Estimation of Off-Label Use of XGEVA® (denosumab) Using Population-Based Databases in Denmark
Amgen Study Number 20101335

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Study Glossary

Abbreviation/term	Definition
AE	Adverse Event
ADR	Adverse Reaction
CI	confidence interval
EMA	European Medicines Agency
EMR	**Electronic Medical Records**
HALT	Hormone-ablation therapy
HCP	Healthcare Practitioner
ICC	Intra-class Correlation Coefficient
ICD-10	International Classification of Diseases, Tenth Revision
IRB	Institutional Review Board
IV	Intravenous
mg	milligrams
Prescription	In this study protocol, any XGEVA prescription is prescribed in secondary care (ie, mainly hospital clinics in Denmark)
RADS	Rådet for Anvendelse af Dyr Sygehusmedin - The Council for Use of Medication in Hospitals
RANKL	Receptor activator of nuclear factor kappa-B ligand
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SC	Subcutaneous
SmPC	Summary of Product Characteristics

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Protocol Synopsis

Study Title: Estimation of Off-Label Use of XGEVA® (denosumab) Using Population-Based Databases in Denmark	
Objectives	Using data from data systems in Denmark, this study is going to evaluate off-label use of XGEVA® (denosumab) after product commercial availability. The study will include 108-200 patients in the Northern Jutland Region of Denmark who receive XGEVA identified from the prescribed treatment data, reported to the Danish National Registry of Patients. The classification of off-label use will be based on age and received diagnoses which are assessed through the Danish National Registry of Patients, through the linkage to the Danish Cancer Registry and medical record review if necessary. The primary objectives of the study include: • To estimate the proportion of patients receiving XGEVA off-label The secondary objectives of the study include: • To estimate the proportion of XGEVA prescriptions that are for off-label indications • To describe the distribution of types of XGEVA off-label use at the prescription level and the patient level • To describe the distribution of XGEVA off-label prescriptions by provider specialty
Study Design	Retrospective analysis of national registry data with chart review
Study Population	The study population will include 108-200 patients who receive a prescription in secondary care of XGEVA during the first year after the initial market availability **or until the minimum sample of 108 is achieved.** These patients will be identified from the Danish National Registry of Patients in the Northern Jutland Region of Denmark. **If the minimum target sample size of 108 XGEVA users is not achieved within the Northern Jutland Region, the study population will be extended to include the Capital Denmark Region, which constitutes the catchment area of the Copenhagen University Hospital.**
Inclusion Criteria	The study will include patients with a prescription for XGEVA® given in secondary care with a maximum of 200 XGEVA users, in the Northern Jutland Region of Denmark during the first 1-year post XGEVA market availability, defined as 12 months after RADS opinion on 24th January 2013[1].
Exclusion Criteria	N/A

[1] **http://www.regioner.dk/~/media/Mediebibliotek_2011/SUNDHED/Medicin/R%C3%A5det%20for%20Anvendelse%20af%20Dyr%20Sygehusmedicin/20130104%20I.%20Behandlingsvejledning%20SRE%20godkendt%20af%20RADS.ashx (Accessed 5th July 2013)**

Definitions of Key Study Variables	Off-label use of XGEVA will be classified according to pre-specified algorithm based on age and diagnosis. Drug prescription will be identified through relevant procedure codes or drug codes. In analyses based on the Northern Jutland Region of Denmark, diagnoses will be assessed through linkage to the Danish Cancer Registry and the Danish National Registry of Patients, and review of medical records during the 6 months prior to the XGEVA prescription. Age will be recorded in years and updated at each XGEVA prescription.
Statistical Considerations	It was estimated that approximately 108 – 200 XGEVA users will be included in analyses in Denmark after the first 1-year of market availability. As prescriptions from the same patient may be correlated, the 95% CI of an observed proportion of off-label use by number of prescriptions in the two data systems were calculated assuming an intra-class correlation coefficient (ICC) of 0.2 or 0. The anticipated precision of the planned analysis is summarized below: • Based on 108 patients, the 95% CIs ranges from 0% - 5.1% for a proportion of off-label use of 1% to 5.2% - 17.5% for a proportion of 10%; and based on estimated 648 prescriptions and assuming ICC of 0, the 95% CIs ranges from 0.3% - 2.0% for a proportion of 1% to 7.8% - 12.6% for a proportion of 10%. The 95% CIs become correspondingly narrower if the actual sample size reaches 200 patients and 1200 prescriptions in the Northern Jutland Region. • The 95% CI of an observed proportion of off-label use by number of prescriptions become wider if assuming ICC of 0.2 rather than 0. **Analysis will assess off-label use during the first 12-month period of commercial availability of XGEVA or after at least 108 patients have been accumulated, whichever comes first. Additional analyses will stratify the 12-month period into 6-month intervals.** The study population will be characterized using descriptive statistics with regard to demographic factors, diagnoses and treatments. The descriptive analysis of off-label use will be conducted at both the prescription level and the patient level. The proportion of prescriptions for off-label use will be calculated as the number of off-label prescriptions divided by the total number of XGEVA prescriptions. The proportion of patients with off-label use will be calculated as the number of patients whose at least one prescription is off-label divided by the total number of patients with an XGEVA prescription. The proportion of XGEVA prescriptions for each type of the off-label use out of all XGEVA prescriptions will be calculated. The proportion of patients receiving the first prescription of XGEVA for each type of the off-label use out of all patients with an XGEVA prescription will also be calculated. The proportion of off-label prescriptions from oncologists, urologist and providers of other specialties will be calculated as total number of off-label prescriptions from all providers of each specialty divided by total number of prescriptions from all providers of the same specialty.

Rationale for Study	European authorities have inquired about potential off-label usage of XGEVA®, which is approved by the EMA for the prevention of skeletal related events in adults with bone metastases from solid tumors. As Amgen has committed to evaluate off-label use of denosumab for all indications, this study is designed to provide data on off-label use of XGEVA. This pharmacovigilance study complements the assessment of off-label use of Prolia® in Study 20090695, entitled "Estimation of Off-Label Use of Prolia (denosumab) in Selected European Countries Using Multiple Observational Databases". This study is going to be based on data linked from registries and other sources in Northern Jutland Region of Denmark, which will allow for accurate assessment of prescriptions and diagnoses, especially those related to cancer patients during the first year post the initial market availability of XGEVA.

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1. OBJECTIVES

This study is planned to evaluate off-label use of XGEVA® (denosumab) based on linkage between the Danish National Registry of Patients, the Danish Cancer Registry and review of medical records for XGEVA users (whenever needed) from the Northern Jutland Region of Denmark. The analyses in Northern Jutland Region of Denmark will include up to 200 patients who receive a prescription of XGEVA during the first 12-months after Rådet for Anvendelse af Dyr Sygehusmedin (RADS) opinion on 24th January 2013. RADS concluded that for patients with bone metastases from prostate and lung cancer, two recommended treatment options are zoledronic acid (IV) and denosumab. For patients with metastases from breast cancer, the choice depends on whether they receive oral or parenteral antineoplastic treatment, in which case the recommended treatment options are: 1) oral clodronate (first choice)/ibandronate (second choice); 2) IV ibandronate (first choice)/zoledronate (second choice); 3) IV pamidronate; 4) SC denosumab. The choice between any of these treatments is based on the treating physician's judgment.

Additional analyses will stratify 12-month observation period into 6-month intervals. The study design is retrospective chart review of XGEVA prescriptions in secondary care being linked to prior diagnoses, and no follow-up of individuals.

Primary objectives of the study include:

- To estimate the proportion of patients receiving XGEVA off-label

Secondary objectives of the study include:

- To estimate the proportion of XGEVA prescriptions that are for off-label indications
- To describe the distribution of types of XGEVA off-label use at the prescription level and the patient level
- To describe the distribution of XGEVA off-label prescriptions by provider specialty

2. BACKGROUND AND RATIONALE

2.1 Disease or Therapeutic Area

Denosumab is a fully human monoclonal antibody of the IgG_2 subclass that binds to and neutralizes the activity of the RANKL. In blocking RANKL, denosumab reduces osteoclast-mediated bone resorption. An enhanced rate of bone remodelling fuelled by osteoclastogenesis mediates diseases such as osteoporosis, arthritic bone destruction, Paget's disease and malignancy-induced bone loss (Romas, 2009). XGEVA (denosumab 120 mg every 4 weeks) is approved by the European Medicines Agency

(EMA) for the prevention of skeletal related events in adults with bone metastases from solid tumors **(European Medicines Agency (EMA), 2012).** Under a different trade name, Prolia® (denosumab 60 mg every 6 months), denosumab has been approved by the EMA as a treatment of osteoporosis in postmenopausal women at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation therapy (HALT) in men with prostate cancer at increased risk of fractures.

Based on the approved indication, examples of the potential for off-label use of XGEVA are shown in Table 1.

Table 1. Selected Diseases with Potential Use of Denosumab

Brand Name	Potential use	Status
Prolia®	Bone loss associated with hormone ablation therapy (HALT) in men with prostate cancer	Approved
Prolia®	Osteoporosis in postmenopausal women at increased risk of fractures (including women with a diagnosis of breast cancer receiving hormone ablation therapy who are at increased risk of fractures*)	Approved
XGEVA®	Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors	Approved
XGEVA®	Giant cell tumor of bone	Trials
XGEVA®	Malignancies at risk of developing bone metastases	Trials
Prolia®	Osteoporosis in men	Approved
Prolia®	Rheumatoid arthritis	Trials
XGEVA®	Hypercalcemia of malignancy	Trials
Prolia®	Glucocorticoid-induced osteoporosis	Theoretical
XGEVA®	Paget's disease	Theoretical

* Per the European Public Assessment Report, the indication valid for postmenopausal osteoporosis ("Postmenopausal women at increased risk of fractures") is also valid for women treated with aromatase inhibitors for non-metastatic breast cancer.

2.2 Rationale for Planned Study

European authorities have inquired about potential off-label usage of XGEVA®, which is indicated for the prevention of skeletal related events in adults with advanced malignancies involving bone. As Amgen has committed to evaluate off-label use of denosumab for all indications, this study is designed to provide data on off-label use of XGEVA in patients with bone metastases in solid tumors. This pharmacovigilance study complements the assessment of off-label use of Prolia® in Study 20090695, "Estimation of Off-Label Use of Prolia (denosumab) in Selected European Countries Using Multiple

Observational Databases". This study is going to be based on data from the selected databases in Denmark with the capacity to assess prescriptions and diagnoses, especially those related to cancer patients during the first year post the initial market availability of XGEVA**.**

2.3 Statistical Inference (Estimation / Hypotheses)

A formal hypothesis will not be tested in this study. Instead we will estimate the proportion of off-label use in Denmark and the associated 95% confidence interval (CI) during the first year of XGEVA commercial availability **or until the minimum sample of 108 is achieved.**

3. STUDY DESIGN

3.1 Study Source Population

Northern Jutland Region of Denmark is the proposed source population for this study. If the minimum target sample size of 108 XGEVA users is not achieved within this study population, the study population will be extended to include the Capital Denmark Region, which constitutes the catchment area of the Copenhagen University Hospital. The combined population of the three regions on 1 January 2013 was 3,584,850 persons (source: Statistics Denmark). This study will use existing population-based databases, which include data on prescriptions/hospital administrations and where the indication can be inferred from the linkage to diagnoses recorded in the Danish Cancer Registry, Danish National Registry of Patients, or medical records (Northern Jutland Region of Denmark). The study design is retrospective analysis of national registry data whereby records of prescriptions/hospital administrations are linked with prior diagnoses. If required, the obtained data may be confirmed by medical chart review. No new data will be collected prospectively. All analytic files constructed for this study will stay with the Aarhus University. Only summary data will be provided to Amgen.

Data systems from one or more European countries may be used as alternative databases for this study if preliminary results suggest the identified database(s) are non-suitable for the purposes of this study. Potential suitability issues may include limited prescriptions (or recording of prescriptions) of XGEVA®, or incomplete recording of the date of prescriptions or diagnoses.

3.2 Study and Source Data

3.2.1 Source Data

In Denmark, XGEVA is prescribed primarily in the hospital setting (secondary care)[2] (source: medstat.dk). The Danish National Registry of Patients records selected treatment administered at hospitals. There is a treatment code for denosumab administration. The hospital visits are tracked via the citizen personal identification number for each patient, which allows linkage to other Danish national registries. These national registries capture health-related data on all citizens through a complex system of interlinkable databases (by a citizen personal identification number that follows each citizen from birth to death). Data cover a broad spectrum of health information including, inpatient hospitalizations, outpatient and emergency hospital visits, outpatient prescriptions, laboratory and pathology results, disease registries (eg., cancer registry), death certificates, and socioeconomic data. A large amount of specialized information from disease registries, such as the Danish Cancer Registry, is available for research. Additionally, medical records from hospital-based outpatient specialist clinics in the Northern Jutland Region will be accessible for the purpose of this study. **The treatment codes in the Danish National Registry of Patients usually have high positive predictive values (Nielsson, 2012; Jespersen, 2012), however, it is unclear what proportion of XGEVA treatment is captured via the treatment code. Furthermore, the Danish National Registry of Patients treatment code does not distinguish between Prolia and XGEVA, necessitating medical record review. Finally, reasons for recording or not recording treatment codes are not known. Therefore, we will additionally gain access to the Electronic Medical Records (EMR) of patients treated in Aarhus University Hospital, with in the catchment area of the Central Denmark Region, which, together with the North Central Region, comprise the Northern Jutland Region. In contrast to the Danish National Registry of Patients, the EMR contains information on dose and brand of administered medication and does not require medical record review to ascertain medication intake. It is envisioned that the use of EMR will allow capture of XGEVA-treated patients not captured by registry records and reduce the potential selection bias that may arise if the registry record is associated with indication. If the target sample size of 108 XGEVA users is not achieved in the Northern Jutland Region, additional patients will be enrolled from hospitals in the Capital Denmark Region.**

[2] **(source: medstat.dk)**

3.2.2 Data Quality

All of the specialized disease registries, including the Danish Cancer Registry, can be linked at the patient level to other national registries using the patient's personal identification number (Sorensen et al, 2008). The automation of these registries has contributed to the collection of comprehensive, high quality data that are widely recognized as valuable sources for the conduct of pharmacoepidemiology studies. Completeness and accuracy of records is generally high, due to laws or other incentives motivating healthcare providers to collect and send the data electronically to their national databases (Furu et al, 2010). A high response rate is expected for chart retrieval. In a recent validation study related to Prolia® in the same Danish region (Study 20090522 Supplemental Activities), researchers obtained 100% of requested charts (Gammelager et al, 2013).

The lag time from the hospital-based medical encounters to the availability of data for analysis in the Danish database is 6-12 months. It may take additional time (1-6 months) to complete medical record abstraction and review for the purpose of this study.

3.3 Selection of Participants

3.3.1 Inclusion (Eligibility) Criteria

In Denmark, the study will include patients with a treatment code for XGEVA, with a maximum of 200 XGEVA users, in the Northern Jutland Region during the first 1-year period after the initial market availability of XGEVA. If there are more than 200 XGEVA users identified in the Northern Jutland Region, the sampling of the first 200 XGEVA users will be identified for inclusion. Because the hospital treatment code for denosumab does not distinguish between XGEVA and Prolia, initially all patients with the denosumab code will be selected. Based on pilot data from the Department of Clinical Epidemiology, denosumab administrations associated with the primary diagnosis of osteoporosis can be excluded as Prolia administrations. Those can be additionally verified by linkage to the regional prescription registry, in which outpatient prescriptions for Prolia are recorded. After screening out Prolia users, XGEVA use for the remaining prescriptions, if required, may be confirmed by medical chart review. Additionally, we will identify and exclude patients who have been enrolled in clinical trial studies to receive XGEVA.

3.4 Definitions

3.4.1 Patient Demographic and Prescriber Characteristics

Patient Age: Will be recorded in years and updated at each XGEVA prescription. Date of birth is encoded in the unique personal identifier and allows calculation of age at any time.

Gender: Male or female. Gender is also encoded within the unique personal identifier.

Prescriber: Primary care or specialty care (eg, oncology or urology) will be determined by reporting the treating clinical department, from which treatment code for denosumab originates in the Danish National Registry of Patients.

3.4.2 XGEVA® Indication

To attribute the indication for which XGEVA was prescribed, the following will be examined (when available):

- Age
- Diagnosis (within 6 months prior to XGEVA prescription or 1 year as a sensitivity analysis), including
  - bone metastasis
  - malignancy without bone metastasis
  - multiple myeloma
  - giant cell tumour of bone
  - bone loss associated with HALT in men with prostate cancer
  - glucocorticoid-induced osteoporosis
  - postmenopausal osteoporosis
  - other types of osteoporosis
  - rheumatoid arthritis
  - hypercalcemia of malignancy
  - Paget's disease

The assessment of diagnosis of bone metastasis will be conducted in a two-step approach. For patients who receive one or more prescriptions of denosumab as recorded in the Danish National Registry of Patients, the linked data from the Danish National Registry of Patients will be searched to identify the diagnosis code for bone metastasis during the period from 6 months (and 1 year as a sensitivity analysis) prior to each XGEVA prescription to 7 days after. In case that subsequent prescriptions lack a diagnosis for bone metastasis, initial diagnosis relevant to an earlier prescription for the same patient will be carried forward for the subsequent prescriptions of the same patient.

For patients with one or more prescription of denosumab that lack a diagnosis of bone metastasis according to the linked data from the Danish National Registry of Patients, medical records dated from 6 months (and 1 year as a sensitivity analysis) prior to each of such XGEVA prescriptions to 7 days after (or during the same hospital admission) will be obtained. Key information related to the potential indication of XGEVA will be collected using a standardized data abstraction form (Appendix A). All the collected medical records and data abstraction forms will be reviewed by an independent research investigator to confirm the presence of diagnosis for bone metastasis as well as other specified disease(s) which may potentially constitute off-label use. In case that subsequent prescriptions lack a diagnosis for bone metastasis or other specified diagnosis, initial diagnosis relevant to an earlier prescription for the same patient will be substituted.

3.4.3 Assessment of Relevant Diagnoses and Treatments

The administrations of XGEVA will be assessed through a two-step approach including search of linked data from the Danish Cancer Registry and Danish National Registry of Patients and review of medical records. Hospital-administered denosumab treatment will be captured (hospital code BWHB42); although dosage is not noted, diagnostic details will be ascertained from review of medical records if insufficient data are available from routine databases**. Administration of XGEVA will be assessed electronically using the EMR system from Aarhus University Hospital**.

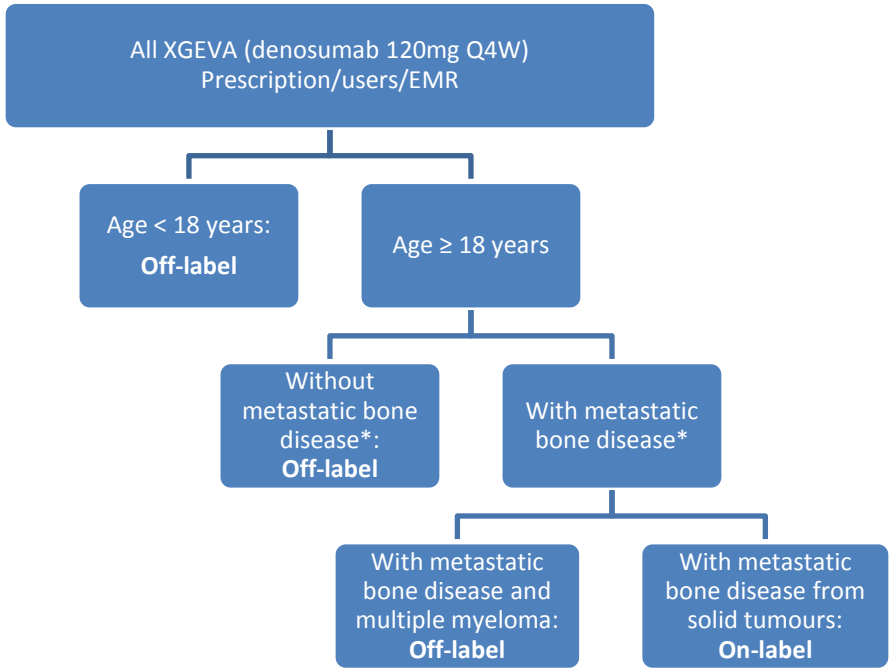
3.4.4 Classification of XGEVA Off-Label Use

Off-label use of XGEVA will be defined as per the product Summary of Product Characteristics, as approved by the EMA (July 15, 2011). The proposed classification tree in Figure 1 capitalizes on the indicated diagnosis and age criteria for XGEVA use. The classification rules of the algorithm may need to be refined based on the performance of the algorithm during the preliminary evaluation given the data availability and reliability during the study period. With the newly approved indications and other updates to the label during the study period, the classification rules of the algorithm will be revised accordingly reflecting the updated label.

Each type of the off-label use of XGEVA according to received diagnosis (malignancy without bone metastasis, multiple myeloma, giant cell tumor of bone, bone loss associated with HALT in men with prostate cancer, glucocorticoid-induced osteoporosis, postmenopausal osteoporosis, other types of osteoporosis, rheumatoid arthritis, hypercalcemia of malignancy, and Paget's disease) will be further distinguished based on

received diagnosis or treatment during the period from the date of each XGEVA prescription plus 7 days for delays in coding through the previous 6 months (and 1 year as a sensitivity analysis).

Figure 1. Classification Algorithms to Categorize Off-label Use



* Identification of metastatic bone disease is based on search of linked data from the Danish Cancer Registry, Danish National Registry of Patients, or medical record review for analyses based on the Northern Jutland Region**/Capital Region (if necessary)** of Denmark

3.5 Validation of Study Variables

In the Northern Jutland Region of Denmark, for patients with one or more prescriptions of XGEVA which lack a diagnosis of bone metastasis according to the linked data from Danish National Registry of Patients, medical records dated from 6 months (and 1 year as a sensitivity analysis) prior to each of such XGEVA prescriptions to 7 days after will be obtained and reviewed to assess received diagnosis and treatment surrounding the time of XGEVA prescription.

3.6 Study Follow-up

There will be no study follow-up as the main objective is to categorize off-label use in a cross-sectional manner. The study will use data from population-based data systems during the 1-year period after the product launch of XGEVA in Denmark.

4. STUDY SIZE

Based on Medicare data and MarketScan® claims in the United States, prevalence of bone metastasis in the general population was estimated as 0.12% after being standardized by age and gender to the 2008 U.S. census data **(Li et al, 2012).** Assuming uptake of XGEVA increases linearly, the average market uptake is estimated to be approximately 5% among all patients with bone metastasis during the first year post the market availability. For the purpose of estimating the number of patients exposed to XGEVA and the number of prescriptions of XGEVA, it is assumed that:

- 0.12% of general population have bone metastasis
- during the first year after XGEVA market entry, 5% of cancer patients with bone metastasis will be treated with XGEVA in Denmark;
- each patient receives an average of 6 prescriptions for XGEVA during the 1-year after the product launch.

Based on these assumptions, the estimated number of patients with one or more XGEVA prescriptions and XGEVA prescriptions in the first year post the market availability in the study population is summarized in Table 2.

Table 2. Estimation of Number of XGEVA Users and Prescriptions in the Northern Jutland Region of Denmark

	Danish Databases
All patients in the data system	1,800,000
Patients with bone metastasis	1,800,000 x 0.12% = 2,160
XGEVA users	2,160 x 5% = 108 Maximum: 200*
XGEVA prescriptions	108 x 6 = 648 Maximum: 1,200

* In case more there are more than 200 XGEVA users identified from the Northern Jutland Region of Denmark, a maximum of 200 users will be sampled and included in the study.

The exact method has been used to estimate the 95% CI of proportions of off-label use by the number of patients and by the number of prescriptions (Agresti, 2002). As prescriptions from the same patient may be correlated, assuming an intra-class correlation coefficient (ICC) of 0.2 or 0, the 95% CI of an observed proportion of off-label use by number of prescriptions in the two data systems are summarized in Table 3 The 95% CI of an observed proportion of off-label use by number of patients in the two data systems are summarized in Table 4. Using a base assumption of 108 patients treated with XGEVA during the first year after commercial availability, the 95% CIs ranges from 0% - 5.1% for a proportion of off-label use of 1% to 5.2% - 17.5% for a proportion of 10%;

and based on estimated 648 prescriptions and assuming ICC of 0, the 95% CIs ranges from 0.3% - 2.0% for a proportion of 1% to 7.8% - 12.6% for a proportion of 10%. The 95% CIs become correspondingly narrower if the actual sample size reaches 200 patients and 1200 prescriptions in the Northern Jutland Region. The 95% CI of an observed proportion of off-label use by number of prescriptions become wider if assuming ICC of 0.2 rather than 0.

Table 3. Calculation of 95% CI of an Observed Proportion of XGEVA Off-Label Use According to Estimated Number of Prescriptions

Proportion of off-label use	Danish Databases			
	N=648		N=1,200	
	ICC*=0	ICC*=0.2	ICC*=0	ICC*=0.2
10%	7.8% – 12.6%	7.0% – 13.8%	8.4% – 11.8%	7.7% – 12.7%
5%	3.4% – 6.9%	2.9% – 8.0%	3.8% – 6.4%	3.4% – 7.1%
1%	0.3% – 2.0%	0.2% – 2.8%	0.5% – 1.7%	0.4% – 2.2%

*Intra-class correlation coefficient for prescriptions from the same patient.

Table 4. Calculation of 95% CI of an Observed Proportion of XGEVA Off-Label Use According to Estimated Number of Users

Proportion of off-label use	Danish Databases	
	N=108	N=200
10%	5.2% – 17.5%	6.2% – 15.0%
5%	1.5% – 10.5%	2.4% – 9.0%
1%	0.0% – 5.1%	0.1% – 3.6%

The assumptions used to estimate sample size were meant to be conservative. However, the actual number of treated patients depends ultimately on reimbursement and medical practice decisions and may be higher or lower than these projections. If the XGEVA treatment cohort includes fewer than 108 patients by the end of the cohort identification period treatment cohort identification will be extended 1 year.

5. STATISTICAL ANALYSIS

The primary statistical analysis will be based on data of off-label use after the initial market availability of XGEVA in Denmark. Stratified analysis will also be conducted separately based on data accumulated during the first year of commercial availability **or after 108 patients have been accumulated, whichever comes first.** Additional analyses will stratify 12-month periods into 6-month intervals.

5.1 Study Endpoints

The endpoints that the study aims to measure will measure off-label use during the 1st year after the market availability and include the following.

Primary endpoints:

- Yes/no regarding whether an individual prescription was on (or off) label
- Yes/no regarding whether the patient was treated on (or off) label

Secondary endpoints:

- XGEVA prescription for each type of off-label use
- Prescriptions that are for off-label use stratified by department that administers treatment

5.2 Patient Characterization

Study population will be characterized with regard to demographic factors, diagnoses and treatments using descriptive statistics. Age will be presented in 5-year categories (including a separate evaluation of patients under age 18 years). Categorical variables will be summarized in frequency tables. Numeric variables will be summarized by presenting the number of observations, mean, standard deviation, quartiles, and median.

For the process of medical record abstraction based on the Northern Jutland Region of Denmark, the proportion of medical records obtained out of all requested will be calculated. Patient characteristics will be described separately for those with medical records successfully obtained and those without.

5.3 Off-Label Use Analyses

5.3.1 Primary Endpoint

The proportion of XGEVA use that is off-label will be calculated on prescription and on a patient basis. The proportion of off-label prescriptions and 95% CI will be estimated taking into consideration the correlation among prescriptions from the same patient. The proportion of patients with off-label use will be calculated as the number of patients whose first prescription is off-label divided by the total number of patients with an XGEVA prescription. Because the diagnosis of bone metastasis for an earlier prescription for an individual can be carried over for subsequent prescription(s), the off-label analysis based on the first prescription on a patient basis is comprehensive to identify all patients with off-label use of XGEVA.

5.3.2 Secondary Endpoints

The proportion of XGEVA prescription for each type of the off-label use (including any pediatric use, malignancy without bone metastasis, multiple myeloma, giant cell tumor of bone, bone loss associated with HALT in men with prostate cancer, glucocorticoid-induced osteoporosis, postmenopausal osteoporosis, other osteoporosis, rheumatoid arthritis, hypercalcemia of malignancy, and Paget's disease) out of all XGEVA prescription will be calculated separately. The proportion of patients receiving the at least one prescription of XGEVA of the off-label use out of all patients with an XGEVA prescription will also be calculated separately.

The proportion of off-label prescription from oncologists, urologists and other specialties will be calculated as total number of off-label prescriptions from all providers of each specialty divided by total number of prescriptions from all providers of the same specialty.

5.4 Sensitivity Analyses

For analyses based on the Northern Jutland Region of Denmark, a sensitivity analysis which looks at diagnosis codes over the 1 year prior to XGEVA prescriptions to assess off-label use will be conducted. In another sensitivity analysis on a patient basis, patients whose multiple diagnoses allow their prescriptions to qualify for both on-label and off-label use will be assigned to on-label use.

5.5 Missing Data

Missing data is a minor concern for analyses based on data from Danish Registries as the Danish National Registry of Patients and the prescription database in combination with the linked data from the Danish Cancer Registry and medical record review is expected to provide comprehensive assessment of diagnoses, treatments and other patient characteristics.

6. STUDY LIMITATIONS

6.1 Potential Bias

Requested patient medical records may not all be obtained. To the extent that medical records which are not obtained differ systematically from those obtained with regard to off-label use patterns, the study results may be biased and not generalizable to all XGEVA users. However, based on experiences from previous similar type of studies, the proportion of obtained medical records out of all requested is expected to be near complete for the specialist clinics, hospital clinics and hospitals and very high for general practitioners. A descriptive analysis of patient characteristics separately for patients with medical records requested and successfully obtained and patients with medical records

requested but not successfully obtained will be performed to provide further evaluation of such potential bias. Furthermore, completeness of recording of administrations of XGEVA is not known.

6.2 Reliability and Validity

Diagnosis code for malignancy with bone metastasis in the Danish National Registry of Patients is likely to be under-recorded (Jensen et al. 2009), therefore the diagnosis of bone metastasis will be more completely assessed through review of medical records. Despite a relatively small European population represented in the Northern Jutland Region of Denmark, the data will provide a comprehensive evaluation of off-label use according to received diagnosis than non-population based databases in Europe.

A longer look-back period (such as for the diagnosis of breast cancer) theoretically could improve the diagnostic classification but may not be feasible given the average enrollment period in the data systems. Six months has been selected based on previous experience but sensitivity will be assessed using one year to determine whether this look-back period should be adjusted.

7. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

Patient medical records will be reviewed by study nurse to abstract recorded diagnoses and prescriptions. Therefore, it is possible that some medical records may contain statements that link adverse events to denosumab therapy.

7.1 Adverse Events

7.1.1 Definition of Adverse Events

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

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

7.1.1.1 Adverse Drug Reactions (ADRs)

AEs that are considered related to the Amgen product(s) are classified as adverse drug reactions (ADRs).

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

7.1.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is any AE as defined above that also:

- 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
- is an "other medically significant event" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other medically significant event" refers to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

7.1.2.1 Serious Adverse Drug Reactions (SADRs)

SAEs that are considered related to the Amgen product(s) are classified as serious adverse drug reactions (SADRs).

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

7.1.2.2 Definition of Other Safety Findings

Other Safety Findings include:

- Medication errors, overdose, misuse, or abuse, whether accidental or intentional, involving an Amgen product, regardless of whether associated with an AE and/or SAEs
- Pregnancy and lactation exposure regardless of whether associated with an AE or and/or SAEs
- Transmission of infectious agents regardless of whether associated with an AE and/or SAEs
- Reports of uses outside the terms for authorized use of the product including off label use when associated with an AE and/or SAEs

7.1.3 Definition of Product Complaints

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

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

- Appearance (eg, broken, cracks, color, particles, odor)
- Labeling (eg, missing, torn, smudged)
- Durability (eg, stability issues)
- Open packaging
- Device damage (eg, pre-filled syringe with bent needle)
- Inability of customer to understand product labeling
- Inability of customer to deliver the product successfully, including partial or incomplete delivery (eg, defective delivery system [syringe])

7.2 Reportable Events and Reporting Timeframes

The research partner (Aarhus University) is responsible for ensuring that all SADRs, product complaints and other safety findings for Amgen products reported by HCPs are submitted to Amgen via the supplied Amgen Safety Reporting Forms. See Appendix B for a sample Adverse Drug Reaction Report Form and Appendix C for sample Pregnancy and Lactation Notification Worksheets. Amgen will not collect data directly from patients; however, since patient medical records may be reviewed to confirm some events, it is possible that some medical records may contain statements that document adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs) in patients receiving

denosumab. Amgen will instruct all medical chart reviewers to report every adverse reaction and SADR, that is, every adverse event case that is specifically documented (or stated) in medical charts to be causally related to denosumab therapy.

All clearly documented SADRs, product complaints and other safety findings, including pregnancy and/or lactation, are to be reported to Amgen within 1 business day of the Aarhus University date of awareness.

ADRs that do not meet serious criteria are to be collected in the study database and must be included in the final study report.

The vendor is to provide event listings to Amgen for purposes of reconciliation per the contractual agreement.

Amgen will report adverse events as required to regulatory authorities in accordance with Pharmacovigilance guidelines and in compliance with local regulations.

8. ETHICAL AND REGULATORY OBLIGATIONS

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy.

9. ADMINISTRATIVE AND LEGAL OBLIGATIONS

9.1 Study Amendments and Study Termination

Amendments must be made only with the prior approval of Amgen. When applicable, the relevant local IRB must be informed of all amendments and give approval. When applicable, Aarhus University Hospital must send a copy of the approval letter from the relevant local IRB to Amgen.

Amgen and Aarhus University Hospital reserve the right to terminate participation in the study according to the study contract. When applicable, Aarhus University Hospital will notify the relevant local IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

9.2 Study Documentation and Archive

Retention of study-related documents is governed by Amgen Policy CCD024r03,

"RECORDS AND INFORMATION MANAGEMENT POLICY".

10. COMMUNICATION OF STUDY RESULTS/PUBLICATION PLAN

The results of these analyses will be summarized in a report that will be submitted to European authorities. The data lag time is approximately 6-12 months for the Danish databases although it may take additional time (1-6 months) to complete medical record abstraction and review for the purpose of this study. It should be noted that the study is dependent on physician prescribing behavior and uptake of XGEVA in Denmark, and it may take longer than 1 year post commercial availability to identify the anticipated 108-200 patients treated with XGEVA.

If after submission of the results to European authorities it is determined that publication of the results in the form of a manuscript is warranted, Amgen's publication policy will be followed. Authorship of the manuscript will follow the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE, 2011). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Any potential conflicts of interest will be disclosed. Authors will adhere to the ICMJE guidelines, specifically, all authors will have (1) made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) participated in drafting the article or revising it critically for important intellectual content; (3) approved the version to be published, and (4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Acquisition of funding, collection of data, or general supervision of the research group does not justify authorship. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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12. APPENDICES

Appendix A. Medical Record Abstraction Form

XGEVA Off-Label Use	**Abstraction ID:**

Medical Records Review to Assess XGEVA® Off-Label Use

Abstraction Coversheet

Patient Study ID:

Treating Hospital Department

Photocopies Attached:
Abstraction Date:
Abstraction Time:
Abstraction Complete: Yes No
If “NO”, then please provide a reason:

XGEVA Off-Label Use	Abstraction ID:

Abstraction Form

As part of the regulatory committed post-marketing pharmacovigilance program, this study is conducted to evaluate potential off-label use of XGEVA among users within 1 year after the initial product market availability. Indications are assessed according to the patient's age and received diagnoses. The purpose of this questionnaire is to collect information regarding received diagnoses for each of the XGEVA administrations.

Please answer the following questions based on information abstracted from the medical records. The time span of medical record abstraction includes but is not necessarily limited to the patient's medical information covering 12 months before to 1 week after the XGEVA treatment specified in Module A. Please expand the time span for abstraction if it is needed to fully describe the medical or medication history relevant to the following questions.

Module A (if required): Verify the Date of XGEVA Administration(s) (pre-populated according to prescription or pharmacy records)

Date receiving the dose of the episode for each of the XGEVA administrations

1st administration date: _____ (MM/DD/YY)

☐ correct; ☐ incorrect, _____(corrected information, if entry is incorrect)

2nd administration date: _____ (MM/DD/YY)

☐ correct; ☐ incorrect, _____(corrected information, if entry is incorrect)

3rd administration date: _____ (MM/DD/YY)

☐ correct; ☐ incorrect, _____(corrected information, if entry is incorrect)

4th administration date: _____ (MM/DD/YY)

☐ correct; ☐ incorrect, _____(corrected information, if entry is incorrect)

5th administration date: _____ (MM/DD/YY)

☐ correct; ☐ incorrect, _____(corrected information, if entry is incorrect)

6th administration date: _____ (MM/DD/YY)

☐ correct; ☐ incorrect, _____(corrected information, if entry is incorrect)

7th administration date: _____ (MM/DD/YY)

☐ correct; ☐ incorrect, _____(corrected information, if entry is incorrect)

XGEVA Off-Label Use ID:	**Abstraction**

8th administration date: _____ (MM/DD/YY)

☐ correct; ☐ incorrect, _____(corrected information, if entry is incorrect)

9th administration date: _____ (MM/DD/YY)

☐ correct; ☐ incorrect, _____(corrected information, if entry is incorrect)

10th administration date: _____ (MM/DD/YY)

☐ correct; ☐ incorrect, _____(corrected information, if entry is incorrect)

11th administration date: _____ (MM/DD/YY)

☐ correct; ☐ incorrect, _____(corrected information, if entry is incorrect)

12th administration date: _____ (MM/DD/YY)

☐ correct; ☐ incorrect, _____(corrected information, if entry is incorrect)

…

XGEVA Off-Label Use ID:	**Abstraction**

Module B: Questions on XGEVA Treatment and Received Diagnoses

1. According to the medical records, is there any mention of dosage for the XGEVA® administration(s) specified in Module A?

   □ **NO.** There is no mention of the dosage for any of the XGEVA administration(s) specified in Module A

   □ **YES.** There is mention of the dosage for some or all of the XGEVA administration(s) specified in Module A

   If **YES**, please specify the dosage and specialty of the prescriber as below, if available.

Administration(s)	**Dose per Administration***	**Specialty of Prescriber**
1st	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____
2nd	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____
3rd	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____
4th	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____
5th	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____
6th	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____
7th	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____
8th	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____

* Dosage field will be set to missing if not recorded

XGEVA Off-Label Use ID:	**Abstraction**

Administration(s)	**Dose per Administration***	**Specialty of Prescriber**
9th	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____
10th	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____
11th	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____
12th	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____
If there are additional administrations, please also specify by the sequence of administration(s)	____ mg total	□ Primary care physicians, □ Oncologists □ Urologists □ Other. Please specify_____

* Dosage field will be set to missing if not recorded

2. Did the patient receive a diagnosis of any of the following diseases according to the available medical records? And if the "Yes", please specify the date of the earliest diagnosis and provide additional required information according to medical records, if available.

Diagnosis	**Presence**	**Date of Diagnosis or treatment (If "Yes")**	**Additional Information (If "Yes")**
Malignancy with bone metastasis	□Yes □ No	__ __/__ __/__ __ (MM/DD/YY)	Was the diagnosis confirmed through radiographic examination? □Yes □ No What was the site of the primary malignancy? _____

XGEVA Off-Label Use ID:	**Abstraction**

Diagnosis	**Presence**	**Date of Diagnosis or treatment (If "Yes")**	**Additional Information (If "Yes")**
Malignancy without bone metastasis	□Yes □ No	__ __/__ __/__ __ (MM/DD/YY)	What was the cancer site? _____
Multiple myeloma	□Yes □ No	__ __/__ __/__ __ (MM/DD/YY)	
Giant cell tumor of bone	□Yes □ No	__ __/__ __/__ __ (MM/DD/YY)	
Prostate cancer treated with HALT*	□Yes □ No	1. Diagnosis of prostate cancer __ __/__ __/__ __ (MM/DD/YY) 2. Start of treatment with HALT after diagnosis of prostate cancer __ __/__ __/__ __ (MM/DD/YY)	What kind of HALT was received? _____
Glucocorticoid-Induced Osteoporosis	□Yes □ No	1. Diagnosis of osteoporosis __ __/__ __/__ __ (MM/DD/YY) 2. Start of treatment with glucocorticoid __ __/__ __/__ __ (MM/DD/YY)	What kind of glucocorticoid was received? _____
Postmenopausal Osteoporosis (including women receiving hormone-ablation therapy [HALT]* for breast cancer)	□Yes □ No	__ __/__ __/__ __ (MM/DD/YY)	What was the cause of menopause? □ Natural menopause □ Hysterectomy □ Treatment with HALT* for breast cancer □ Other. Please specify _____
Other types of osteoporosis	□Yes □ No	__ __/__ __/__ __ (MM/DD/YY)	
Rheumatoid arthritis	□Yes □ No	__ __/__ __/__ __ (MM/DD/YY)	

XGEVA Off-Label Use ID:	**Abstraction**

Diagnosis	**Presence**	**Date of Diagnosis or treatment (If "Yes")**	**Additional Information (If "Yes")**
Hypercalcemia with malignancy	□Yes □ No	1. Diagnosis of malignancy __ __/__ __/__ __ (MM/DD/YY) 2. Diagnosis of hypocalcaemia after diagnosis of malignancy __ __/__ __/__ __ (MM/DD/YY)	
Paget's disease	□Yes □ No	__ __/__ __/__ __ (MM/DD/YY)	

***** HALT treatment include aromatase inhibitors, including (generic name / brand name(s)) letrozole / FEMARA, anastrozole / ARIMIDEX, and exemestane / AROMASIN; and luteinizing-hormone-releasing hormone (gonadotropin-releasing hormone) analogs, including leuprolide / ENANTONE / LUPRON / VIADUR / ELIGARD, goserelin / ZOLADEX, and triptorelin / DECAPEPTYL / TRELSTAR.

Module C: Completion and Review of Abstract Form and Notes

Abstractor: _____

Abstractor's signature: _____

NOTES: If there are any general comments or additional information you would like to add to help us better understand this patient, the medical record, or the information you have provided on the abstraction form, you may do so here. Your comments are encouraged and appreciated!

_____

_____

_____

_____

_____

_____

_____

_____

Appendix B. Sample Safety Reporting Form

AMGEN 201XXXXX	**Adverse Drug Reaction Report** *Notify Amgen of SADRs and Product Complaints Within One Working Day* *SELECT OR TYPE IN A FAX#*	☐New ☐Follow-up

Indicate event type: ☐ AE/Other safety finding ☐ AE/Other safety finding with Product Complaint ☐ Product Complaint only

1. SITE INFORMATION

Site Number	Investigator/Study Doctor	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

3. ADVERSE DRUG REACTON, Other Safety Finding or Product Complaint

Adverse Drug Reaction Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Drug Reaction *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	Is the event serious? No✓	Is the event serious? Yes✓	If Serious, enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the event may have been caused by Amgen drug? See section 10 No✓	Relationship Yes✓	Outcome of Event 01 Resolved 02 Resolving 03 Not resolved 04 Fatal
							✓	
							✓	
							✓	
							✓	
							✓	

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/patient hospitalized? ☐No ☐Yes, If yes, provide date(s) →		

5. SUSPECT AMGEN PRODUCT

	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
Amgen Product: _____ Lot #: _____						
Amgen Product: _____ Lot #: _____						
Amgen Product: _____ Lot #: _____						

6. RELEVANT CONCOMITANT MEDICATIONS (e.g. chemotherapy) If none check here: ☐

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

FORM-015478 Adverse Drug Reaction Report Form v5.0 Effective date: 17-Aug-2012 *ADR Report Form Created: DD-MMM-YYYY*

AMGEN 20XXXXXX

Adverse Drug Reaction Report

Notify Amgen of SADRs and Product Complaints Within One Working Day

☐New ☐Follow-up

Site Number | Subject ID Number

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

8. RELEVANT LABORATORY VALUES *(include baseline values)* If none check here: ☐

Date (Day Month Year)	Test / Unit										

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* If none check here: ☐

Date (Day Month Year)	Additional Tests	Results	Units

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

Signature of Investigator or Designee	Title	Date

FORM-015478 Adverse Drug Reaction Report Form v5.0 Effective date: 17-Aug-2012 *ADR Report Form Created: DD-MMM-YYYY*

Appendix C. Pregnancy and Lactation Notification Worksheets

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

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

Appendix D. Diagnostic Codes, Drug Codes and Procedure Codes

Table D-1. Classification of Diagnostic Codes

Category	Description	ICD-10
Bone metastasis	Secondary malignant neoplasm of bone and bone marrow	C79.5x
Malignancy without bone metastasis	Malignancy—primary or metastatic-- (excluding non-melanoma skin cancer)	C00.xx – C97.xx, excluding C44.xx and C79.5x
Cancer, Breast	In women	C50
Cancer, Prostate	In men	C61
Hematologic malignancy	Multiple myeloma	C90.0 (C90.00 – C90.02)
Osteoporosis	Osteoporosis	M80, M81, M82
Osteoporosis	Senile osteoporosis (postmenopausal)	M80.0, M81.0
Osteoporosis	Post- oophorectomy osteoporosis	M80.1, M81.1
Osteoporosis	Disuse osteoporosis	M80.2, M81.2
Other osteoporosis (drug-induced)	Glucocorticoid- induced osteoporosis	M80.4, M81.4
Osteoporosis	Idiopathic osteoporosis	M80.5, M81.5
Osteoporosis	Other osteoporosis	M80.3, M81.3, M80.8, M81.8 M82
Osteoporosis	Unspecified osteoporosis	M80.9, M81.9
Other bone disease	Osteopenia	M85.8, M85.9
Other bone disease	Paget's disease	M88
Other bone disease	Rheumatoid arthritis	M05, M06
Other bone disease	Neoplasm of uncertain behavior of bone and articular cartilage (inclusive of giant cell tumor of bone)	D48.0
Other bone disease	Hypercalcemia of malignancy (excluding non-melanoma skin cancer)	E83.5C (hypercalcemia without specification) in combination with C00 – C97 (excluding C44)
Fragility fracture	Hip, closed	S72.x, S72.1, S72.2,
Fragility fracture	Distal radius/ulna	S52.x
Fragility fracture	Spine, closed or pathologic	S12.0, S12.1, S12.2, S12.7, S12.9, S22.0, S22.1, S32.x, S42.2, S42.3, S42.4, S42.7, S42.8, M84.4, M84.4A. T08

Amendment 2

Protocol Title:

Estimation of Off-Label Use of XGEVA® (denosumab) in Selected European Countries Using Multiple Observational Databases

Amgen Protocol Number **20101335**

Amendment 2 Date: **28 July 2014**

Rationale:

This amendment is being made to recognize changes and clarify aspects of the protocol as follows:

- Due to limited commercial availability and slow XGEVA uptake and therefore limited possibility to identify sufficient numbers of study subjects (minimum n=108) the study population will be extended to include the Capital Denmark Region, which constitutes the catchment area of the Copenhagen University Hospital. The combined population of the three regions on 1 January 2013 was 3,584,850 persons. The appropriate changes were applied to the protocol.

Description of Changes:

Section: Study Glossary

- Inserted: **EMR – Electronic Medical Records**

Section: Protocol Synopsis, Study Population

- Inserted: **or until the minimum sample of 108 is achieved.**

Section: Protocol Synopsis, Study Population

- Inserted: **If the minimum target sample size of 108 XGEVA users is not achieved within the Northern Jutland Region, the study population will be extended to include the Capital Denmark Region, which constitutes the catchment area of the Copenhagen University Hospital.**

Section: Protocol Synopsis, Statistical Considerations

- Replaced: Analysis will assess off-label use during the first 12-month period of commercial availability of XGEVA or after 200 patients have been accumulated. Additional analyses will stratify the 12-month period into 6-month intervals.

  With: **Analysis will assess off-label use during the first 12-month period of commercial availability of XGEVA or after at least 108 patients have been accumulated, whichever comes first. Additional analyses will stratify the 12-month period into 6-month intervals.**

Section: 3. STUDY DESIGN, 3.1 Study Source Population

- Replaced: Northern Jutland Region of Denmark is the proposed source population for this study (Approximate population: Northern Jutland Region of Denmark, 1.8 million) (Statistics Denmark).

  With: **Northern Jutland Region of Denmark is the proposed source population for this study. If the minimum target sample size of 108 XGEVA users is not achieved within this study population, the study population will be extended to include the Capital Denmark Region, which constitutes the catchment area of the Copenhagen University Hospital. The combined population of the three regions on 1 January 2013 was 3,584,850 persons (source: Statistics Denmark).**

Section: 3. STUDY DESIGN, 3.2 Study and Source Data, 3.2.1 Source Data

- Inserted: **The treatment codes in the Danish National Registry of Patients usually have high positive predictive values (Nielsson, 2012; Jespersen, 2012), however, it is unclear what proportion of XGEVA treatment is captured via the treatment code. Furthermore, the Danish National Registry of Patients treatment code does not distinguish between Prolia and XGEVA, necessitating medical record review. Finally, reasons for recording or not recording treatment codes are not known. Therefore, we will additionally gain access to the Electronic Medical Records (EMR) of patients treated in Aarhus University Hospital, with in the catchment area of the Central Denmark Region, which, together with the North Central**

Region, comprise the Northern Jutland Region. In contrast to the Danish National Registry of Patients, the EMR contains information on dose and brand of administered medication and does not require medical record review to ascertain medication intake. It is envisioned that the use of EMR will allow capture of XGEVA-treated patients not captured by registry records and reduce the potential selection bias that may arise if the registry record is associated with indication. If the target sample size of 108 XGEVA users is not achieved in the Northern Jutland Region, additional patients will be enrolled from hospitals in the Capital Denmark Region.

Section: 3. STUDY DESIGN, 3.4 Definitions, 3.4.3 Assessment of Relevant Diagnoses and Treatments

- Inserted: **Administration of XGEVA will be assessed electronically using the EMR system from Aarhus University Hospital.**

Section: 3. STUDY DESIGN, 3.4 Definitions, 3.4.4 Classification of XGEVA Off-Label Use, footnote of Figure 1

- Inserted: **/Capital Region (if necessary)**

Section: 4. STUDY SIZE

- Replaced: (Arneson et al, manuscript in preparation).

  With: **(Li et al, 2012)**

Section: 5. STATISTICAL ANALYSIS

- Inserted: **or after 108 patients have been accumulated, whichever comes first.**

Section: 10. COMMUNICATION OF STUDY RESULTS/PUBLICATION PLAN

- Deleted: **Data abstraction will continue for up to 200 patients identified as having received XGEVA treatment in Northern Jutland Region of Denmark.**
- Replaced: **Authorship of the manuscript will follow the guidelines proposed by the International Committee of Medical Journal Editors (2004). All authors should have (1) made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) participated in drafting the article or revising it critically for important intellectual content; and (3) approved the version to be published. Potential conflicts of interest should be disclosed.**

With: Authorship of the manuscript will follow the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE, 2011). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Any potential conflicts of interest will be disclosed. Authors will adhere to the ICMJE guidelines, specifically, all authors will have (1) made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) participated in drafting the article or revising it critically for important intellectual content; (3) approved the version to be published, and (4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Acquisition of funding, collection of data, or general supervision of the research group does not justify authorship. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Section: References

- Inserted:

International Committee of Medical Journal Editors (ICMJE). 2011. "Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publications. " http://www.icmje.org/.

Jespersen CG, Borre M, Norgaard M. Validity of the recorded codes of gonadotropin-releasing hormone agonist treatment and orchiectomies in the Danish National Patient Registry. Clin Epidemiol. 2012; 4(145-149.)

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Nielsson MS, Erichsen R, Froslev T, Taylor A, Acquavella J, Ehrenstein V. Positive predictive values of the coding for bisphosphonate therapy among cancer patients in the Danish National Patient Registry. Clin Epidemiol. 2012; 4(233-236.)

- Deleted:

Danish Medicines Agency website, for product number law: http://laegemiddelstyrelsen.dk/en/topics/statistics,-prices-and-reimbursement/product-numbers (Accessed 14-Dec-2011).