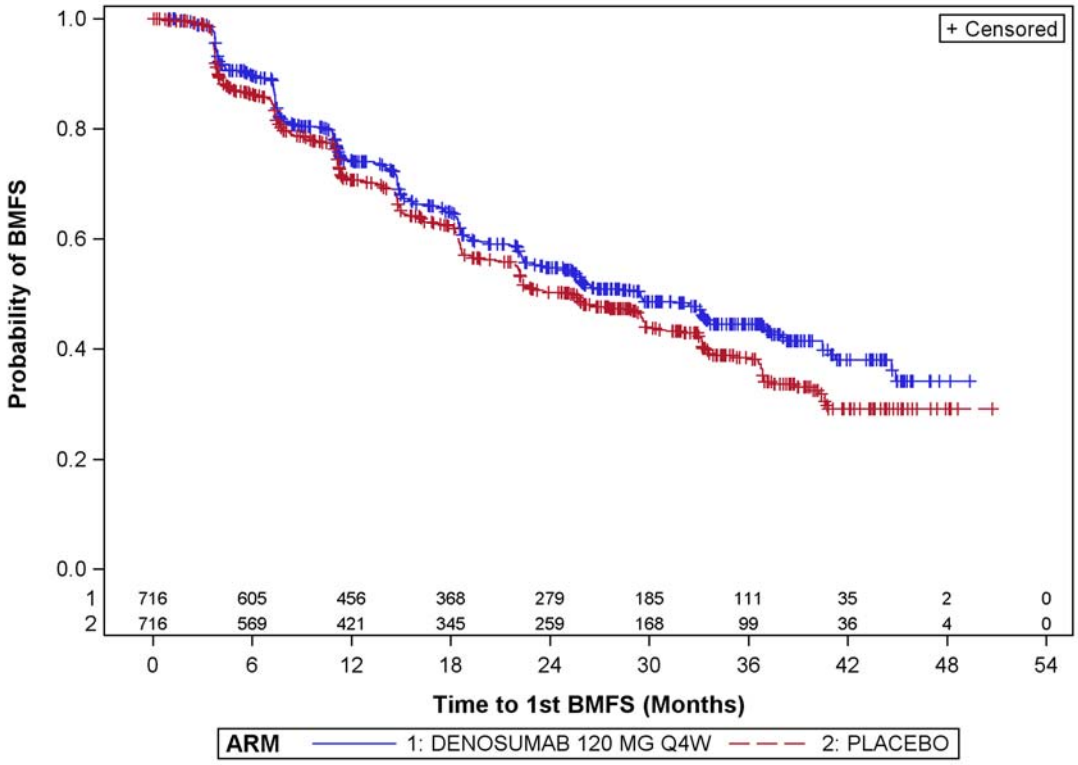


Figure 2 Kaplan-Meier Curve for Time to 1st Bone Metastasis

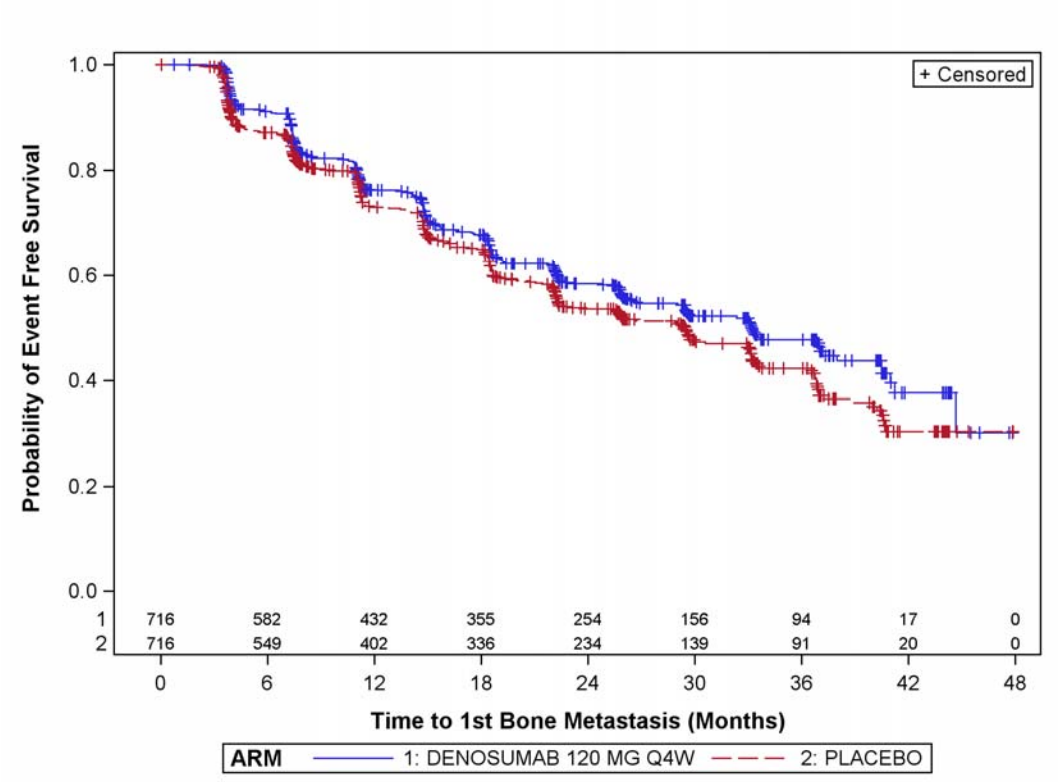


Figure 3 Kaplan-Meier Curve for Overall Survival

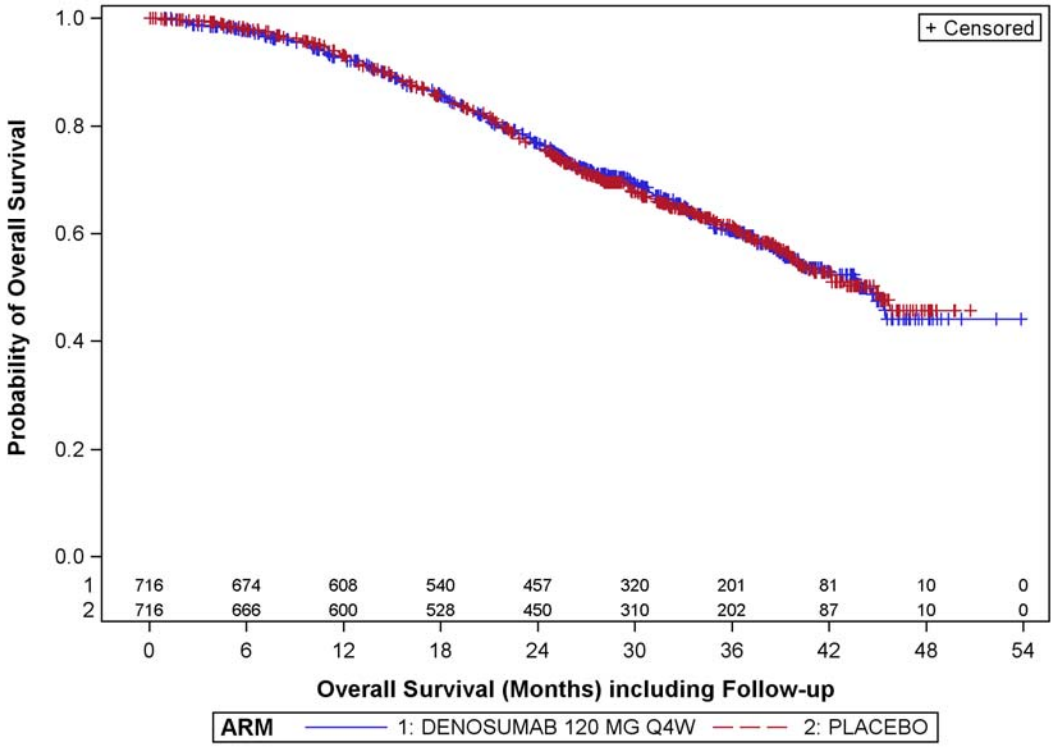
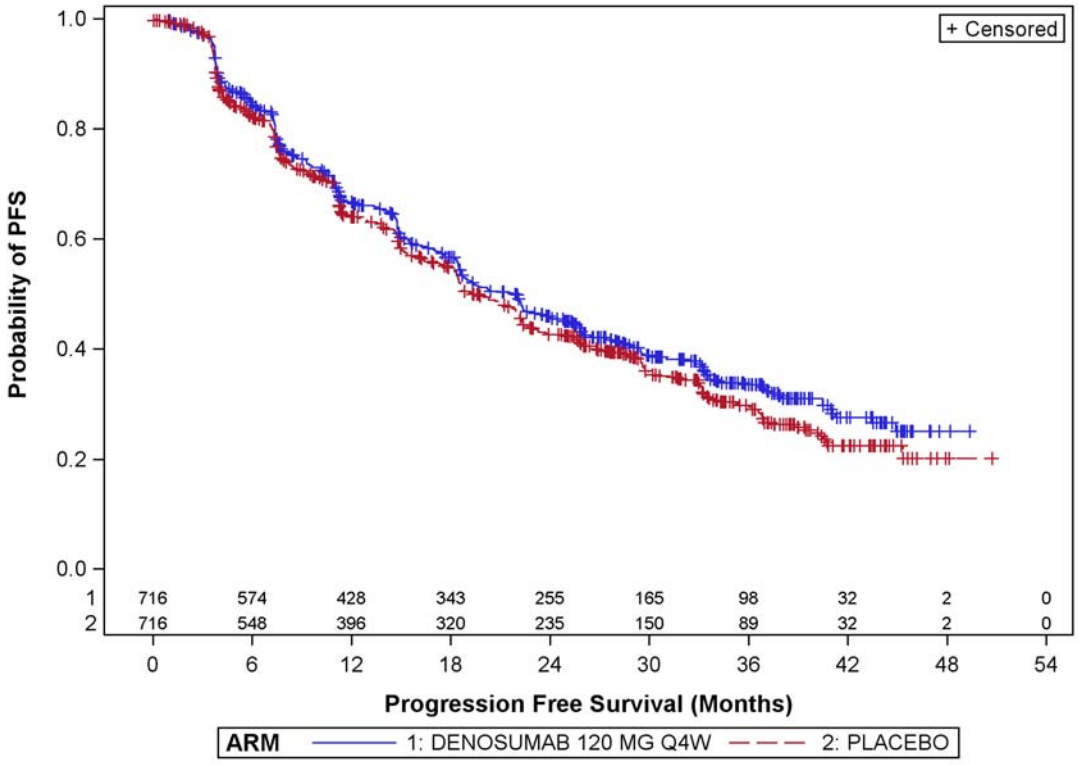


Figure 4 Kaplan-Meier Curve for PFS



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