Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO), Men With Osteoporosis, and Men and Women Who Receive Prolia With Glucocorticoid Exposure in Multiple Observational Databases

Product: Denosumab

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Protocol Synopsis

Title: Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO), Men With Osteoporosis, and Men and Women Who Receive Prolia with Glucocorticoid Exposure in Multiple Observational Databases

Product: Denosumab

Product Current Development/Marketing Phase: Postmarketing safety surveillance

The synopsis summarizes the protocol for the study among women with PMO. The study plan for men with osteoporosis is summarized in. Appendix F. The study plan for men and women who receive Prolia with glucocorticoid exposure is summarized in Appendix H.

Objectives:

Specific objectives of the study are to:

1. Determine incidence rates of adverse events of special interest (AESI) in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and among all women with PMO. The prespecified AESI are:
    - Osteonecrosis of the jaw (ONJ)
    - Atypical femoral fracture leading to hospitalization
    - Fracture healing complications
    - Hypocalcemia leading to hospitalization or emergency room (ER) visit
    - Infection leading to hospitalization, ER visit, or administration of parenteral anti-infective medication
    - Dermatologic adverse events leading to hospitalization or ER visit
    - Acute pancreatitis leading to hospitalization
    - Hypersensitivity leading to hospitalization or ER visit
    - New primary malignancy (excluding non-melanoma skin cancer)
2. Describe characteristics, clinical features, and AESI risk factors in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and all women with PMO.
3. Compare the incidence of the AESI in women with PMO exposed to denosumab to that in women with PMO exposed to bisphosphonates.
4. Describe incidence rates of AESI in postmenopausal women.
5. Describe denosumab utilization patterns in subjects who receive denosumab therapy for treatment of PMO.
6. Describe Prolia utilization patterns in subjects who receive Prolia therapy for unapproved indications (indication, dosage, frequency).

Hypotheses:

This study is descriptive in nature. Incidence rates and associated 95% confidence intervals for each AESI will be estimated in women with PMO in each exposure cohort. While no formal hypotheses will be tested, effect estimates and associated 95% confidence intervals for each AESI will be provided for the denosumab-exposed cohort versus comparable bisphosphonate-exposed cohort(s) with appropriate adjustment for potential confounding factors.

Study Design:

This is a prospective open-cohort study with annual assessment and reporting of descriptive findings from 5 secondary data sources. The study period will include up to 10 years in each data system based on data availability at the time we initiate final analyses. The enrollment period start date is the denosumab international birth date, 26 May 2010. The secondary data sources will be the following:

- US Medicare, including Parts A, B, and D
- Optum Research Database (formerly United HealthCare)
- Scandinavian national health registry databases, including data from Denmark, Sweden, and Norway

Data will be collected for postmenopausal women overall, women with PMO, and subjects who receive Prolia for unapproved indications. Among women with PMO, exposure cohorts will be established based on exposure to denosumab or bisphosphonates. AESI will be identified using validated algorithms based on inpatient and outpatient diagnosis and procedure codes, and, for some AESI, medication codes or laboratory data. Selected AESI (ONJ and atypical femoral fracture) will be confirmed by medical chart review. A report will be produced annually.

Subject Selection Criteria:

Three study populations will be identified based on the following inclusion and exclusion criteria. Subjects in Medicare and Optum Research Database will need to have appropriate plan coverage to be included in any of the following populations. Appropriate plan coverage for the Optum Research Database refers to both pharmacy and medical plan coverage. Appropriate plan coverage for the US Medicare database refers to enrolment in the traditional fee-for-service Medicare (Medicare Parts A and B coverage and not in a Medicare Advantage plan), plus Part D. The requirement of 12-months of continuous enrollment is not relevant for Scandinavian national registries

because all citizens are enrolled in the universal health coverage from birth to death unless they move out of the country.

Inclusion Criteria:

- Postmenopausal women: Postmenopausal status will be determined based on age and defined as women ≥ 55 years old. For the Medicare database, only women ≥ 65 years old will be included in the analysis, given that generally all individuals in the US ≥ 65 years old are eligible for Medicare coverage and data on postmenopausal women less than 65 years old will be available for only a small number of women meeting other specialized eligibility criteria. Data for postmenopausal women (≥ 65 years old) in Medicare will be obtained from the Medicare 5% sample database. To be eligible for this population, all women in the US Medicare database and the Optum Research Database need to be continuously enrolled with appropriate plan coverage for at least 12-months. The index date for postmenopausal women is defined as the date when a patient first satisfies both the age criterion and the minimum continuous enrollment criterion (continuous enrollment criterion applicable for the US Medicare database and the Optum Research Database only).
- Women with PMO: The presence of PMO will be determined utilizing an algorithm based upon definition of postmenopausal women (≥ 65 years old in Medicare or ≥ 55 years old in other data systems), diagnostic codes indicating osteoporosis, diagnostic codes indicating osteoporotic fracture, and/or relevant PMO treatment codes (see Appendix A). A file containing data for all women with PMO in the Medicare database will be requested from CMS. To be eligible for this population, all women in the US Medicare database and the Optum Research Database need to be continuously enrolled with appropriate plan coverage for at least 12-months. In the Optum Research Database and the Scandinavian national registries, a woman must receive a diagnostic code indicating osteoporosis, a diagnostic code indicating osteoporotic fracture, or a relevant PMO treatment code on or after age 55 years old and be alive at the study start date to be eligible for the PMO cohort. The index date for women with PMO is defined as the date when a subject first satisfies both the PMO algorithm and the minimum continuous enrollment criterion (continuous enrollment criterion applicable for the US Medicare database and the Optum Research Database only).
- Subjects who receive Prolia for unapproved indications: To be eligible for this population, all subjects who received at least one dose of Prolia will be included and evaluated for potential Prolia off-label use. In the US Medicare database and the Optum Research Database, subjects need to be continuously enrolled from at least 12-months before the Prolia administration to at least 7-days after the Prolia administration with appropriate plan coverage. The earliest Prolia administration that a subject receives that satisfies the continuous enrollment criteria is defined as the index treatment. US subjects who received Prolia for unapproved indications will be defined as those who receive Prolia but did not receive Prolia for an approved indication as indicated by the approved product information (US Package Insert [USPI] for subjects from the Medicare and Optum Research Database data systems). Scandinavian subject registries reflect diagnoses recorded during hospital-based encounters (inpatient, outpatient, and emergency). To classify missing data and diagnoses resulting

from non-hospital encounters, an "Unclear" classification is assigned to those cases without enough information to be qualified as off-label or on-label use (per the Summary of Product Characteristics [SmPC]). Data from these subjects will be analyzed separately to assess off-label use of Prolia.

Exclusion Criteria:

- Women with PMO: Women with Paget's disease during the 12-month period prior to meeting criteria for inclusion in PMO population will be excluded. Additionally, in US Medicare and Optum Research Database, women with a diagnosis of malignancy (excluding non-melanoma skin cancer) or treatment with chemotherapy, hormonal therapy or radiation therapy for cancer up to 12-months before index date will be excluded. In the Scandinavian national registries, women with a diagnosis of cancer according to the patient registry and/or cancer registry up to 12-months prior to meeting criteria for inclusion in PMO population will be excluded.

Exposure Cohorts:

In the PMO study population, exposure will be defined on the basis of exposure to denosumab, exposure to bisphosphonates overall, or exposure separately to intravenous (IV) or oral bisphosphonates and will take into account changes in therapy over time.

Subject Follow-up:

Follow-up will begin for postmenopausal women and women with PMO at the time they satisfy the patient selection criteria during the study period. All selected postmenopausal women will continue to be followed until the first of the following: disenrollment from the data system, death, or end of the study. All selected women with PMO will continue to be followed until the first of the following: disenrollment from the data system, death, Paget's disease, or end of the study. In addition, in US Medicare and Optum Research Database, the follow-up of women with PMO for AESI other than new primary malignancy will be censored at diagnosis of malignancy (excluding non-melanoma skin cancer), treatment with chemotherapy, hormonal therapy or radiation therapy for cancer. In the Scandinavian national registries, the follow-up of women with PMO for AESI other than new primary malignancy will be censored at the diagnosis of malignancy (excluding non-melanoma skin cancer) according to the patient registry and/or cancer registry. The follow-up for incident events of all AESI will also end at the occurrence of the corresponding AESI.

Ascertainment of Adverse Events of Special Interest:

AESI will be identified using case ascertainment algorithms that incorporate diagnosis, treatment, and, for some AESI, medication codes or laboratory data. Algorithms

incorporating diagnosis codes are based upon International Classification of Disease (ICD) diagnosis codes (ICD-9-CM or ICD-10-CM) for US Medicare, and Optum Research Database, and ICD-10 for the Scandinavian national registries).

Potential cases of ONJ, including all denosumab-exposed and a sample of non-denosumab-exposed ONJ cases in women with PMO from Medicare and the national registries in the Central Denmark Regions and Sweden will be confirmed by medical chart review according to predefined case confirmation criteria. Potential cases of atypical femoral fracture leading to hospitalization in all denosumab-exposed and a sample of non-denosumab-exposed potential cases in women with PMO from the Central Denmark Regions will be confirmed by medical chart and radiographic review according to predefined case confirmation criteria.

Study Size and Estimation of Study Power:

Sample size and power were estimated based on the number of women with PMO.

Estimated person-years of observation among women with PMO that will be available for calculation of AESI incidence rates are based on the assumption that (i) 50% of women with osteoporosis are receiving an osteoporosis medication, and (ii) 5% of women with PMO receiving an osteoporosis medication will be treated with denosumab when the market uptake of denosumab has stabilized. It is further assumed that during the first year after denosumab market entry, only 2.5% of women with PMO who receive treatment will be treated with denosumab. Based upon these assumptions, the overall number of person-years of observation among women with PMO receiving denosumab is estimated to be 90,863, 272,588 and 575,462 patient-years at 2, 5, and 10-years post approval. The number of person-years for individual data systems at 10 years post approval ranges from 19,712 in Optum Research Database to 475,000 in US Medicare. Power was calculated using the Fisher's 2-sided exact test with $\alpha = 0.05$ based on a group ratio of 10:1 between comparator- and denosumab-exposed person-years with up to 10 years of follow-up. There will be nearly 100% power to detect a relative risk of 2 or higher for background rate of 7 cases per 100,000 person-years or higher.

In response to FDA Advice/Information Request received on 16 August 2012 (IND 9837) sample size and power projections for women with PMO were updated after 3-years of Prolia post-launch data were available in all data systems. Updated years 5 and 10 projections and the related tables and figures are in Appendix G.

Statistical Analysis:

Analyses will describe characteristics of, and AESI incidence among women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates overall, women with PMO separately exposed to oral or IV bisphosphonates and all women with PMO. To eliminate the influence of cancer on the risk of AESI, in US Medicare and Optum Research Database, subjects will no longer contribute to the follow-up for any AESI other than new primary malignancy after being diagnosed with malignancy (excluding non-melanoma skin cancer), or receiving treatment with chemotherapy, hormonal therapy or radiation therapy for cancer. In the Scandinavian national registries, subjects will no longer contribute to the follow-up for any AESI other than new primary malignancy after being diagnosed with malignancy (excluding non-melanoma skin cancer) according to the patient registry and/or cancer registry. Person-year adjusted AESI incidence rates will be calculated for each exposure cohort by dividing the total number of events by the total patient-years (sum of subjects' time at risk) from which the events arose.

When there are sufficient numbers of cases, Kaplan-Meier survival curves and/or cumulative incidence function plots will be used to estimate time to first onset of event and Poisson regression models will assess rates of recurrent events.

To compare the risk among the Prolia-exposed cohort and bisphosphonate-exposed cohort in women with PMO we will employ an as-treated, osteoporosis treatment naive user design to assess the adjusted risk ratios (and corresponding 95% confidence intervals) of each AESI separately among subjects who initiate denosumab and subjects who initiate zoledronic acid using inverse-probability of treatment and censoring weighted (IPTCW) estimation functions.

Descriptive statistics will be used to characterize postmenopausal women. In addition, AESI incidence rates will be assessed in this group.

Descriptive statistics will be used to characterize denosumab utilization patterns among women who receive denosumab for the treatment of PMO. Utilization will be assessed by factors including frequency of administration, length of utilization, and the proportion of those treated who discontinue therapy or switch to another osteoporosis medication.

Descriptive statistics will be used to characterize subjects receiving Prolia for unapproved indications.

Analyses will be conducted separately for each specific data system. In addition, results may be combined across data systems using meta-analytic methods, as appropriate.

Reporting:

Safety data from this study will be assessed annually and provided in an annual report. In addition, the annual report will be provided in the Periodic Benefit Risk Evaluation Report (PBRER)/ Periodic Safety Update Report (PSUR). A final report to the regulatory agency will be completed within 6 months following the end of the study. The final report will be comprehensive for all objectives and for the prespecified AESI. Confirmed denosumab-exposed cases of ONJ will be reported in accordance with regional regulatory agency commitments.

Sponsor/Licensee: Amgen Inc.

Study Design Schema

Selected Data System

The US Medicare and Optum Research Database health management data systems and the Scandinavian national health registry systems were selected for the study. These data systems collect routine medical insurance claims information (including inpatient and outpatient medical claims and prescription claims), electronic medical chart information, or health registry information, depending upon specific data system employed.

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Establish Study 20090522 Exposure Cohorts

Women with PMO will be assessed by exposure cohort: all women with PMO, women with PMO who receive denosumab treatment; women with PMO who receive bisphosphonates overall; and women with PMO who separately receive oral or IV bisphosphonate.

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Follow-up of Subjects and AESI Ascertainment

Inpatient and outpatient medical information, including diagnoses, treatments, and prescription information will be analyzed annually to assess adverse events of special interest (AESI) and other study objectives.

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AESI Confirmation

AESI will be identified using validated algorithms based on inpatient and outpatient diagnosis and procedure codes, and, for some AESI, medication codes or laboratory data. Potential cases of ONJ, including all denosumab-exposed and a sample of non-denosumab-exposed ONJ cases in women with PMO from Medicare and the Central Denmark Regions and Sweden will be confirmed by medical chart review according to predefined case confirmation criteria. Potential cases of atypical femoral fracture leading to hospitalization in all denosumab-exposed and a sample of non-denosumab-exposed potential cases in women with PMO from the Central Denmark Region will be confirmed by medical chart and radiographic review according to predefined case-confirmation criteria.

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Annual Assessment and Reporting

All study objectives will be assessed annually based on predefined analysis methods assessed and provided to regulatory agencies in an annual report. In addition, this report will be provided in the Periodic Benefit Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR).

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Final Analysis and Reporting

Final analyses will be completed within 6 months following the end of the study period based on predefined analysis methods and strategies. A final study report will be submitted to regulatory agencies.

Study Glossary and Definition

Abbreviation/Acronym/ Term	Definition
AAOMS	American Association of Oral and Maxillofacial Surgeons
ACR	American College of Rheumatology
AESI	Adverse Event of Special Interest
AFF	Atypical femoral fracture
AHFS	American Hospital Formulary Service
AIPW	Augmented Inverse Probability of treatment and censoring Weighted
ATC	Anatomical Therapeutic Chemical classification
BLA	Biologics License Application
BP	Bisphosphonate
CCI	Charlson Comorbidity Index
CKD	**Chronic Kidney Disease**
CMS	Centers for Medicare and Medicaid Services
Confounders	Extraneous factors that account for a difference in disease frequency between the exposure cohorts; associated factors serving as surrogates for these factors are also commonly called confounders
CPT-4	Current Procedural Terminology, 4th Edition
DOB	Date Of Birth
DOD	Date Of Death
EMA	European Medicines Agency
EMR	Electronic medical record(s)
ER	Emergency room
FDA	US Food and Drug Administration
GIOP	Glucocorticoid-induced osteoporosis
GPRD	General Practice Research Database
HALT	Hormone ablation therapy
HICL	Hierarchical Ingredient Code List
HCPCS	Healthcare Common Procedure Coding System
HMO	Health maintenance organization
ICD-10	International Classification of Diseases – 10th Revision
ICD-9-CM	International Classification of Diseases – 9th Revision, Clinical Modification
IPCW	Inverse Probability Censoring Weighting
IPTCW	**Inverse Probability of Treatment and Censoring Weighting**
IPTW	Inverse Probability Treatment Weighting
ITT	Intention-to-treat

Abbreviation/Acronym/ Term	Definition
IV	Intravenous
Length of disease	Time period from initial diagnosis of the disease to date of study event
MDRR	**Minimal Detectable Relative Risk**
NDC	National Drug Code
NHI	National Health Informatics
NOMESCO	Nordic Medico-Statistical Committee
ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
OXMIS	Oxford Medical Information Systems
PBRER	Periodic Benefit Risk Evaluation Report
PMO	Postmenopausal osteoporosis
PPV	Positive predictive value
P**S**	A propensity score is an estimate of the probability that an observed entity (a person) would undergo the treatment. This probability is sometimes a predictor of outcomes.
PSUR	Periodic Safety Update Report
Q6M	Every 6 months
RA	Rheumatoid arthritis
RANKL	RANK ligand
Selection bias	The introduction of error due to systematic differences in the characteristics between those selected and those not selected for a given study. In a sampling bias, the error is the result of failure to ensure that all members of the reference population have a known chance of selection in the sample.
SERMS	Selective Estrogen Receptor Modulators
SMD	Standardized Mean Difference
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
TNF	Tumor necrosis factor
UAB	University of Alabama at Birmingham
US	United States
USPI	US Package Insert
ZA	Zoledronic acid

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1. INTRODUCTION

Denosumab is a fully human IgG_2 monoclonal antibody that inhibits osteoclast formation, function, and survival, decreasing bone resorption and increasing cortical and trabecular bone mass and bone strength. The favorable benefit-risk profile of Denosumab 60 mg (Prolia®) for the treatment of postmenopausal osteoporosis (PMO) was characterized in the denosumab bone loss Marketing Application; denosumab was shown to be an effective and well tolerated treatment for osteoporosis in women with PMO. Certain adverse events of special interest (AESI) for denosumab will be examined further in the postmarketing environment. This study is one component of the denosumab pharmacovigilance program that will monitor the incidence of these AESI in the postmarketing setting.

After its initial marketing approval, denosumab was subsequently approved in the United States for use in men with osteoporosis and for treatment of glucocorticoid-induced osteoporosis (GIOP) in the US and EU. As a result, these substudies are summarized in Appendix F and Appendix H.

The AESI that will be assessed in this study are as follows:

- osteonecrosis of the jaw (ONJ)
- atypical femoral fracture leading to hospitalization
- fracture healing complications
- hypocalcemia leading to hospitalization or emergency room (ER) visit
- infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication
- dermatologic adverse events leading to hospitalization or ER visit
- acute pancreatitis leading to hospitalization
- hypersensitivity leading to hospitalization or ER visit
- new primary malignancy (excluding non-melanoma skin cancer)

This study will be conducted using several large data systems in several countries including US Medicare, Optum Research Database, and the Scandinavian national health registries (including the national registries of Denmark, Norway, and Sweden).

Analyses will describe and compare, after appropriately adjusting for relevant confounding factors, incidence rates of AESI in women with PMO receiving denosumab, and women with PMO who are not exposed to denosumab therapy but are receiving bisphosphonate therapy. These events will also be described in women who are postmenopausal and in women with PMO.

When denosumab becomes commercially available, new safety issues and concerns may arise through postmarketing safety surveillance processes and may be raised by regulatory agencies worldwide. The study infrastructure and data resources will be available to examine new safety issues and concerns. After careful design and consideration, new safety issues or concerns may be defined as new prespecified AESI to be included in the study protocol through a formal protocol amendment. Such changes will be communicated to regulatory agencies. However, the study itself will not serve as a safety signal detection tool for any non-prespecified adverse events.

2. OBJECTIVES

Specific objectives of the current study are to:

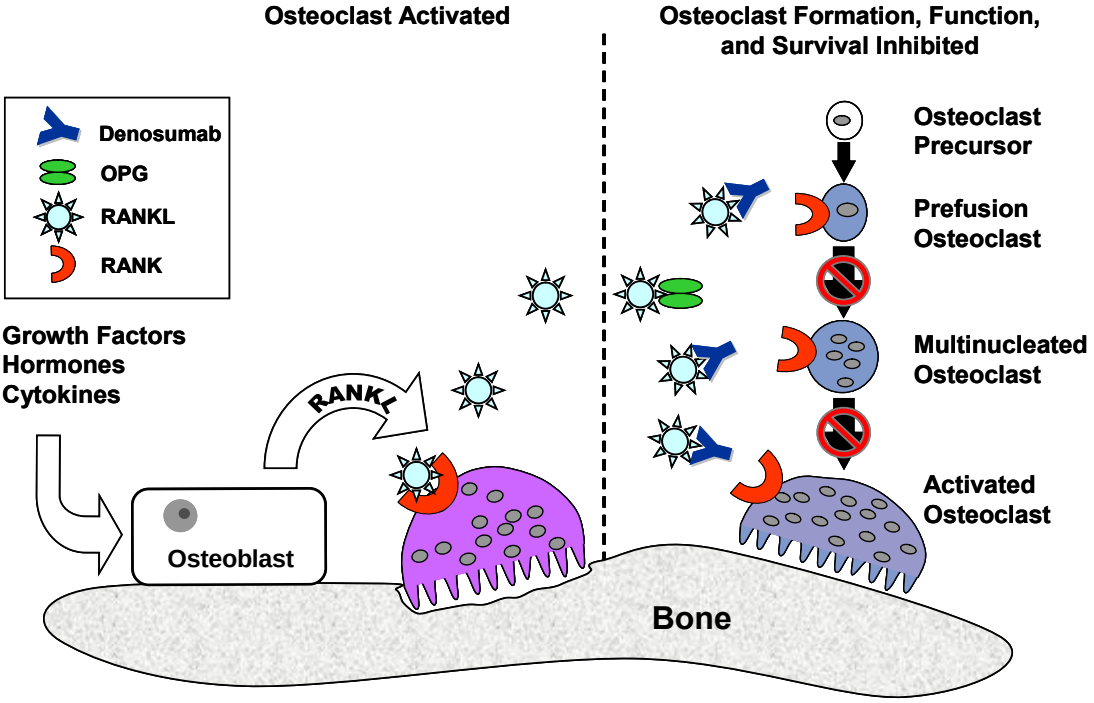
1. Determine incidence rates of adverse events of special interest (AESI) in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and among all women with PMO. The prespecified AESI are:
   - osteonecrosis of the jaw (ONJ)
   - atypical femoral fracture leading to hospitalization
   - fracture healing complications
   - hypocalcemia leading to hospitalization or emergency room (ER) visit;
   - infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication
   - dermatologic adverse events leading to hospitalization or ER visit
   - acute pancreatitis leading to hospitalization
   - hypersensitivity leading to hospitalization or ER visit
   - new primary malignancy (excluding non-melanoma skin cancer)
2. Describe characteristics, clinical features, and AESI risk factors in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and all women with PMO.
3. Compare the incidence of the AESI in women with PMO exposed to denosumab to that in women with PMO exposed to bisphosphonates.
4. Describe incidence rates of AESI in postmenopausal women.
5. Describe denosumab utilization patterns in subjects who receive denosumab therapy for treatment of PMO.
6. Describe Prolia utilization patterns in subjects who receive Prolia therapy for unapproved indications (indication, dosage, frequency).

3. BACKGROUND AND RATIONALE

3.1 Denosumab Therapy for Osteoporosis

Denosumab (also referred to as AMG 162) is a fully human IgG_2 monoclonal antibody that binds to RANK ligand (RANKL), and blocks the interaction of RANKL with RANK. RANKL is a member of the tumor necrosis factor (TNF) superfamily, and is a key mediator in the pathway required for the formation, function, and survival of the cells that resorb bone (osteoclasts). Denosumab binds with high affinity and specificity to RANKL, thereby neutralizing the ligand and suppressing osteoclast-mediated bone turnover.

Figure 3-1. The Osteoprotegerin (OPG)/RANK/RANKL Pathway



Nonclinical and clinical studies conducted to date demonstrate that denosumab is well tolerated and exhibits a favorable safety profile in subjects who were followed for up to 6 years.

3.2 Rationale for the Study

Clinical studies demonstrate that denosumab is well tolerated in subjects followed for up to 6 years. Certain AESI will be examined further in the postmarketing environment. The rationale for these specific AESI are provided in Section 3.3.

Amgen has committed to assess occurrence of these AESI and their public health impact in the postmarketing setting. These assessments will be based upon clinical practice data using standard and enhanced pharmacovigilance approaches. The

proposed study leverages multiple observational data systems that will allow Amgen to proactively evaluate and quantify the incidence of specific AESI observed in the clinical development program, and will also provide a tool and resources for evaluating new safety issues and concerns arising in the postmarketing period.

3.3 Adverse Events of Special Interest

3.3.1 Osteonecrosis of the Jaw (ONJ)

Because suppression of bone turnover has been associated with ONJ in the context of bisphosphonate treatment, ONJ was monitored carefully in the denosumab clinical trial program. ONJ is defined as an area of exposed alveolar or palatal bone, associated with nonhealing after 8 weeks of appropriate care in a patient without prior history of radiation to the head, face, or mouth. This definition was revised in 2014 (Ruggiero et al, 2014) and is currently defined as exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks in a patient without prior history of radiation to jaws or obvious metastatic disease to the jaws. In the denosumab clinical trial program, potential events of ONJ were submitted for review to an independent ONJ Adjudication Committee, which was blinded to treatment. ONJ has been reported rarely in the clinical study program in osteoporosis patients receiving denosumab 60 mg every 6 months; the risk of developing ONJ may increase with duration of exposure. ONJ has also been observed in advanced cancer patients receiving denosumab 120 mg every 4 weeks.

Monitoring for ONJ continues to be a focus of Amgen's comprehensive global postmarketing pharmacovigilance and clinical trial program, which includes routine spontaneous reporting and adjudication in ongoing clinical studies in both PMO and oncology. In addition, ONJ will be assessed as an AESI in this study using expert medical review.

3.3.2 Atypical Femoral Fracture

An atypical femoral fracture is defined as a fracture occurring in a fall from a standing height or less resulting in subtrochanteric or proximal diaphyseal fracture of the femur that has a characteristic appearance on imaging studies of a simple transverse or oblique fracture with beaking of the cortex and diffuse cortical thickening of the proximal femoral shaft (Nevasier et al, 2008). The American Society for Bone and Mineral Research Task Force updated the definition of atypical femoral fracture (Shane et al, 2014) as a fracture located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. In addition, at least 4 of

5 major features must be present. Major features include 1) associated with no trauma or minimal trauma, as in a fall from a standing height or less 2) fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur, 3) complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex, 4) non-comminuted or minimally comminuted, and 5) localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (beaking or flaring). Specifically excluded from the definition of atypical femoral fractures are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumors, miscellaneous bone diseases (eg, Paget's disease, fibrous dysplasia) and periprosthetic fractures.

Cases of atypical femoral fractures have been reported in the osteoporosis literature in association with long-term bisphosphonate use. Some case series have reported a possible association between atypical femoral fractures and long-term alendronate therapy, with low bone turnover as the suggested etiology (Odvina et al, 2010; Odvina et al, 2005; Lenart et al, 2008), while others have not (Abrahamsen et al, 2009). In fact, some case reports have shown evidence of increased cortical remodeling rather than severe suppression as originally hypothesized (Somford et al, 2009; Kwek et al, 2008). The contradictory nature of these reports reflects an area of uncertainty in understanding the relationship between occurrence of atypical femoral fractures and reduction in bone turnover with bisphosphonate therapy.

In the osteoporosis clinical trial program, atypical femoral fractures were reported in patients treated with denosumab. Since the risk of atypical femoral fracture has been associated with long-term bisphosphonate treatment and experience with subjects receiving denosumab for ≥ 4 years is limited, atypical femoral fracture leading to hospitalization will be assessed as an AESI in this study using expert medical review.

3.3.3 Fracture Healing Complications

Fracture repair is a complex, coordinated biological process that relies on wound repair (stem cell recruitment, angiogenesis, mitogenesis), bone-specific anabolism (osteoblast differentiation/ proliferation, bone formation) and catabolism (bone remodeling) (Little et al, 2007). Although most fractures heal without complications, certain fractures are associated with abnormalities in healing. Expected fracture healing times vary significantly by site of fracture, demographic characteristics of

the patient, and comorbidities (Bhandari et al, 2002). The most clinically significant adverse outcome associated with fracture healing is nonunion, which is when bone segments fail to unite and a pseudarthrosis develops.

In the United States, an estimated 5% to 10% of all fractures are complicated by delayed fracture healing or nonunion (Zura et al, 2007; Einhorn, 1995). The development of these complications is influenced by a variety of factors including the patients' general health, lifestyle factors, advanced age, menopausal or pregnancy status, treatment or intervention, and posttreatment complications (Buckwalter et al, 2006; Court-Brown et al, 2006). Nonunion is typically treated with revision surgery when quality of life is expected to be adversely impacted.

In women with PMO, femoral neck fractures account for most nonunion complications, and in this fracture type complications are associated with poor vascular supply to the proximal femur.

Fracture healing in subjects receiving denosumab was carefully evaluated in the denosumab clinical development program. No untoward clinical impact on fracture healing was demonstrated. Nonetheless a theoretical concern exists that use of an anti-resorptive agent may lead to delays in fracture healing by suppressing bone remodeling. Thus, nonunion will be assessed as an AESI in this study.

3.3.4 Hypocalcemia Leading to Hospitalization or ER Visit

Due to the potential for denosumab to lower serum calcium levels, hypocalcemia was monitored carefully in the denosumab clinical program. In denosumab clinical trials, reductions in serum calcium levels were mild, transient, and generally not associated with symptoms. The incidence of clinically significant hypocalcemia was rare. No serious adverse event of hypocalcemia was reported in clinical trials in denosumab-treated subjects with PMO. One serious adverse event of hypocalcemia was reported in a clinical trial in a denosumab-treated subject with nonmetastatic prostate cancer receiving hormone ablation therapy (HALT); the investigator considered this event not related to investigational product. In trials in women with PMO, patients were supplemented with calcium and vitamin D daily. Severe symptomatic hypocalcemia has been reported in post-marketing setting as noted in the USPI and SmPC. The potential for hypocalcemia with denosumab therapy appeared greater in subjects with severe renal impairment or end-stage renal disease compared with those with mild or moderate renal impairment and those with normal renal function. This is likely due to the fact that subjects with severe chronic kidney disease or end-stage renal

disease rely more heavily on bone to provide a source of calcium due to their impaired ability to reabsorb calcium from the urine and to absorb calcium in the gastrointestinal tract.

Due to the potential for denosumab to cause hypocalcemia, hypocalcemia leading to hospitalization or ER visit will be monitored in this study.

3.3.5 Infection Leading to Hospitalization, ER Visit, or Administration of Parenteral Anti-infective Medication

RANKL is expressed on activated T and B cells and in the lymph nodes. Results of a nonclinical study using RANK/RANKL knockout mice suggest that the complete absence of RANKL could interfere with the development of lymph nodes in the fetus (Martin and Gillespie 2001; Fata et al, 2000); however, nonclinical studies suggest that the RANKL/RANK pathway does not play an essential role in the adult immune system (Loser et al, 2006; Padigel et al, 2003; Green et al, 2002; Bachmann et al, 1999). Furthermore, no clinically relevant effect of denosumab treatment was observed on peripheral blood immune cell subset profiles in studies in healthy elderly men, postmenopausal women, or postmenopausal women with low bone mineral density. No evidence of a treatment effect of denosumab on immunoglobulin production was observed. However, because a theoretical risk exists that denosumab could increase the incidence of infections, infection adverse events were prospectively identified as an event of interest in the denosumab clinical trial program.

In the clinical trial program, a greater incidence of serious adverse events of skin infections was observed in denosumab-treated subjects compared with placebo-treated subjects in PMO Study 20030216. In addition, small imbalances in the incidence of serious adverse events of infections of the urinary tract and diverticulitis were observed between the denosumab and placebo treatment groups. Adverse events of infection, including common infections such as pneumonia were generally balanced between treatment groups in the clinical program. Opportunistic infections and fatal adverse events of infection were rare and balanced between treatment groups.

Because of the imbalance observed for skin infections leading to hospitalization in Study 20030216 and because of small treatment differences in some other serious infections, serious infection will be assessed in this study. The AESI of serious infection will be assessed as infections that lead to hospitalization, ER visit, or parenteral treatment with anti-infective medication.

3.3.6 Dermatologic Adverse Events Leading to Hospitalization or ER Visit

In denosumab clinical studies in PMO, the incidence of adverse events related to the skin and subcutaneous tissues was slightly higher in the denosumab group (15.1%) than in the placebo group (12.4%), largely due to a higher incidence of eczema (including events of dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, and eczema), which occurred in 3.1% of subjects in the denosumab group and 1.7% of subjects in the placebo group.

Dermatologic adverse events leading to hospitalization or ER visit will be monitored as an AESI in this study.

3.3.7 Acute Pancreatitis Leading to Hospitalization

Overall, the incidence of pancreatitis in clinical trials was very low in the denosumab clinical program. Serious adverse events of pancreatitis were reported in 8 denosumab-treated subjects (0.2%; 5 cases were acute pancreatitis) and 3 placebo-treated subjects (0.7%; none was reported as acute) in the PMO/HALT program. No pattern was apparent in the time to onset of acute pancreatitis. The incidence of pancreatitis was similar for denosumab- and placebo-treated subjects in the program as a whole, and in most cases, known risk factors for pancreatitis were present, so a causal role of denosumab in the events of acute pancreatitis appears unlikely.

Acute pancreatitis leading to hospitalization will be followed as an AESI in this study. Medication-induced pancreatitis is most likely to be acute rather than chronic, so this study will focus on acute cases. Since the majority of patients with acute pancreatitis encountered in the ER are likely to be eventually hospitalized (Fagenholz et al, 2007), the current study will not search for subjects with diagnostic codes for acute pancreatitis that were associated with ER visits but not with hospitalization.

3.3.8 Hypersensitivity Leading to Hospitalization or ER Visit

Any monoclonal antibody could theoretically be associated with hypersensitivity reactions, including anaphylactic events. Clinically significant hypersensitivity including anaphylaxis associated with denosumab treatment has been reported in the postmarketing setting as noted in USPI.

Hypersensitivity leading to hospitalization or ER visit will be evaluated as an AESI in this study.

3.3.9 New Primary Malignancy

RANKL is expressed on activated T and B cells and in the lymph nodes. Results of a nonclinical study using RANK/RANKL knockout mice suggest that the complete absence of RANKL could interfere with the development of lymph nodes in the fetus (Martin and Gillespie 2001; Fata et al, 2000); however, nonclinical studies suggest that the RANKL/RANK pathway does not play an essential role in the adult immune system (Loser et al, 2006; Padigel et al, 2003; Green et al, 2002; Bachmann et al, 1999). Further, there is no evidence to suggest that denosumab has carcinogenic potential via impairment of immune system.

Data from all denosumab clinical studies were assessed for the overall incidence of malignancy adverse events. Results from clinical studies do not indicate an increased incidence of malignancy in denosumab-treated subjects.

However, due to the theoretical risk of malignancy, new primary malignancy will be assessed as an AESI in this study.

3.4 Study Hypotheses

This study is descriptive in nature. Incidence rates and associated 95% confidence intervals for each AESI will be estimated for women with PMO in each exposure cohort. While no formal hypotheses will be tested, effect estimates and associated 95% confidence intervals for each AESI will be provided for the denosumab-exposed cohort versus comparable bisphosphonate-exposed cohort(s) with appropriate adjustment for potential confounding factors.

4. STUDY PLAN

4.1 Study Design

This is a prospective open cohort study using secondary data sources with annual assessment and reporting of descriptive findings. The secondary data sources to be utilized include:

- US Medicare, including Parts A, B, and D
- Optum Research Database
- Scandinavian national health registry databases, including data from Denmark, Sweden, and Norway

Data will be collected for postmenopausal women overall, women with PMO, and patients who receive Prolia for unapproved indications. Among women with PMO,

exposure cohorts will be established based on exposure to denosumab or bisphosphonates.

AESI will be identified using validated algorithms based on inpatient and outpatient diagnosis and procedure codes, and, for some AESI, medication codes or laboratory data. Selected AESI (ONJ and atypical femoral fracture) will be confirmed by medical chart review. A report will be produced annually.

The study period will include up to 10 years of follow-up in each data system based on data availability at the time we initiate final analyses. The enrollment period start date is the denosumab international birth date, 26 May 2010.

4.2 Description of Data Sources

Several major data systems will be used in this study. These data systems have the following key characteristics:

- Large patient populations with PMO to achieve adequate power to detect increased risk of rare events
- Ability to accurately capture diagnosis, procedure, and medication codes to identify target populations of women with PMO and ascertain occurrence of AESI
- Minimization of potential biases due to loss to follow-up given essentially complete follow-up until death or emigration in the 2 largest data systems (US Medicare and the Scandinavian national registries). This facilitates capture of events that may only occur after long-term therapy or that have moderate to long induction periods. This also obviates concerns about bias due to differential loss to follow-up (eg, by adherence to medication or other factors)
- Access to medical charts to verify occurrence of certain events
- Investigators experienced in pharmacoepidemiology who have the methodologic expertise to refine methods during a long-term follow-up study and to conduct complex multivariate analyses that assure validity of the approaches used to assess risks related to denosumab exposure

Specific data sources are described below.

4.2.1 US Medicare

US Medicare is a comprehensive, nationally representative, population-based data system of US patients ≥ 65 years of age that will include a large proportion of those women who are at high risk of osteoporosis, as well as a substantial majority of the women who will be eligible to receive denosumab in the US. A total of approximately 20.6 million women have pharmacy benefits through Medicare Parts B and D, which can be linked to inpatient hospitalization (Part A) and outpatient clinic or physician office (Part B) claims. It takes Centers for Medicare & Medicaid Services approximately

2 years to format and implement their quality control protocols resulting in a data lag before the data are available to researchers. Patients included in the US Medicare data system are those with full fee-for-service (traditional) Medicare, which currently accounts for approximately 82% of women ≥ 65 years old in the United States. Exclusions are individuals with primary employer coverage (that is, Medicare is the secondary payer, estimated at approximately 3% of the Medicare population [Morrisey, 1993]) and those enrolled in Medicare Advantage (medical care is received in and administered by health maintenance organization [HMO] providers). The proportion of beneficiaries enrolled in Medicare Advantage has varied between 10% and 20%. Subject information is documented from initial enrollment in Medicare until the date of death or to subsequent loss of full Medicare coverage, estimated at < 2% annually, enabling long-term follow-up of subjects. Date (but not cause) of death is routinely captured in the US Medicare data system so as to prevent overpayment of benefits. Medical charts can be retrieved from US Medicare for the confirmation of specific adverse events, as needed.

Selected clinical outcomes will be identified by International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic codes, and up to 6 procedures recorded using Current Procedural Terminology, 4th Edition (CPT-4) codes from the Medicare Parts A, B, and D databases.

The data from US Medicare have frequently been used to characterize drug safety in bone health and in other therapeutic areas, for example, cancer, diabetes, cardiovascular disease, and infectious disease (Hershman et al, 2008; Wang et al, 2008; Wilkinson et al, 2007; Burwen et al, 2007; Setoguchi et al, 2007; Winklemayer et al, 2008). As the largest data system, US Medicare is expected to play a particularly important role in assessing incidence of rare AESI.

4.2.2 Optum Research Database

The subjects included in this study are drawn from a proprietary research database containing eligibility and pharmacy and medical claims data from a large U.S. health plan affiliated with Optum. For 2019, data are available for approximately 14.3 million individuals with medical and pharmacy coverage. The Optum Research Database includes data from approximately 1,379,000 members aged ≥ 55 years old. Data, which are routinely captured, verified, and automated, include claims submitted by healthcare professionals for covered services (claims collected from inpatient, hospital outpatient, ER, surgery centers, physician's office), claims submitted by pharmacies for reimbursement for prescriptions, enrollment data to track plan membership for billing

premiums, and provider data to track participating physicians who have contracted with health plans to provide services to their enrollees. Typically, data pertaining to drugs dispensed in hospitals are unavailable. Optum Research databases continuously receive new information from enrollment, pharmacy, and medical claims. Pharmacy claims data are available within 6 weeks of claim submission, and approximately 6 to 9 months is required to capture and adjudicate 95% of paid medical claims.

The research databases consist of medical and pharmacy administrative claims data from 1993 to the present. Data are relatively complete for all billable medical transactions. Medical transactions that do not result in a bill that would be paid by United HealthCare will not be present. For example, if reimbursement is capitated and there is no requirement to submit a bill for payment, that service may not be included in the database. Claims for subjects with Medicare supplemental coverage provided by United HealthCare may not capture information for encounters or prescriptions paid for by Medicare rather than United HealthCare. Prescription data for subjects with Medicare supplemental coverage may not be captured if subjects reach their drug benefit limits. Because the primary purpose of the United HealthCare data system is to facilitate reimbursement for healthcare provided, data for variables that might be found in a medical chart, but are not used for billing purposes such as height, weight, or smoking, are generally not available. Optum research activities utilize de-identified data from the research database. Chart reviews (with appropriate approvals) are available for pharmacoepidemiologic research studies.

Optum Research database has also been used extensively in evaluating drug safety (Engel-Nitz et al, 2008; Loughlin et al, 2008; Seeger et al, 2007; Yee et al, 2002; Hennessey, 2006; Miller et al, 2003; Loughlin et al, 2002). In 2005, Optum was selected by the US Food and Drug Administration (FDA) to provide support for drug safety monitoring and assessment of potential risks related to pharmaceutical agents, largely due to the extensive data resources and analytic capabilities available.

4.2.3 Scandinavian National Health Registries

Three Scandinavian national health registry systems (Denmark, Norway, and Sweden) capture health-related data on all citizens through a complex system of interlinked databases (linked by a citizen personal identification number that follows each citizen from birth to death). In addition, the data are updated and cleaned once a year for research purposes. These procedures result in a 2-year data lag before data is available to the study sites. Data cover a broad spectrum of health information including

medical records, hospitalizations, prescriptions, laboratory and pathology results, disease registries (eg, cancer registry), death certificates, and socioeconomic data (eg, occupation, job title, and salary). All women are represented in these national registries until death or emigration, providing virtually complete long-term follow-up. Death certificate data are collected electronically, including diagnosis codes for cause of death and the decedent's civil registration number that permits linkage to other national health databases. Thus, a large amount of specialized information from disease- or procedure-specific registries, such as the Danish Hip Fracture Registry or the Danish Hip Arthroplasty Registry, is available for research. All of these specialized registries can be linked at the subject level to other national registries using the subject's personal identification number (Sorensen et al, 2008). Further, 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 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).

All 3 countries use electronic medical records (EMR) and/or paper medical charts. Given that medical care in each country is provided as part of national health systems, records or charts are available for research for the vast majority of individuals, and, with special permission, pathology specimens may be assessed and individual subjects re-examined.

The Scandinavian national registries are widely recognized as valuable sources for the conduct of pharmacoepidemiologic investigations and have been used to investigate the safety profiles of numerous pharmaceuticals (Furu et al, 2010). Many researchers have used these national databases to conduct pharmacoepidemiologic and/or validation studies (Joensen et al, 2009; Christensen et al, 2007; Klemmensen et al, 2007; Krarup et al, 2007).

4.3 Subject Selection Criteria

Three study populations will be identified based on the following inclusion and exclusion criteria. Subjects in Medicare and Optum Research Database will need to have appropriate plan coverage to be included in any of the following populations. Appropriate plan coverage for the United HealthCare database refers to both pharmacy and medical plan coverage. Appropriate plan coverage for the US Medicare database refers to enrolment in traditional fee-for-service Medicare (Medicare Parts A and B coverage and not in a Medicare Advantage plan), plus Part D. The requirement of 12-months of continuous enrollment is not relevant for Scandinavian national registries

because all citizens are enrolled in the universal health coverage from birth to death unless they move out of the country.

4.3.1 Inclusion Criteria

- Postmenopausal women: Postmenopausal status will be determined based on age and defined as women ≥ 55 years old. For the Medicare database, only women ≥ 65 years old will be included in the analysis, given that generally all individuals in the US ≥ 65 years old are eligible for Medicare coverage and data on postmenopausal women less than 65 years old will be available for only a small number of women meeting other specialized eligibility criteria. Data for postmenopausal women (≥ 65 years old) in Medicare will be obtained from the Medicare 5% sample database. To be eligible for this population, all women in the US Medicare database and the Optum Research Database need to be continuously enrolled with appropriate plan coverage for at least 12-months. The index date for postmenopausal women is defined as the date when a subject first satisfies both the age criterion and the minimum continuous enrollment criterion (continuous enrollment criterion applicable for the US Medicare database and the Optum Research Database only).
- Women with PMO: The presence of PMO will be determined utilizing an algorithm based upon definition of postmenopausal women (≥ 65 years old in Medicare or ≥ 55 years old in other data systems), diagnostic codes indicating osteoporosis, diagnostic codes indicating osteoporotic fracture, and/or relevant PMO treatment codes (see Appendix A). A file containing data for all women with PMO in the Medicare database will be requested from CMS. To be eligible for this population, all women in the US Medicare database and the Optum Research Database need to be continuously enrolled with appropriate plan coverage for at least 12-months. In the Optum Research Database and the Scandinavian national registries, a woman must receive a diagnostic code indicating osteoporosis, a diagnostic code indicating osteoporotic fracture, or a relevant PMO treatment code on or after age 55 years old and be alive at the study start date to be eligible for the PMO cohort. The index date for women with PMO is defined as the date when a subject first satisfies both the PMO algorithm and the minimum continuous enrollment criterion (continuous enrollment criterion applicable for the US Medicare database and the Optum Research Database only).
- Subjects who receive Prolia for unapproved indications: To be eligible for this population, all subjects who received at least one dose of Prolia will be included and evaluated for potential Prolia off-label use. In the US Medicare database and the Optum Research Database, subjects need to be continuously enrolled from at least 12-months before the Prolia administration to at least 7-days after the Prolia administration with appropriate plan coverage. The earliest Prolia administration that a subject receives that satisfies the continuous enrollment criteria is defined as the index treatment. These subjects will be defined as those who receive Prolia but did not receive Prolia for an approved indication as indicated by the approved product information (US Package Insert [USPI] for subjects from Medicare and Optum Research Database system and the Summary of Product Characteristics [SmPC] for subjects in the Scandinavian national registries). Data from these subjects will be analyzed separately to assess off-label use of Prolia.

4.3.2 Exclusion Criteria

Women with PMO: Women with Paget's disease during the 12-month period prior to meeting criteria for inclusion in PMO population will be excluded. Additionally, in US Medicare and Optum Research Database, women with a diagnosis of malignancy (excluding non-melanoma skin cancer) or treatment with chemotherapy, hormonal therapy or radiation therapy for cancer up to 12-months before index date will be excluded. In the Scandinavian national registries, women with a diagnosis of cancer according to the patient registry and/or cancer registry up to 12-months prior to meeting criteria for inclusion in PMO population will be excluded.

4.4 Exposure Cohorts

Exposure will be defined on the basis of exposure to denosumab or exposure to bisphosphonates. Exposure cohorts will be defined as follows:

- In the Medicare and United HealthCare databases, denosumab exposure will be identified using CPT-4/Healthcare Common Procedure Coding System (HCPCS) codes (C9272, effective 1 Oct 2010 to 31 Dec 2011; J0897, effective 1 Jan 2012); and National Drug Codes (NDC) (55513071001). Before the assignment of a specific HCPCS code, nonspecific temporary medication codes (J3490–drugs unclassified injection; J3590–unclassified biologic), dose (eg, 60 mg), relevant diagnostic codes, and costs associated with claims based upon these codes will be used to identify denosumab exposures. To rule out potential misclassification from other injectable medications, all injectable drugs that were launched within 2 years of denosumab will be evaluated. In the Scandinavian national registries, denosumab prescriptions will be identified in the national prescription databases based on an Anatomical Therapeutic Chemical classification (ATC) code that has already been assigned to denosumab.
- For each data system, after 6 months of denosumab data are available, an initial evaluation will be conducted to confirm that denosumab exposure can be captured in each data system using the methods described above. Results of this analysis will be communicated in the next annual report to regulatory agencies following completion of the analysis. In addition, in subsequent annual reports, Amgen will report the distribution of identified denosumab exposures by temporary and specific HCPCS codes until temporary codes are no longer being utilized.
- Exposure to bisphosphonates will be identified based upon CPT-4/HCPCS J codes (US data systems) or ATC codes (Scandinavian national registries) in prescription files associated with each data system. The assessment of bisphosphonates includes branded oral bisphosphonates (eg, alendronate [Fosamax®], risedronate [Actonel®], ibandronate [Boniva®/Bonviva®] oral); generic bisphosphonates, including alendronate, neridodronate, and olpadronate; intravenous bisphosphonates including ibandronate IV, and zoledronate [Reclast®/Aclasta®]. Exposure to oral bisphosphonates and IV bisphosphonates will be separately assessed in US Medicare, Optum Research Database, and Norwegian national registries.

Changes in therapy over time will be taken into account. For example, if a subject switches to denosumab from a bisphosphonate during the course of follow-up, she will switch to the denosumab exposure cohort from the bisphosphonate exposure cohort(s).

4.5 Potential Confounding Factors

Variables that will be evaluated as potential confounders in analyses comparing AESI incidence across exposure cohorts include, but are not necessarily limited to, the following:

- Age
- Geographic location (eg, country, state)
- Calendar year
- Fragility fracture history
- Concurrent medication (eg, bisphosphonates); medication use, duration, and dosage
- History of treatment with osteoporosis medication
- Comorbidities (eg, infections, diabetes, and disease or conditions that may increase risk of AESI)
- Variables that may be indicators of health status or health seeking behavior, eg health resource utilization (office visits, ER visits, hospitalizations, cost of services)
- Other comorbidities, medications or procedures empirically selected by the propensity score model as significant predictors of denosumab treatment
- The 12-month period prior to the subject's index date (index date included) will constitute the baseline period. Data collected during the baseline period will be used to define eligibility for inclusion in analyses, ascertainment of postmenopausal or PMO status, and values for baseline covariates as described above.

4.6 Subject Follow-up

Follow-up will begin for postmenopausal women and women with PMO at the time they satisfy the subject selection criteria during the study period (index date excluded). All selected postmenopausal women will continue to be followed until the first of the following: disenrollment from the data system, death, or end of the study. All selected women with PMO will continue to be followed until the first of the following: disenrollment from the data system, death, Paget's disease, or end of the study. In addition, in US Medicare and Optum Research Database, the follow-up of women with PMO for AESI other than new primary malignancy will be censored at diagnosis of malignancy (excluding non-melanoma skin cancer) or treatment with chemotherapy, hormonal therapy or radiation therapy for cancer. In the Scandinavian national registries, the follow-up of women with PMO for AESI other than new primary malignancy will be censored at the diagnosis of malignancy (excluding non-melanoma

skin cancer) according to patient registry and/or cancer registry. The follow-up for incident events of all AESI for both postmenopausal women and women with PMO will also end at the occurrence of the corresponding AESI.

5. ALGORITHMS TO ASCERTAIN ADVERSE EVENTS OF SPECIAL INTEREST

Each AESI case ascertainment algorithm utilizes combinations of inpatient and outpatient ICD diagnosis codes (ICD-9-CM or ICD-10-CM for US Medicare, and Optum Research Database and ICD-10 for the Scandinavian national registries), CPT-4 or HCPCS procedure codes, laboratory or pathology test results, medication used, and/or EMR data.

A comprehensive review of the literature was conducted regarding the development, validation, and application or use of ascertainment algorithms for AESI, particularly among the data systems to be employed in this study. Of particular interest were performance characteristics of the algorithms (sensitivity, specificity, and positive predictive values [PPVs]).

In addition, previous research developed and tested ascertainment algorithms for ONJ (Tennis et al, 2009; Section 5.1), atypical femoral fracture (Narongroeknawin et al, 2012; Section 5.2), and infections leading to hospitalization (Patkar et al, 2009; Thomsen et al, 2009; Section 5.5). These studies assessed the appropriateness of established algorithms via verification against electronic or paper medical charts. Algorithms to identify dermatologic adverse events leading to hospitalization or ER visit have been developed and validated by others as described below (Section 5.6).

Case-ascertainment algorithms developed from Amgen-sponsored studies or the literature are summarized in Appendix B (Table B-1. Through Table B-29). ICD diagnosis codes included in the algorithms were validated either in the literature or by Amgen-sponsored studies in most instances; important diagnosis codes that have not been formally validated were included in some algorithms in order to assure capture of some specific events of interest. Algorithms are generalizable across data systems due to the use of standardized diagnosis, procedure, and medication codes in the US that cross-map to codes used in the Scandinavian national registries. The specific mapping of ICD-9-CM codes to ICD-10 codes is described in Appendix C.

The algorithms for each AESI were designed to be sensitive to capture potential cases of each AESI. The performance of the predefined algorithms, eg, sensitivity and specificity, depends on the available ICD diagnosis codes for each AESI and how these

codes are used in practice. In response to FDA's request, Amgen conducted additional medical record review studies based on the US Medicare database and the Scandinavian national registries to validate selected AESI ascertainment algorithms. The selected AESI in each data system include:

US Medicare:

- Acute pancreatitis leading to hospitalization
- Infections leading to hospitalization, emergency room (ER) visit or administration of parenteral anti-infective medication
- Dermatologic adverse events leading to hospitalization or ER visit
- Fracture healing complications
- Hypocalcaemia leading to hospitalization or ER visit
- New primary malignancy (excluding non-melanoma skin cancer)

Scandinavian national registries:

- Acute pancreatitis leading to hospitalization
- Infections leading to hospitalization, ER visit or administration of parenteral anti-infective medication
- Hypocalcemia leading to hospitalization or ER visit
- New primary malignancy (excluding non-melanoma skin cancer)

The study results were communicated with regulatory agencies [PBRER/PSUR #09 - (Prolia) (27 September 2014 to 26 September 2015)] no refinements to the algorithms were recommended.

The US Department of Health and Human Services (HHS) issued a rule (31 July 2014) requiring US health care providers and health plans to transition to ICD-10-CM/PCS codes on October 1, 2015. The conversions to US ICD-10-CM/PCS are located in the respective tables in the Appendix section [ie, Algorithms Used to Identify Women with Postmenopausal Osteoporosis (Appendix A), Algorithms Used to Identify Adverse Events of Special Interest (Appendix B), Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms (Appendix C)].

5.1 Osteonecrosis of the Jaw

In the US data systems, potential cases of ONJ will be retrieved using the ICD-9-CM codes 733.45 (aseptic necrosis of the jaw), (inflammatory conditions of the jaw), 522.7 (periapical abscess with sinus), and 526.5 (alveolitis of jaw[s]) (Appendix B,Table B-1). In the Scandinavian national registries, potential cases of ONJ are assessed using diagnosis codes for periapical abscess with sinus (K04.6), inflammatory conditions of the

jaw (K10.2), alveolitis of jaws (K10.3), idiopathic aseptic necrosis of bone (M87.0), osteonecrosis due to drugs (M87.1), osteonecrosis due to previous trauma (M87.2), other secondary osteonecrosis (M87.3), other osteonecrosis (M87.8) and osteonecrosis, unspecified (M87.9) (Appendix B,Table B-2). In Norway and Sweden, potential cases of osteonecrosis identified by ICD-10 codes M87.x in sites other than jaw will be excluded using data system-specific value (ie, character or number) in the fifth position of the ICD-10 codes (Appendix B, Table B-2). In all Scandinavian national registries, the identification of potential ONJ cases will be restricted to those with codes for departments of oral and maxillofacial surgery because all ONJ cases are expected to be referred to these departments for treatment (Appendix B, Table B-2). For potential cases associated with denosumab use and for a sample of non-denosumab-exposed cases in women with PMO in the Medicare and national registries in the Central Denmark Region and Sweden, medical charts will be requested and information will be abstracted from available charts and evaluated by an independent medical expert. In response to FDA's information request on 31 January 2017 (IND 009837) Amgen will also conduct an independent study based on the 26 May 2010 to 30 September 2015 United HealthCare data to validate the ascertainment algorithm for potential ONJ cases in women with PMO by medical record review. The study results will be communicated with the regulatory agency. Medical record confirmation of ONJ cannot be conducted in Norway and Denmark (except in the Central Denmark Region), because patients' data are de-identified after linking with the prescription registry, a step necessary to construct the PMO cohort in these data systems. The medical record abstraction procedures in national registries in the Central Denmark Region and Sweden will be developed in compliance with the local privacy laws.

Validation studies included an Amgen-sponsored study by Tennis et al (2009), who conducted an Amgen-sponsored study to assess ICD-9-CM codes used to identify ONJ cases prior to the introduction of code 733.45. Potential ONJ cases were identified in claims databases based upon ICD-9-CM codes 526.4 (inflammatory conditions of the jaw), 522.7 (periapical abscess with sinus), 526.5 (alveolitis of jaw[s]), and 526.89 ("other specified diseases of the jaw") as well as by CPT-4 procedure codes indicating relevant medical procedures performed on the maxillofacial area. Charts were obtained for 94 (58%) of 161 possible cases; 21 were classified by a panel of experts as "probable," 18 cases as "possible," and 55 cases as "not" ONJ. Codes with a PPV value $>$ 30% for probable ONJ have been included in the algorithm for the current study.

Amgen also evaluated the use of the new ICD-9-CM code 733.45 (aseptic necrosis jaw), which was introduced in late 2007. In order to evaluate use of the new code for ONJ, Amgen analyzed data from female cancer patients in United HealthCare data system collected between 2001 and 2008, and found that 99 patients had a diagnosis code of 526.4 (inflammatory conditions of the jaw) over that time period (19 in 2008), and that 4 patients had a diagnosis code of 733.45 (1 patient in 2007 and 3 patients in 2008), suggesting utilization of the new 733.45 ICD-9-CM code.

Based on the study by Tennis et al (2009), codes 526.4, 522.7, and 526.5 will be used in this study since these 3 codes captured 90% (19 of 21) of the probable ONJ cases and had PPVs of 33% to 67%. In addition, the new ICD-9-CM code specific to ONJ (733.45) will be included and will likely increase the PPV of the algorithm. The ICD-10 codes that most closely correspond to these codes are K04.6 (periapical abscess with sinus), K10.2 (inflammatory conditions of the jaws), K10.3 (alveolitis of jaws), and M87.08 (idiopathic aseptic necrosis of bone, other specified site) and these will be used in the Scandinavian national registries.

In the Tennis et al (2009) study cited above, use of dental claims to capture additional cases of ONJ was considered; however, because dental coding is based on procedures and treatments rather than diagnoses, it was not possible to identify codes specific enough to identify potential cases.

It is expected that this algorithm will capture ONJ cases in Stages 2 and 3 and potentially some cases in Stage 1 as classified in the American Association of Oral and Maxillofacial Surgeons (AAOMS) Position Paper, 2014 update (Ruggiero, 2014). Focusing on cases diagnosed by medical professionals should provide greater specificity for ONJ as defined by professional societies (Khosla et al, 2007; AAOMS, 2009; AAOMS, 2007; Ruggiero, 2014). Although use of this proposed algorithm is unlikely to capture Stage 1 cases, such cases may be identified by other pharmacovigilance activities, such as the denosumab active surveillance program or the denosumab clinical trial program.

5.2 Atypical Femoral Fracture Leading to Hospitalization

A validated algorithm to identify nontraumatic subtrochanteric or diaphyseal fractures of the femur, sites where atypical femoral fractures occur, using diagnosis codes and trauma codes (ICD-9-CM codes and E-codes, Appendix B, Table B-3.; ICD-10 codes and Scandinavian Medico-Statistical Committee [NOMESCO] codes, Appendix B, Table B-4) was developed and validated in a study conducted by investigators at the

University of Alabama at Birmingham (UAB) (Narongroeknawin et al, 2012). The algorithm is based upon the following ICD-9-CM codes: 820.22 (fracture of subtrochanteric section of femur closed), 821.00 (fracture of unspecified part of femur closed) or 821.01 (fracture of shaft of femur closed) in the absence of concurrent major trauma that would otherwise explain occurrence of the fracture. Major trauma is indicated by the following E-Codes: E800-E848 (vehicle accidents), E881-E884 (falls, other than falls on stairs and falls on same level), E908-E909 (accidents due to cataclysmic storms and earth surface movements) and E916-E928 ("other" accidents). In the UAB analysis, all patients with subtrochanteric fractures of the femur and a random sample of other femoral fracture types were selected, and medical records and radiology reports were reviewed. Discordance among reviewers was adjudicated by an expert panel comprising 3 radiologists, 2 rheumatologists, and 1 orthopedist. The PPVs of case algorithms to identify nontraumatic subtrochanteric and diaphyseal fractures of the femur varied based on the position and source of the diagnosis codes on medical claims (hospital discharge and surgeons' fracture repair records), ranging from 69% to 89% for subtrochanteric fractures of the femur, from 89% to 98% for diaphyseal fractures of the femur and from 85% to 98% for typical hip fracture.

Nontraumatic subtrochanteric and diaphyseal fractures of the femur were identified with a high PPV; thus, the algorithm was successful in identifying fractures at the characteristic site for atypical femoral fracture. However, very few of the fractures at these sites were identified as having the radiologic characteristics of atypical femoral fracture, resulting in a very low PPV for true atypical femoral fracture (< 15%) (Kenneth Saag, personal communication). For this reason, Amgen will conduct expert medical review of electronic radiographs and medical records to confirm cases of atypical femoral fracture leading to hospitalization for all potential cases among denosumab users and for a sample of non-denosumab-exposed cases in women with PMO. This medical review will only include data from the Central - Denmark Regionwhere electronic copies of radiographs are readily available. In these data systems, radiographs will be obtained for cases of fracture identified by the above algorithm, and the radiographs will be evaluated by medical experts based on standard definition criteria. Thus, incidence rates for atypical femoral fracture will be calculated based only on the radiographically confirmed cases of atypical femoral fracture leading to hospitalization.

Over time, access to electronic imaging for confirmation of atypical femoral fracture leading to hospitalization may become more widespread and new, more specific ICD

codes may become available. In the initial stages, however, this study will be able to calculate rates of atypical femoral fracture leading to hospitalization only in registry data from selected regions of Denmark. The medical record abstraction procedures in selected regions of Denmark will be developed in compliance with the local privacy laws.

5.3 Fracture Healing Complications

The development of fracture healing complications varies significantly by site of fracture, demographic characteristics of the patient, comorbidities, and the type of treatment or intervention applied (Buckwalter et al, 2006; Court-Brown et al, 2006; Bhandari et al, 2002). The most clinically significant adverse fracture healing complication is nonunion, which is when bone segments fail to unite and a pseudarthrosis develops. Nonunion generally requires revision surgery, particularly when quality of life is expected to be adversely impacted.

Based on discussions with practicing orthopedic surgeons, ICD codes for nonunion are reliably used to capture fracture healing complications (ICD 9-CM code, Appendix B, Table B-5. ICD-10 code, Appendix B,Table B-6). Therefore, nonunion is the fracture healing complication that will be most reliably captured in administrative claims databases. Because physicians use diagnostic codes for nonunion to identify fractures that have not healed adequately and require a secondary procedure, the sensitivity and specificity of these diagnostic codes is high. According to the literature and our discussions with surgeons, other ICD codes will have a low PPV because of the high variability in the way they are applied and interpreted; this is due in part to differences in clinical assessment of fracture healing, including radiographic delays or other unspecific clinical symptoms. Therefore, the nonunion diagnostic code is expected to capture the events of greatest clinical significance with the highest PPV. In medical record review studies sponsored by Amgen, the PPV for the algorithm assessing fracture healing complications ranged from approximately 60% in Sweden and Norway national registries to 72% in Denmark national registries. In the US at Group Health Cooperative, the PPV was 89% (Boudreau et al, 2012).

5.4 Hypocalcemia Leading to Hospitalization or ER Visit

Hypocalcemia will be ascertained based upon a primary diagnosis with an ICD diagnosis code for hypocalcemia that is associated with hospitalization or an ER visit (ICD-9-CM 275.41, hypocalcemia; ICD-10 E83.5D, hypocalcemia (Denmark); E83.5, disorders of calcium metabolism (Norway and Sweden); Appendix B, Table B-7. and Table B-8.). Secondary diagnoses of hypocalcemia are excluded, as these cases are

more likely to be caused by electrolyte abnormalities associated with underlying diseases such as chronic renal failure, malabsorption, or hypoparathyroidism, or other electrolyte imbalances, which could represent the primary cause of the hospitalization or ER visit. The algorithm to assess recurrent event(s) of hypocalcemia is summarized in Appendix D. There is no study based on hypocalcemia as the primary diagnosis in large administrative database analyses; however, the ICD-9-CM diagnosis code 275.41 was successfully used to identify secondary hypocalcemia (Baird et al, 2009). Loughlin et al (2008) successfully identified another electrolyte disturbance, ie, hyperkalemia, using ICD-9-CM codes. Symptoms of hypocalcemia, such as tetany, muscle spasm, muscle pain, and abnormal ECG are not specific enough to capture hypocalcemia independent of levels of blood calcium and thus were not incorporated into the algorithm. Similarly, HCPCS procedure codes for injections and infusions of calcium and/or vitamin D and diagnosis for symptoms of hypocalcemia were found to be not feasible or too nonspecific, because procedure codes are not well captured in hospital files. However, because procedure codes are captured better at ER visits, procedure codes are included in the algorithm for ER visits only.

Since the ICD-10 code specific for hypocalcemia (E83.5D) is only available in the Denmark national registry and other Scandinavian national registries use non-specific ICD-10 code for disorders of calcium metabolism (E83.5), the two ICD-10 codes were tested for use in the Scandinavian national registries. In collaboration with our Danish colleagues, a case ascertainment algorithm was tested using data from the Danish national registry for the northern Denmark region. Patients who had been hospitalized with the ICD-10 diagnosis code E83.5 (disorders of calcium metabolism), E83.5D (hypocalcemia) or E58.9 (Dietary calcium deficiency) were identified and their laboratory results, if available, evaluated. A case of hypocalcemia was considered confirmed if the patient had a low calcium measurement at any time during the hospital stay during which an ICD-10 code for calcium was recorded. The E83.5 diagnosis code had a PPV of 20% and the combination of E83.5D and E58.9 diagnosis code had a PPV of 82.9% when compared with laboratory results for hospitalized hypocalcemia (Antonsen et al, 2011).

Blood calcium levels will be summarized among identified cases of hypocalcemia whose laboratory results are available in selected regions of the Scandinavian national registries.

5.5 Infection Leading to Hospitalization, ER Visit, or Administration of Parenteral Anti-infective Medication

Ascertainment of infection leading to hospitalization, ER visit, or administration of parenteral anti-infective medication use among outpatients with infection as primary diagnosis was based upon presence of specific ICD-9-CM codes that are associated with a primary diagnosis of infection. Diagnosis codes for infection are provided in Appendix B (ICD-9-CM codes,Table B-10. ICD-10 codes, Appendix B, Table B-11.). In addition, skin infection (ICD-9-CM codes, ICD-10 codes, Appendix B, Table B-13.) will be analyzed separately. The algorithm to assess recurrent event(s) of infection is summarized in Appendix D. The primary diagnosis of infection is required for case ascertainment so as to exclude infections that are comorbidities, as well as parenteral anti-infective medication use for the treatment or prevention of comorbid infection. The validity of this approach to accurately identify cases of serious infection leading to hospital admission was evaluated by Schneeweiss et al (2007) using the Department of Veterans Affairs administrative database. The PPV of identifying specific bacterial infections leading to hospital admissions varied between 66% and 100%. All conditions combined yielded a PPV of 80%. When the gold-standard definition of bacterial conditions was broadened to hospital admissions due to any acute infectious condition, the PPV increased to 90%. Based upon these findings, investigators concluded that "ICD-9-CM codes of selected serious infections from hospital discharge files can be used as substitutes for chart-based diagnoses." A similar algorithm was used by Smitten et al (2008) to identify infection leading to hospitalization or administration of parenteral antibiotics.

In addition to infections leading to hospitalization or ER visit, infections leading to the outpatient administration of parenteral anti-infective medication will be evaluated. Parenteral anti-infective administration can be identified from either pharmacy dispensing or from outpatient physician visits. For pharmacy dispensing, the eligible event must have a pharmacy claim carrying both the relevant American Hospital Formulary Service (AHFS) code (as listed in Appendix B, Table B-14.) and the corresponding route of intake for that dispensing indicating intravenous injection or intravenous infusion. The AHFS code is a high-level drug code. Each AHFS code includes a number of Hierarchical Ingredient Code List (HICL) codes and National Drug Code (NDC) codes. Parenteral anti-infective medication is also identified by HCPCS codes (Appendix B, Table B-16.) in outpatient files corresponding with the primary outpatient diagnosis for infection. Systemic treatment with antibiotics can also be

identified by the treatment codes (BPHxx) in the Denmark data system (Appendix B, Table B-14.). To be eligible as a case of infection associated with administration of a parenteral anti-infective, both of the following criteria must be fulfilled:

- A primary diagnosis of infection as indicated by the specified ICD-9-CM or ICD-10 code in outpatient file, and
- An administration of intravenous injection or infusion of antibiotics (as specified in Appendix B, Table B-14. and Table B-16.) in the same claim or record of the primary outpatient infection diagnosis.

5.6 Dermatologic Adverse Events Leading to Hospitalization or ER Visit

Ascertainment of dermatologic adverse events will be based upon presence of specific ICD codes for primary diagnosis leading to hospitalization or ER visit. ICD-9-CM and ICD-10 diagnosis codes for dermatologic adverse events overall are provided in Appendix B (Table B-17 and Table B-18., respectively). In addition, bullous dermatoses (Appendix B, Table B-19, and Table B-20, respectively) and erythematous events (Appendix B, Table B-21 and Table B-22., respectively) will be analyzed separately. The algorithm to assess recurrent event(s) of dermatologic adverse events is summarized in Appendix D. Use of ICD-9 codes to identify erythematous events has been validated in the literature. ICD-9-CM code 695.1, which includes erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, was validated in a case-control study using Medicaid claims data (Strom et al, 1991). Medical records were sought for 249 patients and obtained for 128 patients (51.4%). Among the 128 patients for whom charts were obtained, 78 patients (60.9%) were confirmed to have a diagnosis compatible with ICD-9-CM diagnosis code 695.1, while 43 patients (33.6%) had skin diseases other than those represented by ICD-9-CM 695.1. In addition, Gau et al (2008) used the ICD-9-CM code 695.1 to identify cases of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis in the Taiwanese National Health Insurance data system.

5.7 Acute Pancreatitis Leading to Hospitalization

Cases of acute pancreatitis leading to hospitalization will be identified based on hospital claims with a primary ICD-9 diagnosis code of 577.0 or a primary ICD-10 diagnosis code of K85 (Appendix B, Table B-22. And Table B-23).

Two studies have validated the use of ICD-9-CM code 577.0 in inpatient settings using administrative databases (Dore et al, 2009; Eland et al, 2000). In a population-based retrospective follow-up study based on automated hospital discharge data, medical records of 101 patients with a discharge diagnosis code for acute pancreatitis were

reviewed and 82.2% (PPV) of them were confirmed (Eland et al, 2000). In a recent study based on the Ingenix National Health Informatics (NHI) (United HealthCare) data system, inpatient or ER claims associated with acute pancreatitis (ICD-9 diagnosis code of 577.0) were validated against medical record review (Dore et al, 2009). A total of 81 of 141 potential primary diagnoses of acute pancreatitis (PPV = 58%) were confirmed.

In another study based on the Hospital Discharge Registry in North Jutland Country, Denmark, 99 cases of hospitalized acute pancreatitis identified through ICD-8 or ICD-10 codes were validated against hospital medical records, and the PPV was 82% for the correctly recorded diagnosis of a first episode of acute pancreatitis (Floyd et al, 2002).

5.8 Hypersensitivity Leading to Hospitalization or ER Visit

Ascertainment of hypersensitivity will be based upon presence of ICD-9-CM and ICD-10 codes for hypersensitivity adverse events that were either the primary hospital discharge diagnosis or primary diagnosis related to ER visit. Diagnosis codes are provided in Appendix B (ICD-9-CM,Table B-25; ICD-10, Table B-26.). In addition, anaphylactic hypersensitivity will be analyzed separately (ICD-9-CM, Table B-27, ICD-10, Table B-28.). The algorithm to assess recurrent event(s) of hypersensitivity is summarized in Appendix D. Use of ICD-9 codes to identify anaphylaxis has been validated in the literature. ICD-9 codes have been used to identify anaphylaxis in several studies (Johannes et al, 2007; Sheikh and Alves, 2000; Sorenson et al, 1989). A retrospective study based on the United HealthCare data system identified allergic reactions using several ICD-9 codes that are included in the algorithm above, including anaphylaxis (ICD-9-CM code 995.0), drug allergy (ICD-9-CM code 995.2), and allergy (ICD-9-CM 995.3), and this study validated the code for anaphylaxis (Johannes et al, 2007). Medical charts were obtained for 64 of 77 patients (83.1%) for whom medical charts were sought. A diagnosis of anaphylaxis was confirmed in 16 of 28 patients (57.1%) identified based on a claim with ICD-9-CM diagnosis code 995.0. While the non-anaphylactic adverse event codes have not been validated, they are included in the analysis for the sake of completeness.

The use of diagnosis codes other than ICD-9 to identify hypersensitivity has also been supported. In a retrospective cohort study based on the UK General Practice Research Database (GPRD), cases of anaphylaxis were identified by either an Oxford Medical Information System (OXMIS) coded diagnosis of anaphylaxis (n = 783) or with

anaphylaxis noted in the comments field (n=115) (Peng and Jick, 2004). General practitioners were contacted for information relating to the diagnosis for a random sample of patients with a diagnosis code of anaphylaxis (9%) or with "anaphylaxis" in a comment field (43%). Based on the review of medical history from the random sample and derived qualification criteria, the PPV for anaphylaxis was estimated to be 75.3%.

5.9 New Primary Malignancy (Excluding Non-melanoma Skin Cancer)

Malignancies will be identified based on diagnosis codes for neoplasm, excluding non-melanoma skin cancer (ICD-9-CM, Appendix B, Table B-28.; ICD-10,Table B-29). For analysis based on claims data, cases of new primary malignancy will be defined as an inpatient discharge diagnosis with a diagnosis code for a particular cancer or at least 2 outpatient claims with the same cancer diagnosis code occurring 30 to 365 days apart. The performance of the established algorithm to distinguish cases with new primary malignancy from those with pre-existing history of malignancy depends on the length of enrollment and the accuracy and comprehensiveness of the recording of cancer diagnosis and therapy in each data system.

This algorithm has been validated based on ICD-9 codes (Brackley et al, 2006). Cases of all cancer sites combined were identified in the British Columbia Linked Health Data resource using the ICD-9-CM codes described above as primary diagnosis in hospital discharges and were validated against a cancer registry. For the 10-year aggregate data (1990 through 1999), sensitivity for all cancers combined was 78.6%, specificity was 99.0%, PPV was 80.5%, and negative predictive value was 98.9%.

6. POTENTIAL SOURCES OF BIAS IN STUDY DESIGN

There are several key potential sources of bias in the study design.

6.1 Disease Severity

Subjects with more severe conditions and longer durations of disease may tend to receive denosumab rather than other osteoporosis medications. This may cause a bias in the evaluation of long-term safety of denosumab. Without effective methods to reduce or eliminate the bias effect, the study results may not be valid.

To address this issue, various methods through study design such as restriction (eg, subjects with history of fragility fracture) and statistical methods such as propensity scores will be used.

6.2 Bias Associated With Subjects Switching From Another PMO Medication

Several studies have shown that overall compliance and adherence to bisphosphonate therapy may be inadequate to realize levels of treatment effectiveness similar to levels of efficacy observed in clinical trials (Feldstein et al, 2009; Curtis et al, 2008; Siris et al, 2006). It is likely that a large proportion of women initiating treatment with denosumab will be those who are unable to comply with or are intolerant of other osteoporosis therapy, or those who have not achieved an adequate treatment response to other osteoporosis therapy. In addition, women who have received anti-resorptive therapy for long periods of time may be selectively referred to denosumab treatment due to concerns about potential risk of events associated with long-term drug exposure. Such women are also likely to be at increased risk for one or more AESI. Thus, estimated relative risks of adverse events for subjects treated with denosumab may be spuriously high. One approach to address this potential bias inherent in studies of prevalent users is to compare cohorts of initiators with no prior use of osteoporosis therapy.

6.3 Selection Bias Due to Missing Values

The study is based on several health management systems in the US and the Scandinavian national registries. Missing data may pose a problem that should be addressed in specific analyses as bias may be introduced if subjects with missing values are excluded from those analyses. Approaches to handling missing data depend in part upon (i) the type of variable for which data are missing (exposure, outcome or covariate); (ii) whether missingness can be fully assessed (eg, lack of a positive response may signify true missingness as opposed to a failure to record a positive response); and (iii) the proportion of data that are missing for a given variable. Further, important considerations are patterns of missingness and whether such patterns are informative (systematic) or differential with respect to the exposure or outcome variables or covariates. Approaches to address missing data include complete case methods, weighting procedures (Robins et al, 1994), imputation-based procedures, and model-based procedures (Little and Rubin, 2002). Conducting analyses based upon complete cases may lead to biased results, but this bias will generally not be serious when the proportion of subjects with missing variables is small. When a moderate to high proportion of subjects have missing data, weighting methods, imputation or model-based procedures may be useful. Sensitivity analyses assessing the robustness of analysis results using different methods to handle missing data will be conducted.

7. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

Reporting of individual adverse events is not applicable for secondary data collection studies.

8. STUDY SIZE AND ESTIMATION OF STUDY POWER

In response to FDA Advice/Information Request received on 16 August 2012 (IND 9837) sample size and power projections for women with PMO were updated after 3 years of Prolia post-launch data was available in all data systems. Updated years 5 and 10 projections and the related tables and figures are in Appendix G. The following is the original text describing the study size and power estimates.

This study will analyze data both for women with PMO and for all postmenopausal women (defined as women ≥ 65 years old in Medicare and ≥ 55 years old in other data systems); however, study size and study power were estimated based on the number of women with PMO. The expected number of women with PMO in study 20090522 is estimated based on data provided in the Study 20090521 Study Report and projections provided by investigators from each of the data systems.

Estimated person-years of observation among women with PMO that will be available for calculation of AESI incidence rates are based on the assumption that: (i) 50% of women with osteoporosis are receiving an osteoporosis medication (Feldstein et al 2003a, 2003b), and (ii) 5% of women with PMO receiving an osteoporosis medication will be treated with denosumab when the market uptake of denosumab has stabilized. It is further assumed that during the first year after denosumab market entry, only 2.5% of women with PMO who receive treatment will be treated with denosumab. Estimated person-years of exposure are presented by data system and length of follow-up in Table 8-1. Based on these assumptions, the overall number of person-years of observation among women with PMO receiving denosumab is estimated to be 90,863, 272588 and 575,462 at 2, 5, and 10 years post approval. The number of person-years for individual data systems at 10 years post approval ranges from 19,712 in United HealthCare to 475,000 in US Medicare. Actual numbers will vary depending on the time to reach a steady state and the adoption rate of denosumab treatment by the source population for each data system.

Table 8-1. Estimated Exposure to Denosumab Through 10 Years Post Approval of Denosumab by Data System

Data System	Overall Women with PMO (Prevalent Subjects)	Estimated Exposure to Denosumab (Person-years)		
		First 2 Years Post Denosumab Approval (Person-years)	First 5 Years Post Denosumab Approval (Person-years)	First 10 Years Post Denosumab Approval (Person-years)
US Medicare	2,000,000	75,000	225,000	475,000
Denmark	92,000	3,450	10,350	21,850
Norway	92,000	3,450	10,350	21,850
Sweden	156,000	5,850	17,550	37,050
United HealthCare	83,000	3,113	9,338	19,712
Combined	2,423,000	90,863	272,588	575,462

Figure 8-1 illustrates the power to assess relative risk at 10 years post denosumab market entry. Background incidence rates for AESI for the power calculation are from Table 8-2. The power was calculated using the conservative Fisher's 2-sided exact test with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 10:1 between comparator- and denosumab-exposed person-years with up to 10 years of follow-up. The study will have nearly 100% power to detect a relative risk of 2 or higher for AESI with a background incidence rate of ≥ 7 cases per 100,000 person-years or higher, which includes all AESI other than ONJ and atypical femoral fracture. The study will have appreciable power to detect moderately elevated relative risks for rarer AESI. For example, for ONJ (1 case per 100,000 person-years; Sambrook et al, 2006), the study will have over 90% power to detect a relative risk of 3.0 or higher. Furthermore, sensitivity analyses conducted after varying the assumptions concerning PMO prevalence, denosumab exposure prevalence, and the comparator: exposed group ratio resulted in minimal impact to study power.

Figure 8-1. Power Plot for Range of Event Rates for All Data Systems Combined

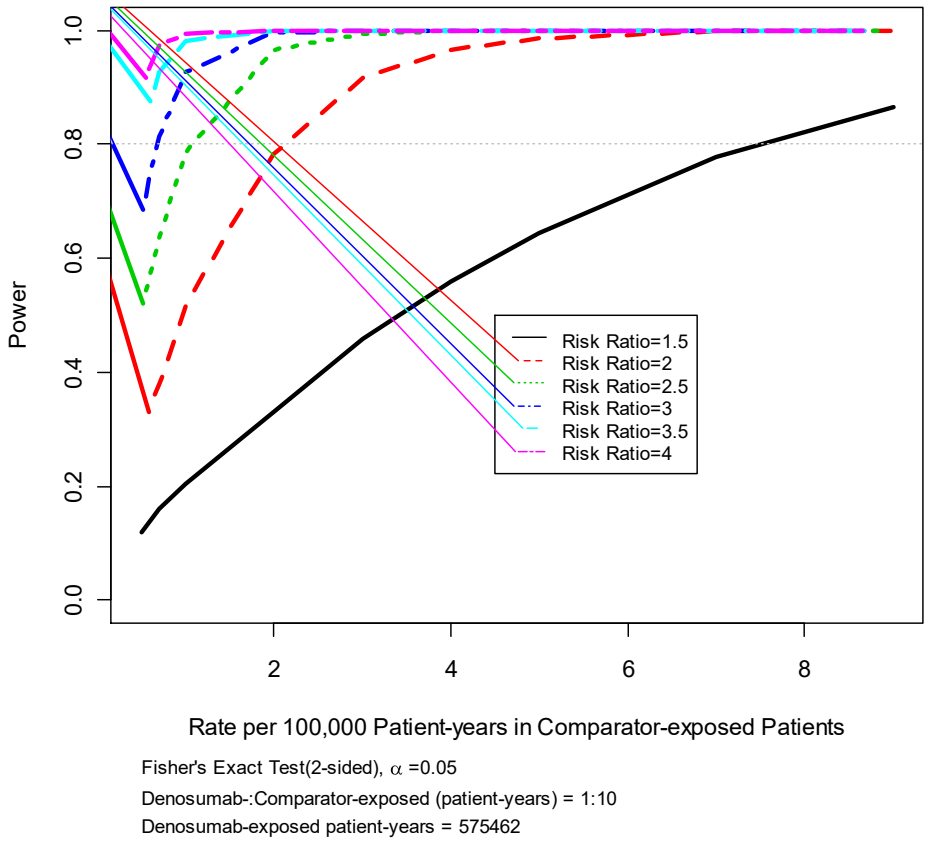


Table of Statistical Power Values for Figure 8-1: Power Plot for Range of Event Rates for All Data Systems Combined

Rate per 100,000 Patient-years in Comparator-exposed Patients	Risk Ratio= 1.5	Risk Ratio= 2.0	Risk Ratio= 2.5	Risk Ratio= 3.0	Risk Ratio= 3.5	Risk Ratio= 4.0
1.0	0.1948	0.5039	0.7839	0.9246	0.9784	0.9939
2.0	0.332	0.7813	0.9675	0.9964	0.9999	1
3.0	0.4541	0.909	0.9954	0.9998	1	1
4.0	0.56	0.9657	0.9997	1	1	1
6.0	0.7252	0.9967	1	1	1	1
8.0	0.8269	0.9994	1	1	1	1

Table values were re-generated using same assumptions as original Figure 8-1

Table 8-2. Background Incidence Rates Used For Power Calculations, With Sources

Adverse Event of Special Interest	Source	Background Incidence Rate (per 100,000 person-years)
ONJ	Sambrook et al, 2006	1
Atypical femoral fracture leading to hospitalization	N/A	Unknown
Fracture healing complications	Study 20090521 US Medicare Report, bisphosphonate group	134
Hypocalcemia leading to hospitalization or ER visit	Study 20090521 US Medicare Report, bisphosphonate group	7
Infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication	Study 20090521 US Medicare Report, bisphosphonate group	8799
Dermatologic adverse events leading to hospitalization or ER visit	Study 20090521 US Medicare Report, bisphosphonate group	207
Acute Pancreatitis leading to hospitalization	Study 20090521 US Medicare Report, bisphosphonate group	137
Hypersensitivity leading to hospitalization or ER visit	Study 20090521 US Medicare Report, bisphosphonate group	217
New primary malignancy (excluding non-melanoma skin cancer)	Study 20090521 US Medicare Report, bisphosphonate group	1353

Currently, the background incidence rate for atypical femoral fracture leading to hospitalization is unknown, and the algorithm to reliably identify atypical femoral fracture leading to hospitalization is a work in progress; thus, a power estimate for assessing relative risk of atypical femoral fracture leading to hospitalization cannot be made at this time. The assessment of atypical femoral fracture leading to hospitalization will be based on data from the Central and North Denmark Regions where electronic radiographs are available.

The power to detect relative risk of each of the AESI in each of the data systems at various time points post denosumab market entry (2 years, 5 years, and 10 years) is presented in Appendix E (Table E-1. through Table E-2). The analyses based on US Medicare data will have ≥ 90% power to detect a relative risk of 3.0 for AESI with incidence ≥ 7 cases per 100,000 person-years at 2 years post denosumab market entry, will achieve ≥ 80% power to detect a relative risk of 2 for all AESI other than ONJ at 5 years post denosumab market entry and will achieve ≥ 80% power to detect a relative

risk of 4 for ONJ at 10 years post denosumab market entry. The analyses based on the Sweden and Denmark (Norway) national registries will have > 90% and ≥ 85% power respectively to detect a relative risk of 2 for fracture healing complications or more common AESI at 5 years post denosumab market entry. ONJ and atypical femoral fractures based on medical record review will not be assessed in United Healthcare. The analyses based on data from United HealthCare will have over 80% power to detect a relative risk of 3.0 and 2.0 or higher for all AESI other than hypocalcemia at 2 years and 5 years, respectively, post denosumab market entry, and over 80% power to detect a relative risk of 5 or higher for hypocalcemia at 10 years post denosumab market entry.

9. STATISTICAL ANALYSIS

Analyses will describe characteristics of, and AESI incidence among, exposure cohorts as defined in Section 4.4.

Analyses will be conducted separately for each data system. In addition, results may be combined across data systems using meta-analytic methods, as appropriate.

Analytic approaches relevant to each study objective are provided below.

9.1 Determination of Incidence Rates of AESI in Women With PMO and by Exposure Cohort

The first objective of the study is to determine incidence rates of AESI in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates overall, women with PMO exposed to oral or IV bisphosphonates and all women with PMO.

To eliminate the influence of cancer, in US Medicare and Optum Research Database, subjects will no longer contribute to the follow-up for any AESI other than new primary malignancy after being diagnosed with malignancy (excluding non-melanoma skin cancer), or receiving treatment with chemotherapy, hormonal therapy or radiation therapy for cancer. In the Scandinavian national registries, subjects will no longer contribute to the follow-up for any AESI other than new primary malignancy after being diagnosed with malignancy (excluding non-melanoma skin cancer) according to patient registry and/or cancer registry. Patient-year-adjusted AESI incidence rates will be calculated for each exposure cohort by dividing the total number of subjects with events by the total patient-years (sum of subjects' time at risk) from which the events arose. The follow-up for incident cases of each AESI will end at the first occurrence of the same event. A subject's time at risk may include only the on-treatment periods or may include both on-treatment and post-treatment periods, depending on the nature of the AESI. For hypocalcemia, infection, dermatologic adverse events, and hypersensitivity, event rates

will also be calculated by including incident as well as recurrent events of the same AESI in the numerator. Incidence and event rates will be calculated as cases per 100,000 person-years and will be standardized by age groups.

9.2 Description of Characteristics, Clinical Features, and AESI Risk Factors in Women With PMO and by Exposure Cohort

The second objective of the study is to describe characteristics, clinical features, and AESI risk factors in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates overall, women with PMO exposed separately to oral bisphosphonates or IV bisphosphonates and all women with PMO.

Descriptive statistics will be used to characterize exposure cohorts with respect to subject characteristics, clinical features, and AESI risk factors. Subject characteristics include, but are not necessarily limited to, age, country/state of residence, concurrent medication use, and comorbid conditions or illnesses. Osteoporosis-related characteristics include calendar year of meeting criteria for inclusion in PMO population, history of fragility fracture, and history of osteoporosis medication use. All of these factors will be evaluated as AESI risk factors. Stratified analyses and/or multiple regression analyses will be used to determine major imbalances in subject or disease characteristics between denosumab-exposed subjects and other exposure cohorts to facilitate the identification of potential confounders in analyses comparing AESI incidence rates across exposure cohorts.

In addition, tabular summaries will describe person-year adjusted AESI event rates and by baseline demographic and clinical characteristics and potential AESI risk factors by exposure cohort. Characteristics of the exposure cohorts and risk factors for AESI among exposure cohorts will be compared using stratified analyses and/or multiple regression analyses to determine major imbalances in subject characteristics between denosumab users and bisphosphonate users to facilitate the identification of potential confounders in comparative analyses between denosumab-exposed subjects and bisphosphonate-exposed subjects.

9.3 Comparison of Incidence Rates of AESI in Women With PMO

The third objective of the study is to compare the incidence of the AESI in women with PMO exposed to denosumab to that in women with PMO exposed to bisphosphonates. As the selection bias resulting from confounding by indication may be appreciable and, in some instances, not measurable, comparative analyses will be inherently challenging to interpret. For these reasons comparative analyses are considered exploratory.

9.3.1 Comparison of AESI Rates in Denosumab-exposed and Bisphosphonate-exposed Cohorts in Women With PMO

Comparative analyses of the AESI will be conducted among women with PMO exposed to Prolia and women with PMO exposed to zoledronic acid.

The study design will follow good practice of pharmacoepidemiology and the USFDA RWE framework (Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, May 2013). To mitigate bias, we will employ an as-treated (Hernan and Robins, 2017; Lund et al, 2015), osteoporosis treatment naive user design, with a minimum 455-day lookback period**,** that sets the cohorts inception date according to the subject's new use of a select osteoporosis treatment (Franklin et al, 2020; Lund et al, 2015; Johnson et al, 2013). To control for confounding, comparison groups should ideally include subjects with the same level of disease severity and treatment pattern (Franklin et al, 2020; U.S. Department of Health and Human Services et al, 2013). Zoledronic acid, more closely meets these criteria and was selected as the active comparator for Prolia. This selection was supported by the findings from 3 studies that used negative control outcomes to assess the comparability of osteoporosis treatment groups for residual confounding in different PMO population, including commercially-insured and Medicare populations (Mcgrath et al, 2020), Studies 20190427 and 20190031) (Appendix I Figures 1, 2, and 3). Propensity score diagnostics and comparability of osteoporosis treatment groups after adjustment of measured confounders will be assessed. A gatekeeping process will be implemented that keeps individuals making these decisions isolated – through their assigned roles and responsibilities – from knowledge about how these decisions might affect outcomes to avoid biased analytic decisions driven by their expected effect on comparative analyses. Sufficiency of number of events and balance in measured covariates between the treatment groups will be evaluated. We will assess the adjusted risk ratios (and corresponding 95% confidence intervals) of each AESI separately among subjects who initiate Prolia and subjects who initiate zoledronic acid using inverse-probability of treatment and censoring weighted (IPTCW) estimation functions (Ozenne et al, 2020; Funk et al, 2011; Aalen, 1978). The use of IPTW and IPCW aims to address the potential confounding due to initial treatment assignment as well as any potentially informative censoring by loss to follow-up (Hubbard et al, 2001; Robins and Finkelstein, 2000). The mean follow-up, all-cause mortality, along with the number and percent of each censoring event will be measured. All-cause mortality will be treated as a competing risk. Negative control outcomes will be included to further assess residual or

unmeasured confounding. Due to the rarity of events (which would be further reduced in a naive user design) and low positive predictive values (PPV - probability that subjects identified using the algorithm truly have the event) of ICD based algorithms, we do not recommend including ONJ or AFF in this comparative analysis. As noted above, medical chart review is already performed for potential cases of ONJ and AFF identified in all Prolia-exposed subjects and a matched sample of bisphosphonate-exposed subjects in applicable data systems. The comparative safety analysis will only be performed in US Medicare. Medicare data, based on sample size and power, is the most fit-for purpose data set to conduct the 20090522 comparative safety analysis between Prolia and IV bisphosphonate users in the naive user design (Appendix I Table I-2a). Medicare is the only data system in which we have the power to detect a minimum relative risk of 1.5 for all 7 (fracture healing complications, hypocalcemia, serious infections, dermatologic adverse events, acute pancreatitis, hypersensitivity, and new primary malignancy) of the AESIs (except hypocalcemia) (Appendix I). In the smaller (Optum and Scandinavian) databases a minimal detectable relative risk of 1.5 was sporadically obtained only for the infection and malignancy adverse events. Using only the US Medicare data should be acceptable because it represents greater than $>$ 80% of women with PMO and $>$ 91% of women receiving Prolia in the current 20090522 study. US Medicare provides national coverage and long-term follow-up to address longer induction periods. We also expect our findings to extrapolate to the EU because Prolia is considered a compound “Insensitive to Ethnic Factors” based on the E5 (R1) (Ethnic Factors in the Acceptability of Foreign Clinical Data) criteria. A compound whose characteristics suggest minimal potential for clinically significant impact by ethnic factors such as genetic polymorphism, age, gender, organ dysfunction etc. on safety, efficacy, or dose response.

At FDA’s recommendation [Ref 01 Dec FDA **2021** ltr], we will evaluate oral BP comparator arms using the naive user design and include ONJ and AFF AESIs as outcomes. FDA acknowledges the limitations of these exploratory analyses as described above. Residual confounding between treatment groups could sire bias that is unfavorable to denosumab. Misclassification can bias the results in either direction (Fox et al, 2005). Lack of power/ precision may obscure a positive association**. At FDA’s recommendation [Ref 20 March 2023 FDA Advise-Information Request] we will conduct additional exploratory post-hoc analyses, including hypothesis testing comparative safety analysis for hypocalcemia stratified by severity category of baseline CKD and descriptive or hypothesis testing analyses, as**

appropriate, of AFF in naïve user, incident new user, and prevalent user cohorts as described by FDA [Ref 20 March 2023 FDA Advise-Information Request]. It is acknowledged that these exploratory post-hoc analyses will be limited by small sample size and rarity of outcome events with associated lack of precision and unstable estimates.

The Manual of Operations for the comparative safety analysis is in Appendix J and provides comprehensive details on the methodology and updated power calculations. The manual includes additional details on key design elements including study period, index dates, censoring, follow-up time, inclusion/exclusion criteria, covariates and propensity score development, subgroup and cumulative exposure analyses.

9.4 Incidence Rates of AESI in Postmenopausal Women

The fourth objective of the study is to describe incidence rates of AESI in postmenopausal women.

AESI incidence rates among postmenopausal women will be calculated as defined above for analytic approaches pertaining to Objective 1 (Section 9.1). Because the postmenopausal women study population is intended to represent the experiences of all postmenopausal women in the general population, women with baseline Paget's disease or malignancy will not be excluded and the follow-up for any AESI other than malignancy will not end at diagnosis or treatment related to cancer in all data systems.

9.5 Denosumab Utilization Patterns in Women With PMO

The fifth objective of the study is to describe denosumab utilization patterns in subjects who received denosumab therapy for treatment of PMO.

Descriptive statistics will be used to characterize denosumab utilization patterns among women who receive denosumab for the treatment of PMO. Utilization will be assessed by factors including frequency of administration, cumulative dosage, and timing of subsequent administrations. Prior, concurrent, or subsequent treatment with other osteoporosis medication will be described. Characteristics of women receiving denosumab for the treatment of PMO will be summarized as described for analyses pertaining to Objective 2 (Section 9.2). Characteristics to be evaluated include, but are not necessarily limited to subject demographic characteristics, medication history and concurrent medications, comorbid conditions and illnesses, and fracture history.

9.6 Prolia Utilization Patterns in Subjects Who Receive Prolia for Unapproved Indications

The sixth objective of the study is to describe Prolia utilization patterns in subjects who receive Prolia therapy for unapproved indications (indication, dosage, frequency).

Analyses assessing use of Prolia for unapproved indications will be descriptive in nature and will include subjects receiving Prolia who receive Prolia for indications that are not included in the applicable product information (Section 4.3). Scandinavian patient registries reflect diagnoses recorded during hospital-based encounters (inpatient, outpatient, and emergency). To classify missing data and diagnoses resulting from non-hospital encounters, an "Unclear" classification is assigned to those cases without enough information to be qualified as off-label or on-label use (per the Summary of Product Characteristics [SmPC]). The total number of subjects receiving Prolia for unapproved indications and the demographic and clinical characteristics of these subjects will be summarized.

10. COMMUNICATION OF STUDY RESULTS TO REGULATORY AGENCIES

The health risk findings of the study associated with Amgen products will be reported to regulatory agencies according to local and international requirements. Confirmed cases of ONJ will be reported in accordance with regional regulatory agency commitments.

10.1 Annual Analysis

Analyses will be conducted annually. Safety data from this study will be assessed and provided in an annual report. In addition, this report will be provided in the PSUR/ PBRER.

10.2 Final Analysis

A final report to regulatory agencies will be completed within 6 months following the end of the study. The final report, will be comprehensive for all objectives and for the specific outcomes of interest.

11. ETHICAL OBLIGATIONS

This study is based upon routinely collected secondary data from 2 US health management systems and national health registry data from 3 Scandinavian countries. Analyses using these data sources will be conducted by investigators who have access to the data through their respective institutions, with analysis findings shared with Amgen in accordance with the data use agreements between Amgen and the investigators (institutions). Study results will only be presented in an aggregate form and individuals will not be identified.

12. REFERENCES

Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. *J Bone Miner Res.* 2009;24(6):1095-1102.

Agresti A. *Categorical Data Analysis.* New York: Wiley: 1990:59–66.

American Association of Oral and Maxillofacial Surgeons (AAOMS). Position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg*. 2007;5:369-376.

American Association of Oral and Maxillofacial Surgeons. Position Paper on Bisphosphonate-related Osteonecrosis of the Jaw 2009 Update. http://www.aaoms.org/docs/position_papers/bronj_update.pdf. Accessed 21 January 2010.

Aalen O. Nonparametric Estimation of Partial Transition Probabilities in Multiple Decrement Models. Ann Stat. 1978;6:534–545.

Antonsen S, Christiansen CF, Norgaard M, Critchlow CW, Sorensen HT. The validation of hypercalcemia and hypocalcemia diagnoses in Danish registries. 27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 14-17, 2011, Chicago, IL (conference website http://www.pharmacoepi.org/meetings/27thconf/index.cfm)

Bachmann MF, Wong BR, Josien R, Steinman RM, Oxenius A, Choi Y. TRANCE, a tumor necrosis family member critical for CD40 ligand-independent T helper cell activation. *J Exp Med*. 1999;189:1025-1031.

Baird GS, Rainey PM, Wener M, Chandler W. Reducing routine ionized calcium measurement. *Clin Chem*. 2009;55:533-540.

Bhandari M, Guyatt GH, Tornetta P, et al. Current practice in the intramedullary nailing of tibial shaft fractures: An international survey*. J Trauma Injury Infection Criti Care.* 2002;53(4):725-732.

Boudreau D, Yu O, Spangler L, et al. Accuracy of ICD-9 codes to identify nonunion and malunion & developing algorithms to improve case-finding of nonunion and malunion. *Bone.* 2012 Nov 19. doi:pii: S8756-3282(12)01357-9. 10.1016/j.bone.2012.11.013.

Brackley ME, Penning MJ, Lesperance ML. In the absence of cancer registry data, is it sensible to assess incidence using hospital separation records? *Int J Equity Health.* 2006;5:12.

Buckwalter JA, Einhorn TA, Marsh JL. Bone and joint healing. In: Bucholz R, Heckman JD, Court-Brown CM, Koval K, Tornetta P, Wirth MA, eds. Rockwood and Green's Fractures in Adults, ed. 6th, vol. 1. Philadelphia:+ LIppincott Williams and Wilkins, 2006:297-311.

Burwen DR, La Voie L, Braun MM, Houck P, Ball R. Evaluating adverse events after vaccination in the Medicare population. *Pharmacoepidemiol Drug Saf.* 2007;16:753-61.

Buckley L, Guiatt G, Fink HA, et al. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Care Res (Hoboken).* 2017;69(8): 1095-1110.

Canalis E, Bilezikian JP, Angeli A, Giustina A. Perspectives on glucocorticoid-induced osteoporosis*. Bone*. 2004;34:593-598.

Center For Drug Evaluation And Research And Center For Biologics Evaluation And Research. Guidance Document. Best Practices For Conducting And Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets. May 2013. Docket Number: FDA-2011-D-0057.

Christensen J, Vestergaard M, Olsen J, Sidenius P. Validation of epilepsy diagnoses in the Danish National Hospital Register. *Epilepsy Res*. 2007;75:162-70.

Court-Brown CM, McQueen MM, Tornetta P. Nonunions and bone defects. In: Tornetta P Einhorn TA, eds. *Trauma*, ed. 1 Philadelphia: Lippincott Williams & Wilkins, 2006:503-19.

Curtis JR, Westfall AO, Cheng H, Lyles K, Saag KG, Delzell E. Benefit of adherence with bisphosphonates depends on age and fracture type: Results from an analysis of 101,038 new bisphosphonate users. *J Bone Miner Res*. 2008;23(9):1435-1441.

Dore DD, Seeger JD, Arnold Chan K. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin*. 2009;25:1019-1027.

Einhorn TA. Enhancement of fracture-healing. *J Bone Joint Surg Am.* 1995;77(6):940-956.

Eland IA, Sturkenboom MJ, Wilson JH, Stricker BH. Incidence and mortality of acute pancreatitis between 1985 and 1995. *Scand J Gastroenterol*. 2000;35:1110-1116.

Engel-Nitz NM, Martin S, Sun P, Buesching D, Fonseca V. Cardiovascular events and insulin therapy: A retrospective cohort analysis. *Diabetes Res Clin Pract.* 2008;81:97-104.

Fagenholz PJ, Castillo CF, Harris NS, Pelletier AJ, Camargo CA Jr. Increasing United States hospital admissions for acute pancreatitis, 1988-2003. *Ann Epidemiol.* 2007;17:491-497.

Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. *Rheumatology (Oxford).* 2011;5011:1982-1990.

Fata JE, Kong YY, Li J, et al. The osteoclast differentiation factor osteoprotegerin-ligand is essential for mammary gland development. *Cell.* 2000;103:41-50.

Feldstein AC, Weycker D, Nichols GA, et al. Effectiveness of bisphosphonate therapy in a community setting. *Bone.* 2009;44:153-159.

Feldstein A, Elmer PJ, Orwoll E, Herson M, Hillier T. Bone mineral density measurement and treatment for osteoporosis in older individuals with fractures: a gap in evidence-based practice guideline implementation. *Arch Intern Med*. 2003a; 163:2165-2172.

Feldstein AC, Nichols GA, Elmer PJ, et al. Older women with fractures: Patients falling through the cracks of guideline-recommended osteoporosis screening and treatment. *J Bone Joint Surg Am*. 2003b;85-A(12):2294-2302.

Floyd A, Pedersen L, Nielsen GL, Thorladcius-Ussing O, Sorensen HT. Secular trends in incidence and 30-day case fatality of acute pancreatitis in North Jutland County, Denmark: a register-based study from 1981-2000. *Scand J Gastroenterol.* 2002;37:1461-1465.

Fox, M. P., et al. (2005). "A method to automate probabilistic sensitivity analyses of misclassified binary variables." Int J Epidemiol 34(6): 1370-1376.

Franklin JM, Patorno E, Desai RJ, et al. Emulating Randomized Clinical Trials with Nonrandomized Real-World Evidence Studies: First Results from the RCT DUPLICATE Initiative. Circulation. 2020.

Funk MJ, Westreich D, Wiesen C, Sturmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. American journal of epidemiology. 2011;173:761-767.

Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sørensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol.* 2010;106:86-94.

Gau SS, Chao PF, Lin YJ, Chang CJ, Gau CS. The association between carbamazepine and valproate and adverse cutaneous drug reactions in patients with bipolar disorder: A nested matched case-control study. *J Clin Psychopharmacol.* 2008;28:509.

Green EA, Choi Y, Flavell RA. Pancreatic lymph node-derived CD4(+)CD25(+) Treg cells: highly potent regulators of diabetes that require TRANCE-RANK signals. *Immunity*. 2002;16:183-91.

Hennessey S. Use of health care databases in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol.* 2006;98(3):311-3.

Hernan MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. The New England journal of medicine. 2017;377:1391-1398.

Hershman DL, McBride RB, Eisenberger A, Tsai WY, Grann VR, Jacobson JS. Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26(19):3159-65.

Hubbard AE, Robins JM, Van Der Laan M. Nonparametric Locally Efficient Estimation of the Treatment Specific Survival Distribution with Right Censored Data and Covariates in Observational Studies. In: Halloran ME, Berry D (eds) Statistical Models in Epidemiology, the Environment, and Clinical Trials The IMA Volumes in Mathematics and its Applications, vol 116 Springer, New York, NY. 2001:1-40.

Joensen AM, Jensen MK, Overvad K, et al. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. *J Clin Epidemiol*. 2009;62(2):188-94.

Johannes CB, Ziyadeh N, Seeger JD, Tucker E, Reiter C, Faich G. Incidence of allergic reactions associated with antibacterial use in a large, managed care organization. *Drug Safety.* 2007;30:706-713.

Johnson ES, Bartman BA, Briesacher BA, et al. The incident user design in comparative effectiveness research. Pharmacoepidemiology and drug safety. 2013;22:1-6.

Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res.* 2004;19(6):893-899.

Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2007;22(10):1479-1491.

Klemmensen AK, Olsen SF, Osterdal ML, Tabor A. Validity of preeclampsia-related diagnoses recorded in a national hospital registry and in a postpartum interview of the women. *Am J Epidemiol*. 2007;166(2):117-124.

Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology*. 2007;28(3):150-154.

Kwek EBK, Goh SK, Koh JSB, Png MA, Howe TS. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? *Injury*. 2008;39:224-231.

Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *New Engl J Med*. 2008;358(12):1304-5.

Little DG, Ramachandaran M, Schindeler A. The anabolic and catabolic responses in bone repair. *J Bone Joint Surg Br*. 2007;89-B:425-433.

Little RJA, Rubin DB. *Statistical Analysis With Missing Data.* 2nd ed. New York: John Wiley; 2002.

Loser K, Mehling A, Loeser S, et al. Epidermal RANKL controls regulatory T-cell numbers via activation of dendritic cells. *Nature Med*. 2006;12:1372-1379.

Loughlin J, Seeger JD, Eng PM, et al. Risk of hyperkalemia in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Contraception.* 2008;78:377-383.

Loughlin JE, Alfredson TD, Ajene AN, et al. Risk for respiratory events in a cohort of patients receiving inhaled zanamivir: A retrospective study. *Clinical Therapeutics.* 2002;24:1786-1799.

Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep. 2015;2:221-228.

Martin TJ, Gillespie MT. Receptor activator of nuclear factor κB ligand (RANKL): another link between breast and bone. *Trends Endocrinol Metabol*. 2001;12:2-4.

Mcgrath LJ, Spangler L, Curtis JR, et al. Using negative control outcomes to assess the comparability of treatment groups among women with osteoporosis in the United States. Pharmacoepidemiology and drug safety. 2020;29:854-863.

Miller DP, Alfredson T, Cook SF, Sands BE, Walker AM. Incidence of colonic ischemia, hospitalized complications of constipation, and bowel surgery in relation to use of alosetron hydrochloride. *Am J Gastroenterol*. 2003;98:1117-1122.

Morrisey MA. Retiree health benefits. *Annu Rev Publ Health*. 1993;14:271-292.

Narongroeknawin P, Shakoory B, Patkar NM, et al. Validation of diagnostic codes for subtrochanteric, diaphyseal, and atypical femoral fractures using administrative claims data. *J Clin Densitom*. 2012 Jan-Mar;15(1):92-102. *Epub 2011* Nov 9.

Nevasier AS, Lane JM, Lenart BA, Edobor-Osula F, Lorich DG. Low-energy femoral shaft fractures associated with alendronate use. *J Orthop Trauma.* 2008;22(5):346-350.

Odvina C, Levy S, Rao S, Zerwekh J, Rao SD. Unusual mid-shaft fractures during long term bisphosphonate therapy. *Clin Endocrinol.* 2010;72:161-168.

Odvina C, Zerwekh JE, Rao S, et al. Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab*. 2005;90(3):1294-1301.

Overman RA, Yeh JY, Deal CL. Prevalence of oral glucocorticoid usage in the United States: a general population perspective. *Arthritis Care Res (Hoboken).* 2013;65(3):294-298.

Ozenne BMH, Scheike TH, Staerk L, Gerds TA. On the estimation of average treatment effects with right-censored time to event outcome and competing risks. Biom J. 2020;62:751-763.

Padigel UM, Kim N, Choi Y, Farrell JP. TRANCE-RANK costimulation is required for IL-12 production and the initiation of a Th1-type response to Leishmania major infection in CD40L-deficient mice. *J Immunol*. 2003;171:5437-5441.

Patkar NM, Curtis JR, Teng GG, et al. Administrative codes combined with medical records based criteria accurately identified bacterial infections among rheumatoid arthritis patients. *J Clin Epidemiol*. 2009;62:321-327.

Patschan D, Loddenkemper K, Buttgereit F. Molecular mechanisms of glucocorticoid induced osteoporosis. *Bone*. 2001;29:498-505.

Peng MM, Jick H. A population-based study of the incidence, cause, and severity of anaphylaxis in the United Kingdom. *Arch Intern Med.* 2004;164:317-319.

Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics. 2000;56:779-788.

Robins JM, Rotnitzky A, Zhao LP. Estimation of regression coefficients when some regressors are not always observed. *J Am Stat Assoc*. 1994;89:846-866.

Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F; American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg 2014;72:1938-56.

Saag KG. Glucocorticoid-induced osteoporosis. *Endocrinol Metab Clin North Am*. 2003;32:135-157.

Sambrook P, Olver I, Goss A. Bisphosphonates and osteonecrosis of the jaw. *Aust Fam Physician.* 2006;35(10):801–803.Schneeweiss S, Robicsek A, Scranton R, Zuckerman D, Solomon DH. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. *J Clin Epidemiol.* 2007;60:397-409.

Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol.* 2007;110:587-593.

Setoguchi S, Glynn RJ, Avorn J, Mogun H, Schneeweiss S. Statins and the risk of lung, breast, and colorectal cancer in the elderly. *Circulation*. 2007;115(1):27-33.

Shane, E., et al. "Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research." J Bone Miner Res. 2014; 29(1): 1-23.

Sheikh A, Alves B. Hospital admissions for acute anaphylaxis: time trend study. *BMJ.* 2000;320:1441.

Siris ES, Harris ST, Rosen CJ, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: Relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clin Proc.* 2006;81:1013-1022.

Smitten AL, Choi HK, Hochberg MC, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. *J Rheumatol.* 2008;35:387-93.

Somford MP, Draijer FW, Thomassen BJ, Chavassieux PM, Boivin G, Papapoulos SE. Bilateral fractures of the femur diaphysis in a patient with rheumatoid arthritis on long-term treatment with alendronate: clues to the mechanism of increased bone fragility. *J Bone Miner Res*. 2009; 24(10):1736-40.

Sorensen HT, Christensen T, Schlosser HK, Pedersen L (eds). *Use of Medical Databases in Clinical Epidemiology.* Report no. 37. Department of Clinical Epidemiology, Aarhus University Hospital, Denmark. 2008.

Sorenson HT, Nielsen B, Nielsen JO. Anaphylactic shock occurring outside hospitals. *Allergy.* 1989;44:288-290.

Strom BL, Carson JL, Halpern AC, et al. Using a claims database to investigate drug-induced Stevens-Johnson syndrome. *Stat Med.* 1991;10:565-76.

Tennis P, Zavras A, Laskarides C, Tan H. Predictive value of ICH and CPT codes for identifying osteonecrosis of the jaw (ONJ). Paper presented at: Twenty-fifth Anniversary International Conference for Pharmacoepidemiology and Therapeutic Risk Management, 18 August 2009. Abstract Number 750343.

Thomsen RW, Schoonen M, Farkas DK, et al. Risk for hospital contact with infection in patients with splenectomy: A population-based cohort study. *Ann Intern Med.* 2009;151;546-555.

Ton FN, Gunawardene SC, Lee H, Neer RM. Effects of low-dose prednisone on bone metabolism. *J Bone Miner Res*. 2005;20:464-470.

Tuck SP, Datta HK. Osteoporosis in the aging male: treatment options. Clin Interv Aging. 2007;2(4):521-36

Van der Laan MJ, Robins JM. *Unified Methods for Censored Longitudinal Data and Causality*. New York: Springer-Verlag; 2002

van Staa TP, Leufkens HG, Abenhaim L, et al. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatology (Oxford).*2000;39:1383-1389

van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int*. 2002;13:777-787.

Wang FT, Xue F, Ding Y, Ng E, Critchlow CW, Dore DD. Predictive values of diagnostic codes for identifying serious hypocalcemia and dermatologic adverse events among women with postmenopausal osteoporosis in a commercial health plan database. *BMC Health Serv Res.* 2018;18(1):263.

Wang FT, Fei Xue, MD, Eva Ng, Critchlow, CW, et al. Performance of an algorithm for identifying serious dermatologic adverse events in commercial health plan claims data. 30th Anniversary International Conference on Pharmacoepidemiology and Therapeutic Risk Management ISPE 2014 Abstract Number: 751237

Wang FW, Uretsky BF, Freeman JL, Zhang D, Giordano SH, Goodwin JS. Survival advantage in Medicare patients receiving drug-eluting stents compared with bare metal stents: real or artifactual? *Catheter Cardiovasc Interv*. 2008;71(5):636-43.

Wilkinson GS, Kuo YF, Freeman JL, Goodwin JS. Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: a population-based analysis. *J Natl Cancer Inst*. 2007;99(13):1016-24.

Winklemayer WC, Setoguchi S, Levin R, Solomon DH. Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. *Arch Intern Med*. 2008;168(21):2368-2375.

Yee CL, Duffy C, Gerbino PG, Stryker S, Noel GJ. Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin. *Pediatr Infect Dis J*. 2002;21:525-529.

Yu Z, van der Laan M. Double robust estimation in longitudinal marginal structural models. *J Stat Plan Inference.* 2006;136(3):1061-1089.

Zura RD, Sasser B, Sabesan V, Pietrobon R, Tucker MC, Olson SA. A survey of orthopaedic traumatologists concerning the use of bone growth stimulators. *J Surg Orthop Adv.* 2007;16(1):1-4.

13. APPENDICES

13.1 Appendix A. Algorithms Used to Identify Women With Postmenopausal Osteoporosis

Table A-1. Osteoporosis Diagnosis Codes and Medication Codes and Case Algorithm Used in the US Medicare and Optum Research Database Systems

Osteoporosis Diagnosis	ICD-9-CM Diagnosis Code	US ICD-10-CM Diagnosis Code
Osteoporosis	733.0x	M80.0- - -, M80.8- - -, M81.0, M81.6, M81.8, Z87.310
Unspecified osteoporosis	733.00	M81.0
Senile osteoporosis (postmenopausal)	733.01	M81.0, M80.0- - -
Idiopathic osteoporosis	733.02	M81.8, M80.8- - -
Disuse osteoporosis	733.03	M81.8, M80.8- - -
Other osteoporosis (drug-induced)	733.09	M81.8, M80.8- - -, M81.6, Z87.310
Case Algorithm for Osteoporosis Diagnosis: Any of the above codes as a primary or secondary discharge diagnosis in an INPATIENT claim record, or one outpatient diagnosis associated with physician evaluation or management.		
Osteoporosis Medication‡	**HCPCS J-code (time period restriction, if any)**	
Zoledronic acid infusion (Reclast)	J3488 (from 01/01/2008)	
Zoledronic acid infusion (Reclast)	Q4095 (from 07/01/2007)	
Zoledronic Acid Infusion (Reclast)*	J3490 (from 04/17/2007)*	
Zoledronic Acid Injection	Q2051(from 07/01/2013)^	
Zoledronic Acid Injection	J3489 (from 01/01/2014)^	
Ibandronate injection	J3490 (from 04/01/2006)*	
Ibandronate injection	J1740 (from 01/01/2007)	
Ibandronate injection	C9229 (from 07/01/2006)	
Calcitonin injection	J0630 (from 01/01/1982)	
Teriparatide	J3110 (from 01/01/2005)	
Denosumab (Prolia)	C9272 (from 10/01/2010)**	
Denosumab (Prolia)†	J3490 (from 06/01/2010)*	
Denosumab (Prolia)†	J3590 (from 06/01/2010)*	
Denosumab (Prolia)	J0897 (from 01/01/2012)**	
Romosozumab (Evenity)	J-3111 (from 10/01/2019)	

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* An algorithm to distinguish between ibandronate, zoledronic acid, and denosumab when coded as J3490 is needed based on the date of claimed code and other data system-specific data availability.

† J3490 and J3590 are to be used to identify Prolia administrations for women with PMO but not men with osteoporosis or men and women with glucocorticoid exposure treated with denosumab because these indications were following the assignment of the denosumab-specific HCPCS code J0897.

^ 07/01/2013 onward an algorithm will be needed to distinguish between Zometa and Reclast in the US data. Effective Jan 1, 2014, the HCPCS code J3489 was developed and is now used to reflect both drugs which have different dosages and administration frequency.

** An algorithm to distinguish between Xgeva and Prolia when coded as J0897 or C9272 is needed for the US data.

Table A-1. Osteoporosis Diagnosis Codes and Medication Codes and Case Algorithm Used in the US Medicare and Optum Research Database Systems

Other Osteoporosis Medications	Dosage
alendronate sodium	70 mg tablet
	70 mg oral solution
	10 mg tablet
	5 mg tablet
	35 mg tablet
alendronate sodium/vitamin D3 tablet (Fosamax plus D)	70 mg alendronate /2800 IU vitamin D3
	70 mg alendronate/5600 vitamin D3
Denosumab (Prolia)	60 mg Injectable, subcutaneous
ibandronate sodium (Boniva)	2.5 mg tablet
	150 mg tablet
risedronate	5 mg tablet
	35 mg tablet
	75 mg tablet
	150 mg tablet
risedronate sodium /calcium carbonate	35 mg risedronate /500 mg calcium
raloxifene (Evista)	60 mg tablet
calcitonin	200 IU/SPRAY
abaloparatide (Tymlos)	3,120 mcg/1.56 mL subcutaneous, 80 mcg dose Pen Injector
romosozumab (Evenity)	105 mg/1.17 mL syringe

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‡ The identification of injectable osteoporosis medication may be supplemented by NDC or other drug codes as appropriate based on the data availability in the data system.

Table A-2. Diagnosis Codes and Case Algorithms for Osteoporotic Fractures

Fracture Site	US ICD-9-CM Code*	US ICD-10-CM Code
Hip, closed	Inpatient primary or secondary diagnosis codes (820.0, 820.2, 820.8, 733.14) OR Carrier line or outpatient claim with CPT in (27220, 27222, 27226-27228, 27254, 27230-27248, 27267-27269) and diagnosis code (820.0, 820.2, 820.8, 733.14)	Inpatient primary or secondary diagnosis codes (S72.0 - - -, S72.1 - - - , S72.2 - - - , S79.0 - - -, M80.051-, M80.052-, M80.059- , M84.451-, M84.452-, M84.459-, M84.659 -) OR Carrier line or outpatient claim with CPT in (27220, 27222, 27226-27228, 27254, 27230-27248, 27267-27269) and diagnosis code (S72.0 - - -, S72.1 - - - , S72.2 - - - , S79.0 - - -, M80.051-, M80.052-, M80.059- , M84.451-, M84.452-, M84.459- , M84.659 -) For all ICD10 codes, include below for the last digit A …… initial encounter for fracture D …… subsequent encounter for fracture with routine healing G …… subsequent encounter for fracture with delayed healing K …… subsequent encounter for fracture with nonunion P …… subsequent encounter for fracture with malunion S ……. sequela
Distal radius/ulna	Inpatient primary or secondary diagnosis code in (813.4, 813.5, 733.12) OR Carrier line or outpatient claim with CPT in (25600, 25605, 25611, 25606, 25607, 25608, 25609, 25620, 25650, 25651, 25652 (includes ulnar styloid)) and diagnosis code in (813.4, 813.5, 733.12)	Inpatient primary or secondary diagnosis code in (S52.5 - - -, S52.6 - - -, S59.0 - - -, S59.2 - - -, M80.031 -, M80.032 -, M80.039 - , M84.431 -, M84.432 -, M84.433 -, M84.434 -, M84.439 -) OR Carrier line or outpatient claim with CPT in (25600, 25605, 25611, 25620, 25606, 25607, 25608, 25609, 25650, 25651, 25652 (includes ulnar styloid)) and diagnosis code in (S52.5 - - - , S52.6 - - -, S59.0 - - -, S59.2 - - -, M80.031 -, M80.032 -, M80.039 -, M84.431 -, M84.432 -, M84.433 -, M84.434 -, M84.439 -)

Footnotes defined on the last page of this table

Table A-2. Diagnosis Codes and Case Algorithms for Osteoporotic Fractures

Fracture Site	US ICD-9-CM Code*	US ICD-10-CM Code
Distal radius/ulna (Continued)		For all ICD10 codes, include below for the last digit A …… initial encounter for fracture D …… subsequent encounter for fracture with routine healing G …… subsequent encounter for fracture with delayed healing K …… subsequent encounter for fracture with nonunion P …… subsequent encounter for fracture with malunion S …… sequela For ICD10 codes start with 'S52.5' and '52.6', additionally include below subcategories for the last digit B …… initial encounter for open fracture type I or II C …… initial encounter for open fracture type IIIA, IIIB, or IIIC E …… subsequent encounter for open fracture type I or II with routine healing F …… subsequent encounter for open fracture type IIIA, IIIB, or IIIC with routine healing H …… subsequent encounter for open fracture type I or II with delayed healing J …… subsequent encounter for open fracture type IIIA, IIIB, or IIIC with delayed M …… subsequent encounter for open fracture type I or II with nonunion N …… subsequent encounter for open fracture type IIIA, IIIB, or IIIC with nonunion Q …… subsequent encounter for open fracture type I or II with malunion R …… subsequent encounter for open fracture type IIIA, IIIB, or IIIC with malunion

Footnotes defined on the last page of this table

Table A-2. Diagnosis Codes and Case Algorithms for Osteoporotic Fractures

Fracture Site	US ICD-9-CM Code*	US ICD-10-CM Code
Spine, closed or pathologic	Inpatient primary or secondary diagnosis code in (805.0, 805.2, 805.4, 805.8, 733.13) OR Carrier line or outpatient claim with CPT in (22510, 22511, 22512, 22513, 22514, 22515, 22520, 22521, 22522, 22523, 22524, 22525, 27200, 27202, 76012, 76013, 22305, 22310, 22315, 22318, 22319, 22325, 22326, 22327, 22328, 77082, 77085-77086) and diagnosis code in (805.0, 805.2, 805.4, 805.8, 733.13) OR Carrier line or outpatient claim with HCPCS in (physician evaluation/management) and diagnosis in (805.0, 805.2, 805.4, 805.8, 733.13)	Inpatient primary or secondary diagnosis code in (S12. (0-6,9) - - -, S22.0 - - -, S32.0 - - -, M48.5 - --, M80.08X-, M80.88 - -, M84.48X-, M84.68X) OR Carrier line or outpatient claim with CPT in (22510, 22511, 22512, 22513, 22514, 22515, 22520, 22521, 22522, 22523, 22524, 22525, 27200, 27202, 76012, 76013, 72291, 72292, 22305, 22310, 22315, 22318, 22319, 22325, 22326, 22327, 22328, 77082, 77085-77086) and diagnosis code in (S12. (0-6,9) - - -, S22.0 - - -, S32.0 - - -, M48.5 - --, M80.08X-, M80.88 - -, M84.48X-, M84.68X) OR Carrier line or outpatient claim with HCPCS in (physician evaluation/management) and diagnosis in (S12. (0-6,9) - - -, S22.0 - - -, S32.0 - - -, M48.5---, M80.08X-, M80.88 - -, M84.48X-, M84.68X) For all ICD10 codes include below for the last digit A …… initial encounter for fracture D …… subsequent encounter for fracture with routine healing G …… subsequent encounter for fracture with delayed healing K …… subsequent encounter for fracture with nonunion P …… subsequent encounter for fracture with malunion S …… sequela For M48.5---, the last digit may only be A, D, G or S

Footnotes defined on the last page of this table

Table A-2. Diagnosis Codes and Case Algorithms for Osteoporotic Fractures

Fracture Site	US ICD-9-CM Code*	US ICD-10-CM Code
Pelvis-closed	Inpatient primary or secondary diagnosis code (808.0, 808.2, 808.4, 808.8) OR Carrier line or outpatient claim with HCPCS in (27193-27194, 27215-27218, 27200, 27202, 27220, 27222, 27226-27228, G0412, G0413, G0414, G0415) and diagnosis code (808.0, 808.2, 808.4, 808.8)	Inpatient primary or secondary diagnosis code (S3210X -, S32.2 - - -, S32.3 - - -, S32.4 - - -, S32.5 - - -, S32.6 - - -, S32.8 - - -, S32.9XX -) OR Carrier line or outpatient claim with HCPCS in (27193-27218, 27220, 27222, 27226-27228, 27254, 27193-27194, 27215-27218, 27220, 27222, 27226-27228, G0412, G0413, G0414, G0415) and diagnosis code (S32.10X -, S32.2 - - -, S32.3 - - -, S32.4 - - -, S32.5 - - -, S32.6 - - -, S32.8 - - -, S32.9XX -) For all ICD10 codes, include below for the last digit A …… initial encounter for fracture D …… subsequent encounter for fracture with routine healing G …… subsequent encounter for fracture with delayed healing K …… subsequent encounter for fracture with nonunion P …… subsequent encounter for fracture with malunion S …… sequela
Other femur-closed	Inpatient primary or secondary diagnosis code (821.0, 821.2, 733.15) OR Carrier line or outpatient claim with CPT in (27220, 27222, 27226-27228, 27230-27248 27254, 27267-27269, 27500-27514) and diagnosis code (821.0, 821.2, 733.15)	Inpatient primary or secondary diagnosis code (S72.3 - - -, S72.4 - - -, S72.8X - -, S72.9 - X -, S79.1 - - -,M80.051-, M80.052-, M80.059-, M80.85 - -, M84.453-, M84.65 (1-3) -, M84.7 - - -) OR Carrier line or outpatient claim with CPT in (27267-27269, 27500-27514) and diagnosis code (S72.3 - - - , S72.4 - - -, S72.8X - -, S72.9 - X -, S79.1 - - - ,M80.051-, M80.052-, M80.059-, M80.85 - -, M84.453-, M84.65 (1-3) -, M84.7 - - -) For all ICD10 codes, include below for the last digit A …… initial encounter for fracture D …… subsequent encounter for fracture with routine healing G …… subsequent encounter for fracture with delayed healing K …… subsequent encounter for fracture with nonunion P …… subsequent encounter for fracture with malunion S …… sequela

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Table A-2. Diagnosis Codes and Case Algorithms for Osteoporotic Fractures

Fracture Site	US ICD-9-CM Code*	US ICD-10-CM Code
Radius/ulna-other	Inpatient primary or secondary diagnosis code (813.0, 813.1, 813.2, 813.3, 813.8, 813.9) OR Carrier line or outpatient claim with **CPT** in (24650, 24655, 24665, 24666, 24670, 24675, 24685, 25500, 25505, 25515, 25520, 25525, 25526, 25530, 25535, 25545, 25560, 25565, 25574, 25575) and diagnosis code (813.0, 813.1, 813.2, 813.3, 813.8, 813.9)	Inpatient primary or secondary diagnosis code (S59.1 - - -, S52.2 - - -, S52.3 - - -, S52.9 - X -, S52.0---, S52.1--B, S52.1--C, M80.83 - -, M84.63 - -) OR Carrier line or outpatient claim with CPT in (24586, 24587, 24620, 24635, 24650, 24655, 24665, 24666, 24670, 24675, 24685, 25500, 25505, 25515, 25520, 25525, 25526, 25530, 25535, 25545, 25560, 25565, 25574, 25575) and diagnosis code (S59.1 - - -, S52.2 - - -, S52.3 - - -, S52.9 - X -, S52.0---, S52.1--B, S52.1--C, M80.83 - -, M84.63 -)
Humerus-closed	Inpatient primary or secondary diagnosis code (812.0, 812.2, 812.4, 733.11) OR Carrier line or outpatient claim with CPT in (23600, 23605, 23615, 23616, 23620, 23625, 23630, 23665, 24500, 24505, 24515, 24516, 24530, 24535, 24538, 24545, 24546, 24560, 24565, 24566, 24575, 24576, 24577, 24579, 24582, 24586, 24587) and diagnosis code (812.0, 812.2, 812.4, 733.11)	Inpatient primary or secondary diagnosis code (S42.2 - - -, S42.3 - - -, S42.4 - - -, S42.9 - --, S49.0 - - -, S49.1 - - -, M80.01 - -, M80.021-, M80.022-, M80.029-, M80.81 - -,M80.82 - - , M84.41 - - ,M84.421-, M84.422-, M84.429-, M84.61 - -.M84.62 - -) OR Carrier line or outpatient claim with CPT in (23600, 23605, 23615, 23616, 23620, 23625, 23630, 23665, 24500, 24505, 24515, 24516, 24530, 24535, 24538, 24545, 24546, 24560, 24565, 24566, 24575, 24576, 24577, 24579, 24582, 24586, 24587) and diagnosis code (S42.2 - - -, S42.3 - - -, S42.4 - - -, S42.9 --, S49.0 - - -, S49.1 - - -, M80.01 - -, M80.021-, M80.022-, M80.029-, M80.81 - -,M80.82 - - , M84.41 - -,M84.421-, M84.422-, M84.429-, M84.61 - - .M84.62 - -) For all ICD10 codes, include below for the last digit A …… initial encounter for fracture D …… subsequent encounter for fracture with routine healing G …… subsequent encounter for fracture with delayed healing K …… subsequent encounter for fracture with nonunion P …… subsequent encounter for fracture with malunion S …… sequela

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Table A-2. Diagnosis Codes and Case Algorithms for Osteoporotic Fractures

Fracture Site	US ICD-9-CM Code*	US ICD-10-CM Code	
Note: One of the above codes AND no concurrent major trauma ECODES:			
E800-E848	Railway, motor vehicle, other road vehicle accidents; water transport accidents; air and space transport accidents; other vehicle accidents		V00-V97.---A
		V00-V09	Pedestrian injured in transport accident
		V10-V19	Pedal cycle rider injured in transport accident
		V20-V29	Motorcycle rider injured in transport accident
		V30-V39	Occupant of three-wheeled motor vehicle injured in transport accident
		V40-V49	Car occupant injured in transport accident
		V50-V59	Occupant of pick-up truck or van injured in transport accident
		V60-V69	Occupant of heavy transport vehicle injured in transport accident
		V70-V79	Bus occupant injured in transport accident
		V80-V89	Other land transport accidents
		V90-V94	Water transport accidents
		V95-V97	Air and space transport accidents
E881-E884	Falls, other than falls on stairs and falls on same level		(Include just A)
		W00.2XXA,	W00.2XXA Other fall from one level to another due to ice and snow, initial encounter
		W11.XXXA - W17.XXXA,	W11 Fall on and from ladder W12 Fall on and from scaffolding W13 Fall from, out of or through building or structure W14 Fall from tree W15 Fall from cliff W16 Fall, jump or diving into water W17 Other fall from one level to another
E908-E909	Accidents due to cataclysmic storms and earth surface movements		(Include just A)
		X34.XXXA-X38.XXXA	X34 Earthquake X35 Volcanic eruption X36 Avalanche, landslide and other earth movements X37 Cataclysmic storm X38 Flood

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Footnotes defined on the last page of this table

Table A-2. Diagnosis Codes and Case Algorithms for Osteoporotic Fractures

Fracture Site	US ICD-9-CM Code*	US ICD-10-CM Code	
E916-E928 (E917 excluded)	Other accidents (struck by falling object, caught accidentally in or between objects, accidents caused by machinery, explosion, firearm, etc.)	W20.- - -A W22.1 - -A - W24.1- -A W28.- - -A – W40. - - -A W49. - - -A W52.- - -A, W85.XXXA- W86.XXXA	(Include just A) W20-W49 Exposure to inanimate mechanical forces <u>Excluding</u> W21.---- Striking against or struck by sports equipment W22.0--- Striking against stationary object W25.---- Contact with sharp glass W26.---- Contact with edge of stiff paper W27.---- Contact with nonpowered hand tool W42.---- Exposure to noise W45. ---- Foreign body or object entering through skin W46.---- Contact with hypodermic needle W52 Crushed, pushed or stepped on by crowd or human stampede W85 Exposure to electric transmission lines W86 Exposure to other specified electric current

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* 4-digit substring unless otherwise specified

Table A-3. Osteoporosis Diagnosis Codes, Medication Codes, and Case Algorithm Used in the Scandinavian National Registries

Case Algorithm for Osteoporosis Diagnosis defined by any of the following:	
ICD-10 Code	**ICD-10 Description**
M80, M81, M82	Osteoporosis
-	
Case Algorithm for Osteoporotic Fracture Diagnosis defined by any of the following:	
Denmark: S72.x*, S52.x, 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, T08	Fracture of hip, radius/ulna, spine, pelvis, femur or humerus. The supplementary character positions which indicate open fractures are not used in Denmark.
Norway and Sweden: S72.x, S52.x, 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, T08; Excluding S72.x1, S12.01, S12.11, S12.21, S12.71, S12.91, S22.01, S22.11, S32.x1, S42.21, S42.31, S42.41, S42.71, S42.81	Fracture of hip, radius/ulna, spine, pelvis, femur or humerus, excluding open fractures of hip, spine, pelvis, femur, or humerus
Note: One of the above codes for osteoporotic fracture diagnosis AND no concurrent major trauma NOMESCO codes (for Denmark) or ICD-10 trauma codes (for Norway and Sweden) on the same day as the fractures described above	
NOMESCO codes	Descriptions
EUP2-EUP9 EUM2-EUM9	Mode of transport: bicycle, moped, motorcycle, motor scooter, passenger car, van, pickup truck, lorry, truck, bus, other specified and unspecified
EUHE02-EUHE08	Falls, all other than falls on the same level

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* x indicates any digit from 0 – 9 available in the coding system

Table A-3. Osteoporosis Diagnosis Codes, Medication Codes, and Case Algorithm Used in the Scandinavian National Registries

Case Algorithm for Osteoporosis Diagnosis defined by any of the following:	
ICD-10 Code	**ICD-10 Description**
M80, M81, M82	Osteoporosis
AUHG02, EUHB, EUHC, EUHD	Other accidents: Contact or collision with animal; collapse, breakage and deformation of material; malfunction and loss of control of machinery, equipment and materials; malfunction and loss of control of transport vehicle machinery
ICD-10 codes	Descriptions
V01-V99	Transport accidents
W02, W11-W17	Falls, all other than falls on the same levels
W20-W49	Accidents due to exposure to inanimate mechanical forces Excluding W21.---- Striking against or struck by sports equipment W22.0 --- Striking against stationary object W25.---- Contact with sharp glass W26.---- Contact with edge of stiff paper W27.---- Contact with nonpowered hand tool W42.---- Exposure to noise W45.---- Foreign body or object entering through skin W46.---- Contact with hypodermic needle
W52 W85-W86	Accidents due to exposure to animate mechanical forces
Case Algorithm for Osteoporosis Medications:	
ATC Code	**ATC Description**
M05BA, M05BB	Bisphosphonate prescription
G03XC01	Raloxifene
M05Bx01	Ipriflavone
M05BX03	Strontium ranelate
M05BX04	Denosumab
H05AA	Teriparatide or parathyroid hormone
H05BA	Calcitonin
M05BX06	Romosozumab (Evenity)
Treatment Code	**Description**
BWHB40, BWHB40A	Treatment with bisphosphonates in hospital

* x indicates any digit from 0 – 9 available in the coding system

13.2 Appendix B. Algorithms Used to Identify Adverse Events of Special Interest Osteonecrosis of the Jaw

Table B-1. ONJ ICD-9-CM and US ICD-10-CM Diagnosis Codes

US ICD-9-CM Codes	US ICD-9-CM Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions
526.4	Inflammatory conditions of jaw	M27.2	Inflammatory conditions of jaws
522.7	Periapical abscess with sinus	K04.6	Periapical abscess with sinus
526.5	Alveolitis of jaw	M27.3	Alveolitis of jaws
733.45	Aseptic necrosis of bone, jaw	M87.180	Osteonecrosis due to drugs, jaw
		M87.08	Idiopathic aseptic necrosis of bone, other site
		M87.28	Osteonecrosis due to previous trauma, other site
		M87.38	Other secondary osteonecrosis, other site
		M87.88	Other osteonecrosis, other site
		M87.9	Osteonecrosis, unspecified*

* M87.9 Osteonecrosis, unspecified from orthopedic surgeons claims are not included in the definition used by Medicare. Optum does not have specialty codes to implement this exclusion.

Table B-2. ONJ ICD-10 Diagnosis Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
K046x	Periapical abscess with sinus
K102x	Inflammatory conditions of jaws, including osteitis of jaws; osteomyelitis of jaws; periostitis of jaws; sequestrum of jaw bone
K103x	Alveolitis of jaws
M87.0	Idiopathic aseptic necrosis of bone
M87.1	Osteonecrosis due to drugs
M87.2	Osteonecrosis due to previous trauma
M87.3	Other secondary osteonecrosis
M87.8	Other osteonecrosis
M87.9	Osteonecrosis, unspecified
Exclude in Norway: M87.0x, M87.1x, M87.8x, M87.9x, where x=1,2,3,4,5,6,7	x in Norway: 1 Shoulder region clavicle scapula 2 Upper arm humerus elbow joint 3 Forearm radius ulna wrist joint 4 Hand carpus fingers metacarpus joints between these bones 5 Pelvic region and thigh buttock femur pelvis hip (joint) sacroiliac joint 6 Lower leg fibula knee joint tibia 7 Ankle and foot metatarsus tarsus toes ankle joint other joints in foot
Exclude in Sweden M87.0x, M87.1x, M87.8x, M87.9x, Where x□ B,C,D,F, G, H	x in Sweden: B shoulder / upper arm C elbow / forearm D wrist / hand F hip / thigh G knee / lower leg H ankle / foot

Admission in a department of oral and maxillofacial surgery (DOMS)*

Atypical Femoral Fracture Leading to Hospitalization

Table B-3. ICD-9-CM and US ICD-10-CM Diagnosis Codes and E-Codes to Identify Non-traumatic Subtrochanteric and Diaphyseal Fracture of the Femur

US ICD-9-CM Codes	US ICD-9-CM Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions
		M84.75-A ^	Atypical femoral fracture, initial encounter for fracture
820.22	Hip, closed Sub/Trochanteric	S72.2--A	subtrochanteric
821.00	Fracture of shaft or unspecified part of femur closed	S72.8X-A S72.9--A	shaft, initial closed
821.01	Fracture of shaft or unspecified part of femur closed	S72.3--A	Unspecified femur, initial closed
Note: One of the above codes AND no concurrent major trauma ICD-9 codes, NOMESCO codes or ICD-10 codes on the same day as the fractures described above ^ New code effective after 10/2017			

Table B-3. ICD-9-CM and US ICD-10-CM Diagnosis Codes and E-Codes to Identify Non-traumatic Subtrochanteric and Diaphyseal Fracture of the Femur

US ICD-9-CM Codes	US ICD-9-CM Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions
E800-E848	Railway, motor vehicle, other road vehicle accidents; water transport accidents; air and space transport accidents; other vehicle accidents	V00-V09	V00-V97.---A Pedestrian injured in transport accident
		V10-V19	Pedal cycle rider injured in transport accident
		V20-V29	Motorcycle rider injured in transport accident
		V30-V39	Occupant of three-wheeled motor vehicle injured in transport accident
		V40-V49	Car occupant injured in transport accident
		V50-V59	Occupant of pick-up truck or van injured in transport accident
		V60-V69	Occupant of heavy transport vehicle injured in transport accident
		V70-V79	Bus occupant injured in transport accident
		V80-V89	Other land transport accidents
		V90-V94	Water transport accidents
		V95-V97	Air and space transport accidents

Table B-3. ICD-9-CM and US ICD-10-CM Diagnosis Codes and E-Codes to Identify Non-traumatic Subtrochanteric and Diaphyseal Fracture of the Femur

US ICD-9-CM Codes	US ICD-9-CM Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions
E881-E884	Falls, other than falls on stairs and falls on same **level**	W00.2XXA, , W11.XXXA-W17.XXXA,	(Include just A) W002XXA Other fall from one level to another due to ice and snow, initial encounter playground equipment W11 Fall on and from ladder W12 Fall on and from scaffolding W13 Fall from, out of or through building or structure W14 Fall from tree W15 Fall from cliff W16 Fall, jump or diving into water W17 Other fall from one level to another

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Table B-3. ICD-9-CM and US ICD-10-CM Diagnosis Codes and E-Codes to Identify Non-traumatic Subtrochanteric and Diaphyseal Fracture of the Femur

US ICD-9-CM Codes	US ICD-9-CM Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions
E908-E909	Accidents due to cataclysmic storms and earth surface movements	X34.XXXA-X38.XXXA	(Include just A) X34 Earthquake X35 Volcanic eruption X36 Avalanche, landslide and other earth movements X37 Cataclysmic storm X38 Flood
E916-E928 (E917 excluded)	Other accidents (struck by falling object, caught accidentally in or between objects, accidents caused by machinery, explosion, firearm, etc.)	W20.---A W22.1 - -A -W24.1- -A W28.- - -A – W40. - - -A W49. - - -A W52.---A W85.XXXA-W86.XXXA	(Include just A) W20-W49 Exposure to inanimate mechanical forces <u>Excluding</u> W21.---- Striking against or struck by sports equipment W22.0--- Striking against stationary object W25.---- Contact with sharp glass W26.---- Contact with edge of stiff paper W27.---- Contact with nonpowered hand tool W42.---- Exposure to noise W45. ---- Foreign body or object entering through skin W46.---- Contact with hypodermic needle W52 Crushed, pushed or stepped on by crowd or human stampede W85 Exposure to electric transmission lines W86 Exposure to other specified electric current

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Table B-4. ICD-10 Diagnosis Codes and NOMESCO Codes Used in the Scandinavian Registries to Identify Nontraumatic Subtrochanteric and Diaphyseal Fracture of the Femur

ICD-10 Code	**ICD-10 Description**
S722x	Subtrochanteric fracture
S723x	Fracture of shaft of femur
S729x	Fracture of femur, part unspecified
Note: One of the above codes AND no concurrent major trauma NOMESCO codes (Denmark) or ICD-10 codes (Norway and Sweden)	
NOMESCO Codes	**Descriptions**
EUP2-EUP9 EUM2-EUM9	Mode of transport: bicycle, moped, motorcycle, motor scooter, passenger car, van, pickup truck, lorry, truck, bus, other specified and unspecified
EUHE02EUHE08	Falls, all other than falls on the same level
AUHG02, EUHB, EUHC, EUHD	Other accidents: Contact or collision with animal; collapse, breakage and deformation of material; malfunction and loss of control of machinery, equipment and materials; malfunction and loss of control of transport vehicle machinery
ICD-10 Codes	**Descriptions**
V01-V99	Transport accidents
W02, W11-W17	Falls, all other than falls on the same levels
W20-W49	Accidents due to exposure to inanimate mechanical forces Excluding W21.---- Striking against or struck by sports equipment W22.0 --- Striking against stationary object W25.---- Contact with sharp glass W26.---- Contact with edge of stiff paper W27.---- Contact with nonpowered hand tool W42.---- Exposure to noise W45.---- Foreign body or object entering through skin W46.---- Contact with hypodermic needle
W52 W85-W86	Accidents due to exposure to animate mechanical forces

Fracture Healing Complications

Table B-5. Fracture Healing Complications ICD-9-CM and US ICD-10-CM Diagnosis Code

US ICD-9-CM Codes	US ICD-9-CM Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions
733.82	Nonunion of fracture	M80.- - - K	Osteoporosis with current pathological fracture
		M84.3- -K	Stress fracture
		M84.4- -K	Pathological fracture, not elsewhere classified
		M84.5- -K	Pathological fracture in neoplastic disease
		M84.6- -K	Pathological fracture in other disease
		S02.- - -K	Fracture of skull and facial bones
		S12.- - -K	Fracture of cervical vertebra and other parts of neck
		S22.- - -K	Fracture of rib(s), sternum and thoracic spine
		S32.- - -K	Fracture of lumbar spine and pelvis
		S42.- - -K	Fracture of shoulder and upper arm
		S49.- - -K	Other and unspecified injuries of shoulder and upper arm
		S52.- - -K, M or N	Fracture of forearm
		S59.- - -K	Other and unspecified injuries of elbow and forearm
		S62.- - -K	Fracture at wrist and hand level
		S72.- - -K, M or N	Fracture of femur
		S79.- - -K	Other and unspecified injuries of hip and thigh
		S82.- - -K, M or N	Fracture of lower leg, including ankle
		S89.- - -K	Other and unspecified injuries of lower leg
		S92.- - -K	Fracture of foot and toe, except ankle

Table B-6. Fracture Healing Complications ICD-10 Diagnosis Codes in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
M841x	Nonunion of fracture [pseudarthrosis]

Hypocalcemia

Table B-7. Hypocalcemia ICD-9-CM and US ICD-10-CM Diagnosis Code

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
275.41	Hypocalcemia	E835.1	Hypocalcemia

Table B-8. Hypocalcemia ICD-10 Diagnosis Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
E835D	Hypocalcemia (Denmark)
E835	Disorders of calcium metabolism (Norway and Sweden)

Infection Leading to Hospitalization, ER Visit, or Administration of Parenteral Anti-Infective Medication

Table B-9. All Infections ICD-9-CM & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
001.xx- 009.xx	Intestinal infectious diseases	A00.-	Cholera
		A01.- -	Typhoid and paratyphoid fevers
		A02.*	Other salmonella infections
		A03.-	Shigellosis
		A04.*	Other bacterial intestinal infections
		A05.-	Other bacterial foodborne intoxications, not elsewhere classified
		A06.*	Amebiasis
		A07.-	Other protozoal intestinal diseases
		A08.*	Viral and other specified intestinal infections
		A09	Infectious gastroenteritis and colitis, unspecified
010.xx- 018.xx	Tuberculosis	A15.-	Tuberculosis of lung
		A17.*	Tuberculosis of nervous system
		A18.*	Tuberculosis of other organs
		A19.-	Miliary tuberculosis

Table B-9. All Infections ICD-9-CM & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
020.xx- 027.xx	Zoonotic bacterial diseases	A20.-	Plague
		A21.-	Tularemia
		A22.-	Anthrax
		A23.-	Brucellosis
		A24.0	Glanders
		A25.-	Rat-bite fevers
		A26.-	Erysipeloid
		A28.-	Other zoonotic bacterial diseases, not elsewhere classified
030.xx	Other bacterial diseases	A30.-	Leprosy [Hansen's disease]
031.xx	Other bacterial diseases	A31.-	Infection due to other mycobacteria
027.xx	Zoonotic bacterial diseases	A32.*	Listeriosis
037	Other bacterial diseases	A35	Other tetanus
032.xx	Other bacterial diseases	A36.*	Diphtheria
033.xx	Other bacterial diseases	A37.*	Whooping cough
034.xx	Other bacterial diseases	A38.-	Scarlet fever
036.xx	Other bacterial diseases	A39.*	Meningococcal infection
038.xx	Other bacterial diseases	A40.-	Streptococcal sepsis
038.xx	Other bacterial diseases	A41.*	Other sepsis
039.xx	Other bacterial diseases	A42.*	Actinomycosis
039.xx	Other bacterial diseases	A43.-	Nocardiosis
035	Erysipelas	A46	Erysipelas
040.xx	Other bacterial diseases	A48.* K90.81, M60.009	Other bacterial diseases, not elsewhere classified
041.xx	Bacterial infection in conditions classified elsewhere and of unspecified site	A49.- B95. * , B96. *	Bacterial infection of unspecified site Other bacterial agents as the cause of diseases classified elsewhere

Table B-9. All Infections ICD-9-CM & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
090.xx- 099.xx	Syphilis and other venereal diseases	A50.*	Congenital syphilis
		A51.*	Primary genital syphilis
		A52.*	Cardiovascular syphilis, unspecified
		A53.0. A53.9	Other and unspecified syphilis
		A54.*	Gonococcal infection
		A55	Chlamydial lymphogranuloma (venereum)
		A56.-	Other sexually transmitted chlamydial diseases
		A57	Chancroid
		A58	Granuloma inguinale
		A63.8	Other specified predominantly sexually transmitted diseases
		A64	Unspecified sexually transmitted disease
		M02.3*	Reiter's disease
100.xx- 104.xx	Other spirochetal diseases	A27.*	Leptospirosis
		A65	Nonvenereal syphilis
		A66.-	Yaws
		A67.-	Pinta [carate]
		A69.0	Necrotizing ulcerative stomatitis
		A69.1	Other Vincent's infections
		A69.21	Meningitis due to Lyme disease
		A69.8	Other specified spirochetal infections
		A69.9	Spirochetal infection, unspecified
		A74.81	Chlamydial peritonitis
		B25.0	Cytomegaloviral pneumonitis

Table B-9. All Infections ICD-9-CM & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
110.xx- 118.xx	Mycoses	B35.-	Dermatophytosis
		B36.-	Other superficial mycoses
		B37.*	Candidiasis
		B38.*	Coccidiodomycosis
		B39.-	Histoplasmosis
		B40.*	Blastomycosis
		B41.-	Paracoccidiodomycosis
		B42.*	Sporotrichosis
		B43.-	Chromomycosis and pheomycotic abscess
		B44.*	Aspergillosis
		B45.-	Cryptococcosis
		B46.-	Zygomycosis
		B47.-	Eumycetoma
		B48.-	Rhinosporidiosis
		B49	Unspecified mycosis
130.xx- 136.xx	Other infectious and parasitic diseases	A59.*	Trichomoniasis
		B58. *	Toxoplasma
		B59	Pneumocystosis
		B60.1-, B60.2, B60.8	Other protozoal diseases
		B64	Unspecified protozoal disease
		B85. -	Pediculosis and phthiriasis
		B86	Scabies
		B87.*	Myiasis
		B83.4, B88.-	Other Infestations
		B89	Unspecified parasitic disease
		B99.8, B99.9	Other and unspecified infectious diseases
		D86. *	Sarcoidosis
		L94.6	Ainhum
		M35.2	Behçet's disease
		D73.3	Abscess of spleen

Table B-9. All Infections ICD-9-CM & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
289.59	Splenic abscess	G00.*	Bacterial meningitis, not elsewhere classified
320.xx	Bacterial meningitis	G01	Meningitis in bacterial diseases classified elsewhere
		B45.1, G02	Meningitis in other infectious and parasitic diseases classified elsewhere
321.x	Meningitis due to other nonbacterial organisms	G03.0	Nonpyogenic meningitis
322.x	Meningitis of unspecified cause	G03.1	Chronic meningitis
		G03.8	Meningitis due to other specified causes
		G03.9	Meningitis, unspecified
		G04.2 G05.-	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere
323.xx	Encephalitis, myelitis, and encephalomyelitis		Intracranial and intraspinal abscess and granuloma

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Table B-9. All Infections ICD-9-CM & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
324.xx	Intracranial and intraspinal abscess	G06.-, G07.-	Intracranial and intraspinal abscess and granuloma in diseases classified elsewhere
373.0x	Blepharitis	H01.0- - -	Blepharitis
373.4	Infective dermatitis of eyelid of types resulting in deformity	H01.8	Other specified inflammations of eyelid
373.5	Other infective dermatitis of eyelid	H01.8	Other specified inflammations of eyelid
380.1x	Infective otitis externa	H60.0-	Abscess of external ear
		H60.1-	Cellulitis of external ear
		H60.2-	Malignant otitis externa
		H60.3-	Other infective otitis externa
		H62.*-	Otitis externa in other diseases classified elsewhere
382.xx	Suppurative and unspecified otitis media	H66.*	Suppurative and unspecified otitis media
		H67.-	Otitis media in diseases classified elsewhere
381.5x	Eustachian tube (ear) salpingitis	H68.0- -	Eustachian salpingitis
383.0x	Acute mastoiditis	H70.0- -	Acute mastoiditis
421.x	Endocarditis	I33.0,I33.9, I39	Acute and subacute endocarditis
289.2	Nonspecific mesenteric lymphadenitis	I88.0	Nonspecific mesenteric lymphadenitis
460	Acute nasopharyngitis (common cold)	J00.-	Acute nasopharyngitis [common cold]
461.xx	Acute sinusitis	J01.-	Acute sinusitis
462.	Acute pharyngitis	J02.8, J02.9	Acute pharyngitis
463.	Acute tonsillitis	J03.80, J03.81 J03.90, J03.91	Acute tonsillitis
464.xx	Acute laryngitis and tracheitis	-	
		J04.*, J05.*	Acute laryngitis and tracheitis
465.xx	Acute upper respiratory infections of multiple or unspecified sites	, J06.-	Acute upper respiratory infections of multiple and unspecified sites
466.xx	Acute bronchitis and bronchiolitis	J20. - , J21. -	Acute bronchitis and bronchiolitis

Table B-9. All Infections ICD-9-CM & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
		J32.-	Chronic sinusitis
475	Peritonsillar abscess	J36	Peritonsillar abscess
480xx-486xx, 487.0	Pneumonia, influenza with pneumonia	B77.81	Ascariasis pneumonia
		J10.*	Influenza due to other identified influenza virus
		J11.*	Influenza due to unidentified influenza virus
		J12.*	Viral pneumonia, not elsewhere classified
		J13	Pneumonia due to Streptococcus pneumoniae
		J14	Pneumonia due to Hemophilus influenzae
		J15.*	Bacterial pneumonia, not elsewhere classified
		J16.-	Pneumonia due to other infectious organisms, not elsewhere classified
		J17	Pneumonia in diseases classified elsewhere
		J18.-	
488.11, 488.12	Influenza due to identified 2009 H1N1 influenza virus with pneumonia/with other respiratory manifestations	J10.08, J10.1	Influenza due to other identified influenza virus with other specified pneumonia/ with other respiratory manifestations
511.1	Pleurisy with effusion or mention of bacterial cause other than TB,	J90	Pleural effusion, not elsewhere classified
528.3	Cellulitis and abscess of mouth	K12.2	Cellulitis and abscess of mouth
528.5	Cellulitis of lips	K13.0	Diseases of lips
		K35.-	Acute appendicitis
		K36	Other appendicitis
		K37	Unspecified appendicitis
		K38.-	Other diseases of appendix

Table B-9. All Infections ICD-9-CM & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
562.x1, 562.x3	Diverticulitis of small intestine and colon	K57.x2, K57.x3	Diverticulitis of small intestine and colon
566	Abscess of anal and rectal regions	K61.-	Abscess of anal and rectal regions
575.0	Acute Cholecystitis	K81.0	Acute cholecystitis
684	Impetigo	L01.*	Impetigo, unspecified
680.x	Carbuncle and furuncle	L02.-2, L02.-2-, L02.-3, L02.-3-	Carbuncle and furuncle
681.xx	Cellulitis and abscess of finger and toe	L03.-, L02.51-, L02.61-	Cellulitis of finger/ toe. Abscess of hand/foot
682.x	Other cellulitis and abscess	L02.-1, L02.-1-, L03.*	Other cellulitis and abscess

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Table B-9. All Infections ICD-9-CM & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
683	Acute lymphadenitis	L04.-	Acute lymphadenitits
686.xx	Other local infections of skin and subcutaneous tissue	L08.*, L88, B78.1, E83.2, L92.8, L98.0	Pyoderma Pneumococcal arthritis and polyarthritis
711.0x 711.4x 711.9x	Infective arthritis (bacterial)	M00.*	Pyogenic arthritis
		M01.*	Direct infections of joint in infectious and parasitic diseases classified elsewhere
		M02.8*	Other reactive arthropathies
728.86	Necrotizing fasciitis	M72.6	Necrotizing fasciitis
730.xx	Osteomyelitis, periostitis, and other infections involving bone	M86.*	Osteomyelitis
		M46.2-	Osteomyelitis
		M46.3-	Infection of intervertebral disc (pyogenic)
590.xx	Infections of kidney	N10.-	Acute tubulo-interstitial nephritis
		N16	Renal tubulo-interstitial disorders in diseases classified elsewhere
		N28.8-	Pyeloureteritis cystica
		N11.-	Chronic tubulo-interstitial nephritis
		N12	Tubulo-interstitial nephritis, not specified as acute or chronic
		N13.6	Pyonephrosis
		N15.1	Renal and perinephric abscess
		N15.9	Renal tubulo-interstitial disease, unspecified
595.xx	Cystitis	N30.-	Cystitis
597.xx, 099.4x	Urethritis, not sexually transmitted, urethral syndrome; Other nongonococcal urethritis	N34.-	Urethritis and urethral syndrome
599	Urinary tract infection	N39.0	Urinary tract infection, site not specified
790.7x	Bacteremia	R78.81	Bacteremia

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Table B-10. All Infections ICD-10 Diagnosis Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
A00xx	Cholera
A01 xx	Typhoid and paratyphoid fevers
A02 xx	Other salmonella infections
A03 xx	Shigellosis
A04 xx	Other bacterial intestinal infections
A05 xx	Other bacterial foodborne intoxications, not elsewhere classified
A06 xx	Amebiasis
A07 xx	Other protozoal intestinal diseases
A08 xx	Viral and other specified intestinal infections
A09 xx	Infectious gastroenteritis and colitis, unspecified
A15 xx	Respiratory tuberculosis
A16 xx	Respiratory tuberculosis, not confirmed bacteriologically or histologically
A17 xx	Tuberculosis of nervous system
A18 xx	Tuberculosis of other organs
A19 xx	Miliary tuberculosis
A20 xx	Plague
A21xx	Tularaemia
A22 xx	Anthrax
A23 xx	Brucellosis
A24 xx	Glanders and melioidosis
A25xx	Rat-bite fevers
A26 xx	Erysipeloid
A27 xx	Leptospirosis
A28 xx	Other zoonotic bacterial diseases, not elsewhere classified
A30 xx	Leprosy [Hansen's disease]
A31 xx	Infection due to other mycobacteria
A32 xx	Listeriosis
A34 xx	Obstetrical tetanus
A35 xx	Other tetanus
A36xx	Dphtheria
A37 xx	Whooping cough
A38xx	Scarlet fever

Table B-10. All Infections ICD-10 Diagnosis Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
A40 xx	Streptococcal sepsis
A41 xx	Other sepsis
A42 xx	Actinomycosis
A43xx	Nocardiosis
A44 xx	Bartonellosis
A46 xx	Erysipelas
A48 xx	Other bacterial diseases, not elsewhere classified
A49 xx	Bacterial infection of unspecified site
A51 xx	Early syphilis
A52 xx	Late syphilis
A53 xx	Other and unspecified syphilis
A54xx	Gonococcal infection
A55 xx	Chlamydial lymphogranuloma (venereum)
A56xx	Other sexually transmitted chlamydial diseases
A57 xx	Chancroid
A58 xx	Granuloma inguinale
A59 xx	Trichomoniasis
A60 xx	Anogenital herpesviral [herpes simplex] infections
A63 xx	Other predominantly sexually transmitted diseases, not elsewhere classified
A64 xx	Unspecified sexually transmitted disease
A65xx	Nonvenereal syphilis
A66 xx	Yaws
A67xx	Pinta (carate)
A691xx	Other Vincent's infections
A698xx	Other specified spirochetal infections
A699xx	Spirochaetal infection, unspecified
B35 xx	Dermatophytosis
B36 xx	Other superficial mycoses
B37 xx	Candidiasis
B38xx	Coccidiodomycosis
B39xx	Histoplasmosis
B40xx	Blastomycosis
B41xx	Paracoccidiodomycosis

Table B-10. All Infections ICD-10 Diagnosis Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
B42xx	Sporotrichosis
B43 xx	Chromomycosis and pheomycotic abscess
B44 xx	Aspergillosis
B45 xx	Cryptococcosis
B46 xx	Zygomycosis
B48 xx	Other mycoses, not elsewhere classified
B49 xx	Unspecified mycosis
B55 xx	Leishmaniasis
B58xx	Toxoplasmosis
B59 xx	Pneumocystosis
B60xx	Other protozoal diseases not elsewhere classified
B64 xx	Unspecified protozoal disease
B85 xx	Pediculosis and phthiriasis
B86 xx	Scabies
B87 xx	Myiasis
B88 xx	Other infestations
B95 xx	*Streptococcus*, *Staphylococcus*, and *Enterococcus* as the cause of diseases classified elsewhere
B96 xx	Other bacterial agents as the cause of diseases classified elsewhere
B99 xx	Other and unspecified infectious diseases
D733xx	Diseases of spleen
G00 xx	Bacterial meningitis, not elsewhere classified
G03xx	Meningitis due to other and unspecified causes
G04xx	Encephalitis, myelitis and encephalomyelitis
G042 xx	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified
G05 xx	Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere
G06 xx	Intracranial and intraspinal abscess and granuloma
H66 xx	Suppurative and unspecified otitis media
H67 xx	Otitis media in diseases classified elsewhere
H70 xx	Mastoiditis and related conditions
I33 xx	Acute and subacute endocarditis
I39 xx	Endocarditis and heart valve disorders in diseases classified elsewhere
J00 xx	Acute nasopharyngitis [common cold]
J01 xx	Acute sinusitis

Table B-10. All Infections ICD-10 Diagnosis Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
J02 xx	Acute pharyngitis
J03 xx	Acute tonsillitis
J04 xx	Acute laryngitis and tracheitis
J05 xx	Acute obstructive laryngitis [croup] and epiglottitis
J06 xx	Acute upper respiratory infections of multiple and unspecified sites
J10 xx	Influenza due to other influenza virus; code first any associated lung abscess (J85.1)
J11xx	Influenza virus, not identified
J12 xx	Viral pneumonia, not elsewhere classified
J13 xx	Pneumonia due to *Streptococcus pneumoniae*
J14 xx	Pneumonia due to *Hemophilus influenzae*
J15 xx	Bacterial pneumonia, not elsewhere classified
J16xx	Pneumonia due to other infectious organisms, not elsewhere classified
J17 xx	Pneumonia in diseases classified elsewhere
J18 xx	Pneumonia, unspecified organism
J20 xx	Acute bronchitis
J21 xx	Acute bronchiolitis
J32xx	Chronic sinusitis
J36 xx	Peritonsillar abscess
J948xx	Other specified pleural conditions
K35 xx	Acute appendicitis
K36xx	Acute appendicitis
K37xx	Unspecified appendicitis
K38xx	Other diseases of appendix
K57xx	Diverticular disease of intestine
K61 xx	Abscess of anal and rectal regions
K81 xx	Cholecystitis
K122xx	Cellulitis and abscess of mouth
K130xx	Diseases of lips
L01xx	Impetigo
L02 xx	Cutaneous abscess, furuncle and carbuncle
L03 xx	Cellulitis and acute lymphangitis
L08 xx	Other local infections of skin and subcutaneous tissue
M011x	Tuberculous arthritis

Table B-10. All Infections ICD-10 Diagnosis Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
M013x	Arthritis in other bacterial diseases classified elsewhere
M726x	Necrotizing fascitis
M86 xx	Osteomyelitis
N10xx	Acute tubulo-interstitial nephritis
N11xx	Chronic tubulo-interstitial nephritis
N12xx	Tubulo-interstitial nephritis, not specified as acute or chronic
N151x	Renal and perinephric abscess
N159x	Renal tubulo-interstitial disease, unspecified
N30 xx	Cystitis
N34xx	Urethritis and urethral syndrome
N390x	Urinary tract infection, site not specified
R788x	Findings of other substances, not normally found in blood

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Table B-11. Skin Infection ICD-9 & US ICD-10-CM Diagnosis Codes

ICD-9-CM Code	ICD-9-CM Description	ICD-10-CM Code	ICD-10-CM Description
035	Erysipelas	A46	Erysipelas
373.0x	Blepharitis	H01.0- -	Blepharitis
373.4	Infective dermatitis of eyelid of types resulting in deformity	H01.8	Other specified inflammations of eyelid
373.5	Other infective dermatitis of eyelid	H01.8	Other specified inflammations of eyelid
380.1x	Infective otitis externa	H60.0-	Abscess of external ear
		H60.1-	Cellulitis of external ear
		H60.2-	Malignant otitis externa
		H60.3-	Other infective otitis externa
		H62.*	Otitis externa in other diseases classified elsewhere
528.3	Cellulitis and abscess of mouth	K12.2	Cellulitis and abscess of mouth
528.5	Diseases of lips	K13.0,	Diseases of lips
680.xx to 682.xx	Carbuncle and furuncle, Other cellulitis and abscess	L02.*, L0.3*	Cutaneous abscess, furuncle and carbuncle
684.	Impetigo	L01. *	Impetigo
686.xx	Other local infections of skin and subcutaneous tissue	L08. *, L88, B78.1, E83.2, L92.8, L98.0	Other local infections of skin and subcutaneous tissue
728.86	Necrotizing fasciitis	M72.6	Necrotizing fasciitis

Table B-12. Skin Infection ICD-10 Diagnosis Used in the Scandinavian Registries

ICD-10 code	ICD-10 Description
H010x	Blepharitis
H03xx	Disorders of eyelid in diseases classified elsewhere
H600x	Abscess of external ear
H601x	Cellulitis of external ear
H602x	Malignant otitis externa
H603x	Other infective otitis externa
H62xx	Disorders of external ear in diseases classified elsewhere
K122x	Cellulitis and abscess floor of mouth
K130x	Diseases of lips
K61xx	Abscess of anal and rectal regions
L02xx	Cutaneous abscess, furuncle and carbuncle
L03xx	Cellulitis and acute lymphangitis
L01xx	Impetigo
L08xx	Other local infections of skin and subcutaneous tissue
M726x	Necrotizing fasciitis
A46xx	Erysipelas

Table B-13. AHFS Code for Parenteral Anti-infective Medications

08.12 Antibacterial agents
08.12 Antibiotics
08.12.02 Aminoglycosides
08.12.04 Antifungals
08.12.04 Fungicides
08.12.06 Cephalosporins
08.12.07 Miscellaneous B-Lactam antibiotics
08.12.08 Chloramphenicols
08.12.12 Macrolides
08.12.12 Erythromycins
08.12.16 Penicillins
08.12.18 Quinolones
08.12.20 Sulfonamides
08.12.24 Tetracyclines
08.12.28 Miscellaneous antibiotics
08.14 Antifungals
08.16 Antituberculars
08.18 Antivirals
08.18 Virucides
08.22 Quinolones
08.24 Sulfonamides
08.26 Sulfones
08.28 Antitreponemal agents
08.32 Trichomonacides
08.36 Urinary anti-infectives
08.36 Urinary germicides

Table B-14. HCPCS Codes for IV Anti-infective Medications

HCPCS Code	Definition
S9494	Home infusion therapy, antibiotic, antiviral, or antifungal therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately, per diem) (do not use this code with home infusion codes for hourly dosing schedules S9497-S9504)
S9497	Home infusion therapy, antibiotic, antiviral, or antifungal therapy; once every three hours; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
S9500	Home infusion therapy, antibiotic, antiviral, or antifungal therapy; once every 24 hours; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
S9501	Home infusion therapy, antibiotic, antiviral, or antifungal therapy; once every 12 hours; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
S9502	Home infusion therapy, antibiotic, antiviral, or antifungal therapy; once every eight hours, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
S9503	Home infusion therapy, antibiotic, antiviral, or antifungal; once every six hours; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
S9504	Home infusion therapy, antibiotic, antiviral, or antifungal; once every four hours; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
J0120	Injection, tetracycline, up to 250 mg
J0200	Injection, alatrofloxacin mesylate, 100 mg
J0278	Injection, amikacin sulfate, 100 mg
J0285	Injection, amphotericin B, 50 mg

Table B-14. HCPCS Codes for IV Anti-infective Medications

HCPCS Code	Definition
J0287	Injection, amphotericin B lipid complex, 10 mg
J0288	Injection, amphotericin B cholesteryl sulfate complex, 10 mg
J0289	Injection, amphotericin B liposome, 10 mg
J0290	Injection, ampicillin sodium, 500 mg
J0295	Injection, ampicillin sodium/sulbactam sodium, per 1.5 g
J0348	Injection, anidulafungin, 1 mg
J0456	Injection, azithromycin, 500 mg
J0530	Injection, penicillin G benzathine and penicillin G procaine, up to 600,000 units
J0540	Injection, penicillin G benzathine and penicillin G procaine, up to 1,200,000 units
J0550	Injection, penicillin G benzathine and penicillin G procaine, up to 2,400,000 units
J0560	Injection, penicillin G benzathine, up to 600,000 units
J0570	Injection, penicillin G benzathine, up to 1,200,000 units
J0580	Injection, penicillin G benzathine, up to 2,400,000 units
J0637	Injection, caspofungin acetate, 5 mg
J0690	Injection, cefazolin sodium, 500 mg
J0692	Injection, cefepime HCl, 500 mg
J0694	Injection, cefoxitin sodium, 1 g
J0696	Injection, ceftriaxone sodium, per 250 mg
J0697	Injection, sterile cefuroxime sodium, per 750 mg
J0698	Cefotaxime sodium, per g

Table B-14. HCPCS Codes for IV Anti-infective Medications

HCPCS Code	Definition
J0710	Injection, cephapirin sodium, up to 1 g
J0713	Injection, ceftazidime, per 500 mg
J0715	Injection, ceftizoxime sodium, per 500 mg
J0720	Injection, chloramphenicol sodium succinate, up to 1 g
J0743	Injection, cilastatin sodium imipenem, per 250 mg
J0744	Injection, ciprofloxacin for intravenous infusion, 200 mg
J0770	Injection, colistimethate sodium, up to 150 mg
J0878	Injection, daptomycin, 1 mg
J1335	Injection, ertapenem sodium, 500 mg
J1364	Injection, erythromycin lactobionate, per 500 mg
J1450	Injection, fluconazole, 200 mg
J1455	Injection, foscarnet sodium, per 1,000 mg
J1580	Injection, garamycin, gentamicin, up to 80 mg
J1590	Injection, gatifloxacin, 10 mg
J1835	Injection, itraconazole, 50 mg
J1840	Injection, kanamycin sulfate, up to 500 mg
J1850	Injection, kanamycin sulfate, up to 75 mg
J1890	Injection, cephalothin sodium, up to 1 g

Table B-14. HCPCS Codes for IV Anti-infective Medications

HCPCS Code	Definition
J1956	Injection, levofloxacin, 250 mg
J2010	Injection, lincomycin HCl, up to 300 mg
J2020	Injection, linezolid, 200 mg
J2185	Injection, meropenem, 100 mg
J2248	Injection, micafungin sodium, 1 mg
J2280	Injection, moxifloxacin, 100 mg
J2460	Injection, oxytetracycline HCl, up to 50 mg
J2510	Injection, penicillin G procaine, aqueous, up to 600,000 units
J2540	Injection, penicillin G potassium, up to 600,000 units
J2543	Injection, piperacillin sodium/tazobactam sodium, 1 g/0.125 g (1.125 g)
J2700	Injection, oxacillin sodium, up to 250 mg
J2770	Injection, quinupristin/dalfopristin, 500 mg (150/350)
J3243	Injection, tigecycline, 1 mg
J3260	Injection, tobramycin sulfate, up to 80 mg
J3320	Injection, spectinomycin dihydrochloride, up to 2 g
J3370	Injection, vancomycin HCl, 500 mg
J3465	Injection, voriconazole, 10 mg
c9001	linezolid injection, per 200mg
c9019	injection, caspofungin acetate, 5 mg
c9116	injection, ertapenem sodium, per 1 gram vial

Table B-14. HCPCS Codes for IV Anti-infective Medications

HCPCS Code	Definition
c9124	injection, daptomycin, per 1 mg
c9227	injection, micafungin sodium, per 1 mg
c9228	injection, tigecycline, per 1 mg
j0286	injection, amphotericin b, any lipid formulation, 50 mg
j0558	injection, penicillin g benzathine and penicillin g procaine, 100,000 units
j0559	injection, penicillin g benzathine and penicillin g procaine, 2500 units
j0561	injection, penicillin g benzathine, 100,000 units
j1362	injection, erythromycin gluceptate, per 250 mg
s0016	injection, amikacin sulfate, 500 mg
s0024	injection, ciprofloxacin, 200 mg
s0029	injection, fluconazole, 400 mg
s0072	injection, amikacin sulfate, 100 mg
s0080	injection, pentamidine isethionate, 300 MG
s0081	injection, piperacillin sodium, 500 mg
s0085	injection, gatifloxacin, 200 mg
s0096	injection, itraconazole, 200 mg

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Table B-15. Treatment Codes for IV Anti-infective Medications

Treatment code (DK)	Description
BPHxx	Systemic treatment with antibiotics

* Only available in Denmark

Dermatologic Adverse Events Leading to Hospitalization or ER Visit

Table B-16. Dermatologic Adverse Events ICD-9 and US ICD-10-CM Diagnosis Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
694.4	Pemphigus. Pemphigus: NOS, erythematosus, foliaceus, malignant, vegetans, vulgaris	L10.-	Pemphigus
694.5	Pemphigoid	L12.0, L12.8, L12.9	Bullous pemphigoid; Other pemphigoid
694.6x	Benign mucous membrane pemphigoid	L12.1	Cicatricial pemphigoid
694.xx	Bullous dermatoses	L10.* L12.0, L12.1, L12.2, L12.8, L12.9 L13.- L14.- L40.1	Pemphigus Bullous pemphigoid; Other pemphigoid Other bullous disorders Bullous disorders in diseases classified elsewhere Generalized pustular psoriasis
694.9	Unspecified bullous dermatoses	L13.9	Bullous disorder, unspecified
708.x	Urticaria	L50.-	Urticaria
695.10	Erythema multiforme, unspecified	L510, L51.9	Nonbullous Erythema multiforme, Erythema multiforme, unspecified
695.11	Erythema multiforme minor	L51.8	Other erythema multiforme
695.12	Erythema multiforme major	L51.8	Other erythema multiforme
695.13	Stevens-Johnson syndrome	L51.1	Stevens-Johnson syndrome
695.14	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome	L51.3	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
695.15	Toxic epidermal necrolysis	L12.3 -, L51.2	Acquired epidermolysis bullosa , Toxic epidermal necrolysis [Lyell]
695.19	Other erythema multiforme	L51.8	Other erythema multiforme

Table B-16. Dermatologic Adverse Events ICD-9 and US ICD-10-CM Diagnosis Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
695.5x	Exfoliation due to erythematous conditions according to extent of body surface involved. Code first erythematous condition causing exfoliation, such as: Ritter's disease (695.81) (Staphylococcal) scalded skin syndrome (695.81) Stevens-Johnson syndrome (695.13) Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome (695.14) toxic epidermal necrolysis (695.15)"	L49.-	Exfoliation due to erythematous condition according to extent of body surface involved.
696.1	Other psoriasis	L40.- (excluding L40.5-)	Psoriasis (excluding Arthropathic psoriasis)
782.1	Rash and other nonspecific skin eruption	R21.-	Rash and other nonspecific skin eruption

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Table B-17. Dermatologic Adverse Events ICD-10 Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
L10xx	Pemphigus
L12xx	Pemphigoid
L13xx	Other bullous disorders
L14xx	Bullous disorders in diseases classified elsewhere
L50xx	Urticaria
L511x	Bullous erythema multiforme
L512x	Toxic epidermal necrolysis [Lyell]
L518x	Other erythema multiforme
L519x	Erythema multiforme, unspecified
L538x	Other specified erythematous condition
R21xx	Rash and other nonspecific skin eruption

Table B-18. Bullous Adverse Events ICD-9 and US ICD-10-CM Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM description
694.xx	Bullous dermatoses	L10.*	Pemphigus
		L12.0, L12.1, L12.2, L12.8, L12.9	Bullous pemphigoid; Other pemphigoid
		L13.-	Other bullous disorders
		L14.-	Bullous disorders in diseases classified elsewhere
		L40.1	Generalized pustular psoriasis

Table B-19. Bullous Adverse Events ICD-10 Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
L10xx	Pemphigus
L12xx	Pemphigoid
L13xx	Other bullous disorders
L14xx	Bullous disorders in diseases classified elsewhere

Table B-20. Serious Erythematous Adverse Events ICD-9 and US ICD-10-CM Codes

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM description
695.10	Erythema multiforme, unspecified	L51. 0, L51.9	Erythema multiforme
695.11	Erythema multiforme minor	L51.8	
695.12	Erythema multiforme major	L51.8	
695.13	Stevens-Johnson syndrome	L51.1	
695.14	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome	L51.3	
695.15	Toxic epidermal necrolysis	L12.3 -, L51.2	
695.19	Other erythema multiforme	L51.8	
695.5x	Exfoliation due to erythematous conditions according to extent of body surface involved. Code first erythematous condition causing exfoliation, such as: Ritter's disease (695.81) (Staphylococcal) scalded skin syndrome (695.81) Stevens-Johnson syndrome (695.13) Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome (695.14) toxic epidermal necrolysis (695.15)"	L49.-	Exfoliation due to erythematous condition according to extent of body surface involved.

Table B-21. Serious Erythematous Adverse Events ICD-10 Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
L511x	Bullous erythema multiforme
L512x	Toxic epidermal necrolysis [Lyell]
L518x	Other erythema multiforme
L519x	Erythema multiforme, unspecified
L538x	Other specified erythematous condition

Acute Pancreatitis Leading to Hospitalization

Table B-22. Pancreatitis ICD-9 & US ICD-10-CM Diagnosis Codes

US ICD-9 Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM Description
577.0	Acute pancreatitis	K85.0	Idiopathic acute pancreatitis[a]
		K85.0-	Idiopathic acute pancreatitis[a]
		K85.1	Biliary acute pancreatitis[a]
		K85.1-	Biliary acute pancreatitis[a]
		K85.3	Drug induced acute pancreatitis[a]
		K85.3-	Drug induced acute pancreatitis[a]
		K85.8	Other acute pancreatitis[a]
		K85.8-	Other acute pancreatitis[a]
		K85.9	Acute pancreatitis[a]
		K85.9-	Acute pancreatitis[a]

[a]Note:K85.0 - K85.9 did not require a 5th digit until October 2016. From October 2015 through September 2016, the 4-digit ICD-10 code was used.

Table B-23. Pancreatitis ICD-10 Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
K85	Acute pancreatitis

Hypersensitivity Leading to Hospitalization or ER Visit

Table B-24. Hypersensitivity ICD-9 & US ICD-10-CM Diagnosis Codes

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Code	US ICD-10-CM Description
288.3	Eosinophilia. Eosinophilia allergic, hereditary, idiopathic, secondary. Eosinophilic leukocytosis	D72.1	Eosinophilia
713.6	Arthropathy associated with hypersensitivity reaction	M02.2- M02.2--	Postimmunization arthropathy, unspecified site
		M36.4	Arthropathy in hypersensitivity reactions classified elsewhere

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Table B-24. Hypersensitivity ICD-9 & US ICD-10-CM Diagnosis Codes

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Code	US ICD-10-CM Description
995.0	Other anaphylactic shock. Allergic shock NOS or due to adverse effect of correct medicinal substance properly administered. Anaphylactic reaction NOS or due to adverse effect of correct medicinal substance properly administered. Anaphylaxis NOS or due to adverse effect of correct medicinal substance properly administered	T78.2XXA	Anaphylactic shock, unspecified, initial encounter
		T88.6XXA	Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, initial encounter
995.3	Allergy, unspecified	T78.40XA	Allergy, unspecified, initial encounter
		T78.49XA	Other allergy, initial encounter
995.20, 995.27, 995.29	Other and unspecified adverse effect of drug, medicinal and biological substance (due) to correct medicinal substance properly administered. Adverse effect to correct medicinal substance properly administered. Allergic reaction to correct medicinal substance properly administered. Hypersensitivity to correct medicinal substance properly administered Idiosyncrasy due to correct medicinal substance properly administered. Drug: hypersensitivity NOS reaction NOS	T88.7XXA	Unspecified adverse effect of drug or medicament, initial encounter
		T50.905A	Adverse effect of unspecified drugs, medicaments and biological substances, initial encounter
		T50.995A	Adverse effect of other drugs, medicaments and biological substances, initial encounter

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Table B-25. Hypersensitivity ICD-10 Diagnosis Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
D721x	Eosinophilia (Eosinophilia: allergic, hereditary)
M364x	Arthropathy in hypersensitivity reactions classified elsewhere
M022x	Postimmunization arthropathy
T782x	Anaphylactic shock, unspecified
T886x	Anaphylactic shock due to adverse effect of correct drug or medicament properly administered
T887x	Unspecified adverse effect of drug or medicament
T784x	Allergy, unspecified

Table B-26. Anaphylaxis ICD-9 Diagnosis Codes & US ICD-10-CM

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM description
995.0	Other anaphylactic shock. Allergic shock NOS or due to adverse effect of correct medicinal substance properly administered. Anaphylactic reaction NOS or due to adverse effect of correct medicinal substance properly administered. Anaphylaxis NOS or due to adverse effect of correct medicinal substance properly administered	T78.2XXA	Anaphylactic shock, unspecified, initial encounter
		T88.6XXA	Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, initial encounter

Table B-27. Anaphylaxis ICD-10 Diagnosis Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-10 Description
T886x	Anaphylactic shock due to adverse effect of correct drug or medicament properly administered
T782x	Anaphylactic shock, unspecified

New Primary Malignancy (Excluding Non-melanoma Skin Cancer)

Table B-28. Malignancy ICD-9 & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Codes	US ICD-9-CM Descriptions	US ICD-10-CM Codes	US ICD-10-CM Description
140.xx	Lip	C00.-	Malignant neoplasm of lip
141.xx	Tongue	C01.-	Malignant neoplasm of base of tongue
		C02.-	Malignant neoplasm of other and unspecified parts of tongue
142.xx	Major salivary glands	C07.-	Malignant neoplasm of parotid gland
		C08.-	Malignant neoplasm of other and unspecified major salivary glands
143.xx	Gum	C03.-	Malignant neoplasm of gum
144.xx	Floor of mouth	C04.-	Malignant neoplasm of floor of mouth
145.xx	Mouth unspecified	C05.-	Malignant neoplasm of palate
		C06.*	Malignant neoplasm of other and unspecified parts of mouth
146.xx	Oropharynx	C09.-	Malignant neoplasm of tonsil
		C10.-	Malignant neoplasm of oropharynx
147.xx	Nasopharynx	C11.-	Malignant neoplasm of nasopharynx
148.xx	Hypopharynx	C12	Malignant neoplasm of pyriform sinus
		C13.-	Malignant neoplasm of hypopharynx
149.xx	Lip other and ill-defined	C14.-	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
150.xx	Esophagus	C15.-	Malignant neoplasm of esophagus
151.xx	Stomach	C16.-	Malignant neoplasm of stomach

Table B-28. Malignancy ICD-9 & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Codes	US ICD-9-CM Descriptions	US ICD-10-CM Codes	US ICD-10-CM Description
152.xx	Small intestine	C17.-	Malignant neoplasm of small intestine
153.xx	Colon	C18.-	Malignant neoplasm of colon
154.xx	Rectum	C19	Malignant neoplasm of rectosigmoid junction
		C21.-	Malignant neoplasm of anus and anal canal
		C20	Malignant neoplasm of rectum
155.xx	Liver	C22.-	Malignant neoplasm of liver and intrahepatic bile ducts
156.xx	Gallbladder & bile ducts	C23	Malignant neoplasm of gallbladder
		C24.-	Malignant neoplasm of other and unspecified parts of biliary tract
157.xx	Pancreas	C25.-	Malignant neoplasm of pancreas
158.xx	Retroperitoneum/peritoneum	C48.-	Malignant neoplasm of retroperitoneum and peritoneum
159.xx	Digestive organ/peritoneum other ill-defined	C26.-	Malignant neoplasm of other and ill-defined digestive organs
160.xx	Nasal cavities, middle ear & accessory sinus	C30.-	Malignant neoplasm of nasal cavity and middle ear
		C31.-	Malignant neoplasm of accessory sinuses
161.xx	Larynx	C32.-	Malignant neoplasm of larynx
162.xx	Lung, bronchus & trachea	C33	Malignant neoplasm of trachea
		C34.*	Malignant neoplasm of bronchus and lung

Table B-28. Malignancy ICD-9 & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Codes	US ICD-9-CM Descriptions	US ICD-10-CM Codes	US ICD-10-CM Description
163.xx	Pleura	C38.-	Malignant neoplasm of heart, mediastinum and pleura
163.xx	Pleura		
		C45.-	Mesothelioma
164.xx	Thymus, heart & mediastinum	C37	Malignant neoplasm of thymus
		C38.-	Malignant neoplasm of heart, mediastinum
165.xx	Respiratory, intrathoracic other ill-defined	C39.-	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs
170.xx	Bone and articular cartilage	C40.*	Malignant neoplasm of bone and articular cartilage of limbs
		C41.-	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
171.xx	Connective and other soft tissue	C47.*	Malignant neoplasm of peripheral nerves and autonomic nervous system
		C49.*	Malignant neoplasm of other connective and soft tissue
172.xx	Melanoma	C43.*	Malignant melanoma of skin
		D03.*	Melanoma in situ
174.xx	Female breast	C50.- - -	Malignant neoplasm of breast
175.xx	Male breast	C50.- - -	Malignant neoplasm of breast
176.xx	Kaposi sarcoma	C46.*	Kaposi's sarcoma
179	Uterus, part unspecified	C55	Malignant neoplasm of uterus, part unspecified
180.xx	Cervix	C53.-	Malignant neoplasm of cervix uteri
181.xx	Placentia	C58	Malignant neoplasm of placenta

Table B-28. Malignancy ICD-9 & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Codes	US ICD-9-CM Descriptions	US ICD-10-CM Codes	US ICD-10-CM Description
182.xx	Body of uterus	C54.-	Malignant neoplasm of corpus uteri
183.xx	Ovary, fallopian tube, broad ligament, parametrium, round ligament, other specified sites of uterine adnexa	C56.-	Malignant neoplasm of ovary
		C57.*	Malignant neoplasm of unspecified fallopian tube
184.xx	Female genital other and unspecified	C51.-	Malignant neoplasm of vulva
		C52.-	Malignant neoplasm of vagina
185.xx	Prostate	C61	Malignant neoplasm of prostate
186.xx	Testis	C62.- -	Malignant neoplasm of testis
187.xx	Penis and male other	C60.-	Malignant neoplasm of penis
		C63.*	Malignant neoplasm of other and unspecified male genital organs
188.xx	Bladder	C67.-	Malignant neoplasm of bladder
189.xx	Kidney/Renal	C64.-	Malignant neoplasm of kidney, except renal pelvis
		C65.-	Malignant neoplasm of renal pelvis
		C66.-	Malignant neoplasm of ureter
		C67.-	Malignant neoplasm of bladder
		C68.-	Malignant neoplasm of other and unspecified urinary organs
190.xx	Eye	C69.- -	Malignant neoplasm of eye and adnexa

Table B-28. Malignancy ICD-9 & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Codes	US ICD-9-CM Descriptions	US ICD-10-CM Codes	US ICD-10-CM Description
191.xx	Brain	C71.-	Malignant neoplasm of brain
192.xx	Malignant neoplasm of other and unspecified parts of nervous system	C70.-	Malignant neoplasm of meninges
		C72.*	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
193	Malignant neoplasm of thyroid gland	C73	Malignant neoplasm of thyroid gland
194.xx	Other Endocrine glands and related structures	C74.- -	Malignant neoplasm of adrenal gland
		C75.-	Malignant neoplasm of other endocrine glands and related structures
195.xx	Other and ill-defined sites	C76.*	Malignant neoplasm of other and ill-defined sites
199.xx	Without specification of sites	C80.-	Malignant neoplasm without specification of site
200.xx	Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic structure	C83.- -	Non-follicular lymphoma
		C85.-	Other specified and unspecified types of non-Hodgkin lymphoma
		C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
		C96.-	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
201.xx	Hodgkin's Lymphoma	C81.-	Hodgkin lymphoma

Table B-28. Malignancy ICD-9 & US ICD-10-CM Diagnosis Codes

US ICD-9-CM Codes	US ICD-9-CM Descriptions	US ICD-10-CM Codes	US ICD-10-CM Description
202.xx	Other lymphoid and histiocytic tissue	C82.- -	Follicular lymphoma
		C84.- -	Mature T/NK-cell lymphomas
		C85.- -	Other specified and unspecified types of non-Hodgkin lymphoma
		C96.-	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
		C91.4-	Hairy cell leukemia
202.xx	Other lymphoid and histiocytic tissue	C86.-	Other specified types of T/NK-cell lymphoma
203.x0	Multiple myeloma	C90.- 0	Multiple myeloma and malignant plasma cell neoplasms
		C88.2, C88.3, C88.8, C88.9	Other malignant immunoproliferative diseases
204.x0	Lymphoid leukemia	C91.- 0	Lymphoid Leukemia
205.x0	Myeloid leukemia	C92.- 0	Myeloid leukemia
206.x0	Monocytic leukemia	C93.-0	Monocytic leukemia
207.x0	Other specified leukemia	C94.-0	Other leukemias of specified cell type
207.x0	Other specified leukemia	D45.-	Polycythemia vera
208.x0	Leukemia unspecified	C95.-0	Leukemia of unspecified cell type
		C96.-, C94.6	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
209.0 to 209.3	Malignant carcinoid tumors, Merkel cell carcinoma	C7A. *, C4A. *	Malignant carcinoid tumors; Merkel cell carcinoma

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Table B-29. Malignancy ICD-10 Diagnosis Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-9 Description
C00xx	Malignant neoplasm of lip
C01xx	Malignant neoplasm of base of tongue
C02xx	Malignant neoplasm of other and unspecified parts of tongue
C03xx	Malignant neoplasm of gum
C04xx	Malignant neoplasm of floor of mouth
C05xx	Malignant neoplasm of palate
C06xx	Malignant neoplasm of other and unspecified parts of mouth
C07xx	Malignant neoplasm of parotid gland
C08xx	Malignant neoplasm of other and unspecified major salivary glands
C09xx	Malignant neoplasm of tonsil
C10xx	Malignant neoplasm of oropharynx
C11xx	Malignant neoplasm of nasopharynx
C12xx	Malignant neoplasm of pyriform sinus
C13xx	Malignant neoplasm of hypopharynx
C14xx	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C15xx	Malignant neoplasm of oesophagus
C16xx	Malignant neoplasm of stomach
C17xx	Malignant neoplasm of small intestine
C18xx	Malignant neoplasm of colon
C19xx	Malignant neoplasm of rectosigmoid junction
C20xx	Malignant neoplasm of rectum
C21xx	Malignant neoplasm of anus and anal canal
C22xx	Malignant neoplasm of liver and intrahepatic bile ducts
C23xx	Malignant neoplasm of gallbladder
C24xx	Malignant neoplasm of other and unspecified parts of biliary tract
C25xx	Malignant neoplasm of pancreas
C26xx	Malignant neoplasm of other and ill-defined digestive organs
C30xx	Malignant neoplasm of nasal cavity and middle ear
C31xx	Malignant neoplasm of accessory sinuses
C32xx	Malignant neoplasm of larynx
C33xx	Malignant neoplasm of trachea

Table B-29. Malignancy ICD-10 Diagnosis Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-9 Description
C34xx	Malignant neoplasm of bronchus and lung
C37xx	Malignant neoplasm of thymus
C38xx	Malignant neoplasm of heart, mediastinum and pleura
C39 xx	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs
C40xx	Malignant neoplasm of bone and articular cartilage of limbs
C41xx	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C43xx	Malignant melanoma of skin
C450x	Mesothelioma of pleura
C46xx	Kaposi's sarcoma
C47xx	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48xx	Malignant neoplasm of retroperitoneum and peritoneum
C49xx	Malignant neoplasm of other connective and soft tissue
C50xx	Malignant neoplasm of breast
C51xx	Malignant neoplasm of vulva
C52xx	Malignant neoplasm of vagina
C53xx	Malignant neoplasm of cervix uteri
C54xx	Malignant neoplasm of corpus uteri
C55xx	Malignant neoplasm of uterus, part unspecified
C56xx	Malignant neoplasm of ovary
C57xx	Malignant neoplasm of other and unspecified female genital organs
C58xx	Malignant neoplasm of placenta
C60xx	Malignant neoplasm of penis
C61xx	Malignant neoplasm of prostate
C62xx	Malignant neoplasm of testes
C63xx	Malignant neoplasm of other and unspecified male genital organs
C64xx	Malignant neoplasm of kidney, except renal pelvis
C65xx	Malignant neoplasm of renal pelvis
C66xx	Malignant neoplasm of ureter
C67xx	Malignant neoplasm of bladder

Table B-29. Malignancy ICD-10 Diagnosis Codes Used in the Scandinavian Registries

ICD-10 Code	ICD-9 Description
C68xx	Malignant neoplasm of other and unspecified urinary organs
C69xx	Malignant neoplasm of eye and adnexa
C70xx	Malignant neoplasm of meninges
C71xx	Malignant neoplasm of brain
C75xx	Malignant neoplasm of other endocrine glands and related structures
C76xx	Malignant neoplasm of other and ill-defined sites
C80xx	Malignant neoplasm without specification of site
C81xx	'Hodgkin's disease '
C82xx	'Follicular [nodular] non-Hodgkin's lymphoma '
C83xx	'Diffuse non-Hodgkin's lymphoma '
C84xx	Peripheral and cutaneous T-cell lymphomas
C85xx	'Other and unspecified types of non-Hodgkin's lymphoma '
C88xx	Malignant immunoproliferative diseases
C90xx	Multiple myeloma and malignant plasma cell neoplasms
C91xx	Lymphoid leukaemia
C92xx	Myeloid leukaemia
C93xx	Monocytic leukaemia
C94xx	Other leukaemias of specified cell type
C95xx	Leukaemia of unspecified cell type
C96xx	Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue

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13.3 Appendix C. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms

Table C-1. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: ONJ

US ICD-9 Codes	US ICD-9 Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
526.4	Inflammatory conditions of jaw	M27.2	Inflammatory conditions of jaws	K10.2	Inflammatory conditions of jaws,
522.7	Periapical abscess with sinus	K04.6	Periapical abscess with sinus	K04.6	Periapical abscess with sinus
526.5	Alveolitis of jaw	M27.3	Alveolitis of jaws	K10.3	Alveolitis of jaws
733.45	Aseptic necrosis of bone, jaw	M87.180 M87.08 M87.28 M87.38 M87.88 M87.9	Osteonecrosis due to drugs, jaw Idiopathic aseptic necrosis of bone, other site Osteonecrosis due to previous trauma, other site Other secondary osteonecrosis, other site Other osteonecrosis, other site Osteonecrosis, unspecified	M87.0 M87.1 M87.2 M87.3 M87.8 M87.9	Idiopathic aseptic necrosis of bone, other specified site Osteonecrosis due to drugs, jaw Osteonecrosis due to previous trauma Other secondary osteonecrosis Other osteonecrosis Osteonecrosis, unspecified

Table C-2. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Atypical Femoral Fracture Leading to Hospitalization

US ICD-9 Codes	US ICD-9 Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
		M84.75-A ^	Atypical femoral fracture, initial encounter for fracture		
820.22	Subtrochanteric, closed	S72.2--A	subtrochanteric	S72.2	Subtrochanteric fracture
821.00	Unspecified part of femur, closed	S72.8X-A, S72.9--A	Fracture of unspecified femur, initial closed	S72.9	Fracture of femur, part unspecified
821.01	Shaft of femur, closed	S72.3--A	Unspecified fracture of femur, initial closed	S72.3	Fracture of shaft of femur
Note: One of the above codes AND no concurrent major trauma ICD-9 codes, NOMESCO codes or ICD-10 codes on the same day as the fractures described above					

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Table C-2. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Atypical Femoral Fracture Leading to Hospitalization

US ICD-9-CM Codes	US ICD-9-CM Descriptions	NOMESCO Codes	Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
E800-E848	Railway, motor vehicle, other road vehicle accidents; water transport accidents; air and space transport accidents; other vehicle accidents	EUP2-EUP9 EUM2-EUM9	Mode of transport: bicycle, moped, motorcycle, motor scooter, passenger car, van, pickup truck, lorry, truck, bus, other specified and unspecified	V00-V09 V10-V19 V20-V29 V30-V39 V40-V49 V50-V59 V60-V69 V70-V79 V80-V89 V90-V94 V95-V97	V00-V97.---A Pedestrian injured in transport accident Pedal cycle rider injured in transport accident Motorcycle rider injured in transport accident Occupant of three-wheeled motor vehicle injured in transport accident Car occupant injured in transport accident Occupant of pick-up truck or van injured in transport accident Occupant of heavy transport vehicle injured in transport accident Bus occupant injured in transport accident Other land transport accidents Water transport accidents Air and space transport accidents	V01-V99	Transport accidents

Table C-2. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Atypical Femoral Fracture Leading to Hospitalization

US ICD-9-CM Codes	US ICD-9-CM Descriptions	NOMESCO Codes	Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
E881-E884	Falls, other than falls on stairs and falls on same level	EUHE02-EUHE08	Falls, all other than falls on the same level	W00.2XXA,	(Include just A) W00.2XXA Other fall from one level to another due to ice and snow, initial encounter W11 Fall on and from ladder W12 Fall on and from scaffolding W13 Fall from, out of or through building or structure	W02, W11-W17	Falls, all other than falls on the same levels

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Table C-2. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Atypical Femoral Fracture Leading to Hospitalization

US ICD-9-CM Codes	US ICD-9-CM Descriptions	NOMESCO Codes	Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
E881-E884 (continued)				W11.XXXA - W17.XXXA,	W14 Fall from tree W15 Fall from cliff W16 Fall, jump or diving into water W17 Other fall from one level to another		
E908-E909	Accidents due to cataclysmic storms and earth surface movements			X34.XXXA-X38.XXXA	(Include just A) X34 Earthquake X35 Volcanic eruption X36 Avalanche, landslide and other earth movements X37 Cataclysmic storm X38 Flood	W20-W49 Excluding W21.---- Striking against or struck by sports equipment W22.0 --- Striking against stationary object W25.---- Contact with sharp glass W26.---- Contact with edge of stiff paper W27.---- Contact with nonpowered hand tool W42.---- Exposure to noise W45.---- Foreign body or object entering through skin W46.---- Contact with hypodermic needle	Accidents due to exposure to inanimate mechanical forces

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Table C-2. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Atypical Femoral Fracture Leading to Hospitalization

US ICD-9-CM Codes	US ICD-9-CM Descriptions	NOMESCO Codes	Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
E916-E928 (E917 excluded)	Other accidents (struck by falling object, caught accidentally in or between objects, accidents caused by machinery, explosion, firearm, etc.)	AUHG02, EUHB, EUHC, EUHD	Other accidents: Contact or collision with animal; collapse, breakage and deformation of material; malfunction and loss of control of machinery, equipment and materials; malfunction and loss of control of transport vehicle machinery	W20.---A W22.1 - -A - W24.1- -A W28.- - -A – W40. - - -A W49. - - -A W52.---A, W85.XXXA- W86.XXXA	(Include just A) W20-W49 Exposure to inanimate mechanical forces Excluding W21.---- Striking against or struck by sports equipment W22.0--- Striking against stationary object W25.---- Contact with sharp glass W26.---- Contact with edge of stiff paper W27.---- Contact with nonpowered hand tool W42.---- Exposure to noise W45. ---- Foreign body or object entering through skin W46.---- Contact with hypodermic needle W85 Exposure to electric transmission lines W86 Exposure to other specified electric current	W52 W85-W86	Accidents due to exposure to animate mechanical forces

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Table C-3. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Fracture Healing Complications

US ICD-9 Codes	US ICD-9 Descriptions	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
733.82	Nonunion of fracture	M80.- - - K	Osteoporosis with current pathological fracture	M84.1	Nonunion of fracture [pseudarthrosis]
		M84.3- -K	Stress fracture		
		M84.4- -K	Pathological fracture, not elsewhere classified		
		M84.5- -K	Pathological fracture in neoplastic disease		
		M84.6- -K	Pathological fracture in other disease		
		S02.- - -K	Fracture of skull and facial bones		
		S12.- - -K	Fracture of cervical vertebra and other parts of neck		
		S22.- - -K	Fracture of rib(s), sternum and thoracic spine		
		S32.- - -K	Fracture of lumbar spine and pelvis		
		S42.- - -K	Fracture of shoulder and upper arm		
		S49.- - -K	Other and unspecified injuries of shoulder and upper arm		
		S52.- - -K, M or N	Fracture of forearm		
		S59.- - -K	Other and unspecified injuries of elbow and forearm		
		S62.- - -K	Fracture at wrist and hand level		
		S72.- - -K, M or N	Fracture of femur		
		S79.- - -K	Other and unspecified injuries of hip and thigh		
		S82.- - -K, M or N	Fracture of lower leg, including ankle		
		S89.- - -K	Other and unspecified injuries of lower leg		
		S92.- - -K	Fracture of foot and toe, except ankle		

Note:
- - -K is specific for subsequent encounter for fracture with nonunion
- - -M is specific for subsequent encounter for open fracture type I or II with nonunion
- - -N is specific for subsequent encounter for open fracture type IIIA, IIIB, or IIIC with nonunion

Table C-4. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Hypocalcemia

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
275.41	Hypocalcemia	E835.1	Hypocalcemia	E83.5D	Hypocalcemia (Denmark)
				E83.5	Disorders of calcium metabolism (Norway and Sweden)

Table C-5. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Infection

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
001.xx-009.xx	Intestinal infectious diseases	A00.- A01.- A02.- A03.- A04.* A05.- A06.- A07.- A08.- A09.-	Cholera Typhoid and paratyphoid fevers Other salmonella infections Shigellosis Other bacterial intestinal infections Other bacterial foodborne intoxications, not elsewhere classified Amebiasis Other protozoal intestinal diseases Viral and other specified intestinal infections Infectious gastroenteritis and colitis, unspecified	A00xx-A09xx	Intestinal infectious diseases

Table C-5. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Infection

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
010.xx-018.xx	Tuberculosis	A15.- A17.- A18.0- A19.-	Tuberculosis of lung Tuberculosis of nervous system Tuberculosis of bones and joints Miliary tuberculosis	A15xx-A19xx	Tuberculosis
020.xx-027.xx	Zoonotic bacterial diseases	A20.- A21.- A22.- A23.- A24.0 A25.- A26.- A28.- A32.*	Plague Tularemia Anthrax Brucellosis Glanders Rat-bite fevers Erysipeloid Other zoonotic bacterial diseases, not elsewhere classified Listeriosis	A20xx-A28xx, A32.x	Certain zoonotic bacterial diseases, Listeriosis
030.xx-041.xx	Other bacterial diseases	A30.- A31.- A35.- A36.-, A37.- A38.- A39.- A40.- A41.- A42.-, A43.- A46 A48.- A49.- K90.81, M60.009 B95. *, B96. *	Leprosy [Hansen's disease] Infection due to other mycobacteria Other tetanus Diphtheria, Whooping cough Scarlet fever Meningococcal infection Streptococcal sepsis Other sepsis Actinomycosis, Nocardiosis Erysipelas Other bacterial diseases, not elsewhere classified Bacterial infection of unspecified site	A30x-A31.x, A35.x-A49.x, B95.x-B96.x	Other bacterial diseases, Bacterial, viral & other infectious agents (except B97 Viral in this category is elsewhere)

Table C-5. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Infection

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
090.xx-099.xx	Syphilis and other venereal diseases	A50.- A51.0 A52.00 A53.- A54.- A55.- A56.- A57.- A58.- A63.8 A64.-	Congenital syphilis Primary genital syphilis Cardiovascular syphilis, unspecified Other and unspecified syphilis Gonococcal infection Chlamydial lymphogranuloma (venereum) Other sexually transmitted chlamydial diseases Chancroid Granuloma inguinale Other specified predominantly sexually transmitted diseases Unspecified sexually transmitted disease	A50xx-A58.x, A60xx, ,A63.8, A64xx	Infections with a predominantly sexual mode of transmission
100.xx-104.xx	Other spirochetal diseases	A65 A66.- A67.- A69.0 A69.1 A69.21 A69.8 A69.9 A74.81 B25.0	Nonvenereal syphilis Yaws Pinta [carate] Necrotizing ulcerative stomatitis Other Vincent's infections Meningitis due to Lyme disease Other specified spirochetal infections Spirochetal infection, unspecified Chlamydial peritonitis Cytomegaloviral pneumonitis	A65.x-A67.x, A69.1, A69.8, A69.9	Other spirochetal diseases

Table C-5. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Infection

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
110.xx-118.xx	Mycoses	B35.- B36.- B37.- B38.- B39.- B40.- B41.- B42.- B43.- B44.- B45.- B46.- B47.- B48.- B49.-	Dermatophytosis Other superficial mycoses Candidiasis Coccidiodomycosis Histoplasmosis Blastomycosis Paracoccidiodomycosis Sporotrichosis Chromomycosis and pheomycotic abscess Aspergillosis Cryptococcosis Zygomycosis Eumycetoma Rhinosporidiosis Unspecified mycosis	B35xx-B49.x	Mycoses
130.xx-136.xx	Other infectious and parasitic diseases	A59.*, B58.*, B59, B60.1-, B60.2, B60.8, B64 B83.4 B85.- B86 B87.* B88.-, B89 B99.8 B99.9 D86.* , L94.6 M35.2	Trichomoniasis, Toxoplasma, Pediculosis , Other and Unspecified protozoal diseases	B58.x-B64, B85xx-B89.x, B99xx	Protozoal diseases, Pediculosis, acariasis and other infestations, Other infectious diseases Pediculosis, acariasis and other infestations, Other infectious diseases
289.2	Nonspecific mesenteric lymphadenitis	I88.0	Nonspecific mesenteric lymphadenitis	I88.0	Nonspecific mesenteric lymphadenitis

Table C-5. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Infection

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
289.59	Splenic abscess	D73.3 G00.- G01.- G03.0 G03.1 G03.8 G03.9	Abscess of spleen Bacterial meningitis, not elsewhere classified Meningitis in bacterial diseases classified elsewhere Nonpyogenic meningitis Chronic meningitis Meningitis due to other specified causes Meningitis, unspecified	D73.3	Abscess of the spleen
320.xx	Bacterial meningitis	G00. *, G01	Bacterial meningitis, not elsewhere classified		
321.x	Meningitis due to other nonbacterial organisms	B45.1, G02	Meningitis in other infectious and parasitic diseases classified elsewhere		
322.x	Meningitis of unspecified cause	G06.-	Intracranial and intraspinal abscess and granuloma	G03.x	Meningitis due to other and unspecified causes
323.xx	Encephalitis, myelitis, and encephalomyelitis	G04.2 G05.-	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere	G04.x-G05xx	Encephalitis, myelitis and encephalomyelitis, Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere
324.xx	Intracranial and intraspinal abscess	G07.-	Intracranial and intraspinal abscess and granuloma in diseases classified elsewhere	G06xx-G07.x	Intracranial and intraspinal abscess and granuloma, Intracranial and intraspinal abscess and granuloma in diseases classified elsewhere

Table C-5. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Infection

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
373.0x	Blepharitis	H01.0-	Blepharitis	H01.0	Blepharitis
373.4x	Infective dermatitis of eyelid of types resulting in deformity	H01.8	Other specified inflammations of eyelid	H03.x	Disorders of eyelid in diseases classified elsewhere
373.5x	Other infective dermatitis of eyelid	H01.8	Other specified inflammations of eyelid	H03.x	Disorders of eyelid in diseases classified elsewhere
380.1x	Infective otitis externa	H60.0- H60.1- H60.2- H60.3- H62.-	Abscess of external ear Cellulitis of external ear Malignant otitis externa Other infective otitis externa Otitis externa in other diseases classified elsewhere	H60.0, H60.1, H60.2, H60.3, H62.x	Abscess of external ear, Cellulitis of external ear, Malignant otitis externa, Other infective otitis externa, Disorders of external ear in diseases classified elsewhere
381.5x	Eustachian tube (ear) salpingitis	H68.0-	Eustachian salpingitis	H68.0	Eustachian salpingitis
382.xx	Suppurative and unspecified otitis media	H66.- H67.-	Suppurative and unspecified otitis media Otitis media in diseases classified elsewhere	H66xx, H67xx	Suppurative and unspecified otitis media, Otitis media in diseases classified elsewhere

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Table C-5. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Infection

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
383.0x	Acute mastoiditis	H70.0-	Acute mastoiditis	H70xx, H95.0, H95.1	Mastoiditis and related conditions, Recurrent cholesteatoma of postmastoidectomy cavity, Other disorders following mastoidectomy
460	Acute nasopharyngitis (common cold)	I88.0	Nonspecific mesenteric lymphadenitis	J00	Acute nasopharyngitis [common cold]
461.xx	Acute sinusitis	J00.-	Acute nasopharyngitis [common cold]	J01xx	Acute sinusitis
462.xx	Acute pharyngitis	J01.-	Acute sinusitis	J02xx	Acute pharyngitis
463.xx	Acute tonsillitis	J02.0	Streptococcal pharyngitis	J03xx	Acute tonsillitis
464.xx	Acute laryngitis and tracheitis	J03.0- J04.-	Streptococcal tonsillitis Acute laryngitis and tracheitis	J04xx, J05xx	Acute laryngitis and tracheitis, Acute obstructive laryngitis [croup] and epiglottitis
465.xx	Acute upper respiratory infections of multiple or unspecified sites	J05.-	Acute obstructive laryngitis [croup] and epiglottitis	J06xx	Acute upper respiratory infections of multiple and unspecified sites

Table C-5. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Infection

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
466.xx	Acute bronchitis and bronchiolitis	J20.9 J21.0 J21.8	Acute bronchitis, unspecified Acute bronchiolitis due to respiratory syncytial virus Acute bronchiolitis due to other specified organisms	J20xx-J21.x	Acute bronchitis, Acute bronchiolitis
473.x	Chronic sinusitis	J32.-	Chronic sinusitis	J32.x	Chronic sinusitis
475	Peritonsillar abscess	J34.0 J36	Abscess, furuncle and carbuncle of nose Peritonsillar abscess	J36	Peritonsillar abscess
480xx-486xx, 487.0	Pneumonia, influenza with pneumonia	J10.- J11.- J12.- J13.- J14.- J15.0 J16.- J17.- J18.- J20.-	Influenza due to other identified influenza virus Influenza due to unidentified influenza virus Viral pneumonia, not elsewhere classified Pneumonia due to Streptococcus pneumoniae Pneumonia due to Hemophilus influenzae Pneumonia due to Klebsiella pneumoniae Pneumonia due to other infectious organisms, not elsewhere classified Pneumonia in diseases classified elsewhere Acute bronchitis	J10.0, J11.0, J12xx-J18.x	Influenza with pneumonia, Pneumonia

Table C-5. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Infection

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
487.xx	Influenza	J06.-	Acute upper respiratory infections of multiple and unspecified sites	J10.x, J11.x	Influenza due to other identified influenza virus, Influenza, virus not identified
488.11, 488.12	Influenza due to identified 2009 H1N1 influenza virus with pneumonia/with other respiratory manifestations	J10.08, J10.1	Influenza due to other identified influenza virus with other specified pneumonia/ with other respiratory manifestations		
511.1	Pleurisy with effusion or mention of bacterial cause other than TB,	J90.-	Pleural effusion, not elsewhere classified	J94.8	Other specified pleural conditions
528.3	Cellulitis and abscess of mouth	K12.2	Cellulitis and abscess of mouth	K12.2	Cellulitis and abscess floor of mouth
528.5	Cellulitis of lips	K13.0	Diseases of lips	K13.0	Diseases of lips
566	Cellulitis of anus	K57.- K61.-	Diverticular disease of intestine Abscess of anal and rectal regions	K61xx	Abscess of anal and rectal regions
575.0	Acute Cholecystitis	K81.0-	Acute cholecystitis	K81.0	Acute Cholecystitis
590.xx	Infections of kidney	N10.- N11.- N12.- N13.6 N15.1 N15.9	Acute tubulo-interstitial nephritis Chronic tubulo-interstitial nephritis Tubulo-interstitial nephritis, not specified as acute or chronic Pyonephrosis Renal and perinephric abscess Renal tubulo-interstitial disease, unspecified	N10-N12, N15.1, N15.9	Acute tubulo-interstitial nephritis, Chronic tubulo-interstitial nephritis, Tubulo-interstitial nephritis, not specified as acute or chronic, Renal and perinephric abscess, Renal tubulo-interstitial disease, unspecified

Table C-5. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Infection

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
595.xx	Cystitis	N30.-	Cystitis	N30xx	Cystitis
597.xx, 099.4x	Urethritis, not sexually transmitted, urethral syndrome; Other nongonococcal urethritis	N34.-	Urethritis and urethral syndrome	N34.x	Urethritis and urethral syndrome
680.x	Carbuncle and furuncle	L02.-2, L02.-2-, L02.-3, L02.-3-	Carbuncle and furuncle	L02xx	Cutaneous abscess, furuncle and carbuncle
681.xx	Cellulitis and abscess of finger and toe	L02.51-, L02.61-, L03.-	Cellulitis of finger/ toe. Abscess of hand/foot	L03.0	Cellulitis of finger and toe
682.x	Other cellulitis and abscess	L02.-1, L02.-1-,, L03.*	Cutaneous abscess of face, Other cellulitis and abscess	L03.1-L03.9	Other and unspecified Cellulitis
683	Acute lymphadenitis	L04.-	Acute lymphadenitits	L04.x	Acute lymphadenitis
684	Impetigo	K90.81 L01.-	Whipple's disease Impetigo, unspecified	L01.x	Impetigo
686.xx	Other local infections of skin and subcutaneous tissue	L08. *, L88, B78.1, E83.2, L92.8, L98.0	Other local infections of skin and subcutaneous tissue	L08xx	Other local infections of skin and subcutaneous tissue
728.86	Necrotizing fasciitis	M72.6	Necrotizing fasciitis	M72.6	Necrotizing fasciitis

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Table C-5. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Infection

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Descriptions	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
730.xx	Osteomyelitis, periostitis, and other infections involving bone	M86.-, M46.2- M46.3-	Osteomyelitis Infection of intervertebral disc (pyogenic)	M86xx	Osteomyelitis
790.7x	Bacteremia	R78.81	Bacteremia	R78.8	Findings of other substances, not normally found in blood
540.xx-543.xx	Appendicitis, Other diseases of appendix	K13.0 K35.- K36.- K37.- K38.-	Diseases of lips Acute appendicitis Other appendicitis Unspecified appendicitis Other diseases of appendix	K35xx-K38.x	Acute appendicitis, Other appendicitis, Other diseases of appendix
562.xx	Diverticulitis	K57.-	Diverticular disease of the intestine	K57xx	Diverticular disease of the intestine
035	Erysipelas	A43.-	Nocardiosis	A46	Erysipelas
599.0	Urinary tract infection	N39.0	Urinary tract infection, site not specified	N39.0	Urinary tract infection, site not specified
421.x	Endocarditis	I33.-	Acute and subacute endocarditis	I33xx, I39xx	Acute and subacute endocarditis, Endocarditis and heart valve disorders in diseases classified elsewhere
711.4x	Infective arthritis (bacterial)	M00.* M01.* M02.1* M02.3* M02.8*	Direct infections of joint in infectious and parasitic diseases classified elsewhere Reiter's disease Other reactive arthropathies	M01.1x, M01.3x	Tuberculous arthritis, Arthritis in other bacterial diseases classified elsewhere

Table C-6. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Dermatologic Adverse Events

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Code	US ICD-10-CM description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
694.4	Pemphigus. Pemphigus: NOS, erythematosus, foliaceus, malignant, vegetans, vulgaris	L10.-	Pemphigus	L10.x	Pemphigus
694.5	Pemphigoid	L12.-	Bullous pemphigoid	L12.x	Pemphigoid
694.6x	Benign mucous membrane pemphigoid	L12.1	Cicatricial pemphigoid	L12.1	Cicatricial pemphigoid
694.xx	Bullous dermatoses	L10.*	Pemphigus	L10.x, L12.x, L13.x, L14.x	Pemphigus, Pemphigoid, Other bullous disorders, Bullous disorders in diseases classified elsewhere
		L12.0, L12.1, L12.2, L12.8, L12.9	Bullous pemphigoid; Other pemphigoid		
		L13.-	Other bullous disorders		
		L14.-	Bullous disorders in diseases classified elsewhere		
		L40.1	Generalized pustular psoriasis		
694.9	Unspecified bullous dermatoses	L13.9	Bullous disorder, unspecified	L13.9	Bullous disorder, unspecified

Table C-6. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Dermatologic Adverse Events

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Code	US ICD-10-CM description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
695.1	Erythema multiforme, unspecified	L51.0, L51.9	Erythema multiforme	L51.9	Erythema multiforme, unspecified
695.11	Erythema multiforme minor	L51.8		L51.8	Other erythema multiforme
695.12	Erythema multiforme major	L51.8		L51.8	Other erythema multiforme
695.13	Stevens-Johnson syndrome	L51.1		L51.1	Bullous erythema multiforme
695.14	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome	L51.3		L51.8	Other erythema multiforme
695.15	Toxic epidermal necrolysis	L12.3 -, L51.2		L51.2	Toxic epidermal necrolysis [Lyell]
695.19	Other erythema multiforme	L51.8		L51.8	Other erythema multiforme

Table C-6. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Dermatologic Adverse Events

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Code	US ICD-10-CM description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
695.5x	Exfoliation due to erythematous conditions according to extent of body surface involved. Code first erythematous condition causing exfoliation, such as: Ritter's disease (695.81) (Staphylococcal) scalded skin syndrome (695.81) Stevens-Johnson syndrome (695.13) Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome (695.14) toxic epidermal necrolysis (695.15)"	L49.-	Exfoliation due to erythematous condition according to extent of body surface involved.	L53.8	Other specified erythematous condition
782.1	Rash and other nonspecific skin eruption	R21.-	Rash and other nonspecific skin eruption	R21	Rash and other nonspecific skin eruption
708.x	Urticaria	L50.-	Urticaria	L50.0	Allergic urticaria

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Table C-7. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Pancreatitis

US ICD-9-CM Code	US ICD-9-CM Description	US ICD-10-CM Code	US ICD-10-CM description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
577.0	Acute pancreatitis	K85.0 K85.0-	Idiopathic acute pancreatitis	K85.x	Acute pancreatitis
		K85.1 K85.1-	Biliary acute pancreatitis		
		K85.3 K85.3-	Drug induced acute pancreatitis		
		K85.8 K85.8-	Other acute pancreatitis		
		K85.9	Acute pancreatitis[a]		
		K85.9 K85.9-	Acute pancreatitis[a]		

[a] Note: K85.9 did not require a 5th digit until October 2016. From October 2015 through September 2016, the 4-digit ICD-10 K85.9 was used.

Table C-8. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Hypersensitivity

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
288.3	Eosinophilia. Eosinophilia allergic, hereditary, idiopathic, secondary. Eosinophilic leukocytosis	D72.1	Eosinophilia	D72.1	Eosinophilia (Eosinophilia: allergic, hereditary)
713.6	Arthropathy associated with hypersensitivity reaction	M02.2 - -	Postimmunization arthropathy, unspecified site	M36.4, M02.2x	Arthropathy in hypersensitivity reactions classified elsewhere, Postimmunization arthropathy
		M36.4	Arthropathy in hypersensitivity reactions classified elsewhere		

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Table C-8. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Hypersensitivity

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
995.0	Other anaphylactic shock. Allergic shock NOS or due to adverse effect of correct medicinal substance properly administered. Anaphylactic reaction NOS or due to adverse effect of correct medicinal substance properly administered. Anaphylaxis NOS or due to adverse effect of correct medicinal substance properly administered	T78.2XXA, T88.6XXA	Anaphylactic shock, unspecified, initial encounter Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, initial encounter	T78.2, T88.6	Anaphylactic shock, unspecified, Anaphylactic shock due to adverse effect of correct drug or medicament properly administered
995.20, 995.27, 995.29	Other and unspecified adverse effect of drug, medicinal and biological substance (due) to correct medicinal substance properly administered. Adverse effect to correct medicinal substance properly administered. Allergic reaction to correct medicinal substance properly administered. Hypersensitivity to correct medicinal substance properly administered Idiosyncrasy due to correct medicinal substance properly administered. Drug: hypersensitivity NOS reaction NOS	T88.7XXA T50.905A T50.995A	Unspecified adverse effect of drug or medicament, initial encounter Adverse effect of unspecified drugs, medicaments and biological substances, initial encounter Adverse effect of other drugs, medicaments and biological substances, initial encounter	T88.7	Unspecified adverse effect of drug or medicament

Table C-8. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: Hypersensitivity

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
995.3	Allergy, unspecified	T78.40XA	Allergy, unspecified, initial encounter	T78.4	Allergy, unspecified
		T78.49XA	Other allergy, initial encounter		

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Table C-9. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: New Primary Malignancy (Excluding Non-melanoma Skin Cancer)

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
140.xx	Lip	C00.-	Malignant neoplasm of lip	C00	Malignant neoplasm of lip
141.xx	Tongue	C01.-	Malignant neoplasm of base of tongue	C01,C02	Malignant neoplasm of base of tongue, malignant neoplasm of other and unspecified parts of tongue
		C02.-	Malignant neoplasm of other and unspecified parts of tongue		
142.xx	Major salivary glands	C07.-	Malignant neoplasm of parotid gland	C07,C08	Malignant neoplasm of parotid gland, malignant neoplasm of other and unspecified major salivary glands
		C08.-	Malignant neoplasm of other and unspecified major salivary glands		
143.xx	Gum	C03.-	Malignant neoplasm of gum	C03	Malignant neoplasm of gum

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Table C-9. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: New Primary Malignancy (Excluding Non-melanoma Skin Cancer)

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
144.xx	Floor of mouth	C04.-	Malignant neoplasm of floor of mouth	C04	Malignant neoplasm of floor of mouth
145.xx	Mouth unspecified	C05.-	Malignant neoplasm of palate	C05, C06	Malignant neoplasm of palate, Malignant neoplasm of other and unspecified parts of mouth
		C06.-	Malignant neoplasm of other and unspecified parts of mouth		
146.xx	Oropharynx	C09.-	Malignant neoplasm of tonsil	C09,C10	Malignant neoplasm of tonsil, Malignant neoplasm of oropharynx
		C10.-	Malignant neoplasm of oropharynx		
147.xx	Nasopharynx	C11.-	Malignant neoplasm of nasopharynx	C11	Malignant neoplasm of nasopharynx
148.xx	Hypopharynx	C12.-	Malignant neoplasm of pyriform sinus	C12,C13	Malignant neoplasm of pyriform sinus, Malignant neoplasm of hypopharynx
		C13.-	Malignant neoplasm of hypopharynx		
149.xx	Lip other and ill-defined	C14.-	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx	C14	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
150.xx	Esophagus	C15.-	Malignant neoplasm of esophagus	C15	Malignant neoplasm of oesophagus
151.xx	Stomach	C16.-	Malignant neoplasm of stomach	C16	Malignant neoplasm of stomach
152.xx	Small intestine	C17.-	Malignant neoplasm of small intestine	C17	Malignant neoplasm of small intestine

Table C-9. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: New Primary Malignancy (Excluding Non-melanoma Skin Cancer)

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
153.xx 209.0 – 209.3	Colon Malignant carcinoid tumors	C18.-	Malignant neoplasm of colon	C18	Malignant neoplasm of colon
154.xx	Rectum	C19.-	Malignant neoplasm of rectosigmoid junction	C19,C21,C20	Malignant neoplasm of rectosigmoid junction, malignant neoplasm of anus and anal canal, malignant neoplasm of rectum
		C21.-	Malignant neoplasm of anus and anal canal		
		C20.-	Malignant neoplasm of rectum		
155.xx	Liver	C22.-	Malignant neoplasm of liver and intrahepatic bile ducts	C22	Malignant neoplasm of liver and intrahepatic bile ducts
156.xx	Gallbladder & bile ducts	C23.-	Malignant neoplasm of gallbladder	C23, C24	Malignant neoplasm of gallbladder, malignant neoplasm of other and unspecified parts of biliary tract
		C24.-	Malignant neoplasm of other and unspecified parts of biliary tract		
157.xx	Pancreas	C25.-	Malignant neoplasm of pancreas	C25	Malignant neoplasm of pancreas
158.xx	Retroperitoneum/ peritoneum	C48.-	Malignant neoplasm of retroperitoneum and peritoneum	C48	Malignant neoplasm of retroperitoneum and peritoneum
159.xx	Digestive organ/peritoneum other ill-defined	C26.-	Malignant neoplasm of other and ill-defined digestive organs	C26	Malignant neoplasm of other and ill-defined digestive organs

Table C-9. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: New Primary Malignancy (Excluding Non-melanoma Skin Cancer)

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
160.xx	Nasal cavities, middle ear & accessory sinus	C30.-	Malignant neoplasm of nasal cavity and middle ear	C30,C31	Malignant neoplasm of nasal cavity and middle ear, Malignant neoplasm of accessory sinuses
		C31.-	Malignant neoplasm of accessory sinuses		
161.xx	Larynx	C32.-	Malignant neoplasm of larynx	C32	Malignant neoplasm of larynx
162.xx	Lung, bronchus & trachea	C33.-	Malignant neoplasm of trachea	C33,C34	Malignant neoplasm of trachea, Malignant neoplasm of bronchus and lung
		C34.-	Malignant neoplasm of bronchus and lung		
163.xx	Pleura	C38.-	Malignant neoplasm of pleura	C38.0, C45.0	Malignant neoplasm of heart, mediastinum and pleura, Mesothelioma
164.xx	Thymus, heart & mediastinum	C37.-	Malignant neoplasm of thymus	C37, C38.0-C38.3, C38.8	Malignant neoplasm of thymus, Malignant neoplasm of heart, mediastinum
		C38.-	Malignant neoplasm of heart, mediastinum		
165.xx	Respiratory, intrathoracic other ill-defined	C39.-	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs	C39	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs

Table C-9. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: New Primary Malignancy (Excluding Non-melanoma Skin Cancer)

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
170.xx	Bone and articular cartilage	C40.-	Malignant neoplasm of bone and articular cartilage of limbs	C40,C41	Malignant neoplasm of bone and articular cartilage of limbs, Malignant neoplasm of bone and articular cartilage of other and unspecified sites
		C41.-	Malignant neoplasm of bone and articular cartilage of other and unspecified sites		
171.xx	Connective and other soft tissue	C47.-	Malignant neoplasm of peripheral nerves and autonomic nervous system	C47,C49	Malignant neoplasm of peripheral nerves and autonomic nervous system, Malignant neoplasm of other connective and soft tissue
		C49.-	Malignant neoplasm of other connective and soft tissue		
172.xx	Melanoma	C43.-	Malignant melanoma of skin	C43	Malignant melanoma of skin
		D03.-	Melanoma in situ		
174.xx	Female breast	C50.-	Malignant neoplasm of breast	C50	Malignant neoplasm of breast
175.xx	Male breast	C50.-	Malignant neoplasm of breast	C50	Malignant neoplasm of breast
176.xx	Kaposi sarcoma	C46.-	Kaposi's sarcoma	C46	'Kaposi's sarcoma '
179	Uterus, part unspecified	C55.-	Malignant neoplasm of uterus, part unspecified	C55	Malignant neoplasm of uterus, part unspecified

Table C-9. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: New Primary Malignancy (Excluding Non-melanoma Skin Cancer)

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
180.xx	Cervix	C53.-	Malignant neoplasm of cervix uteri	C53	Malignant neoplasm of cervix uteri
181.xx	Placentia	C58.-	Malignant neoplasm of placenta	C58	Malignant neoplasm of placenta
182.xx	Body of uterus	C54.-	Malignant neoplasm of corpus uteri	C54	Malignant neoplasm of corpus uteri
183.xx	Ovary, fallopian tube, broad ligament, parametrium, round ligament, other specified sites of uterine adnexa	C56.-	Malignant neoplasm of ovary	C56, C57.0-C57.4	Malignant neoplasm of ovary, Malignant neoplasm of fallopian tube, broad ligament, parametrium, round ligament, other specified sites of uterine adnexa
		C57.-	Malignant neoplasm of unspecified fallopian tube		
184.xx	Female genital other and unspecified	C51.-	Malignant neoplasm of vulva	C51,C52,C57.7-C57.9	Malignant neoplasm of other and unspecified female genital organs, Malignant neoplasm of vulva, Malignant neoplasm of vagina
		C52.-	Malignant neoplasm of vagina		
		C57.-	Malignant neoplasm of unspecified fallopian tube		
185.xx	Prostate	C61.-	Malignant neoplasm of prostate	C61	Malignant neoplasm of prostate

Table C-9. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: New Primary Malignancy (Excluding Non-melanoma Skin Cancer)

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
186.xx	Testis	C62.-	Malignant neoplasm of testis	C62.x	Malignant neoplasm of testes
187.xx	Penis and male other	C60.-	Malignant neoplasm of penis	C60.x, C63.x	Malignant neoplasm of penis, Malignant neoplasm of other and unspecified male genital organs
		C63.-	Malignant neoplasm of other and unspecified male genital organs		
188.xx	Bladder	C67.-	Malignant neoplasm of bladder	C67.x	Malignant neoplasm of bladder
189.xx	Kidney/Renal	C64.-	Malignant neoplasm of kidney, except renal pelvis	C64,C65,C66, C67,C68	Malignant neoplasm of kidney, except renal pelvis, Malignant neoplasm of renal pelvis, Malignant neoplasm of ureter, Malignant neoplasm of bladder, Malignant neoplasm of other and unspecified urinary organs
		C65.-	Malignant neoplasm of renal pelvis		
		C66.-	Malignant neoplasm of ureter		
		C67.-	Malignant neoplasm of bladder		
		C68.-	Malignant neoplasm of other and unspecified urinary organs		
190.xx	Eye	C69.-	Malignant neoplasm of eye and adnexa	C69	Malignant neoplasm of eye and adnexa
191.xx	Brain	C71.-	Malignant neoplasm of brain	C71	Malignant neoplasm of brain

Table C-9. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: New Primary Malignancy (Excluding Non-melanoma Skin Cancer)

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
192.xx	Malignant neoplasm of other and unspecified parts of nervous system	C70.-	Malignant neoplasm of meninges	C70, C72.0, C72.1, C72.5, C72.9	Malignant neoplasm of meninges, spinal cord, cauda equina, Other and unspecified cranial nerves, central nervous system, unspecified
		C72.-	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system		
193	Malignant neoplasm of thyroid gland	C73.-	Malignant neoplasm of thyroid gland	C73	Malignant neoplasm of thyroid gland
194.xx	Other Endocrine glands and related structures	C74.-	Malignant neoplasm of adrenal gland	C74,C75	Malignant neoplasm of thyroid gland, Malignant neoplasm of adrenal gland, Malignant neoplasm of other endocrine glands and related structures
		C75.-	Malignant neoplasm of other endocrine glands and related structures		
195.xx	Other and ill-defined sites	C76.-	Malignant neoplasm of other and ill-defined sites	C76	Malignant neoplasm of other and ill-defined sites
199.xx	Without specification of sites	C80.-	Malignant neoplasm without specification of site	C80	Malignant neoplasm without specification of site

Table C-9. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: New Primary Malignancy (Excluding Non-melanoma Skin Cancer)

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
200.xx	Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic structure	C83.-	Non-follicular lymphoma	C83.x, C85.0, C96.3	Diffuse non-Hodgkin's lymphoma, Lymphosarcoma, True histiocytic lymphoma
		C84.- -	Anaplastic large cell lymphoma		
		C85.-	Other specified and unspecified types of non-Hodgkin lymphoma		
		C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue		
		C96.-	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue		
201.xx	Hodgkin's Lymphoma	C81.-	Hodgkin lymphoma	C81	'Hodgkin's disease '
202.xx	Other lymphoid and histiocytic tissue	C82.-	Follicular lymphoma	C82.x,C83.6, C84,C85, C96.0-C96.2, C91.4	Follicular [nodular] non-Hodgkin's lymphoma, Undifferentiated (diffuse), Peripheral and cutaneous T-cell lymphomas, Other and unspecified types of non-Hodgkin's lymphoma, Letterer-Siwe disease, Malignant histiocytosis, Malignant mast cell tumour, Hairy-cell leukaemia
		C84.-	Mature T/NK-cell lymphomas		
		C85.-	Other specified and unspecified types of non-Hodgkin lymphoma		
		C96.-	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue		
		C91.-0	Lymphoid leukemia		
		C86.-	Other specified types of T/NK-cell lymphoma		

Table C-9. Mapping of ICD-9-CM to ICD-10 Diagnosis Codes Used in Case Ascertainment Algorithms: New Primary Malignancy (Excluding Non-melanoma Skin Cancer)

US ICD-9 Code	US ICD-9 Description	US ICD-10-CM Codes	US ICD-10-CM Description	Scandinavian ICD-10 Codes	Scandinavian ICD-10 Descriptions
203.xx	Multiple myeloma	C90.-	Multiple myeloma and malignant plasma cell neoplasms	C90,C88.7	Multiple myeloma and malignant plasma cell neoplasms, Malignant immunoproliferative diseases
		C88.2, C88.3, C88.8, C88.9	Other malignant immunoproliferative diseases		
204.x0	Lymphoid leukemia	C91.-0	Lymphoid Leukemia	C91	Lymphoid leukaemia
205.x0	Myeloid leukemia	C92.-	Myeloid leukemia	C92	Myeloid leukaemia
206.x0	Monocytic leukemia	C93.-0	Monocytic leukemia	C93	Monocytic leukaemia
207.x0	Other specified leukemia	C94.-0	Other leukemias of specified cell type	C94	Other leukaemias of specified cell type
		D45.-	Polycythemia vera		
208.xx	Leukemia unspecified	C95.-0	Leukemia of unspecified cell type	C95,C96.7, C96.9	Leukaemia of unspecified cell type, Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue
		C96.-	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue		

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13.4 Appendix D. Algorithms to Assess Recurrent Event(s) for Selected AESI

AESI	Recurrent Event Patterns
Infection	consecutive case-qualifying events with a gap of ≥ 30* days in between which is free of any oral, IV or IM anti-infective medications
Hypocalcemia	Consecutive case-qualifying events with the second event not associated with IV calcium administration and is ≥ 30* days apart from the first event or Consecutive case-qualifying events with the second event associated IV calcium administration on any different date from the first event§
Hypersensitivity	consecutive case-qualifying events with a gap of ≥ 30* days in between which is free of any IV or IM corticosteroid, subcutaneous or IM epinephrine, or IV or IM antihistamine medications
Dermatologic adverse events	consecutive case-qualifying events with a gap of ≥ 30* days in between which is free of any oral, IV, IM or topical corticosteroid medications

* For each eligible recurrent event, exclude the first 30-day period, which is free of any AESI-specific treatment, following the prior event. If another case-qualifying diagnosis or AESI-specific treatment occurred during the first 30-day following the prior event, this diagnosis or treatment will reset the counting of the 30-day period which will be excluded from the analysis. (eg, if a woman received a claim for infection leading to ER visit on May 1 2011, received a treatment with IV antibiotic on May 15 2011, another diagnosis for infection leading to hospitalization on May 25, 2011, and another diagnosis for infection leading to ER visit on August 1st, the period from May 1 2011 up to June 24 (30 days after May 25, 2011 will be excluded from denominator when calculating recurrent rate of infection))

§ Inclusion of IV calcium administration in the hypocalcemia recurrent event algorithm is dependent on individual data system characteristics.

13.5 Appendix E. Power to Detect Adverse Events of Special Interest in Each of the Data Systems

Table E-1. Power to Detect Relative Risk for the Adverse Events of Special Interest, US Medicare[a]

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		2 Years Post Launch								
ONJ	1	0%	0%	1%	1%	2%	4%	10%	18%	57%
Fracture healing complications	134	99%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	7	18%	48%	74%	90%	97%	99%	100%	100%	100%
Serious infection	8799	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	207	100%	100%	100%	100%	100%	100%	100%	100%	100%
Pancreatitis	137	99%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	217	100%	100%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1353	100%	100%	100%	100%	100%	100%	100%	100%	100%
		5 Years Post Launch								
ONJ	1	2%	5%	12%	21%	31%	43%	63%	79%	99%
Fracture healing complications	134	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	7	42%	88%	99%	100%	100%	100%	100%	100%	100%

[a] Power calculated using the Fisher's 2-sided exact text with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 1:1 between denosumab- and comparator-exposed person-years for ONJ and 10:1 for other AESI.

Table E-1. Power to Detect Relative Risk for the Adverse Events of Special Interest, US Medicare[a]

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		5 Years Post Launch (continued)								
Serious infection	8799	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	207	100%	100%	100%	100%	100%	100%	100%	100%	100%
Pancreatitis	137	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	217	100%	100%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1353	100%	100%	100%	100%	100%	100%	100%	100%	100%
		10 Years Post Launch								
ONJ	1	6%	18%	33%	52%	70%	83%	95%	99%	100%
Fracture healing complications	134	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	7	72%	100%	100%	100%	100%	100%	100%	100%	100%
Serious infection	8799	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	207	100%	100%	100%	100%	100%	100%	100%	100%	100%
Pancreatitis	137	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	217	100%	100%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1353	100%	100%	100%	100%	100%	100%	100%	100%	100%

[a] Power calculated using the Fisher's 2-sided exact text with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 1:1 between denosumab- and comparator-exposed person-years for ONJ and 10:1 for other AESI.

Table E-2. Power to Detect Relative Risk for the Adverse Events of Special Interest, United HealthCare[a]

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		2 Years Post Launch								
Fracture healing complications	134	15%	39%	65%	83%	93%	97%	100%	100%	100%
Serious hypocalcemia	7	3%	5%	7%	10%	13%	16%	22%	28%	54%
Serious infection	8799	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	207	20%	54%	81%	95%	99%	100%	100%	100%	100%
Pancreatitis	137	16%	40%	66%	85%	94%	98%	100%	100%	100%
Serious hypersensitivity	217	22%	56%	84%	96%	99%	100%	100%	100%	100%
Malignancy	1353	81%	100%	100%	100%	100%	100%	100%	100%	100%
		5 Years Post Launch								
Fracture healing complications	134	35%	81%	98%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	7	6%	11%	17%	23%	30%	39%	52%	65%	93%

[a] Power calculated using the Fisher's 2-sided exact text with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 10:1 between denosumab- and comparator-exposed person-years.

Table E-2. Power to Detect Relative Risk for the Adverse Events of Special Interest, United HealthCare[a]

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		5 Years Post Launch (continued)								
Serious infection	8799	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	207	50%	94%	100%	100%	100%	100%	100%	100%	100%
Pancreatitis	137	36%	82%	97%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	217	51%	94%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1353	100%	100%	100%	100%	100%	100%	100%	100%	100%
		10 Years Post Launch								
Fracture healing complications	134	62%	98%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	7	8%	18%	29%	43%	55%	67%	82%	92%	100%
Serious infection	8799	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	207	79%	100%	100%	100%	100%	100%	100%	100%	100%
Pancreatitis	137	63%	98%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	217	81%	100%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1353	100%	100%	100%	100%	100%	100%	100%	100%	100%

[a] Power calculated using the Fisher's 2-sided exact text with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 10:1 between denosumab- and comparator-exposed person-years.

Table E-3. Power to Detect Relative Risk for Adverse Events of Special Interest, Denmark/Norway[a]

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		2 Years Post Launch								
ONJ	1	0%	0%	0%	0%	0%	0%	0%	0%	0%
Fracture healing complications	134	17%	44%	71%	86%	95%	98%	100%	100%	100%
Serious hypocalcemia	7	3%	6%	7%	11%	14%	18%	25%	31%	58%
Serious infection	8799	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	207	23%	59%	85%	96%	99%	100%	100%	100%	100%
Pancreatitis	137	17%	44%	69%	87%	96%	99%	100%	100%	100%
Serious hypersensitivity	217	24%	61%	87%	97%	100%	100%	100%	100%	100%
Malignancy	1353	85%	100%	100%	100%	100%	100%	100%	100%	100%
		5 Years Post Launch								
ONJ	1	0%	0%	0%	0%	0%	0%	0%	0%	0%
Fracture healing complications	134	37%	85%	98%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	7	6%	12%	18%	26%	34%	41%	57%	70%	94%

[a] Power calculated using the Fisher's 2-sided exact text with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 1:1between denosumab- and comparator-exposed person-year for ONJ and 10:1 for other AESI.

Table E-3. Power to Detect Relative Risk for Adverse Events of Special Interest, Denmark/Norway[a]

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		5 Years Post Launch (continued)								
Serious infection	8799	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	207	54%	96%	100%	100%	100%	100%	100%	100%	100%
Pancreatitis	137	38%	85%	99%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	217	55%	96%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1353	100%	100%	100%	100%	100%	100%	100%	100%	100%
		10 Years Post Launch								
ONJ	1	0%	0%	0%	0%	0%	0%	0%	0%	2%
Fracture healing complications	134	66%	99%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	7	9%	20%	32%	45%	59%	70%	86%	94%	100%
Serious infection	8799	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	207	82%	100%	100%	100%	100%	100%	100%	100%	100%
Pancreatitis	137	67%	99%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	217	85%	100%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1353	100%	100%	100%	100%	100%	100%	100%	100%	100%

[a] Power calculated using the Fisher's 2-sided exact text with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 1:1between denosumab- and comparator-exposed person-year for ONJ and 10:1 for other AESI.

Table E-4. Power to Detect Relative Risk for Adverse Events of Special Interest, Sweden[a]

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		2 Years Post Launch								
ONJ	1	0%	0%	0%	0%	0%	0%	0%	0%	0%
Fracture healing complications	134	24%	63%	88%	98%	100%	100%	100%	100%	100%
Serious hypocalcemia	7	5%	7%	12%	17%	22%	26%	38%	47%	78%
Serious infection	8799	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	207	34%	80%	97%	100%	100%	100%	100%	100%	100%
Pancreatitis	137	25%	64%	89%	98%	100%	100%	100%	100%	100%
Serious hypersensitivity	217	35%	82%	98%	100%	100%	100%	100%	100%	100%
Malignancy	1353	97%	100%	100%	100%	100%	100%	100%	100%	100%
		5 Years Post Launch								
ONJ	1	0%	0%	0%	0%	0%	0%	0%	0%	1%
Fracture healing complications	134	57%	97%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	7	8%	16%	28%	38%	50%	61%	79%	89%	100%

[a] Power calculated using the Fisher's 2-sided exact text with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 1:1 between denosumab- and comparator-exposed person-years for ONJ and 10:1 for other AESI.

Table E-4. Power to Detect Relative Risk for Adverse Events of Special Interest, Sweden[a]

Outcomes	Background Incidence Rate (per 100,000 Person-years)	Relative Risk								
		1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		5 Years Post Launch (continued)								
Serious infection	8799	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	207	75%	100%	100%	100%	100%	100%	100%	100%	100%
Pancreatitis	137	58%	97%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	217	76%	100%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1353	100%	100%	100%	100%	100%	100%	100%	100%	100%
		10 Years Post Launch								
ONJ	1	0%	0%	0%	0%	0%	0%	1%	2%	12%
Fracture healing complications	134	86%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypocalcemia	7	13%	28%	48%	66%	79%	89%	97%	99%	100%
Serious infection	8799	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious dermatologic adverse events	207	96%	100%	100%	100%	100%	100%	100%	100%	100%
Pancreatitis	137	87%	100%	100%	100%	100%	100%	100%	100%	100%
Serious hypersensitivity	217	97%	100%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1353	100%	100%	100%	100%	100%	100%	100%	100%	100%

[a] Power calculated using the Fisher's 2-sided exact text with $\alpha = 0.05$ (Agresti, 1990) based on a group ratio of 1:1 between denosumab- and comparator-exposed person-years for ONJ and 10:1 for other AESI.

13.6 Appendix F. Substudy: Men With Osteoporosis Treated With Denosumab

INTRODUCTION

After its initial marketing approval for postmenopausal osteoporosis, the use of Prolia in men with osteoporosis was approved in the United States. In this substudy, descriptive analyses of data from men with osteoporosis treated with denosumab in the United States (US) Medicare data system and Optum Research Database will be provided for the 9 adverse events of special interest (AESI; see the Objectives Section of this Amendment) evaluated in Study 20090522.

A fixed-cohort design will be employed, and crude and age-standardized AESI incidence rates will be provided. In the fixed-cohort, subjects are not allowed to leave and rejoin the cohort once they were included in the Prolia cohort; yet, a subject satisfying eligibility criteria for the Prolia cohort can join the cohort throughout the study period. Incidence rates stratified by age, osteoporosis treatment at baseline, previous fragility fracture, and occurrence of the relevant AESI during the baseline period will also be provided, as will descriptive analyses of baseline covariates and denosumab utilization patterns.

OBJECTIVES

In men with osteoporosis treated with denosumab, objectives of the substudy are to describe:

1. subject characteristics, clinical features, AESI risk factors, and subject follow-up
2. incidence rates of AESI, including:
   - osteonecrosis of the jaw (ONJ)
   - non-traumatic subtrochanteric and diaphyseal fracture
   - fracture healing complications
   - hypocalcemia leading to hospitalization or emergency room (ER) visit;
   - infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication
   - dermatologic adverse events leading to hospitalization or ER visit
   - acute pancreatitis leading to hospitalization
   - hypersensitivity leading to hospitalization or ER visit
   - new primary malignancy (excluding non-melanoma skin cancer)
3. denosumab utilization patterns

BACKGROUND AND RATIONALE

Denosumab Therapy for Osteoporosis

Denosumab (also referred to as AMG 162) is a fully human IgG_2 monoclonal antibody that binds to RANK ligand (RANKL), and blocks the interaction of RANKL with RANK. RANKL is a member of the tumor necrosis factor (TNF) superfamily, and is a key mediator in the pathway required for the formation, function, and survival of the cells that resorb bone (osteoclasts). Denosumab binds with high affinity and specificity to RANKL, thereby neutralizing the ligand and suppressing osteoclast-mediated bone turnover.

Clinical studies to date demonstrate that denosumab 60 mg is well tolerated in men. It has a favorable safety profile in male patients followed up to 5 years. No additional safety issues have been identified in men, demonstrating that the safety profile of denosumab is similar in men and women.

Rationale

Clinical studies demonstrate that denosumab is well tolerated in men. Amgen now will include men with osteoporosis treated with denosumab in the ongoing post-marketing safety Study 20090522 to assess safety in the post-marketing environment. The proposed inclusion of men in Study 20090522 leverages the existing study infrastructure, and the pharmacoepidemiologic and methodologic expertise of the current investigator teams. Importantly, male denosumab users will be ascertained from the large US Medicare database and the Optum Research Database used in Study 20090522, which will allow Amgen to proactively evaluate and quantify the incidence of specific AESI among men with osteoporosis treated with denosumab. The addition of men will also provide resources for evaluating new safety issues and concerns among male users that may arise in the postmarketing period.

Adverse Events of Special Interest (AESI)

The following AESI, all currently included in Study 20090522, will also be studied in men: osteonecrosis of the jaw (ONJ), non-traumatic subtrochanteric and diaphyseal fracture, fracture healing complications, hypocalcemia leading to hospitalization or emergency room (ER) visit, infections leading to hospitalization or ER visit or administration of parenteral anti-infective medication, dermatologic adverse events leading to hospitalization or ER visit, acute pancreatitis leading to hospitalization, hypersensitivity leading to hospitalization or ER visit, and new primary malignancy. Confirmation of atypical femoral fracture will not be performed in this substudy as radiographs are not available in the Medicare and Optum Research Database systems.

HYPOTHESES

This substudy is descriptive in nature. As such, no pre-specified hypotheses will be tested in this substudy. Rates and associated 95% confidence intervals for each AESI will be estimated for men with osteoporosis treated with denosumab.

SUBSTUDY DESIGN

This is a prospective fixed cohort study of men with osteoporosis treated with denosumab in the US Medicare and Optum Research Database. The study period will include up to 7 years of follow-up in each data system based on data availability at the time we initiate final analyses. The enrollment period begins upon approval of the indication for the treatment in men with osteoporosis (20 Sep 2012), with annual assessment and reporting of descriptive findings. AESI will be identified using validated algorithms based on inpatient and outpatient diagnosis and procedure codes, and, for some AESI, medication codes or laboratory data (ie, the same algorithms used for postmenopausal women and women with PMO). Osteonecrosis of the jaw will be confirmed by medical chart review in the US Medicare database.

DESCRIPTION OF DATA SOURCE

US Medicare

The US Medicare database is a comprehensive, nationally representative, population-based data system of US subjects ≥ 65 years of age. Key characteristics, including available data and average follow-up time, are described in the Study 20090522 Protocol (Section 4.2.1). In 2010, there were a total of 21,879,333 male US residents enrolled in Medicare. Of these men, approximately 16,806,969 were ≥ 65 years of age as of 01 Apr 2010, representing 97% of the US general population of men in this age group in 2010. A total of 5,295,029 (32%) of these men had Parts A, B and D coverage for at least 1 month (when they also were age 65+), and 26% had Parts A, B and D coverage for all months in the year in which they were ≥65 years.

Optum Research Database Optum Research Database is administrative database that provides data for 15 million patient lives per year. Optum Research Database is described in the Study 20090522 Protocol (Section 4.2.1). In 2012, a total of 6,234,500 men were enrolled for at least one day in the database and a total of 3,961,976 men were continuously enrolled throughout the year.

SUBJECT SELECTION CRITERIA FOR SUBSTUDY

Subjects in Medicare and Optum Research Database will need to have appropriate plan coverage to be included in the study population. Appropriate plan coverage for the Optum Research Database refers to both pharmacy and medical plan coverage. Appropriate plan coverage for the US Medicare database refers to enrolment in traditional fee-for-service Medicare (Medicare Parts A and B coverage and not in a Medicare Advantage plan), plus Part D. The population included in this substudy will be identified based on the following inclusion and exclusion criteria.

Inclusion Criteria

Men ≥ 65 years old in the Medicare database or ≥ 30 years old in Optum Research Database who receive at least one denosumab 60 mg injection will be included. Additionally, all men need to be continuously enrolled for at least 12 months prior to start of follow-up. A diagnosis of osteoporosis or osteoporotic fracture would not be required because it is known that male osteoporosis is under-diagnosed. The exclusion of subjects with cancer or Paget disease (as described in the Exclusion Criteria Section) will ensure that subjects treated with Prolia is for osteoporosis but not for other indications. The index date will be the date of first administration of Prolia on or after male substudy start date after fulfilling both the database specific age and 12-month enrollment criteria..

Exclusion Criteria

Men with a diagnosis of malignancy (excluding non-melanoma skin cancer) or treatment with chemotherapy, hormonal therapy or radiation therapy for cancer up to 12 months before the index date will be excluded. Men with Paget's disease during the 12-month period prior to the index date will also be excluded.

Exposure Cohort

Exposure will be defined on the basis of exposure to denosumab 60 mg. Denosumab exposure will be identified using NDC codes and HCPCS codes (C9272, J0897).

COVARIATES

Variables that will provide descriptive characteristics of men with osteoporosis treated with denosumab may include, but not necessarily be limited to the following:

- age
- age groups (eg, ≥ 65 and < 75, ≥ 75) for US Medicare
- age groups (eg, 30-44, 45-54, 55-64, 65-74, ≥ 75) for Optum Research Database

- geographic location (eg, state)
- calendar year of meeting eligibility criteria for the substudy
- osteoporosis diagnosis
- fragility fracture history

history of treatment with osteoporosis medication (bisphosphonates, Selective Estrogen Receptor Modulators (SERMS), calcitonin, teraparatides, denosumab, romosozumab, abaloparatide)

- concurrent medications that are risk factors for relevant AESI
- Charlson's Comorbidity Index (CCI)
- comorbidities (eg, infections, diabetes, and disease or conditions that may be indicative of secondary osteoporosis or increase risk of AESI)
- variables that may be indicators of health status or health seeking behavior, eg,health resource utilization (office visits, ER visits, hospitalizations, cost of services)

The 12-month period prior to the subject's index date (inclusive) will constitute the baseline period. Data collected during the baseline period will be used to define eligibility for inclusion in analyses and values for baseline covariates described above.

SUBJECT FOLLOW-UP

Subject follow-up among eligible men will begin the day after the index date and continue to the first of the following: disenrollment from the data system, death, and diagnosis of Paget's disease, diagnosis of malignancy (excluding non-melanoma skin cancer), treatment with chemotherapy, hormonal therapy or radiation therapy for cancer, switching to bisphosphonates or other osteoporosis medications or end of the substudy. The follow-up for incident events of all AESI will also end at the occurrence of the corresponding AESI. The assessment of bisphosphonate and other osteoporosis medications follows the same method as in the study among women with PMO (Study 20090522 Protocol, Appendix A, Table A-1 and Table A-3).

ALGORITHMS TO ASCERTAIN ADVERSE EVENTS OF SPECIAL INTEREST

Algorithms to ascertain AESI have been developed in Study 20090522 and will be applied to men (Study 20090522 Protocol, Appendix B, and Table B-1-Table B-29). Each AESI case ascertainment algorithm utilizes combinations of inpatient and outpatient ICD diagnosis codes (ICD-9-CM), CPT-4 or HCPCS procedure codes, laboratory or pathology test results, medication used, and/or EMR data. A comprehensive review of the literature was conducted regarding the development,

validation, and application or use of ascertainment algorithms for AESI in studies including both men and women (Study 20090522 Protocol, Section 5). Amgen also conducted additional medical record review studies based on the US Medicare database and the Scandinavian national registries to validate selected AESI ascertainment algorithms. The study results were communicated with regulatory agencies [PBRER/PSUR #09 - (Prolia) (27 September 2014 to 26 September 2015)].

Consistent with Study 20090522, all potential cases of ONJ in men with osteoporosis treated with denosumab will undergo medical chart review in US Medicare, when available. Potential cases of atypical femoral fracture in men with osteoporosis treated with denosumab will not be confirmed through medical chart review.

POTENTIAL SOURCES OF BIAS IN STUDY DESIGN

There are several study design issues to be considered to appropriately interpret the study results.

DISEASE SEVERITY

Men who receive denosumab for the treatment of osteoporosis, especially shortly after the approval of the indication, are likely to have more severe conditions and longer durations of the disease considering that male osteoporosis is under-diagnosed and under-treated in general (Tuck and Datta, 2007).

BIAS ASSOCIATED WITH SUBJECTS SWITCHING FROM ANOTHER OSTEOPOROSIS MEDICATION

It is possible that men treated with denosumab for osteoporosis may have received bisphosphonates or other osteoporosis medications. These men may be unable to comply with or are intolerant of other osteoporosis medications or have not achieved an adequate treatment response. In addition, men who have received anti-resorptive therapy for long periods of time may be selectively referred to denosumab treatment due to concerns about potential risk of events associated with long-term drug exposure. Such men are also likely to be at increased risk for one or more AESI. The influence of bisphosphonate and other osteoporosis medications before the treatment of denosumab on the incidence rates of AESI will be evaluated through stratified analysis by osteoporosis medications received during baseline period.

SELECTION BIAS DUE TO MISSING VALUES

Since this substudy is based on US Medicare and Optum Research Databases, missing data are possible and may introduce bias if subjects with missing values are excluded

from the analyses. The handling of missing data will follow the same strategy as for the analysis among women with PMO (Study 20090522 Protocol, Section 6.3).

SAFETY DATA COLLECTION, RECORDING, AND REPORTING

Safety data collection, recording and reporting for men with osteoporosis treated with denosumab will follow the same plan as for women with PMO (Study 20090522 Protocol, Section 7).

SAMPLE SIZE AND PRECISION OF ESTIMATION

Sample size is calculated based on the estimated number and patient-years of males with osteoporosis in the US Medicare Database (≥ 65 years old) and the United Healthcare database (≥ 30 years old) and the assumption that 0.25% of males with osteoporosis will receive denosumab for the first 2 years post approval and 0.50% thereafter. The expected number of person-years of observation in the US Medicare database is 3,152, 12,610, and 18,915 at 2, 5, and 7 years post approval (Table F- 1.). The expected number of person-years of observation in the United Healthcare databaseis 115, 458, and 687 at 2, 5, and 7 years post approval (Table F- 1.). The actual numbers will vary depending on the adoption rate of denosumab treatment.

The background incidence rates of AESI were estimated based on literature review, and feasibility analysis in the US Medicare database and United Healthcare database are provided in Table F-2.

In the US Medicare database, the precision estimation is based on the exact method for ONJ and hypocalcemia. The normal approximation method is used for other relatively more common AESI. The 95% confidence interval (per 100,000 person-years) for ONJ is estimated to be (0, 119) based on 3,152 person-years at year 2, (0, 31) based on 12,610 person-years at year 5, and (0, 22) based on 18,915 person-years at year 7. The 95% confidence interval (per 100,000 person-years) for hypocalcemia is estimated to be (0, 131) based on 3,152 person-years at year 2, (0, 43) based on 12,610 person-years at year 5, and (0, 32) based on 18,915 person-years at year 7.

The half-width of the 95% confidence intervals for other relatively more common AESI are provided in Table F-3. The half-widths were calculated using the normal approximation to the Poisson distribution. For example, the 95% confidence interval for the incidence rate of pancreatitis is estimated to be 173±73 per 100,000 person-years based on 12,610 person-years at year 5.

In the United Healthcare database, the precision estimation is based on the normal approximation method (Table F-3). The half-width of the confidence intervals for each AESI are much wider, corresponding to a smaller sample size in this database. Medical chart review will not be conducted for ONJ in United HealthCare and therefore precision estimations are not provided.

Table F- 1. Estimated Exposure to Denosumab in Men With Osteoporosis Through 7 Years Post Approval in US Medicare Database

Data System	Estimated Annual Male Osteoporosis in 100% Sample (Person-years)	Estimated Exposure to Denosumab (Person-years)		
		First 2 Years Post Denosumab Approval (Person-years)	First 5 Years Post Denosumab Approval (Person-years)	First 7 Years Post Denosumab Approval (Person-years)
US Medicare	630,484	3,152	12,610	18,915
United HealthCare	22,907	115	458	687

Table F-2. Summary of Background Incidence Rates of AESI in Men With Osteoporosis Based on Literature Review and Amgen's Feasibility Analysis US Medicare and United Healthcare Databases

AESI	Source	Background Incidence Rate (per 100,000 person-years)
ONJ	Sambrook et al., 2006	1
Atypical femoral fracture leading to hospitalization	N/A	Unknown
Fracture healing complications	Amgen's analysis in US Medicare[a]	347
	United HealthCare[b]	771
Hypocalcemia leading to hospitalization	Amgen's analysis in US Medicare[a]	7
	United HealthCare[b]	47
Serious infection	Amgen's analysis in US Medicare[a]	11799
	United HealthCare[b]	8705
Serious dermatologic adverse events	Amgen's analysis in US Medicare[a]	196
	United HealthCare[b]	202
Pancreatitis	Amgen's analysis in US Medicare[a]	173
	United HealthCare[b]	178
Serious hypersensitivity	Amgen's analysis in US Medicare[a]	202
	United HealthCare[b]	170
New primary malignancy	Amgen's analysis in US Medicare[a]	2557
	United HealthCare[b]	1634

[a] The analysis was conducted among men ≥65 years old and with osteoporosis in US Medicare from 2004 – 2009. Cases of AESI were identified using the same ascertainment algorithm as in Appendix B.
[b] The analysis was conducted among men ≥ 30 years old with osteoporosis and without cancer in United Healthcare from 2005 – 2010.

Table F-3. Half-width of the 95% Confidence Interval of the Estimate of Incidence Rates for AESI[a], US Medicare[b] and United Healthcare[c]

			Half-width of the 95% Confidence Interval		
AESI	**Source**	**Background Incidence Rate (per 100,000 Person-years)**	**2 Years Post Launch**	**5 Years Post Launch**	**7 Years Post Launch**
Hypocalcemia	United HealthCare	47	±396	±199	±162
Pancreatitis	US Medicare	173	±145	±73	±59
	United HealthCare	178	±771	±386	±315
Serious dermatologic adverse events	US Medicare	196	±155	±77	±63
	United HealthCare	202	±821	±412	±336
Serious hypersensitivity	US Medicare	202	±157	±78	±64
	United HealthCare	170	±754	±378	±308
Fracture healing complications	US Medicare	347	±206	±103	±84
	United HealthCare	771	±1605	±804	±657
New primary malignancy	US Medicare	2557	±558	±279	±228
	United HealthCare	1634	±2336	±1171	±956
Serious infection	US Medicare	11799	±1199	±600	±490
	United HealthCare	8705	±5392	±2702	±2206

[a] Half-width of the 95% confidence intervals was calculated for AESI incidence rates using the normal approximation to the Poisson distribution.
[b] The exposure to denosumab in US Medicare among men ≥ 65 years old and with osteoporosis is estimated to be 3152, 12610 and 18915 person-years at 2, 5, and 7 years post approval respectively.
[c] The exposure to denosumab in United Healthcare among men ≥ 30 years old with osteoporosis and without cancer is estimated to be 115, 458, and 687 person-years at 2, 5, and 7 years post approval respectively

STATISTICAL METHODS OF ANALYSIS

Descriptive analyses of data for men with osteoporosis treated with denosumab in the US Medicare and Optum Research Database systems will be provided, including description of subject characteristics, clinical features, risk factors of AESI, and subject follow-up. In addition, crude and age-standardized AESI incidence rates and event rates and denosumab utilization patterns will be described for this population.

Analytic approaches relevant to each study objective are provided below.

Objective 1: Describe Subject Characteristics, Clinical Features, AESI Risk Factors and Subject Follow-up in Men With Osteoporosis Treated With Denosumab

Subject characteristics, clinical features and AESI risk factors assessed during baseline will be described. Summary of enrollment and subject follow-up will also be described.

Objective 2: Determine Rates of AESI in Men With Osteoporosis Treated With Denosumab

The crude estimates of incidence rates (and 95% confidence interval) and estimates standardized to the Year 2010 US census age distribution will be calculated in men with osteoporosis treated with denosumab. Stratified analyses will be conducted as appropriate using important confounders such as age, history of osteoporosis medication (bisphosphonate and other osteoporosis medications) at baseline, and history of fracture at baseline. In addition, event rates (and 95% confidence intervals) assessing both first and subsequent events of the same AESI will be provided for hypocalcemia, infection, hypersensitivity, dermatologic adverse events and their subtypes.

Incidence rates (and 95% confidence intervals) stratified by cumulative dose of bisphosphonate treatment received during baseline period will also be provided to explore the effect of long-term exposure of bisphosphonate on risk of ONJ, non-traumatic subtrochanteric and diaphyseal fracture, fracture healing complication and new primary malignancy.

Estimation of incidence rates of the algorithm-identified potential ONJ and confirmed ONJ (in the US Medicare database only) based on expert review results will be provided. For expert review of ONJ, the proportion of medical charts that are obtained out of the total number requested will be calculated. The positive predictive value (PPV) of the established algorithm against reviewed case status will be calculated as the number of

confirmed cases divided by the number of potential cases for which medical charts are reviewed.

Depending on the nature of the AESI, time at risk may include on-treatment periods only, or both on-treatment and posttreatment periods. For all AESI, analyses will be conducted based on time at risk defined by the on-treatment period only. In addition, for ONJ and non-traumatic subtrochanteric and diaphyseal fracture and fracture healing complications, analyses will also be performed based on time at risk which includes both on-treatment and up to the first year of the posttreatment period. For new primary malignancy, additional analyses will be performed based on time at risk, which includes both on-treatment and up to the first 5 years of the posttreatment period. The length of posttreatment period included in AESI-specific analyses is defined according to the potential latency period for that AESI.

Cumulative incidence will be graphically displayed using Kaplan-Meier curves and/or cumulative incidence function plots. Simultaneous confidence intervals (95% confidence bands) will be provided to represent the uncertainty in the estimate of the curve.

Objective 3: Describe Denosumab Utilization Patterns Among Men With Osteoporosis Treated With Denosumab

Descriptive statistics will be used to characterize denosumab utilization patterns in men with osteoporosis treated with denosumab. Factors to be assessed include frequency of administration, cumulative dosage, and timing of subsequent administrations. Prior, concurrent, or subsequent treatment with other osteoporosis medications will be described. Stratification by key subject characteristics will be considered as appropriate.

COMMUNICATION OF STUDY RESULTS TO REGULATORY AGENCIES

Study results will be submitted to regulatory agencies following the same plan as results from Study 20090522 (Study 20090522 Protocol, Section 10).

ETHICAL OBLIGATIONS

This substudy is based upon routinely collected data from US Medicare and Optum Research Database systems. Analyses using these data sources will be conducted by investigators who have access to the data through their respective institutions, with analysis findings shared with Amgen in accordance with the data use agreement between Amgen and the investigators (institutions). Study results will be presented only in an aggregate form, and individuals will not be identified.

13.7 Appendix G. Sample Size and Power Projections for Women With PMO Re-estimated After 3-years of Prolia Post-launch Data was Available in all Data Systems

Sample size and power projections for women with PMO were updated after 3- years of Prolia post-launch data was available in all data systems. By 2016, 4 annual reports have been completed, and the expected number of women with PMO have been re-estimated based on data provided in the existing annual study reports using projections by simple linear regression from each of the data systems (Table G-1). The data-reporting period begins on 26 May 2010 for all data systems and the end date range differs by data system, from 31Dec2013 (US Medicare and Scandinavian countries) to 31 March 2015 (United HealthCare). The overall number of person-years of observation among women with PMO exposed to denosumab is estimated to be approximately 175,798 and 413,098 at 5 and 10 years post approval, respectively. The number of person-years of exposure to denosumab in individual data systems at 10 years post approval ranges from about 5,247 in Norway to 363,268 in US Medicare. The updated estimation is lower than the original estimation described in Table 8-1 of the Protocol.

Table G-1. Reported and Estimated Exposure to Denosumab Through 10 Years Post Approval of Denosumab by Data System

Data System	Reported Exposure to Denosumab in the Annual Reports (Person-years)[a b]				Estimated Exposure to Denosumab (Person-years)[c]	
	Year 2 Annual Report	Year 3 Annual Report	Year 4 Annual Report	Year 5 Annual Report	First 5 Years Post Denosumab Approval (Person-years)[d]	First 10 Years Post Denosumab Approval (Person-years)
US Medicare	1,015	14,924	57,545	126,086	154,351	363,268
Denmark	53	1,173	3,775	7,581	9,442	22,035
Norway	2	107	622	1,873	2,183	5,247
Sweden	3	555	2,260	4,789	5,918	13,949
United HealthCare	275	908	2,005	3,039	3,904	8,599
Combined	1,348	17,667	66,207	143,368	175,798	413,098

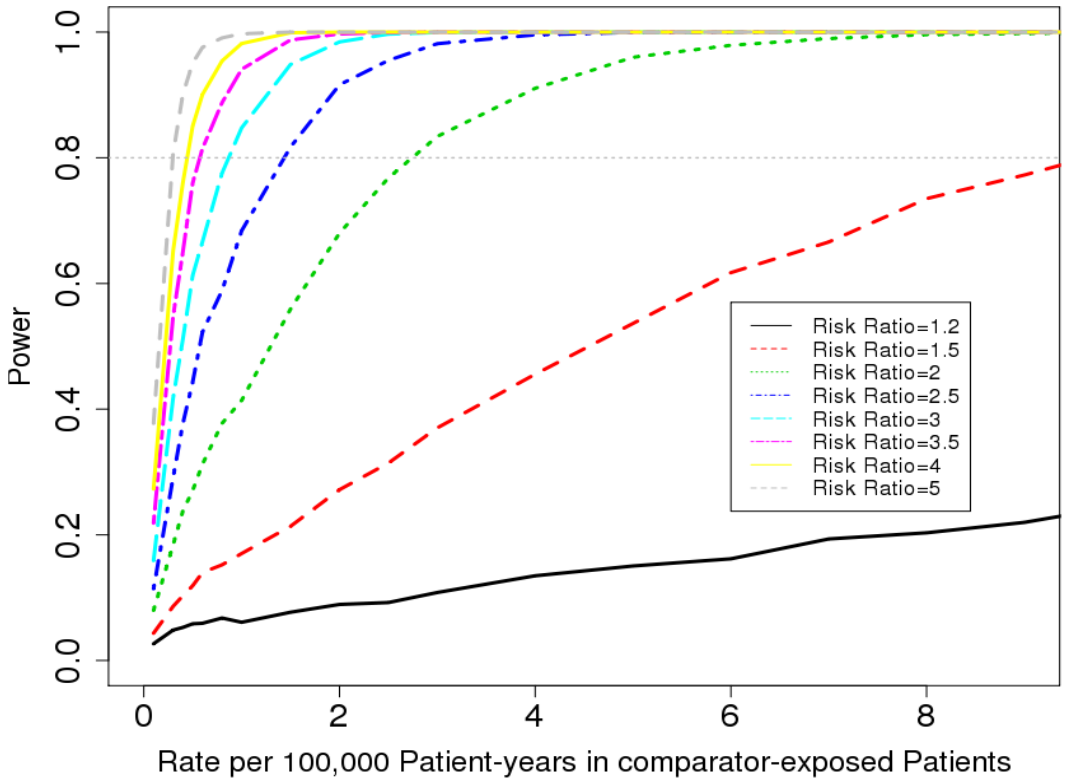
[a] The data reporting period of the Year 2 annual report is 26 May 2010-29 February 2012 for United HealthCare and 26 May 2010-31 December 2010 for other data systems. For the later reports, all data systems have one-year increment in the reporting period from the Year 3 to Year 5 annual reports. (Names of the annual reports received begin in Year 2)
[b] The denosumab exposure is based upon on-treatment period.
[c] The estimation is projected by simple linear regression using the report year as the predictor and person-years as the dependent variable for each data system.
[d] When at least 5 years of data is available (from each data system) post denosumab approval.

Table G-2. Background Incidence Rates Used For Power Calculations - Reported Rates From the Year 5 Annual Report

	Background Incidence Rate (per 100,000 person-years)[a]				
Adverse Event of Special Interest	US Medicare	Denmark	Norway	Sweden	United HealthCare
ONJ[b c]	47	47.8	35.3	18.6	27.8
Subtrochanteric or diaphyseal femoral fracture[b c]	149	178.3	190.9	191.8	255.6
Fracture healing complications[c]	156	31.8	85.4	179.4	146.4
Hypocalcemia leading to hospitalization[d]	6	8.3	11.2	27.9	13.1
Infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication[d]	9,481	4034.1	3767.8	5029.9	6047.9
Dermatologic adverse events leading to hospitalization or ER visit[d]	236	48.2	34.1	119.2	138
Acute pancreatitis leading to hospitalization[d]	118	56.9	45.2	87.4	105.7
Hypersensitivity leading to hospitalization or an ER visit[d]	231	68.8	79.6	140.3	150.8
New primary malignancy (excluding non-melanoma skin cancer)[e]	1,802	1527.3	1853.7	1722.4	892

[a] Background rate is from the exposure cohort of Any Bisphosphonates Only and appropriate time at risk period of on-treatment with or without post-treatment.
[b] Defined using ICD code algorithm (ie, not confirmed by medical record review)
[c] The rate is based on the time at risk of on-treatment plus one year of post-treatment
[d] The rate is based on the time at risk of on-treatment only
[e] The rate is based on the time at risk of on-treatment plus five years of post-treatmentUsing the same approach of Fisher's 2-sided exact test with $\alpha = 0.05$ (Agresti, 1990) as in the original estimation (Section 8 of the Protocol), power to assess relative risk at 10 years post denosumab market entry (Figure G-1) was calculated based on a ratio of 1:20 between denosumab-exposed and comparator person-years with up to 10 years of follow-up. The ratio 1:20 (changed from 1:10 used in the original calculations) is based on the projected patient-years at 10 years post denosumab approval combined all data systems. Using the combined data from all data systems, after 10 years of follow-up, the study will have nearly 100% power to detect a relative risk of 2 or higher for AESI with a background incidence rate of ≥ 7 cases per 100,000 person-years or higher. The study will have appreciable power to detect moderately elevated relative risks for rarer AESI.

Figure G-1. Statistical Power at 10 Years Post Denosumab Market Entry for a Range of Event Rates (All Data Systems Combined)



Fisher's Exact Test (2-sided), α =0.05
Denosumab:Comparator-exposed (patient-years) = 1:20
Denosumab-exposed patient-years = 413098

Table of Statistical Power Values for Figure G-1: Statistical Power at 10 Years Post Denosumab Market Entry for a Range of Event Rates (All Data Systems Combined)

Rate per 100,000 Patient-years in Comparator-exposed Patients	Risk Ratio= 1.2	Risk Ratio= 1.5	Risk Ratio= 2	Risk Ratio= 2.5	Risk Ratio= 3	Risk Ratio= 3.5	Risk Ratio= 4	Risk Ratio= 5
1.0	0.069	0.1661	0.4224	0.6735	0.8471	0.9412	0.9788	0.9979
2.0	0.0895	0.2702	0.678	0.9142	0.9855	0.9982	0.9997	1
3.0	0.1106	0.3726	0.8342	0.9793	0.9993	1	1	1
4.0	0.1285	0.4602	0.913	0.9951	0.9999	1	1	1
6.0	0.1596	0.6087	0.9809	0.9997	1	1	1	1
8.0	0.1975	0.7228	0.9957	1	1	1	1	1

Table values were re-generated using same assumptions as original Figure G-1

Based on the reported background rates (Table G-2) and projected patient-years from the study (Table G-1), the updated power to detect relative risk of each of the ICD algorithm defined AESI in each of the data systems at various time points post denosumab market entry (5 years and 10 years) is presented in Table G-4 trough Table G-8. For all AESI other than serious hypocalcaemia, the analyses based on US Medicare data will achieve > 95% power to detect a relative risk of 1.5 at both 5 and 10 years post denosumab market entry. The analyses based on data from United HealthCare will have over 80% power to detect a relative risk of 3.0 and 2.5 or higher, respectively, for all AESI other than hypocalcemia and ONJ at 5 years and 10 years post denosumab market entry. The analyses based on the Denmark national registries will have > 85% to detect a relative risk of 3.5 and 2.5 or higher, respectively, for all AESI other than serious hypocalcaemia at 5 years and 10 years post denosumab market entry. The analyses based on the Norway national registries will have > 80% power to detect a relative risk of 4.0 for serious hypersensitivity or more common AESI at 5 years post denosumab market entry and for all AESI other than serious hypocalcaemia at 10 years post denosumab market entry. The analyses based on the Sweden national registries will have > 80% to detect a relative risk of 3.0 and 2.5 or higher, respectively, for all AESI other than serious hypocalcaemia and ONJ at 5 years and 10 years post denosumab market entry.

Medical chart review was performed for the potential events identified by the ICD algorithm for ONJ (US Medicare, Denmark, and Sweden data systems) and subtrochanteric or diaphyseal femoral fractures (Denmark data system) observed in all denosumab-exposed subjects and a matched sample of bisphosphonate-exposed subjects. As of year 2016, only US Medicare and Denmark have provided annual reports on the analysis with the medical review cases, US Medicare has 1 annual report and Denmark has 2 annual reports (Table G-3). With the limited number of annual reports on the medically reviewed events, the subject-years cannot be projected for the 5 years or 10 years post denosumab approval. In addition, the extremely low number of confirmed cases (0-2 cases) that were used for the calculation of the background incidence rates can result in very imprecise estimates, therefore power analysis was not conducted for the rates based on medical chart reviewed cases. This will be re-evaluated when all data systems have 5 years of data post-Prolia market entry.

Table G-3. Background Incidence Rates for the AESI With Medical Review

	Background Incidence Rate Number of events/Patient-years (per 100,000 person-years)[a]	
Adverse Event of Special Interest	US Medicare[b]	Denmark[c]
ONJ	1/63,600 (2.0)	2/2630 (97.2)
Atypical femoral fracture[b] [c]	NA	1/2648 (38.9)

[a] Background rate is from the exposure cohort of Any Bisphosphonates Only and based on the time at risk period of on-treatment plus one year of post-treatment (described in annual reports)
[b] From the Year 4 annual report (the only report from US Medicare)
[c] From the Year 5 annual report (the most recent report from Denmark)

Tables Table G-4 - Table G-8 Projected Power at 5 and 10 Years Post Launch for Select Relative Risks From 1.2 to 10.0 are Provided for Algorithm Defined AESIs (without medical review) in Each Data System. These Projections Have Been Updated Based on the Data From Reporting Period Starting From 26 May 2010 for all Data Systems and the Ending From 31 Dec 2013 (US Medicare and Scandinavian countries) to 31 March 2015 (United HealthCare) by Different Data Systems

Table G-4. Algorithm Defined AESIs Without Medical Review, US Medicare[a]

Outcomes	Background Incidence Rate (per 100 000 Person-Years)	Relative Risk[a]									
		1.2	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		5 Years Post Launch									
ONJ	47	36%	96%	100%	100%	100%	100%	100%	100%	100%	100%
Subtrochanteric Fractures	149	82%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Fracture Healing Complications	156	83%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1802	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Hypocalcaemia	6	9%	29%	73%	94%	99%	100%	100%	100%	100%	100%
Serious Infection	9,481	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Dermatologic Adverse Events	236	95%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Pancreatitis	118	71%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Hypersensitivity	231	94%	100%	100%	100%	100%	100%	100%	100%	100%	100%

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Table G-4. Algorithm Defined AESIs Without Medical Review, US Medicarea

Outcomes	Background Incidence Rate (per 100 000 Person-Years)	Relative Risk[a]									
		1.2	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		10 Years Post Launch									
ONJ	47	69%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Subtrochanteric Fractures	149	99%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Fracture Healing Complications	156	99%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1,802	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Hypocalcaemia	6	15%	55%	97%	100%	100%	100%	100%	100%	100%	100%
Serious Infection	9,481	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Dermatologic Adverse Events	236	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Pancreatitis	118	96%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Hypersensitivity	231	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

[a] Power calculated using the Fisher's 2-sided exact test with alpha=0.05 between Prolia and bisphosphonate (BP) exposed person-years.

Table G-5. Algorithm Defined AESIs Without Medical Review, United HealthCare[a]

Outcomes	Background Incidence Rate (per 100 000 Person-Years)	Relative Risk[a]									
		1.2	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		5 Years Post Launch									
ONJ	28	5%	9%	18%	28%	40%	51%	62%	77%	88%	100%
Subtrochanteric Fractures	256	10%	33%	76%	95%	100%	100%	100%	100%	100%	100%
Fracture Healing Complications	146	8%	21%	53%	79%	92%	99%	100%	100%	100%	100%
Malignancy	892	21%	76%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Hypocalcaemia	13	3%	5%	10%	15%	21%	27%	35%	48%	60%	88%
Serious Infection	6,048	85%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Dermatologic Adverse Events	138	8%	20%	53%	78%	93%	98%	100%	100%	100%	100%
Pancreatitis	106	7%	17%	43%	70%	86%	94%	98%	100%	100%	100%
Serious Hypersensitivity	151	8%	21%	54%	81%	94%	99%	100%	100%	100%	100%

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Table G-5. Algorithm Defined AESIs Without Medical Review, United HealthCare[a]

Outcomes	Background Incidence Rate (per 100 000 Person-Years)	Relative Risk[a]									
		1.2	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		10 Years Post Launch									
ONJ	28	7%	14%	30%	51%	68%	81%	89%	97%	99%	100%
Subtrochanteric Fractures	256	16%	57%	99%	100%	100%	100%	100%	100%	100%	100%
Fracture Healing Complications	146	11%	37%	85%	98%	100%	100%	100%	100%	100%	100%
Malignancy	892	39%	98%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Hypocalcaemia	13	5%	8%	18%	29%	43%	53%	63%	79%	89%	100%
Serious Infection	6,048	99%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Dermatologic Adverse Events	138	11%	36%	83%	98%	100%	100%	100%	100%	100%	100%
Pancreatitis	106	10%	30%	73%	93%	99%	100%	100%	100%	100%	100%
Serious Hypersensitivity	151	12%	39%	85%	99%	100%	100%	100%	100%	100%	100%

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[a] Power calculated using the Fisher's 2-sided exact test with alpha=0.05 between Prolia and bisphosphonate (BP) exposed person-years.

Table G-6. Algorithm Defined AESIs Without Medical Review, Denmark[a]

Outcomes	Background Incidence Rate (per 100 000 Person-Years)	Relative Risk[a]									
		1.2	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		5 Years Post Launch									
ONJ	48	7%	17%	47%	73%	88%	96%	99%	100%	100%	100%
Subtrochanteric Fractures	178	12%	48%	92%	100%	100%	100%	100%	100%	100%	100%
Fracture Healing Complications	32	6%	15%	36%	58%	76%	87%	94%	99%	100%	100%
Malignancy	1,527	64%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Hypocalcaemia	8	4%	7%	13%	22%	31%	39%	49%	65%	75%	97%
Serious Infection	4,034	96%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Dermatologic Adverse Events	48	7%	19%	45%	73%	89%	96%	99%	100%	100%	100%
Pancreatitis	57	8%	20%	52%	77%	92%	98%	99%	100%	100%	100%
Serious Hypersensitivity	69	9%	22%	58%	85%	96%	99%	100%	100%	100%	100%

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Table G-6. Algorithm Defined AESIs Without Medical Review, Denmark[a]

Outcomes	Background Incidence Rate (per 100 000 Person-Years)	Relative Risk[a]									
		1.2	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		10 Years Post Launch									
ONJ	48	10%	32%	77%	97%	98%	100%	100%	100%	100%	100%
Subtrochanteric Fractures	178	23%	80%	99%	100%	100%	100%	100%	100%	100%	100%
Fracture Healing Complications	32	9%	23%	61%	87%	97%	98%	100%	100%	100%	100%
Malignancy	1527	93%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Hypocalcaemia	8	5%	11%	24%	41%	56%	71%	81%	92%	97%	100%
Serious Infection	4034	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Dermatologic Adverse Events	48	10%	33%	77%	96%	99%	100%	100%	100%	100%	100%
Pancreatitis	57	10%	36%	83%	98%	100%	100%	100%	100%	100%	100%
Serious Hypersensitivity	69	11%	41%	92%	99%	100%	100%	100%	100%	100%	100%

[a] Power calculated using the Fisher's 2-sided exact test with alpha=0.05 between Prolia and bisphosphonate (BP) exposed person-years.

Table G-7. Algorithm Defined AESIs Without Medical Review, Norway[a]

Outcomes	Background Incidence Rate (per 100 000 Person-Years)	Relative Risk[a]									
		1.2	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		5 Years Post Launch									
ONJ	35	5%	8%	15%	23%	33%	42%	51%	66%	78%	97%
Subtrochanteric Fractures	191	7%	18%	45%	70%	87%	95%	98%	100%	100%	100%
Fracture Healing Complications	85	6%	13%	28%	45%	60%	75%	83%	94%	98%	100%
Malignancy	1,854	24%	83%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Hypocalcaemia	11	3%	5%	9%	13%	16%	20%	25%	34%	42%	69%
Serious Infection	3,768	44%	99%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Dermatologic Adverse Events	34	5%	8%	16%	24%	33%	43%	51%	67%	77%	97%
Pancreatitis	45	3%	7%	13%	25%	36%	45%	56%	73%	85%	99%
Serious Hypersensitivity	80	6%	11%	26%	43%	58%	71%	82%	93%	98%	100%

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Table G-7. Algorithm Defined AESIs Without Medical Review, Norway[a]

Outcomes	Background Incidence Rate (per 100 000 Person-Years)	Relative Risk[a]									
		1.2	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		10 Years Post Launch									
ONJ	35	6%	12%	27%	45%	61%	74%	83%	94%	98%	100%
Subtrochanteric Fractures	191	9%	32%	76%	96%	100%	100%	100%	100%	100%	100%
Fracture Healing Complications	85	7%	18%	46%	73%	89%	96%	99%	100%	100%	100%
Malignancy	1,854	47%	99%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Hypocalcaemia	11	4%	6%	11%	19%	26%	33%	42%	57%	69%	93%
Serious Infection	3,768	78%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Dermatologic Adverse Events	34	6%	12%	27%	45%	60%	73%	82%	94%	98%	100%
Pancreatitis	45	7%	14%	33%	53%	71%	83%	90%	98%	99%	100%
Serious Hypersensitivity	80	7%	17%	45%	70%	88%	95%	98%	100%	100%	100%

[a] Power calculated using the Fisher's 2-sided exact test with alpha = 0.05 between Prolia and bisphosphonate (BP) exposed person-years.
Hypocalcemia is ascertained based upon a primary diagnosis with a more general ICD diagnosis code for disorders of calcium metabolism.

Table G-8. Algorithm Defined AESIs Without Medical Review, Sweden[a]

Outcomes	Background Incidence Rate (per 100 000 Person-Years)	Relative Risk[a]									
		1.2	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		5 Years Post Launch									
ONJ	19	4%	8%	18%	29%	42%	53%	64%	78%	89%	100%
Subtrochanteric Fractures	192	11%	35%	81%	98%	100%	100%	100%	100%	100%	100%
Fracture Healing Complications	179	10%	34%	78%	97%	100%	100%	100%	100%	100%	100%
Malignancy	1,722	52%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Hypocalcaemia	28	6%	10%	25%	39%	55%	67%	78%	90%	97%	100%
Serious Infection	5,030	91%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Dermatologic Adverse Events	119	9%	24%	62%	87%	97%	100%	100%	100%	100%	100%
Pancreatitis	87	8%	22%	53%	79%	92%	98%	99%	100%	100%	100%
Serious Hypersensitivity	140	10%	28%	70%	92%	99%	100%	100%	100%	100%	100%

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Table G-8. Algorithm Defined AESIs Without Medical Review, Sweden[a]

Outcomes	Background Incidence Rate (per 100 000 Person-Years)	Relative Risk[a]									
		1.2	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	10.0
		10 Years Post Launch									
ONJ	19	6%	15%	34%	54%	71%	85%	92%	98%	100%	100%
Subtrochanteric Fractures	192	18%	65%	99%	100%	100%	100%	100%	100%	100%	100%
Fracture Healing Complications	179	17%	63%	98%	100%	100%	100%	100%	100%	100%	100%
Malignancy	1,722	84%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Hypocalcaemia	28	6%	16%	42%	66%	84%	94%	97%	100%	100%	100%
Serious Infection	5,030	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Serious Dermatologic Adverse Events	119	13%	48%	92%	100%	100%	100%	100%	100%	100%	100%
Pancreatitis	87	11%	37%	84%	98%	100%	100%	100%	100%	100%	100%
Serious Hypersensitivity	140	15%	53%	96%	100%	100%	100%	100%	100%	100%	100%

[a] Power calculated using the Fisher's 2-sided exact test with alpha = 0.05 between Prolia and bisphosphonate (BP) exposed person-years.
Hypocalcemia is ascertained based upon a primary diagnosis with a more general ICD diagnosis code for disorders of calcium metabolism.

13.8 Appendix H. Substudy: Men and Women Who Receive Prolia With Glucocorticoid Exposure

INTRODUCTION

Prolia® (denosumab 60 mg every 6 months [Q6M]) was previously approved in the US and EU for bone loss conditions, including treatment of postmenopausal women with osteoporosis at high/increased risk of fracture, male osteoporosis, and bone loss in patients undergoing hormone ablation for cancer. A new indication for treatment of Glucocorticoid-induced Osteoporosis (GIOP) was approved in the US and EU in 2018, and therefore this population was added to the existing 20090522 Study.

OBJECTIVES

The objectives of the substudy are to describe in men and women who receive Prolia with glucocorticoid exposure:

- subject characteristics, clinical features, AESI risk factors, and subject follow-up
- incidence rates of AESI, including:
  - ONJ
  - non-traumatic subtrochanteric and disaphyseal femoral fracture
  - fracture healing complications
  - hypocalcemia leading to hospitalization or ER visit
  - infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication
  - dermatologic adverse events leading to hospitalization or ER visit
  - acute pancreatitis leading to hospitalization
  - hypersensitivity leading to hospitalization or ER visit
  - new primary malignancy (excluding non-melanoma skin cancer)
- denosumab utilization patterns

BACKGROUND AND RATIONALE

Denosumab Therapy for Osteoporosis

Denosumab (also referred to as AMG 162) is a fully human IgG_2 monoclonal antibody that binds to RANKL and blocks the interaction of RANKL with RANK. RANKL is a key mediator in the pathway required for the formation, function, and survival of the cells that resorb bone (osteoclasts). Denosumab binds with high affinity and specificity to RANKL, thereby neutralizing the ligand and inhibiting osteoclast-mediated bone turnover.

Glucocorticoid use and Glucocorticoid-induced Osteoporosis

Glucocorticoids are commonly used to treat a variety of chronic inflammatory conditions, such as giant cell arteritis, polymyalgia rheumatica, rheumatoid arthritis (RA), asthma, chronic obstructive pulmonary disease, and dermatologic conditions, due to their anti-inflammatory and immunosuppressive effects.

Glucocorticoid use disrupts the normal bone remodeling process and is associated with a rapid and transient increase in bone resorption, followed by a decrease in bone formation that occurs even with low doses, begins early, and persists throughout the duration of use (Ton et al, 2005; Canalis et al, 2004; Saag, 2003; Patschan et al, 2001). Rapid bone loss (3% to 27% of bone mineral density) occurs during the first 6 to 12 months of glucocorticoid treatment, followed by a slower decline (Saag, 2003; van Staa et al, 2002). More than 10% of patients who receive long-term glucocorticoid treatment are diagnosed with a clinical fracture, and 30 to 40% have radiographic evidence of vertebral fractures (Buckley et al, 2017).

Oral glucocorticoids were estimated to be used by 1.2% of the US population aged ≥ 20 years between 1999 and 2008, and 65% of the glucocorticoid users reported usage ≥ 90 days (Overman et al, 2013). In the population aged ≥ 18 in the UK, mean prevalence of oral glucocorticoid prescriptions was 0.85% for all types of glucocorticoid usage and 0.75% for long-term therapies (ie, ≥ 3 months) between 1989 and 2008 (Fardet et al, 2011). Glucocorticoid use increases with age (Kanis et al, 2004; van Staa et al, 2000).

Rationale

A new indication for Prolia, treatment of GIOP, was approved on 18 May 2018 in the US. Men and women who receive Prolia with glucocorticoid exposure are included in the ongoing study 20090522 to assess safety in the post-marketing environment.

The inclusion of men and women who receive Prolia with glucocorticoid-exposure in Study 20090522 leverages the existing study infrastructure, and the pharmacoepidemiologic and methodologic expertise of the current investigator teams. Importantly, adult denosumab users with glucocorticoid exposure will be ascertained from the large US Medicare Database and the Optum Research Database (previously called United Healthcare) used in Study 20090522, which will allow Amgen to proactively evaluate and quantify the incidence of specific AESI among men and women who receive Prolia with glucocorticoid exposure.

AESIs

The following AESIs, all currently included in Study 20090522, will also be studied in men and women who receive Prolia with glucocorticoid exposure: ONJ, non-traumatic subtrochanteric and disaphyseal femoral fracture, fracture healing complications, hypocalcemia leading to hospitalization or ER visit, infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication, dermatologic adverse events leading to hospitalization or ER visit, acute pancreatitis leading to hospitalization, hypersensitivity leading to hospitalization or ER visit, and new primary malignancy (excluding non-melanoma skin cancer). Confirmation of atypical femoral fracture will not be performed in this substudy, as radiographs are not available in the Medicare and Optum Research Database data systems.

HYPOTHESES

This substudy is descriptive in nature. As such, no pre-specified hypotheses will be tested. Rates and associated 95% confidence intervals for each AESI will be estimated for adults with glucocorticoid-associated osteoporosis treated with denosumab.

SUBSTUDY DESIGN

This is a prospective cohort study of men and women who receive Prolia with glucocorticoid exposure conducted using secondary data including US Medicare and data from the Optum Research Database. The enrollment period will begin upon the US approval of the indication for the "treatment of osteoporosis associated with newly initiating or sustained systemic glucocorticoid therapy in men and women at high risk for fracture" (18 May 2018) and continue through the end of Study 20090522, with annual reporting of descriptive findings. Crude and age-standardized AESI incidence rates will be provided. Adverse events of special interest will be identified using algorithms from the 20090522 study based on inpatient and outpatient diagnosis and procedure codes, and, for some AESIs, medication codes (ie, the same algorithms that are used for postmenopausal women and women with PMO). Osteonecrosis of the jaw will be confirmed by medical chart review in the US Medicare database.

DESCRIPTION OF DATA SOURCE

US Medicare

The US Medicare database is a comprehensive, nationally representative, population-based data system of US subjects ≥ 65 years of age. Key characteristics, including available data and average follow-up time, are described in Section 4.2.1. It takes Centers for Medicare & Medicaid Services approximately 2 years to format and

implement their quality control protocols resulting in a data lag before the data are available to researchers. In 2015, there were a total of 25,257,685 male and 30,238,537 female US residents enrolled in Medicare. Of these men and women, approximately 20,694,854 and 25,936,099 were ≥ 65 years of age as of 2015, representing 98% (of total 21,090,217** men ≥ 65 years of age) and 97% (of total 26,670,635** women ≥ 65 years of age) of the US general population of men and women in this age group in 2015**. A total of ~16,476,797 (35.35%) of these men and women had Parts A, B, and D coverage (not in a Medicare Advantage plan) for all months in the year in which they were ≥ 65 years.

**These are estimates for 2015 based on 2010 census.

Optum Research Database

Optum Research Database is an administrative database that provides eligibility data, medical claims, and pharmacy claims from a large, commercial health plan affiliated with Optum for 15 million patient lives per year. The Optum Research Database is described in Section 4.2.1. In 2015, approximately 5.33 million adult men and 5.51 million women were enrolled for at least 1 day in the database and approximately 5.88 million (56.18%) of them were continuously enrolled throughout the year.

SUBJECT SELECTION CRITERIA FOR SUBSTUDY

Subjects to be included in the substudy are those in Medicare and Optum Research Database with appropriate health plan coverage. Appropriate health plan coverage for the Optum Research database refers to both pharmacy and medical plan coverage. Appropriate plan coverage for the US Medicare database refers to enrollment in traditional fee-for-service Medicare (Medicare Parts A and B coverage and not in a Medicare Advantage plan), plus Part D. The population included in this substudy will be identified based on the following inclusion and exclusion criteria.

Inclusion Criteria

Men and women identified from Medicare or Optum Research Database who are ≥ 65 years old (or ≥ 30 years old in Optum) on or before receiving at least 1 denosumab 60 mg injection or fill after approval date of Prolia for treatment of glucocorticoid-induced osteoporosis (18 May 2018) will be included. This includes both new and prevalent users of denosumab. The index date is defined as the date of the first denosumab administration on or after the approval date fulfilling both the database specific age,

12-month enrollment criteria, and has received a 90-day average daily dose equivalent ≥ 7.5 mg of prednisone at any time during the previous 12 months.

Exclusion Criteria

Men and women with a diagnosis of malignancy (excluding non-melanoma skin cancer) or treatment with chemotherapy, hormonal therapy or radiation therapy for cancer up to 12 months before the index date will be excluded. Men and women with Paget's disease during the 12-month period prior to the index date will also be excluded. The exclusion of subjects with cancer or Paget's disease will ensure that subjects included in the substudy are receiving denosumab for the treatment of osteoporosis, and not for other indications.

Exposure Cohort

Exposure will be defined based on exposure to denosumab 60 mg and glucocorticoids. We will identify a cohort of men and women who receive Prolia with glucocorticoid exposure (rather than glucocorticoid-induced osteoporosis), as there is no universally accepted clinical case definition for glucocorticoid-induced osteoporosis, no specific ICD-10 codes, or algorithms to identify glucocorticoid-induced osteoporosis in the literature, and no information on indication of medication use in 20090522 databases.

A glucocorticoid exposure of an average daily dose ≥ 7.5mg of prednisone or equivalent was chosen because it is the dose included in the label of the new indication and is used as the cut point for the highest increase in fracture risk in glucocorticoid-treated individuals (Buckley et al, 2017). Average daily dose will be assessed on a 90-day basis because glucocorticoids are often prescribed PRN (as needed) leaving the actual daily dose unknown (ie, the dose used each day could vary). A 12-month period was chosen because glucocorticoid treatment is a potentially reversible risk factor for glucocorticoid-induced osteoporosis.

Sites will base their glucocorticoid definition on those listed under American Hospital Formulary Service Pharmacologic-Therapeutic Classification
(AHFS PTF 68:04 - Adrenals), to be identified from ICD-10-CM procedure, HCPCS, and NDC codes. Claims for oral, IV, and injected glucocorticoids will be included. Glucocorticoid dose will be analyzed and reported in terms of prednisone equivalents. Denosumab exposure will be identified using NDC codes and HCPCS codes (HCPCS C9272, J0897).

COVARIATES

Variables that will provide descriptive characteristics of men and women who receive Prolia with glucocorticoid exposure may include:

- sex
- age
  - age groups (eg, ≥ 65 and < 75, ≥ 75) for US Medicare
  - age groups (eg, 30-39, 40- 49, 50-54, 55-64, 65-69, 70-74, ≥ 75 for Optum Research
    - The fracture risk categories in glucocorticoid treated subjects in the American College of Rheumatology (ACR) guidelines are divided by ≥ or < 40 years of age
- geographic location (region)
- calendar year of meeting eligibility criteria for the substudy
- fragility fracture history
- history of treatment with osteoporosis medication (bisphosphonates, SERMS, calcitonin, teriparatide, denosumab, romosozumab, abaloparatide)
- history of medications that are risk factors for relevant AESI including treatment duration, cumulative dose
- CCI
- comorbidities (eg, infections, diabetes, and diseases or conditions that may be indicative of secondary osteoporosis [other than glucorticoid use] or increase risk of AESI, key underlying inflammatory conditions, chronic kidney disease)
- variables that may be indicators of health status or health seeking behavior, eg, health resource utilization (office visits, ER visits, hospitalizations)

The 12-month period prior to the index date (inclusive) will constitute the baseline period. Although the follow-up period for this study begins at the earliest on 18 May 2018, data prior to 18 May 2017 will be used to assess exposure to covariates during a 12-month baseline period. Data collected during the baseline period will be used to define eligibility for inclusion in study and values for baseline covariates described above.

SUBJECT FOLLOW-UP

Subject follow-up among eligible men and women will begin the day after the index date and continue to the first of the following: disenrollment from the data system, death, diagnosis of Paget's disease, diagnosis of malignancy (excluding non-melanoma skin cancer), treatment with chemotherapy, hormonal therapy or radiation therapy for cancer, end of the denosumab on-treatment (or on-treatment plus post-treatment) episode, switching to bisphosphonates or other osteoporosis medications or end of currently available data. The follow-up for incident events of all AESI will also end at the

occurrence of the corresponding AESI. The assessment of bisphosphonate and other osteoporosis medications follows the same method as in the study among women with PMO (Table A-1). Subjects retreated with Prolia can be brought back into the cohort if they have received a 90-day average daily dose equivalent ≥ 7.5mg of prednisone at any time during the previous 12 months. Therefore, a subject may have multiple retreatment index dates and multiple segments of patient-years for the retreatment period of denosumab.

ALGORITHMS TO ASCERTAIN ADVERSE EVENTS OF SPECIAL INTEREST

Algorithms to ascertain AESI have been developed in Study 20090522 (Table B-1, Table B-3, Table B-5, Table B-7, Table B-9, Table B-11, Table B-13, Table B-14, Table B-15, Table B-16, Table B-18, Table B-20, Table B-22, Table B-24,Table B-28) and will be used in the Men and Women Who Receive Prolia with Glucocorticoid Exposure substudy. Each AESI case ascertainment algorithm utilizes combinations of inpatient or outpatient ICD diagnosis codes (ICD-10-CM), CPT-4 or HCPCS procedure codes, and/or medication used. A comprehensive review of the literature was conducted regarding the development, validation, and application or use of ICD-9-CM ascertainment algorithms for AESI in studies including both men and women (Section 5). Chart studies for hypocalcemia and dermatologic adverse events were also conducted within the Optum database in support of the 522 Study (Wang et al, 2018). Amgen conducted additional medical record review studies based on the US Medicare database to validate selected AESI ICD-9-CM ascertainment algorithms. The study results were communicated to regulatory agencies [PBRER/PSUR #09 (Prolia) (27 September 2014 to 26 September 2015)]. ICD-10-CM algorithms were converted from these ICD-9 algorithms. The PPV for the ICD-10-CM based algorithms for ONJ in the Medicare and Optum databases are being evaluated (response submitted on 31 Jan 2018 as Seq No 1150 to IND 9837).

Consistent with Study 20090522, all potential cases of ONJ in men and women who receive Prolia with glucocorticoid exposure will undergo medical chart review in US Medicare, when available. Potential cases of atypical femoral fracture in men with osteoporosis treated with denosumab will not be confirmed through medical chart review.

POTENTIAL SOURCES OF BIAS IN STUDY DESIGN

There are several study design issues to be considered to appropriately interpret the study results.

DISEASE SEVERITY

Men and women who receive Prolia with glucocorticoid exposure, especially shortly after the approval of the indication, are likely to have more severe conditions and longer durations of the disease.

BIAS ASSOCIATED WITH SUBJECTS SWITCHING FROM ANOTHER OSTEOPOROSIS MEDICATION

Men and women who receive Prolia with glucocorticoid exposure may have received bisphosphonates or other osteoporosis medications. These subjects may be unable to comply with or are intolerant of other osteoporosis medications or have not achieved an adequate treatment response. In addition, subjects who have received anti-resorptive therapy for long periods of time may be selectively referred to denosumab treatment due to concerns about potential risk of events associated with long-term drug exposure. Such subjects are also likely to be at increased risk for one or more AESI.

SELECTION BIAS DUE TO MISSING VALUES

Since this substudy is based on US Medicare and the Optum Research Database, missing data are possible and may introduce bias if subjects with missing values are excluded from the analyses. The handling of missing data will follow the same strategy as for the analysis among women with PMO (Section 6.3).

SAFETY DATA COLLECTION, RECORDING, AND REPORTING

Safety data collection, recording and reporting for men and women who receive Prolia with glucocorticoid exposure will follow the same plan as for women with PMO (Section 7).

SAMPLE SIZE AND PRECISION OF ESTIMATION

Estimates of the size of the glucocorticoid associated osteoporosis cohort (the number of patient-years of denosumab exposure in subjects with a history of glucocorticoid use) and the half-widths for the 9 AESIs are presented in Table H-1.

Table H-1. Half-width of the 95% Confidence Interval of the Estimate of Incidence Rates for AESI[a, b], US Medicare and Optum Research Database

Source	Background Incidence Rate (per 100,000 Person-years)	Estimated Person years	Half Width of the 95% Confidence Interval (per 100,000 Person-years)
US Medicare			
Dermatologic Events	238	4040	±150
Infection	9803	4040	±965
Hypocalcemia	62	4040	±77
Acute Pancreatitis	127	4040	±110
Hypersensitivity	254	4040	±155
Fracture Healing Complications	236	3909	±152
AFF (non-traumatic subtronchanteric and diaphyseal fracture)	105	3909	±102
ONJ	80	3909	±89
New Primary Malignancy	1756	2319	±539
Optum Research Database			
Dermatologic Events	115	110	±635
Infection	7448	110	±5102
Hypocalcemia	37	110	±362
Acute Pancreatitis	53	110	±430
Hypersensitivity	69	110	±491
Fracture Healing Complications	318	127	±983
AFF	223	127	±823
ONJ	100	127	±552
New Primary Malignancy	465	101	±1330

[a] Half-width of the 95% confidence intervals was calculated for AESI incidence rates using the normal approximation to the Poisson distribution.

[b] The exposure to denosumab was estimated based on the simple linear regression from each of the data systems using the existing data in the previous 20090522 reports (up to Year 6 annual report)

The background incident rates are based on ICD algorithms and, for ONJ and AFF, without medical chart review from Year 6 annual report.

The time at risk for dermatological events, infection, hypocalcemia, acute pancreatitis, and hypersensitivity is based on on-treatment period only, on-treatment period plus 1 year post-treatment for fracture healing, ONJ and AFF (non-traumatic subtrochanteric and diaphyseal fracture) and on-treatment period plus 5-years post-treatment for new primary malignancy.

The estimates of denosumab patient-years includes the time from May 2018 (Prolia US approval date for glucocorticoid-induced osteoporosis indication) to the end of data collection for the 20090522 study. The number of person-years among the women and men exposed to denosumab were estimated based on the data provided in the existing annual reports using projections by simple linear regression from each of the two data systems separately.

An internal analysis of bisphosphonate users in Marketscan database was used to estimate the percent of subjects with glucocorticoid use who were defined as those receive systemic glucocorticoid continuously for at least 90 days within 1 year prior to the bisphosphonate administration date. The projected Prolia-treated person-years were further multiplied by those percentages to obtain the estimated person-years in the subjects who have a history of glucocorticoid use (Table H-1).

Background incidence-rates (Table H-1) are obtained from US Medicare and Optum Research Database Year 6 annual report [CSR YR 6 ref] and are algorithm based from the women with PMO population. Among the 9 AESIs, the time at risk for dermatological adverse events, serious infection, hypocalcemia, acute pancreatitis, and hypersensitivity is based on on-treatment period only, on-treatment period plus 1 year post-treatment for fracture healing, ONJ and atypical femoral fracture (AFF) (non-traumatic subtrochanteric and diaphyseal fracture) and on-treatment period plus 5-years post-treatment for new primary malignancy. The half-widths were calculated using the normal approximation to Poisson distribution, same approach as in the Appendix F Substudy of Men with Osteoporosis Treated With Denosumab.

STATISTICAL METHODS OF ANALYSIS

Descriptive analyses of the data for men and women who receive Prolia with glucocorticoid exposure in the US Medicare and Optum Research data systems will be provided, including description of subject characteristics, clinical features, risk factors of AESI, and subject follow-up. In addition, crude and age-standardized AESI incidence rates and denosumab utilization patterns will be described for this population.

Analytic approaches relevant to each study objective are provided below.

Objective 1: Describe subject characteristics, clinical features, AESI risk factors, and subject follow-up in men and women who receive Prolia with glucocorticoid exposure.

Subject characteristics, clinical features, and AESI risk factors assessed during baseline will be described. Summary of enrollment and subject follow-up will also be described.

Objective 2: Determine Rates of AESI in men and women who receive Prolia with glucocorticoid exposure.

The crude estimates of incidence rates (and 95% confidence interval) and estimates standardized to the Year 2010 US census age distribution will be calculated in men and women who receive Prolia with glucocorticoid exposure. Stratified analyses will be conducted as appropriate using key confounders/covariates. Estimation of incidence rates of the algorithm-identified potential ONJ and confirmed ONJ (in the US Medicare database only) based on expert review results will be provided.

Depending on the nature of the AESI, time at risk may include on-treatment periods only, or both on-treatment and post-treatment periods. For dermatological adverse events, serious infection, hypocalcemia, acute pancreatitis, and hypersensitivity, analysis will be based on on-treatment period only, on-treatment period plus 1 year post-treatment for fracture healing, ONJ and non-traumatic subtrochanteric and diaphyseal femoral fracture, analysis will be performed based on on-treatment period plus 5 years post-treatment for new primary malignancy. The length of post-treatment period included in AESI-specific analyses is defined according to the potential latency period for that AESI. Each subtype of event was treated as an independent outcome and was not censored by occurrence of the parent category AESI.

Cumulative incidence will be graphically displayed using Kaplan-Meier curves and/or cumulative incidence function plots (when at least one event was recorded during the study period). Simultaneous confidence intervals (95% confidence bands) will be provided to represent the uncertainty in the estimate of the curve.

Objective 3: Describe denosumab utilization patterns among men and women who receive Prolia with glucocorticoid exposure.

Descriptive statistics will be used to characterize denosumab utilization patterns in men and women who receive Prolia with glucocorticoid exposure. Factors to be assessed

include frequency of administration, cumulative dosage, and timing of subsequent administrations as well as treatment with other osteoporosis medications will be described.

COMMUNICATION OF STUDY RESULTS TO REGULATORY

AGENCIES

Substudy results will be submitted to regulatory agencies as available following the same plan as results from Study 20090522 (Section 10)

ETHICAL OBLIGATIONS

This substudy is based upon routinely collected data from US Medicare and the Optum Research Database systems. Analyses using these data sources will be conducted by investigators who have access to the data through their respective institutions, with analysis findings shared with Amgen in accordance with the data use agreement between Amgen and the investigators (institutions). Study results will be presented only in an aggregate form, and individuals will not be identified.

13.9 Appendix I. Minimal Detectable Relative Risk for the Comparative Safety Analysis in the 20090522 Study

Minimal Detectable Relative Risk (MDRR) for the Comparative Safety Analysis of the 9 AESIs in the 20090522 Study

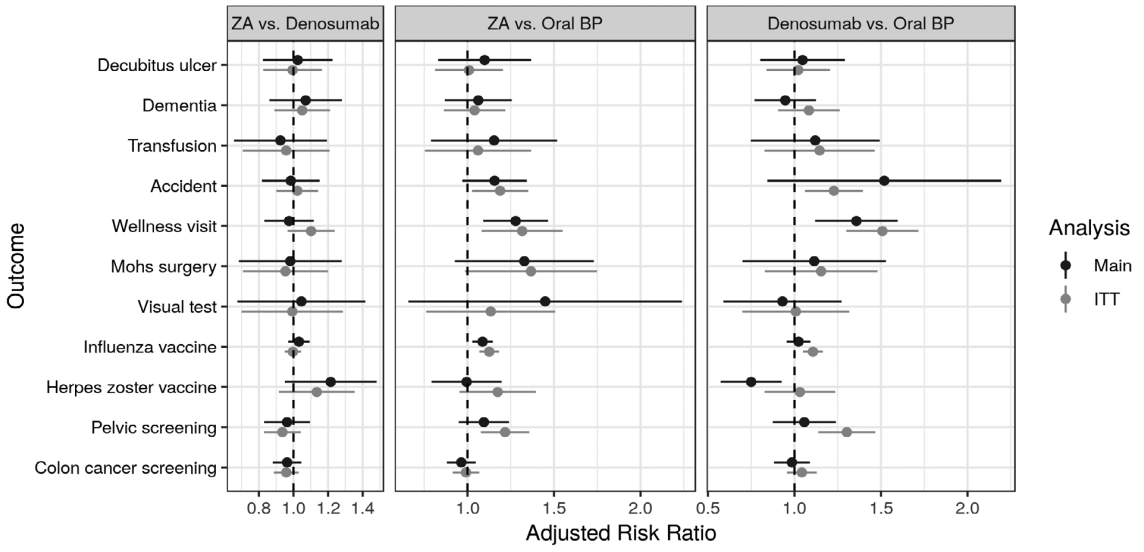
1. Background

Study 20090522, entitled “Denosumab Global Safety Assessment Among Women with Postmenopausal Osteoporosis (PMO), Men With Osteoporosis, and Men and Women Who Receive Prolia With Glucocorticoid Exposure in Multiple Observational Databases”, is descriptive in nature and reports subject characteristics, utilization patterns and incidence rates for 9 AESIs. For describing incidence rates, exposure to medication for PMO is considered as time-varying, that is, a subject’s exposure status may change over time as the subject discontinues one treatment and starts another. The third objective is to compare the incidence of the AESI in women with PMO exposed to denosumab to that in women with PMO exposed to bisphosphonates. As the potential selection bias resulting from confounding by indication may be appreciable and, in some instances, not measurable, comparative analyses will be inherently challenging to interpret. For these reasons comparative analyses are considered exploratory and different design methods have been explored for use in the 20090522 study.

Per FDA guidance (Center For Drug Evaluation And Research And Center For Biologics Evaluation And Research, May 2013), to draw valid conclusions, a comparative analysis requires a fit-for-purpose data source and strong study design considerations, including comparator selections, and identification and handling of confounders, and adequate sample size and statistical power. Comparison groups should ideally include subjects with the same distributions of both measured and unmeasured risk factors of the study outcome. One method for controlling for confounding is through study design. An active comparator - naive user design helps control for confounding, does not deplete susceptible subjects, captures early events following initiation, aligns eligibility, exposure and start of follow-up, ensures the correct temporal assessment between exposure and covariates, avoids the problem of adjusting for characteristics that may be in the causal pathway and may aid in the evaluation of cumulative effects of drug exposure on AESI. (Franklin et al, 2020; Lund et al, 2015; Johnson et al, 2013)

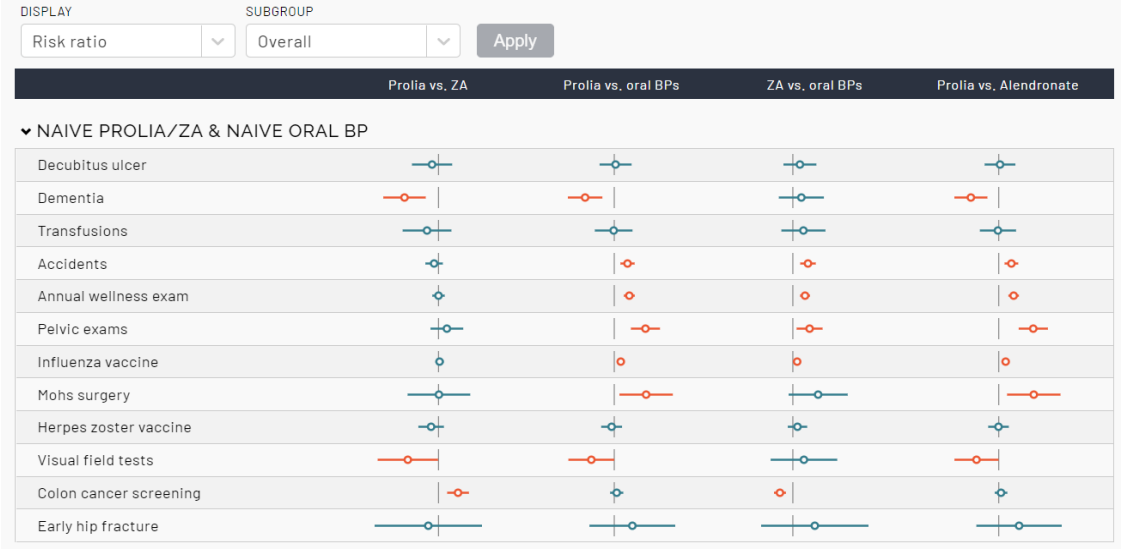
Our previous work [(Mcgrath et al, 2020), Studies 20190427 and 20190031] using negative control outcomes to assess the comparability of osteoporosis treatment groups suggested that our best comparator for Prolia in the naive user design would be IV bisphosphonate (Figure I-1, I-2, I-3). A previous correspondence with FDA also mentioned a switcher and prevalent user designs. [Prolia IR 3.23.20]

Figure I-1. Treatment Naive Design in MarketScan data, 12-month Cumulative Risk Ratios of Negative Control Outcomes For Exposure Contrasts Including Injectable Osteoporosis Treatments. (Mcgrath et al, 2020)



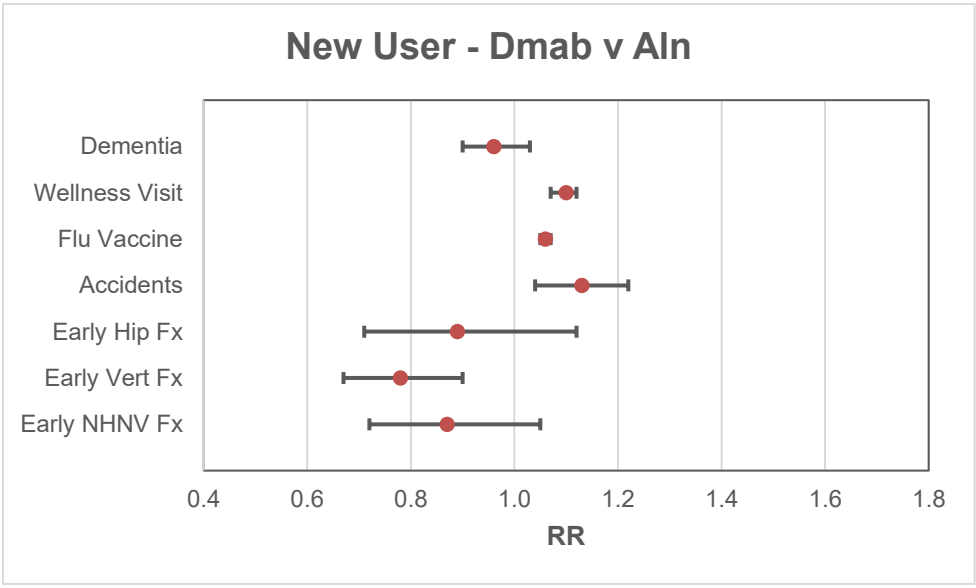
ZA zoledronic acid, BP bisphosphonate

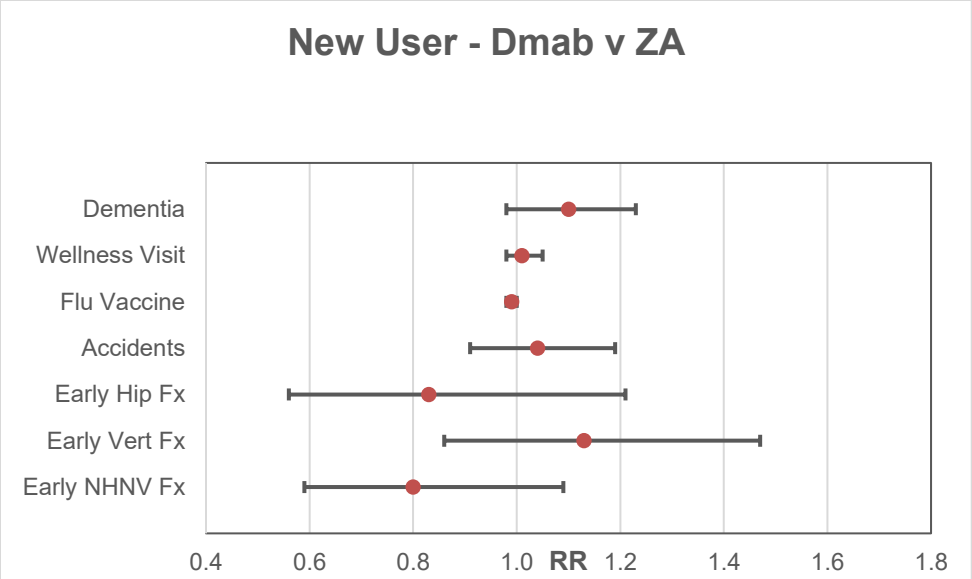
Figure I-2. Treatment Naive in Optum Research Database, 12-month Cumulative Risk Ratios of Negative Control Outcomes For Exposure Contrasts Including Injectable Osteoporosis Treatments (Study 20190427)



ZA zoledronic acid, BP bisphosphonate

Figure I-3. Treatment Naive in Medicare, Relative Risk of Negative Control Outcomes For Exposure Contrasts Including Prolia Treatments (Study 20190031)





ALN Alendronate, FX fracture, Vert vertebral, NHNV non-hip non-vertebral

The current analysis informs adequate sample size and statistical power for naive users (Prolia vs IV bisphosphonate), switcher (Prolia vs oral bisphosphonate; Prolia vs IV bisphosphonate) and prevalent designs (Prolia vs oral bisphosphonate; Prolia vs IV bisphosphonate). To inform our confidence in obtaining valid estimates in the 20090522 comparative safety analysis, the smallest relative risk between treatments that can be statistically detected with the probability of at least 80% that the null hypothesis is rejected, if a specific alternative hypothesis is true, was calculated for the projected sample size of the 20090522 study in the final year.

2. Methods

The methods for calculating the minimal detectable relative risk (MDRR) (considering statistical power (80%) and available sample size) for the 20090522 comparative safety analyses were provided to the sites (Amgen estimated the power for the Optum site). The expected number of subjects at the end of the study for each study design was estimated based on exposure data from the annual reports and using projections by simple linear regression for each of the data systems. Background incidence rates by exposure cohort for each AESI were taken based on the most recent annual report data (Year 9) in each data system at the time of the MDRR analysis.

It is anticipated that methods for final comparative analysis will employ inverse probability of treatment and censoring weighting (IPTCW). Methods to calculate statistical power for inverse probability (IP) weighted estimators have not yet been developed. Statistical power for such estimators is a function of the sample size,

number of outcomes, and the variability in the IP weights. Here, a standard normal approximation is extended for the statistical power for the difference in two binomials (Fundamentals of Biostatistics, Rosner [1997], page 418) to account for variance inflation due to IP weights. The variance of the IP weights from previous studies assessing comparability of osteoporosis treatment groups was used to compute a variance inflation for these calculations.

Using this extended standard normal approximation accounting for variance inflation of the IP weights, the expected number of subjects at the end of the study, and background incidence rates for each AESI, the MDRR for each AESI was derived for each study design by data system.

3. Results

The projected number of subjects in the final 20090522 report for each study design is presented in Table I-1. The naive user cohort is the largest group in the Scandinavian counties; the other study designs contained limited numbers of Prolia users. Prevalent users are the largest cohort in the US sites, but the naive user design contained the largest number of Prolia users.

Table I-1. Projected Number of Subjects For Each PMO Exposure Groups by Cohort For Last Study Report Delivered in 2022

Cohort	Exposure Group	Number of subjects				
		Medicare	Optum	Denmark	Norway	Sweden
Naive user		882,247	35,877	93,454	62,388	133,415
	Prolia	107,702	6,481	4,440	2,999	4,598
	BP Oral	705,282	26,103	88,825	56,161	126,211
	BP IV	69,263	3,293	189	3,228	2,606
Switcher		35,181	12,565	505	324	695
	Prolia	5,665	3,653	96	21	46
	BP Oral	20,266	6,548	373	111	473
	BP IV	9,250	2,364	36	192	176
Prevalent		1,350,171	201,089	44,661	42,256	65,707
	Prolia	36,986	1,477	259	63	88
	BP Oral	1,233,836	194,659	43,997	41,427	64,629
	BP IV	79,349	4,953	405	766	990

BP bisphosphonate

For the purpose of the MDRR analysis, we set the effect size (smallest deviation from the null that we would be able to detect) at a RR of 1.5. We consider differences in AESIs with a relative risk of less than 1.5 to not be clinically meaningful. This threshold was based on the non-inferiority margin used in a US Medicare study that assessed the hazard of infection between zoledronic acid and Prolia biologic-treated rheumatoid arthritis subjects. (Curtis et al, 2015) In the Medicare data, using the naive user design, this threshold was met for all algorithm defined AESIs except AFF (defined using the specific ICD 10 Code M84.75-A) & hypocalcemia (Table I-2a). A similar pattern is noted with the prevalent user design (Table I-2c). The Medicare data is less fit using the switcher design, but the results are better than those reported for the remaining data systems (Table I-2b). In the remaining smaller databases, a minimal detectable relative risk of 1.5 or less (shaded cells) was sporadically obtained for the infection and malignancy adverse events across study designs.

Table I-2a. Naive User Design: Minimum Detectable Relative Risk Between Prolia and IV Bisphosphonate With 80% Power at Study End for Algorithm Defined Events

	Medicare	Optum	Denmark	Norway	Sweden
Osteonecrosis of the jaw (algorithm defined)	1.48	10.8	-	7.5	-
AFF defined using the specific ICD 10 Code M84.75-A	-	-	NA	NA	NA
Fracture healing complications	1.3	3.2	-	3.1	2.5
Fracture healing complications restricted to previous hip fracture	1.14	-	-	-	2.0
Hypocalcemia	1.98	-	-	-	4.9
Infections	1.04	1.2	1.8	1.4	1.3
Dermatologic adverse events	1.28	3.0	-	7.5	3.7
Acute pancreatitis	1.36	4.2	5.1	7.5	4.9
Hypersensitivity	1.24	3.0	-	5.7	3.7
New primary malignancy	1.08	1.9	2.3	1.6	1.4

- RR is not defined due to incidence proportion of 0.

Table I-2b. Switcher Design: Minimum Detectable Relative Risk Between Prolia and Oral Bisphosphonate With 80% Power at Study End for Algorithm Defined Events

	Medicare	Optum	Denmark	Norway	Sweden
Osteonecrosis of the jaw	5.56	9.2	-	-	-
AFF defined using the specific ICD 10 Code M84.75-A	NaN	15.8	NA	NA	NA
Fracture healing complications	2.76	3.9	-	-	20.3
Fracture healing complications restricted to previous hip fracture	1.64	-			16.3
Hypocalcemia	7.14	15.8	-	-	-
Serious Infections	1.18	1.3	2.5	4.2	3.2
Dermatologic adverse events	2.16	3.9	-	-	20.4
Acute pancreatitis	2.8	5.0	-	-	-
Hypersensitivity	2.2	4.1	-	-	20.4
New primary malignancy	1.5	2.0	5.0	6.1	4.0

- RR is not defined due to incidence proportion of 0.

Table I-2c. Prevalent User Design: Minimum Detectable Relative Risk Between Prolia and Oral Bisphosphonate or IV Bisphosphonate With 80% Power at Study end for Algorithm Defined Events

		Medicare	Optum	Denmark	Norway	Sweden
Osteonecrosis of the jaw (algorithm defined)	**Prolia vs. Oral BP**	2.06	7.9	10.6	33.7	39.1
	Prolia vs. IV BP	1.62	20.4	-	-	-
AFF defined using the specific ICD 10 Code M84.75-A	**Prolia vs. Oral BP**	72.34	19.51	NA	NA	NA
	Prolia vs. IV BP	-	-	NA	NA	NA
Fracture healing complications	**Prolia vs. Oral BP**	1.66	4.3	27.6	31.5	13.3
	Prolia vs. IV BP	1.38	4.0	-	21.8	12.8
Fracture healing complications restricted to previous hip fracture	**Prolia vs. Oral BP**	1.22	-	-	-	9.7
	Prolia vs. IV BP	1.16	-	-	-	8.5
Hypocalcemia	**Prolia vs. Oral BP**	5.52		100.4	71.7	40.7
	Prolia vs. IV BP	5.08	-	-	-	38.6
Infections	**Prolia vs. Oral BP**	1.08	1.4	1.7	2.4	2.2
	Prolia vs. IV BP	1.06	1.3	1.9	2.5	2.2
Dermatologic adverse events	**Prolia vs. Oral BP**	1.52	4.1	12.7	35.6	21.7
	Prolia vs. IV BP	1.4	3.7	-	-	-
Acute pancreatitis	**Prolia vs. Oral BP**	1.74	5.2	10.2	26.9	19.7
	Prolia vs. IV BP	1.5	5.2	-	38.9	15.8
Hypersensitivity	**Prolia vs. Oral BP**	1.52	4.4	10.5	22.5	15.6
	Prolia vs. IV BP	1.36	3.7	16.0	38.9	15.8
New primary malignancy	**Prolia vs. Oral BP**	1.18	2.2	2.2	3.2	2.7
	Prolia vs. IV BP	1.12	2.2	2.8	3.5	2.7

- RR is not defined due to incidence proportion of 0. BP bisphosphonate

4. Discussion

The MDRR analysis indicates the Medicare data, based on sample size and power, is most fit-for purpose data set to conduct the 20090522 comparative safety analysis between Prolia and IV bisphosphonate users in the naive user design for fracture healing complications, hypocalcemia, infections, dermatologic adverse events, acute pancreatitis, hypersensitivity, and new primary malignancy. The Medicare sample size in the switcher design is less sufficient but is better than the remaining data systems. Only using the US Medicare data should be acceptable because it represents great than > 80% of women with PMO and > 91% of women receiving Prolia in the 20090522 study. US Medicare provides national coverage and long-term follow-up for most US citizens and permanent residents after they reach 65 years of age. We also expect our findings to extrapolate to the EU because Prolia is considered a compound "Insensitive to Ethnic Factors" based on the E5 (R1) (Ethnic Factors in the Acceptability of Foreign Clinical Data) criteria. A compound whose characteristics suggest minimal potential for clinically significant impact by ethnic factors such as genetic polymorphism, age, gender, organ dysfunction etc. on safety, efficacy, or dose response. The limitation to this approach is lack of evidence of reproducibility from within the study.

There is less power in the switcher design and the switcher design is considered to be an inferior design because it could potentially introduce confounding by past bisphosphonate use a potential confounder for some of our AESIs. (Lo 2019; Ou et al, 2017; Zura et al, 2016; Molvik and Khan, 2015, Lo 2010) The prevalent user designs is not favored because those who stop taking the drug can be sick stoppers or results in depletion of susceptible subjects and those who adhere can be healthy users, have tolerated the medication well or have benefited from treatment, both of which can result in under ascertainment of harms. Duration of use among prevalent users can also differ by drug exposure that may cause bias if it remains unadjusted and measured subject characteristics can be the cause or consequence of drug use. (Schneeweiss et al, 2007; Ray, 2003)

Although in the naive user design, the power for the comparative safety analysis is adequate for algorithm identified osteonecrosis of the jaw and subtrochanteric and diaphyseal fractures of the femur (the location of atypical femur fracture) using Medicare data, as noted in the RTQ-on-Study-522_23July2020, because of low PPV (6% to 28% in US data systems) and low number of events of ONJ (12-43 algorithm identified potential cases in prevalent Prolia users in Scandinavian data systems in the 2020

interim report), we recommend not pursing a comparative safety analysis for ONJ, above what has been accomplished through 1:1 propensity score matching and adjudication the precision of the risk estimate would be low. Also, misclassification of study outcome is expected to be substantial, as the magnitude of misclassification bias is affected most by false positives and bias expands with more rare outcomes. (Newcomer et al, 2019) For similar reasons, a comparative safety analysis of atypical femur fracture will also not be conducted.

5. Conclusion

The third objective in the 20090522 study is to compare the incidence of the AESI in women with PMO exposed to Prolia to that in women with PMO exposed to bisphosphonates. This analysis provides further evidence supporting the recommendation made in Amgen's RTQ-on-Study-522_23July2020 correspondence to conduct this comparative safety analyses for adverse events of special interests (fracture healing complications, hypocalcemia, infections, dermatologic adverse events, acute pancreatitis, hypersensitivity, and new primary malignancy) using Medicare data and a naive user-IV bisphosphonate comparator design.

6. References

Curtis JR, Xie F, Yun H, Saag KG, Chen L, Delzell E. Risk of hospitalized infection among biologic-treated rheumatoid arthritis patients concurrently treated with denosumab. Arthritis & Rheumatology. 2015.

Franklin JM, Patorno E, Desai RJ, et al. Emulating Randomized Clinical Trials with Nonrandomized Real-World Evidence Studies: First Results from the RCT DUPLICATE Initiative. Circulation. 2020.

Johnson ES, Bartman BA, Briesacher BA, et al. The incident user design in comparative effectiveness research. Pharmacoepidemiology and drug safety. 2013;22:1-6.

Lo JC, O'Ryan FS, Gordon NP, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons 2010;68:243-253.

Lo JC, Grimsrud CD, Ott SM, et al. Atypical femur fracture incidence in women increases with duration of bisphosphonate exposure. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2019;30:2515-2520.

Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep. 2015;2:221-228.

Mcgrath LJ, Spangler L, Curtis JR, et al. Using negative control outcomes to assess the comparability of treatment groups among women with osteoporosis in the United States. Pharmacoepidemiology and drug safety. 2020;29:854-863.

Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. American journal of epidemiology. 2003;158:915-920.

Schneeweiss S, Patrick AR, Sturmer T, et al. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. Medical care. 2007;45:S131-142.

Zura R, Xiong Z, Einhorn T, et al. Epidemiology of Fracture Nonunion in 18 Human Bones. JAMA Surg 2016;151:e162775.

13.10 Appendix J. Comparative Safety Analysis MOP

PROLIA® (DENOSUMAB)

20090522 Comparative Safety Analysis

Manual of Operations

Study 20090522: Denosumab Global Safety Assessment Among Women with Postmenopausal Osteoporosis (PMO), Men with Osteoporosis, and Men and Women Who Receive Prolia With Glucocorticoid Exposure in Multiple Observational Databases

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13.10.1 Table of Contents

13.10.2 Revisions and Updates

Version	Date	Section: Update: Reason
1.0	*2021.07.23*	*Original*
2.0	*2022.03.22*	*Amendment 1 Includes analyses requested by FDA 01 Dec 21 Ltr*
3.0	*2022.05.10*	*Amendment 2 Revised the entry criteria of the cohort for the fracture healing complication comparative safety analysis*
4.0	*2022.09.19*	*Amendment 3 Updated in response to FDA's 12 July 2022 Advice Information Request letter*
5.0	***2023.04.28***	***Amendment 4 Updated in response to FDA's 20 Mar 2023 Advice Information Request letter***

13.10.3 Rationale and Background

13.10.3.1 Diseases and Therapeutic Area

Osteoporosis is a silent skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture (Camacho et al, 2020). Management of osteoporosis includes non-pharmacological treatment (eg, diet, exercise plan, calcium and vitamin D supplementation) and pharmacological therapy. Osteoporosis medications are standardized; dosage amounts are standard and do not increase over time, nor are medications indicated for combined use (Riek and Towler 2011). The disease is often undertreated and adherence to medication is low.

Denosumab is a fully human IgG2 monoclonal antibody that binds to RANK ligand (RANKL), and blocks the interaction of RANKL with RANK. RANKL is a member of the tumor necrosis factor (TNF) superfamily and is a key mediator in the pathway required for the formation, function, and survival of the cells that resorb bone (osteoclasts). Denosumab binds with high affinity and specificity to RANKL, thereby neutralizing the ligand and suppressing osteoclast-mediated bone turnover. Denosumab was first approved on 26 May 2010 [the international birth date] for the treatment of women with postmenopausal osteoporosis (PMO) at increased risk of fractures. After its initial marketing approval, denosumab was subsequently approved in the United States for treatment of bone loss in men receiving androgen deprivation therapy for prostate cancer and for treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer at high risk for fracture (16 September 2011), use in men with

osteoporosis (20 September 2012) and for treatment of glucocorticoid-induced osteoporosis (GIOP) in patients at high risk of fracture (18 May 2018).

Bisphosphonates (BP) slow bone resorption by attaching to the bone surface and inhibiting osteoclast function (Lewiecki, 2010). This class of drugs is characterized by a long skeletal half-life. Oral bisphosphonates include alendronate, risedronate, and ibandronate, and have been used to treat osteoporosis for more than 20 years and have historically been used as first-line therapy. Alendronate, the most commonly used oral bisphosphonate, is indicated for both treatment and prevention of osteoporosis in postmenopausal women as well as treatment to increase bone mass in men with osteoporosis, treatment of glucocorticoid-induced osteoporosis, and treatment of Paget's disease. Zoledronic acid (ZA) was approved in 2007. It has a more similar route and frequency of administration to Prolia than oral BPs which minimizes the risk of informative or differential censoring in a comparative analysis. It is given as a 5 mg single dose intravenously every 12 months and has the same indications as oral bisphosphonates.
(https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020560 accessed 28 January 2021)

Other osteoporosis drugs include bone-builders such as parathyroid hormone and parathyroid hormone-related protein analogs (teriparatide (infrequently used) and abaloparatide (approved 2017)) and a sclerostin inhibitor (romosozumab) (approved 2019).

13.10.3.2 Rationale

During the Prolia BLA APPROVAL (June 1, 2010), FDA determined that analysis of spontaneous postmarketing adverse events would not be sufficient to assess a signal of select events and required Amgen to conduct a long-term observational study in administrative databases to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in postmenopausal women administered Prolia. Study 20090522, entitled "Denosumab Global Safety Assessment Among Women with Postmenopausal Osteoporosis (PMO), Men with Osteoporosis, and Men and Women Who Receive Prolia With Glucocorticoid Exposure in Multiple Observational Databases" was implemented in response. This study is mostly descriptive in nature, describing risk factors, utilization and incidence rates and associated 95% confidence intervals for 9 AESI annually. The third objective of this study is to compare the incidence of the AESI in women with PMO

exposed to denosumab (Prolia®, referred to as denosumab going forward) to that in women with PMO exposed to bisphosphonates. As the potential selection bias resulting from confounding by indication may be appreciable and, in some instances, not measurable, comparative analyses was described as exploratory. This document provides guidance to sites on performing the comparative analysis.

13.10.3.3 Feasibility and Futility Considerations

The 20090522 study is a retrospective cohort study from 5 secondary data sources; 2 US, US Medicare including Parts A, B, and D and Optum (formerly United HealthCare) and 3 Scandinavian national health registry databases, including data from Denmark, Sweden, and Norway that assesses 9 Adverse Events of Special Interest (AESI). The comparative study will only be conducted in the US Medicare data system and it was originally recommended not to include osteonecrosis of the jaw (ONJ) or atypical femur fractures (AFF) AESIs.

Per FDA guidance (Center For Drug Evaluation And Research And Center For Biologics Evaluation And Research, May 2013), to draw valid conclusions, a comparative analysis requires a fit-for-purpose data source and strong study design considerations, including comparator selections, and identification and handling of confounders, and adequate sample size and statistical power. To provide the most robust analysis possible, Amgen has been evaluating different designs and associated power, comparator selections and handling of confounders. A naïve user i.e. naïve user of any type of osteoporosis medications, active comparator design was chosen for the primary comparative analysis for reasons outlined in Section 13.10.13.10.5.1. Due to power considerations, we will also restrict the comparative analysis to the US Medicare data (Section 13.10. 13.10.5.5 below).

Due to the rarity of events (which would be further reduced in a naïve user design) and low positive predictive values (PPV - probability that subjects identified using the algorithm truly have the event) of ICD based algorithms, it was recommended that 2 of these events, osteonecrosis of the jaw and atypical femur fracture, not be included in the comparative analysis (Table 1). These 2 events are routinely adjudicated in all denosumab users and a 1:1 matched sample of bisphosphonate users in Central Denmark. X-rays are required for atypical femur fracture adjudication and are only available for the Central Denmark region. In the 2010 to 2017 data < 5 cases of atypical femur fracture have been confirmed in denosumab users. Osteonecrosis of the jaw is also adjudicated in all denosumab users and a 1:1 matched sample of bisphosphonate

users in US Medicare and Sweden data systems, however balance of measured baseline covariate between the denosumab and bisphosphonate matched groups has only been achieved in the Medicare system.

Table 1. Feasibility of Comparative Analysis for not including AFF and ONJ: PPV and Number of Events for AESIs in Denosumab-only Users by Data System in Current YR 10 Study Design (includes naïve users, prevalent users, and switchers)

	Medicare (Largest)	Optum	Denmark	Sweden	Norway
ONJ – algorithm PPV %	26[a]	6	78 [a,b]	81[a]	NA
ONJ – algorithm (N potential cases)[c]	1398	20	50	16	19
ONJ[a] – confirmed cases (N)	23	NA	10[b]	6	NA
ONJ[a] – confirmed – distribution of measured covariates	Balanced	NA	Not balanced	Not balanced	NA
AFF – algorithm PPV (%) (x-rays central Denmark only)			12%[a,b]		
AFF[a] – confirmed (N)	NA	NA	< 5 [a,b]	NA	NA
AFF[a] – confirmed - distribution of measured covariates			Not balanced		
AFF – algorithm specific ICD10 (N potential cases)	10	0	NA	NA	NA

"AESI-adverse events of special interest; AFF = atypical femoral fracture; BP = bisphosphonates; ICD = International Classification of Diseases; N = number; NA = not applicable; ONJ = osteonecrosis of the jaw; ORSR = observational research study report; PMO = postmenopausal osteoporosis PPV = positive-predictive value; The PPV is the proportion of potential cases identified through the ICD-based case ascertainment algorithm that are confirmed as true cases through medical chart review."

[a] PPV 2010 - 2017. Confirmed ONJ and AFF data is from 2010 to 2017 data. ICD 10 M84.75-A data is from 2016 to 31 December 2017 in US Medicare and 31 March 2019 for Optum Research. PMO Denosumab users are 1:1 propensity-score matched with BP exposed women with PMO to create a cohort that is followed to identified potential cases using case ascertainment algorithms that are subsequently confirmed through medical record review. Sources: PPV for ONJ and AFF: Table 8-9 of Year 9 report. Confirmed Denosumab-only cases of AFF: Table 8-14 of Year 9 report, Confirmed Denosumab-only cases of ONJ: Table 8-10 of Year 9 report. AFF algorithm specific ICD10 Table 8-13 of Year 9 report

[b] Central Denmark

[c] Data years 26 May 2010, and the data availability dates of 31 December 2018 for US Medicare and Scandinavian national registries, and 31 March 2020 for Optum Research Database.

13.10.3.4 Statistical Inference (Estimation or Hypothesis[es])

The outcomes will be compared between treatment groups under the hypothesis that there exists no relative difference in risk of outcomes between subjects initiating treatment with denosumab versus those initiating treatment with zoledronic acid for 7 AESIs as defined in the 20090522 study (hypocalcemia leading to hospitalization or emergency room (ER) visit; infections leading to hospitalization, ER visit, or

administration of parenteral anti-infective medication; dermatologic adverse events leading to hospitalization or ER visits; acute pancreatitis leading to hospitalization; hypersensitivity leading to hospitalization or ER visit; new primary malignancy (excluding non-melanoma skin cancer) and fracture healing complications).

13.10.4 Research Question and Objectives

The question under investigation is whether the use of denosumab increases the risk of select AESIs. The below analyses assess if the incidence of seven AESI are comparable among women with PMO initiating denosumab and women with PMO initiating zoledronic acid.

13.10.4.1 Primary

The primary objective is to

a) Describe the prevalence of baseline covariates by treatment group

b) Assess comparability of baseline measured characteristics between treatment groups, after inverse probability of treatment weighting adjustment. Comparability will be assessed using standardized mean differences (see Section 13.10.13.10.5.3.3).

c) To evaluate the primary etiologic question of whether Denosumab has a biologic effect on the following AESIs, we will assess the relative risk with 95% confidence intervals among postmenopausal women with osteoporosis who initiated treatment with denosumab and those who initiated treatment with zoledronic acid.

AESIs

- Fracture healing complications
- New primary malignancy (excluding non-melanoma skin cancer)
- Hypocalcemia leading to hospitalization or emergency room (ER) visit
- Infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication
- Dermatologic adverse events leading to hospitalization or ER visit
- Acute pancreatitis leading to hospitalization,
- Hypersensitivity leading to hospitalization or ER visit

13.10.4.2 Secondary

The secondary objective is to assess the risk difference and 95% confidence interval of the following AESIs among postmenopausal women with osteoporosis who initiated treatment with denosumab and those who initiated treatment with zoledronic acid if a relative association (95% confidence interval excludes null) exists to better characterize the public health impact of the association.

- Fracture healing complications
- New primary malignancy (excluding non-melanoma skin cancer)
- Hypocalcemia leading to hospitalization or emergency room (ER) visit
- Infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication
- Dermatologic adverse events leading to hospitalization or ER visit
- Acute pancreatitis leading to hospitalization,
- Hypersensitivity leading to hospitalization or ER visit

13.10.5 Research Methods

13.10.5.1 Study Design

This comparative safety analysis is being conducted within the 20090522 retrospective cohort study using secondary data. A naïve user design is being employed for the primary objective to evaluate if denosumab increases the risk of 7 AESIs. A naïve user design has the advantage of ensuring the correct temporal assessment between exposure and covariates, capturing early events following initiation, and aligning eligibility, exposure, and start of follow-up.

The active comparator arms were selected based on results from three studies that used negative control outcomes to assess the comparability of osteoporosis treatments after adjustment for measured confounders (Mcgrath et al, 2020), Studies 20190427 and 20190031). Zoledronic acid was selected as the best active comparator in the naïve user design (Table 2).

Table 2. Naïve user full cohort: Proportion of negative control outcomes with null risk-difference associations

Comparison	MarketScan (N=11)	Optum (N=12)	Medicare (N=7)	Total
Prolia vs. ZA	91%	83%	86%	90%
Prolia vs. Oral BP	82%	50%	57%	67%

The balance of measured baseline covariates between comparison groups will be assessed. Inverse probability of treatment and censoring weighted (IPTCW) adjusted risk ratios will be estimated using a semi-parametric cumulative incidence estimator, to compare the risk of outcome among subjects initiating treatment with denosumab relative to the reference group initiating treatment with zoledronic acid. These analyses will be further detailed by estimating risk differences as a secondary objective when associations (95% confidence interval excludes null) are observed.

13.10.5.2 Setting and Study Population

The study population is a sample of the PMO study population included in the Medicare databases as part of the post marketing Study 20090522, entitled, "Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO), Men With Osteoporosis, and Men and Women Who Receive Prolia With Glucocorticoid Exposure in Multiple Observational Databases."

13.10.5.2.1 Study Period

We will use all available 20090522 PMO Medicare data from 26 May 2006 through 31 December 2019, with subjects entering the exposure cohort from 30 September 2011 through 31 December 2017. This allows for a minimum 15-month baseline period and potential for at least 24 months of follow-up, although 24 months of follow-up is not required.

13.10.5.2.2 Selection and Number of Sites

Due to power considerations, we will restrict the comparative analysis to the US Medicare data. In the Year 10 annual 20090522 report, of the 5 data systems, US Medicare represented 84% of women with PMO and 91% of women receiving Prolia in the study.

13.10.5.2.3 Subject/Patient/Healthcare Professional Eligibility

13.10.5.2.3.1 Inclusion Criteria

Women eligible for inclusion met the criteria for PMO specified in the 20090522 study. For the comparative safety analysis, eligibility criteria also include

- Administration/prescription/dispensing of denosumab or zoledronic acid.
- Cohorts
  - Naïve user (osteoporosis treatment naive): The treatment initiation index date is the first administration/prescription/dispensing of denosumab or zoledronic acid on or after the 20090522 PMO index date and occurring between 30 September 2011 through 31 December 2017. Subjects with less than 455 days of continuous health plan enrollment preceding the index date are excluded. Zoledronic acid is given yearly; a 455 day (ie, 15 month) minimal look-back period will enable assessment of past use of zoledronic acid and any BP use to determine whether a patient is a naïve user (Choi et al, 2017). If more baseline data is available, the look-back period will extend further.
  - Subjects are excluded for evidence of prior use (previous claim within available historical claims; no maximum time between medications) of any type of osteoporosis drug (eg, bisphosphonates, Denosumab, teriparatide, or raloxifene).

Naïve User Exposure cohort	Description of exposure group
Denosumab	No prior use of (in all available data) Denosumab BP Oral BP IV Teriparatide Raloxifene
ZA	No prior use of (in all available data) Denosumab BP Oral BP IV Teriparatide Raloxifene

- The index date (for description of baseline covariates and start of risk) for the fracture healing complications cohort is the date of the first closed hip fracture that occurs after treatment initiation in the **naïve** user cohort prior to 01 Jan 2018. Restricting the analysis only to subjects that experience a closed hip fracture reduces potential confounding by fracture location and severity. However, if the number of fracture healing complication events is lower than 30 events across both treatment groups, we will expand the cohort to include fractures occurring at other locations including those near the hip (other femur fracture closed and closed pelvic fractures) and humerus (Mills 2017; Zura 2017).

13.10.5.2.3.2 Exclusion Criteria

Women will be excluded from the analysis if they have any of the following conditions or receive any of the following treatments on or during the 455 days preceding the naïve new user index date (the baseline period).

- Paget's disease of bone,
- Cancer (excluding non-melanoma skin cancer),
- Treatment with chemotherapy,
- Treatment with hormonal therapy for cancer,
- Treatment with radiation or radiation therapy for cancer, or
- Prevalent specific AESI during baseline (prevalent baseline acute AESIs (infection, hypocalcemia, hypersensitivity, dermatologic events) occurring on the index date will not be excluded)

13.10.5.2.4 Matching

N/A

13.10.5.2.5 Baseline Period

The baseline period will be defined as 455 days on or before the index date (index date included). Data collected during the baseline period will be used to define values for baseline covariates as described above.

13.10.5.2.6 Study Follow-up

Subjects will be followed from the index date (ie, treatment initiation) until the first of the following: date of a given outcome, death, treatment discontinuation or switching (the minimum of: end of study medication plus 60 days or start of different OP medication), disenrollment (defined as >60 day gap in enrollment), first diagnosis of Paget's disease or cancer (excluding non-melanoma skin cancer) as described in the 20090522 study, treatment with chemotherapy, hormonal therapy or radiation therapy for cancer, or end of available data in database. At-risk person-time during follow-up will be assessed separately for each outcome of interest.

13.10.5.3 Variables

13.10.5.3.1 Exposure Assessment

The same algorithms used to ascertain exposure in the 20090522 study will be used in the comparative safety analysis. The exposure cohorts are detailed in Section 13.10.13.10.5.2.3.1 above.

13.10.5.3.2 Outcome Assessment

The same algorithms used to ascertain adverse events of special interest outcomes in the 20090522 study will be used in the comparative safety analysis. The following outcomes will be assessed in the comparative safety analysis.

- Fracture healing complications
- New primary malignancy (excluding non-melanoma skin cancer)
- Hypocalcemia leading to hospitalization or emergency room (ER) visit
- Infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication
- Dermatologic adverse events leading to hospitalization or ER visit
- Acute pancreatitis leading to hospitalization,
- Hypersensitivity leading to hospitalization or ER visit

13.10.5.3.3 Covariate Assessment

The baseline potential confounders, demographics, and AESI risk factors listed in the 20090522-study protocol and manual of operation for matching of denosumab and bisphosphonates users for ONJ and AFF adjudication will be used in the comparative safety analysis to develop propensity scores and censoring weights. Variables assessed on or 455 days prior to the index date will be included. Inverse-probability of treatment and censoring weights will be used to address confounding in initial treatment assignment and potentially informative censoring by loss to follow-up (Robins and Finkelstein, 2000). Appropriate variables for inclusion in a propensity score are either true confounders (because inclusion of these covariates reduces bias) or are variables that are related to the outcome (because these variables increase precision). We will not include variables that are related to the exposure but not to the outcome as these will increase the variance of the estimated exposure effect without decreasing bias (Brookhart et al, 2006). In addition to the variables included in the propensity score matching of denosumab and bisphosphonate users for ONJ and AFF adjudication, the propensity score for the comparative safety analysis may include interaction terms for before and after Oct 1, 2015 for the ICD 9 to ICD 10 code revision, history of fragility fracture type (hip, closed; distal radius/ulna; humerus -closed, other femur closed, pelvis-closed, distal radius/ulna – other, spine, closed or pathologic; other – prior to index date), number of fragility fractures, seasonality (quarter) of index date, number of different medications (count of number of distinct therapeutic classes – ATC level 3), kyphosis, osteoarthritis, use of nonsteroidal anti-inflammatory drugs, opiates, and anticoagulants. For fracture healing complications, the following baseline covariates prior to the index date will also be included in the propensity score for this analysis, duration of prior zoledronic acid, oral BP, or denosumab use (Appendix 13.10.13.10.7.2 Variables considered during creation of propensity score). Variables with no positivity in both groups were not included (Westreich and Cole, 2010).

We will use logistic regression to estimate propensity scores for all contrasts of interest in the full cohort, full cohorts with size differences >10% due to exclusion criteria (prevalent cases), cohorts that include different baseline covariates, and subgroups. The propensity scores will be used to create inverse-probability of treatment weights (IPTW) to standardize the distribution of key covariates between the two treatment groups. Denosumab users will be assigned weights equal to the inverse of their propensity scores (1/PS) and individuals in the comparator group will be assigned weights equal to the inverse of one minus their propensity scores [1/(1 – PS)]. To avoid allowing a few

individuals with large weights to dominate the weighted analysis, we will use stabilized weights (Xu et al, 2010; Robins et al, 2000). Stabilized weights are the standard IPTW multiplied by the marginal probability of exposure. Time-varying covariates will not be employed since we anticipate that most AESIs will occur in the first few years of follow-up.

Weights calculated from the propensity score will be used to create a 'pseudo-population' in which the distribution of measured baseline covariates is independent of treatment assignment. We expect that after applying propensity score methods, most of the covariates will have a standardized mean difference (SMD) <0.1. This means that weighting has balanced the distribution of measured covariates between treatment groups. Residual imbalance may remain after applying propensity score weights, as evidenced by variables with SMD ≥ 0.1. We will assess the magnitude of the SMD, importance of the covariates as confounders, and the number of covariates falling outside of this value.

The propensity score evaluation process will be iterative considering interaction terms, including continuous variables as splines, higher order terms, different categorizations, review of histograms for positivity assumption and weights for trimming and refitting of model etc. Following the gating process, this will be done prior to availability of any outcome information to avoid biased analytic decisions driven by their expected effect on comparative analyses.

A similar method will be used to construct the censoring weights for all comparisons. Total follow up time (mean & median) and numbers, percent and days to first (and any) type of censoring will be reviewed (Section 13.10.13.10.5.7.2.2). The date of censoring will be the earliest of each of the censoring types. If any of the events occur on the same day, the reasons for censoring will be assigned according to this hierarchy: medical (including death) > treatment discontinuation > disenrollment > admin. Inverse probability of censoring (IPC) weights will be generated to account for dependent censoring ie, censoring weights are applied to the uncensored population to weight them up to resemble the overall uncensored population at baseline. The censoring model will be estimated using a time to event Cox proportional hazards regression with a composite censoring variable. The variables used in the treatment propensity model above will be used in the censoring model. If the number of covariates need to be reduced to achieve model convergence, we will remove covariates with small cell counts in cross-tabs with censoring indicators. We will try to keep strong predictors in the

model, if this is not possible, we may need to exclude those subjects. There is no routine diagnostic approach for censoring models. The variables to be used in propensity score models, censoring models, and outcome models are recorded and stored with the R code used to generate results.

To assess unmeasured confounding, the 4 non-fracture negative control outcomes that were evaluated in the Medicare Negative Control study 20190031 (dementia, wellness visit , influenza vaccine, accidents) will also be evaluated using the same inverse probability of treatment and censoring weights and models used for the primary comparison of denosumab and zoledronic acid in the naive users cohort. Follow-up for negative control outcomes will begin the day after the index date. The one-year risk ratio and risk difference (and corresponding 95% confidence intervals) will be estimated. Prevalent dementia during baseline will be an exclusion criterion in the dementia negative control analysis. Negative control outcomes will be defined as they were in the 20190031 study. Residual confounding will be indicated if the 95% confidence interval of the risk ratio excludes 1 or if the risk difference excludes 0. The extent of residual confounding will be further characterized as the risk ratio being ≤ 0.85 or ≥ 1.15 or the risk difference being 1% or greater.

13.10.5.3.4 Validity and Reliability

As outlined in the 20090522 protocol, published, validated algorithms are used to identify AESIs. Further algorithm validation was performed in the individual databases for US ICD9 and EU ICD 10 based algorithms. [ORSR 20140404, Table 3 and Table 4.] The ICD-10 code specific for hypocalcemia is only available in the Denmark national registry. Norway and Sweden use nonspecific ICD-10 codes for disorders of calcium metabolism that may not accurately capture hypocalcemia precluding comparison across all countries.

Table 3. Overall Summary of Medical Review: Confirmed Cases and Associated PPV for Selected AESI and Their Subtypes by Data System

	US Medicare (Total Cases)		Scandinavian Data Systems (Total Cases)	
	Confirmed Cases[a]	PPV [b]	Confirmed Cases[a]	PPV [b]
AESI	n	% (95% CI)	n	% (95% CI)
Acute pancreatitis *	82	83.7 (75.1, 89.7)	113	87.6 (80.8, 92.2)
Dermatologic AEs **	82	86.3 (78.0, 91.8)	85	92.4 (85.1, 96.3)
Dermatologic subtype: bullous dermatoses	4	100.0 (51.0, 100.0)	37	92.5 (80.1, 97.4)
Dermatologic subtype: erythematous	1	100.0 (20.7, 100.0)	8	100.0 (67.6, 100.0)
Fracture healing complication	63	71.6 (61.4, 80.0)	N/A	N/A
Hypocalcemia **	74	82.2 (73.1, 88.8)	8	13.1 (6.8, 23.8)
Infections **	87	87.9 (80.0, 92.9)	120	87.6 (81.0, 92.1)
Infection subtype: skin infection	9	100.0 (70.1, 100.0)	6	75.0 (40.9, 92.9)
New primary malignancy [c]	65	75.6 (65.5, 83.4)	111	88.1 (81.3, 92.7)
Hypersensitivity **	N/A	N/A	45	54.2 (43.6, 64.5)
Hypersensitivity subtype: anaphylactic hypersensitivity	N/A	N/A	7	87.5 (52.9, 97.8)

AEs = adverse events; AESI = adverse event(s) of special interest; CI = confidence interval; N/A = not applicable; PPV = positive predictive value

[a] Confirmed by medical review
[b] PPV calculated as the number of confirmed cases after medical review divided by the number of obtained medical charts with sufficient information.
[c] New primary malignancy, excluding nonmelanoma skin cancer
* leading to hospitalization
**leading to hospitalization or ER visit (Note: for AESI of Infections, includes infections leading to administration of parenteral anti-infective medication.)

Table 4. Scandinavian Data Systems: Summary of Medical Review Positive Predictive Value for Selected AESI and Their Subtypes for Women With Postmenopausal Osteoporosis

	Norway				Denmark				Sweden			
	Obt	Insuff	Conf	PPV	Obt	Insuff	Conf	PPV	Obt	Insuff	Conf	PPV
AESI	n	n (%)	n	% (95% CI)	n	n (%)	n	% (95% CI)	n	n (%)	n	% (95% CI)
Acute pancreatitis *	54	14 (25.9)	37	92.5 (80.1, 97.4)	42	2 (4.8)	33	82.5 (68.1, 91.3)	49	0 (0.0)	43	87.8 (75.8, 94.3)
Dermatologic AEs **, [a]	N/A	N/A	N/A	–	50	0 (0.0)	46	92.0 (81.2, 96.8)	50	8 (16.0)	39	92.9 (81.0, 97.5)
Dermatologic subtype: bullous dermatoses	N/A	N/A	N/A	–	30	0 (0.0)	28	93.3 (78.7, 98.2)	10	0 (0.0)	9	90.0 (59.6, 98.2)
Dermatologic subtype: erythematous	N/A	N/A	N/A	–	4	0 (0.0)	4	100.0 (51.0, 100.0)	4	0 (0.0)	4	100.0 (51.0, 100.0)
Hypersensitivity **, [a]	N/A	N/A	N/A	–	38	3 (7.9)	17	48.6 (33.0, 64.4)	51	3 (5.9)	28	58.3 (44.3, 71.2)
Hypersensitivity subtype: anaphylactic	N/A	N/A	N/A	–	3	0 (0.0)	3	100.0 (43.9, 100.0)	5	0 (0.0)	4	80.0 (37.6, 96.4)
Hypocalcemia **	14	0 (0.0)	2	14.3 (4.0, 39.9)	2	0 (0.0)	1	50.0 (9.5, 90.5)	45	0 (0.0)	5	11.1 (4.8, 23.5)
Infections **	60	15 (25.0)	39	86.7 (73.8, 93.7)	50	2 (4.0)	43	89.6 (77.8, 95.5)	44	0 (0.0)	38	86.4 (73.3, 93.6)
Infection subtype: skin infection	6	1 (16.7)	3	60.0 (23.1, 88.2)	0	0 (0.0)	0	0.0 (0.0, 0.0)	3	0 (0.0)	3	100.0 (43.9, 100.0)
New primary malignancy [b]	48	8 (16.7)	38	95.0 (83.5, 98.6)	50	4 (8.0)	41	89.1 (77.0, 95.3)	43	3 (7.0)	32	80.0 (65.2, 89.5)

AEs = adverse events; AESI = adverse event(s) of special interest; CI = confidence interval; Conf = confirmed; Insuff = cases with insufficient information; N/A = not applicable; Obt = obtained; PPV = positive predictive value

[a] Dermatologic AEs and hypersensitivity were only assessed in Denmark and Sweden, per protocol.

[b] New primary malignancy, excluding nonmelanoma skin cancer

* leading to hospitalization

** leading to hospitalization or ER visit (Note: for AESI of Infections, includes infections leading to administration of parenteral anti-infective medication.)

13.10.5.4 Data sources

The data sources for the comparative safety analysis are those as described in the main PMO 20090522 study. Medicare data through 31 December 2019 will be used in this analysis.

13.10.5.5 Study Size

Medicare data, based on sample size and power, is the most fit-for-purpose data set to perform the 20090522 naive user comparative safety analysis between denosumab and zoledronic acid. The Medicare data system accounts for 91% of women receiving denosumab in the 20090522 study. Power tables for the comparative safety analysis were update based on the number of exposed subjects in the naïve user cohort using the available 2018 Medicare data (Table 5 and Table 6) that will be used in these analyses.

The methods for comparative safety analysis employ inverse probability of treatment and censoring weighting (IPTCW). Methods to calculate statistical power for inverse probability (IP) weighted estimators have not yet been developed. Statistical power for such estimators is a function of the sample size, number of outcomes, and the variability in the IP weights. Here, a standard normal approximation is extended for the statistical power for the difference in two binomials (Fundamentals of Biostatistics, Rosner [1997], page 418) to account for variance inflation due to IP weights. The variance of the IP

weights from previous studies assessing comparability of osteoporosis treatment groups was used to compute a variance inflation for these calculations.

Table 5. Number of subjects for each PMO exposure group using the naive user design based on the Year 10 Annual Report Annual report.

Treatment Group	N	
	All AESI Cohort (other than fracture healing) Total N = 518,037	Fracture healing cohort Total N = 7,562
Prolia	76,245	1,189
ZA	34,481	560
Oral BP	405,905	5,791
IV BP	35,887	582
Any BP	441,792	6,373

ZA zoledronic acid, BP bisphosphonate, IV intravenous

Table 6. Statistical power based on Year 10 Annual Report and minimum detectable relative risk of 1.2, 1.5, 2.0, and 3.0 for Naïve User study design analysis

Adverse Event of Special Interest	Treatment Comparison	Minimum detectable relative risk = 1.2	Minimum detectable relative risk = 1.5	Minimum detectable relative risk = 2.0	Minimum detectable relative risk = 3.0
Osteonecrosis of the jaw (ONJ) (Algorithm)	Prolia VS Oral BP	36	95	100	100
	Prolia VS ZA	23	83	100	100
	Prolia VS Any BP	38	96	100	100
Hypocalcemia leading to hospitalization	Prolia VS Oral BP	9	27	65	97
	Prolia VS ZA	8	26	71	100
	Prolia VS Any BP	10	32	73	99
Infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication	Prolia VS Oral BP	100	100	100	100
	Prolia VS ZA	100	100	100	100
	Prolia VS Any BP	100	100	100	100
Dermatologic adverse events leading to	Prolia VS Oral BP	75	100	100	100
	Prolia VS ZA	42	99	100	100

Adverse Event of Special Interest	Treatment Comparison	Minimum detectable relative risk = 1.2	Minimum detectable relative risk = 1.5	Minimum detectable relative risk = 2.0	Minimum detectable relative risk = 3.0
hospitalization or ER visit	**Prolia VS Any BP**	77	100	100	100
Acute pancreatitis leading to hospitalization	**Prolia VS Oral BP**	46	99	100	100
	Prolia VS ZA	24	86	100	100
	Prolia VS Any BP	48	99	100	100
Hypersensitivity leading to hospitalization or an ER visit	**Prolia VS Oral BP**	75	100	100	100
	Prolia VS ZA	53	100	100	100
	Prolia VS Any BP	78	100	100	100
Fracture healing complications restricted to previous hip fracture	**Prolia VS Oral BP**	12	42	87	100
	Prolia VS ZA	6	15	41	89
	Prolia VS Any BP	12	43	87	100
New primary malignancy (excluding non-melanoma skin cancer)	**Prolia VS Oral BP**	100	100	100	100
	Prolia VS ZA	100	100	100	100
	Prolia VS Any BP	100	100	100	100
Atypical Femur Fracture defined using the specific ICD 10 Code M84.75-A	**Prolia VS Oral BP**	Not calculated. There were no cases in any exposure cohort using the n**aive** user design.			
	Prolia VS ZA				
	Prolia VS Any BP				

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ZA zoledronic acid, BP bisphosphonate, IV intravenous

For most AESIs, there is greater than 80% power to detect a RR of 1.5. The power is lower for fracture healing complications and hypocalcemia. In our naïve user cohort, no cases of the rare atypical femur fracture outcome were identified.

13.10.5.6 Data Management

13.10.5.6.1 Obtaining Data Files

The analysis includes US Medicare data previously obtained for the post marketing Study 20090522, entitled, “Denosumab Global Safety Assessment Among Women With

Postmenopausal Osteoporosis (PMO), Men With Osteoporosis, and Men and Women Who Receive Prolia With Glucocorticoid Exposure in Multiple Observational Databases."

13.10.5.6.2 Linking Data Files

Not applicable

13.10.5.6.3 Review and Verification of Data Quality

When FASTER receives data from CMS it is read into SAS files. The first step of QA/QC procedures is to compare the number of records in each SAS file to the file summaries provided by CMS to make sure the number of records exactly match. We then compare the number of records by each file type across all past years of data to evaluate any temporal trends and make sure that the change in numbers is either expected or explainable. Once the data has been read, we perform basic statistical analyses such as PROC FREQ, PROC MEANS, PROC UNIVARIATE depending on variable type (character, numeric, date, etc.) on each variable in each file to evaluate completeness and identify extreme or impossible values for example age greater than 110 or date of birth (DOB) later than end of current data year. We also confirm that variables that are expected to be never missing, including but not limited to subject ID, claim ID, DOB etc. are not missing. Such records, if found, are flagged. In addition, we have built in internal validity checks to enumerate and flag subjects with multiple DOBs, multiple sex code, multiple date of deaths (DOD) or if a subject had a non-missing DOD in past but has claims in later years.

13.10.5.7 Data Analysis

13.10.5.7.1 Planned Analyses

13.10.5.7.1.1 Primary Analysis

13.10.5.7.2 Planned Method of Analysis

13.10.5.7.2.1 General Considerations

To compare the risk of outcomes between subjects who initiate denosumab and subjects who initiate zoledronic acid, the baseline characteristics will be used to create propensity scores (Section 13.10.13.10.5.3.3). Sufficient comparability (based on quantitative assessment of balance in covariates after IPTW) will be assessed between the two exposure groups, cumulative risks will be calculated by each treatment group using inverse-probability of treatment and censoring weighted (IPTCW) estimation functions (Ozenne et al, 2020). Adjusted cumulative incidence by treatment (with 95% confidence bands) will be plotted and adjusted risk ratios (and corresponding 95% confidence intervals) will be tabulated for each adverse event of special interest for the primary

objective. Adjusted risk differences (and corresponding 95% confidence intervals) will be tabulated for the secondary objective if relative associations (95% confidence excludes null) are observed. A gatekeeping process will be implemented and documented by the external investigators that keeps individuals making these decisions isolated – through their assigned roles and responsibilities – from knowledge about how these decisions might affect outcomes to avoid biased analytic decisions driven by their expected effect on comparative analyses (Appendix 13.10.7.1). The majority of the analysis will be run using the Causal Studio remote application.

13.10.5.7.2.2 Missing or Incomplete Data and Lost to Follow-up

For the naive user cohort, for each exposure group, follow-up (days) will be reported (mean & median) and graphed (up to 5 years) and the number, percent and days to each censoring event (and death) and to the first of any censoring event (and death) for each outcome will be tabulated for each time point (Section 13.10.13.10.5.7.2.4). If we encounter potential survivor bias with varying lengths of follow-up, we will perform an intent-to-treat sensitivity analysis restricted to subjects with a specified length of follow-up. (Section 13.10.13.10.5.7.2.6.4).

13.10.5.7.2.3 Analysis

13.10.5.7.2.3.1 Description of Study Enrollment

Attrition tables including frequencies and proportions of subjects included in the naive user analysis set will be provided. The tables will summarize the selection of the study population starting from the 20090522-source population of postmenopausal women with osteoporosis based on a stepwise implementation of study eligibility criteria. Since exclusions have already been applied in the 365-day baseline period for the 20090522 study, the results presented in this analysis will represent exclusion from -365 to -455 days pre-index date.

13.10.5.7.2.3.2 Description of Subject/Patient Characteristics

Demographic and clinical characteristics (see Section 13.10.13.10.5.3.3 Covariate Assessment) will be summarized for the new user cohort by treatment groups both before and after weighting (and trimming if needed) with standardized mean difference calculated. Categorical variables will be presented as number and proportion/ percent of subjects and continuous variables presented as mean with standard deviation and/or median with range, as appropriate.

13.10.5.7.2.4 Analysis of the Primary Endpoint(s)

Study endpoints include:

AESIs

- Fracture healing complications
- New primary malignancy (excluding non-melanoma skin cancer)
- Hypocalcemia leading to hospitalization or emergency room (ER) visit
- Infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication
- Dermatologic adverse events leading to hospitalization or ER visit
- Acute pancreatitis leading to hospitalization,
- Hypersensitivity leading to hospitalization or ER visit

For each comparison, propensity scores will be calculated for each subject using multivariable logistic regression modeling based on subject baseline demographic and clinical characteristics. We will assess if sufficient comparability (based on quantitative assessment of balance in baseline characteristics) can be achieved between the two treatment groups (Section 13.10.13.10.5.3.3 Covariate Assessment). The final assessment will be made by an independent Gatekeeper (Appendix 13.10.7.1) and documented.

The risk of the outcomes will be compared between the two treatment groups via inverse probability of treatment weight (IPTW) and inverse probability of censoring weight (IPCW) methods. Each outcome will be assessed separately. We will estimate the cumulative risk of each outcome using augmented inverse-probability of treatment and censoring weighted (AIPW) estimation functions. (Ozenne et al, 2020) The AIPW estimator is doubly robust – if either the treatment/censoring model or the outcome model is properly specified, then the estimate is consistent. The AIPW provides an estimate of the cumulative risk of the outcome by time t, within the overall subject population. It is explicitly targeting the same parameter (estimand) that would be obtained in an RCT conducted in the overall population.

Death will be treated as a competing risk in the main analysis. We will use a semi-parametric estimator of cumulative incidence of the focal event (eg, AESI) at time t, which must occur before the competing event (eg, death). This estimator extends the Nelson-Aalen estimator of the cumulative hazard function in the presence of right censoring to account for dependent censoring (Ozenne et al, 2020; Aalen, 1978). This method does not estimate hazards and does not suffer from the many known problems associated with these models (Hernan et al., 2010). Results of treatment associations with each outcome when death is considered as a competing risk will be presented.

The outcome model will be estimated using Cox proportional hazards regression and may also include known predictors of the outcome.

Adjusted cumulative risk by treatment and risk ratios (with 95% confidence bands) will be plotted (up to 5-years) and adjusted risk ratios (and corresponding 95% confidence intervals) will be estimated at 1 year for each adverse event of special interest for the primary objective.

13.10.5.7.2.5 Analysis of Secondary and Exploratory Endpoint(s)

For the second objective, if the primary analysis indicates an association (95% confidence intervals exclude the null), adjusted risk differences for each outcome will be plotted (up to 5- years) and tabulated at 1 year for naive users of denosumab and naive users of zoledronic acid.

Unadjusted cumulative risk (with death as a competing risk with no propensity score or censoring adjustment) and 95% confidence intervals will be described and calculated for each exposure group at 1 year for qualitative assessment of adjustment influence.

Also, the number of subjects, person-years and number of events will be described and unadjusted incidence rates (number of subjects with events/person-years) and age-standardized (as done in the 20090522 study), and cumulative risks will also be calculated for all available follow-up time to allow comparison of incidence results between the naive user and prevalent user design used in the 20090522 study. In addition, the latter analyses will also be multiplied by the respective PPV for descriptive purposes.

13.10.5.7.2.6 Sensitivity Analyses

13.10.5.7.2.6.1 Subgroup Analysis

Analyses to assess residual bias will be conducted for outcomes in the naive user denosumab and zoledronic acid comparison with an adequate number of events (n=30 across both treatment arms). Thirty is an arbitrary number, however the opinion of the research team was this was an appropriate cut point as 5 to 10 cases in a single arm can interfere with a model's stability.

- The analyses for the primary end points will be repeated for each outcome (except for fracture healing) in a subgroup of subjects who had a fracture within the 12 months prior to the index date. This analysis provides additional restriction for disease severity.
- The analyses for the primary end points will be repeated for each outcome in a subgroup of subjects with no renal disease. Denosumab, unlike zoledronic acid,

is not contraindicated in subjects with creatinine clearance less than 35 mL/min or in those with evidence of acute renal impairment. Therefore, we expect that subjects treated with denosumab will have a higher prevalence of renal impairment than subjects treated with zoledronic acid. Because renal insufficiency may be a strong indicator for hypocalcemia risk, we expect that our crude association would be biased away from the null with denosumab treated subjects at an increased baseline risk of the outcomes. This bias could still occur in the stratified analysis if the diagnosis of stage 1 and 2 CKD is under reported through diagnostic codes but impacts a physician's prescribing choice. On the other hand, stage 1 and 2 CKD would be a weaker indicator of for hypocalcemia risk than later stages.

- The analyses for the primary end points will be repeated for each outcome in a subgroup of subjects during more recent years. This analysis provides additional control for confounding as the previous negative control outcome studies evaluating osteoporosis treatment comparability indicated more residual confounding in the early years of Prolia prescribing. To align with US ICD 10 revisions, subjects entering the naive user cohort on or after Oct 1, 2015 will be included in this analysis.

13.10.5.7.2.6.2 Stratified Analysis

None

13.10.5.7.2.6.3 Other Sensitivity Analysis – Different Potential Induction Periods

The number of subjects, person-years and number of events will be described at 3-months and 6-months from the treatment initiation index date for AESIs with anticipated early induction periods (hypocalcemia leading to hospitalization or emergency room (ER) visit, dermatologic adverse events leading to hospitalization or ER visit, hypersensitivity, infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication, acute pancreatitis leading to hospitalization) and at 5-years from the index date for AESIs with anticipated later induction periods (bone related and new primary malignancy excluding non-melanoma skin cancer). Adjusted risk ratios (and corresponding 95% confidence intervals) will be estimated at 3-months and 6-months for AESIs with anticipated early induction periods and at 5-years for AESIs with anticipated later induction periods, as allowed by adequate sample size at these time periods. If the risk ratios in these analyses indicate an association, adjusted risk differences (and corresponding 95% confidence intervals) will be estimated at 3-months and 6-months for AESIs with anticipated early induction periods and at 5-years for AESIs with anticipated later induction periods.

The specific biologic induction periods for the AESIs with anticipated later induction periods have not been fully flushed out. To explore differing induction/latency periods adjusted risk ratios (and corresponding 95% confidence intervals) will be estimated

starting from 1, 2, 3, 4, and 5 years after the initial medication. These analyses will be performed by assigning new index dates at the designated time point, but the censoring criteria will not change. These analyses may be limited from lower number of events and lack of precision.

As requested by EMA (EMEA/H/C/001120/LEG/041.1), to explore the incidence with different durations of exposure, a 1-year adjusted cumulative risk ratios (with 95% confidence intervals) will be estimated for subgroups of subjects with up to 3 years of treatment and subjects with >3 years of exposure for the bone related (osteonecrosis of the jaw and atypical femur fracture) and malignancy AESI. For the latter analysis, time at risk will start at 3 years of treatment. As long-term exposure to osteoporosis medication is infrequent under the real-world settings, sample size may be limited in this analysis.

13.10.5.7.2.6.4 Other Sensitivity Analysis - Intention to treat analysis

The analyses of the primary outcome will be repeated using a "first treatment carried forward" approach (intention to treat (ITT) ie, not censor for medication nonadherence. This will help to elucidate how sensitive the results are to healthy adherer bias. In addition to presenting the 1-year cumulative risk ratio, this will also be calculated at 5 years for bone related and malignancy events. However, this approach could also introduce misclassification error that would increase with time. In a safety analysis, this could introduce bias toward the null and mask concerns.[Lund 2015] Also, in the fracture healing complication analysis, denosumab has a shorter dose interval than zoledronic acid and higher opportunity to switch to an anabolic treatment after the initial fracture which could favor the analysis toward denosumab.

13.10.5.7.2.6.5 Exploratory Analysis – FDA recommendations

As discussed earlier, the positive predictive value of osteonecrosis of the jaw algorithm is low with the potential for outcome misclassification and the number of atypical femur fracture identified using ICD 10 M84.75-A code is low.

In addition, three negative control outcomes studies indicated more residual confounding with oral bisphosphonates than zoledronic acid, when used as a comparator arm for Prolia. Within the context of the acknowledged limitations, we plan to conduct comparisons of algorithm identified osteonecrosis of the jaw and atypical femur fracture AESIs and include oral BP comparator arms as exploratory analyses to the naive user study per the agency's request [Ref 01 Dec FDA **2021** ltr].

Algorithm identified osteonecrosis of the jaw, an outcome event with anticipated later induction period, will be compared between women with PMO initiating denosumab and women initiating zoledronic acid as described in sections 13.10.13.10.5.7.2.1 -- 13.10.13.10.5.7.2.6.4, under the hypothesis that there exists no relative difference in risk. The treatment initiation index date for the osteonecrosis of the jaw analyses is the first administration/prescription/dispensing of denosumab or zoledronic acid on or after the 20090522 PMO index date and occurring between September 30, 2011, through December 31, 2017 (as done for other AESIs). The baseline period for these analyses will be defined as 455 days on or before the index date.

FDA recommends the use of sensitivity analyses to determine the impact of various study decisions relating to outcome definition. Such analyses can be helpful in determining the potential impact of varying assumptions such as limiting or expanding outcome definitions on study results to facilitate better interpretations of study results in light of significant uncertainty. (U.S. Department of Health and Human Services et al, 2013) The osteonecrosis of the jaw algorithm used in the 20090522 study was developed to optimize sensitivity. Uncertainty around bias due to misclassification from the resultant low positive predictive value will be assessed by including the following criteria in the algorithm.

Criteria

1. Restrict ONJ algorithm to potential osteonecrosis of the jaw events with oral antibiotic use within 30 days post claims-based date. (Lin et al, 2014) In observational case registry studies in adults with a diagnosis of cancer and a new diagnosis of ONJ, 80% received antibiotics. (Ehrenstein et al, 2021; Schiodt et al, 2018) We will include the most common (≥ 2%) antibiotics observed in the registry.(Schiodt et al, 2018)

   Oral antibiotics include

   Tetracyclines (AHFS 8:12.24.XX
   Clindamycin (AHFS 8:12.28.20
   Metronidazole/ Flagyl/ Metronidazol (AHFS 8:30.92 - Miscellaneous Antiprotozoals)
   Penicillins (AHFS 8:12.16.xx)
   Cephalosporins (AHFS 8:12.06.XX)
   Fluoroquinolone (AHFS 8:12.18 – Quinolones)
   Macrolide (AHFS 8:12.12.xx)
2. Restrict osteonecrosis of the jaw codes used in the algorithm to only include specific ICD9 or ICD10 codes that identify a confirmed case of ONJ in the YR 10 20090522 annual report plus ICD-10 code M87.08 (Osteonecrosis due to drugs)
   a. ICD-9 code 733.45 (Aseptic necrosis of bone, jaw)

b. ICD-9 code 526.4 (Inflammatory conditions of jaw)
c. ICD-9 code 526.5 (Alveolitis of jaw)
d. ICD-10 code K04.6 (Periapical abscess with sinus)
e. ICD-10 code M87.08 (Osteonecrosis due to drugs)
f. ICD-10 code M87.8 (Other osteonecrosis, other site)

3. Restrict osteonecrosis of the jaw codes to those that are primary diagnoses
4. Restrict osteonecrosis of the jaw codes to those from select facility and provider claims
    a. Maxillofacial Surgery
    b. Oral Surgery
    c. General Dentistry

Using the 20090522 prevalent denosumab users matched 1:1 to BP users, PPV for the ONJ algorithm will be calculated by exposure (only denosumab and any bisphosphonate) at time of potential osteonecrosis of the jaw event identification in the data. In addition, for each revised algorithm criterion and for combined criteria 1 and 2, the overall PPV (as calculated in the 20090522 study) and the 1-year adjusted cumulative risk ratio will be calculated using the revised algorithms.

For the osteonecrosis of the jaw analysis, we will also apply a correction for the margin of error introduced by the low PPV. We will use a correction method based on estimates of the positive predictive value, since information on the negative predictive value, sensitivity, and specificity of osteonecrosis of the jaw algorithms in US data are lacking.(Ehrenstein et al, 2021). This method will provide corrected estimates of the relative risk under outcome misclassification with nondifferential sensitivity based on estimates of the observed relative risk and positive predictive values among PMO patients exposed to denosumab and those exposed to bisphosphonates (Brenner and Gefeller, 1993). With such a rare event, we anticipate the specificity to be very high and nondifferential.

No cases of atypical femur fracture (ICD 10 M84.75-A code), an event with anticipated later induction period, were identified in any of the exposure cohorts in the naive user design. Consequently, the analyses for the primary relative risk and secondary relative differences outcomes comparing denosumab (n =10) to intravenous (n=5), oral (n=57) , and any bisphosphonate (n=62) for this AESI will be run in the original 20090522 PMO cohorts employing a prevalent user design with exposure cohort index date being met on or after October 1, 2016. An ICD code specific for atypical femur fracture was not available before that time. A U.S. ICD 9 code was not available for atypical femur fracture. Although the U.S. transitioned to ICD-10 in October of 2015, coding systems

undergo regular revision, and new codes may be added over time. Several new codes for atypical femur fracture that previously did not exist under the original ICD-10 were added in 2016 that went into effect 10/1/2016.

Subjects in the 20090522 PMO cohort who were under follow-up (not censored by death, loss of coverage, Paget's disease, Malignancy) as of 01 Oct 2016 and PMO index date was less than or equal to 31 Dec 2017 will be included in this analysis. The index date (for exclusions, baseline covariates and follow-up) is the date of the first exposed day on or after 01 Oct 2016 in follow-up for the treatments of interest (denosumab, oral bisphosphonates (Alendronate, Risedronate, Ibandronate), or IV bisphosphonate (zoledronic acid, Ibandronate)). Subjects will not re-enter same cohort but can be in a different exposure cohort. Exclusions occurring during baseline (Paget's disease or Malignancy) are applied including less than 455 days of Medicare enrollment and concurrent exposure (based on days' supply) to multiple osteoporosis treatments on index date. To exclude prevalent atypical femur fracture in the year prior to introduction of code M84.75, subjects with subtrochanteric fracture during October 1, 2015 - October 1, 2016 will be excluded. Follow-up will start the day following the index date with censoring occurring at the earliest of death, loss of coverage, 12/31/2019, Paget's disease, malignancy, switching to a different OP medication, or discontinuation treatment. Primary outcomes will be calculated for Prolia and IV BP and Prolia and any BP comparisons.

Covariates for duration of prior zoledronic acid, oral BP, or denosumab use will be included in the propensity score for this analysis. The baseline period for these analyses will be defined as 455 days on or before the index date. However, as we are using the 20090522 PMO cohort, not all subjects will have 455 days of baseline for inclusion. Also, due to the low number of cases, features and risk factors of the atypical femur fracture (ICD 10 M84.75-A code) cases will be described by treatment. This will help to assess potential confounding by previous use of osteoporosis medication that can occur in a prevalent user design and to assess events that occur earlier than the anticipated induction period.

Per the Agency request, we will also perform comparisons between subjects initiating denosumab and those initiating oral bisphosphonate and comparisons between subjects initiating denosumab and those initiating any bisphosphonate (either oral or IV (zoledronic acid or ibandronate)) as described in sections 13.10.13.10.5.7.2.1 -- 13.10.13.10.5.7.2.6.4, under the hypothesis that there exists no relative difference in risk

of 8 algorithm defined AESIs as defined in the 20090522 study (hypocalcemia leading to hospitalization or emergency room (ER) visit , infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication, dermatologic adverse events leading to hospitalization or ER visits, acute pancreatitis leading to hospitalization, hypersensitivity leading to hospitalization or ER visit, osteonecrosis of the jaw, new primary malignancy (excluding non-melanoma skin cancer) and fracture healing complications). Due to the large number of oral bisphosphonate users compared to denosumab users, treatment blinding will not be effective with the addition of these analyses. As described in Section 13.10.13.10.5.3.3, unmeasured confounding will be assessed using the 4 non-fracture negative control outcomes that were evaluated in the Medicare Negative Control study 20190031 (dementia, wellness visit, influenza vaccine, accidents) for each of the comparisons including oral bisphosphonates.

Inclusion criteria for cohorts that include oral bisphosphonates

- Naive user (osteoporosis treatment naive): The treatment initiation index date is the first administration/prescription/dispensing of Denosumab or oral bisphosphonate (or first of either oral bisphosphonate or IV bisphosphonate) on or after the 20090522 PMO index date and occurring between 30 September 2011 through 31 December 2017. Subjects with less than 455 days of continuous health plan enrollment preceding the index date are excluded.
- Subjects are excluded for evidence of prior use (previous claim within available historical claims; no maximum time between medications) of any type of osteoporosis drug (eg, bisphosphonates, Denosumab, teriparatide, or raloxifene). In addition to the other exclusions noted in Section 13.10.13.10.5.2.3.2.

Naive User Exposure cohort	**Description of exposure group**
Oral BP	No prior use of (in all available data) Denosumab BP Oral BP IV Teriparatide Raloxifene
Any BP (oral or IV)	No prior use of (in all available data) Denosumab BP Oral BP IV Teriparatide Raloxifene

An additional sensitivity analysis employing a 14 day or 10% gap allowance (whichever is larger) for all treatments will be performed to explore how results are influenced by the study methodology **[Ref 12 Jul 2022 Advice-Information Request]** .

13.10.5.7.2.6.6 Exploratory Post-hoc Analysis – FDA recommendations [Ref 20 Mar 2023 FDA letter]

At FDA's recommendation [Ref 20 Mar 2023 FDA letter], additional post-hoc exploratory analyses will be conducted as described below.

To evaluate risk of hypocalcemia in relation to severity of baseline chronic kidney disease (CKD), we will perform hypocalcemia analyses stratified by CKD stages 1-2, 3, 4, 5-ESRD, and unknown or unspecified. Due to the limited number of subjects in some of these stratified groups, we will also stratify by CKD stages 1-3 and 4-ESRD. For these hypocalcemia analyses stratified by CKD, adjusted cumulative risk and risk ratios (and corresponding 95% confidence intervals) will be estimated at 1 year in the 3 comparisons (denosumab/zoledronic acid, denosumab/oral bisphosphonate, and denosumab /any bisphosphonate).

For AFF, in addition to the analysis employing the prevalent user cohort described in section 11.6.5.7.2.6.5, we will perform the analyses of AFF in the following user cohorts, per FDA's recommendations:

1) **Naïve user cohort**

2) **Incident new user cohort with no use of Prolia or any BP during the baseline period of 455 days prior to index date**

3) **A modified prevalent user cohort based on the definitions below per FDA's recommendations:**

   Including subjects who only used the cohort-defining drug during the baseline period (455 days on or before the index date), i.e.,

   - **Prolia cohort: Use of Prolia (but not oral BP or IV BP) is allowed during the baseline period prior to the date of the first Prolia exposure on or after October 1, 2016**

   - **Any BP cohort: Use of any BP (but not Prolia) is allowed during the baseline period prior to the date of the first BP exposure on or after October 1, 2016**

- **Oral BP cohort: Use of oral BP (but not Prolia or IV BP) is allowed during the baseline period prior to the date of the first oral BP exposure on or after October 1, 2016**

- **IV BP cohort: Use of IV BP (but not Prolia or oral BP) is allowed during the baseline period prior to the date of the first IV BP exposure on or after October 1, 2016**

These analyses of AFF in additional user cohorts will entail the construction of new patient cohorts. For each comparison (denosumab/zoledronic acid, denosumab/oral bisphosphonate, and denosumab /any bisphosphonate), if no events of AFF are observed across both exposure groups, only descriptive information (eg, number of subjects and person-years) will be provided. In each comparison (denosumab/zoledronic acid, denosumab/oral bisphosphonate, and denosumab /any bisphosphonate), if there is at least 1 AFF event in one exposure group and no AFF events in the other exposure group, descriptive analyses using unadjusted and untrimmed incidence rates (eg, number of subjects with event / person-years) will be provided. In each comparison (denosumab/zoledronic acid, denosumab/oral bisphosphonate, and denosumab /any bisphosphonate), if there is at least 1 AFF event in both exposure groups, comparative analyses will be conducted, including generation of propensity scores, assessment of diagnostics, creation of censoring weights, and estimation of adjusted 1- year cumulative risk and risk ratios; descriptive analyses using unadjusted and untrimmed incidence rates (eg, number of subjects with event / person-years) will also be provided. For each comparison (denosumab/zoledronic acid, denosumab/oral bisphosphonate, and denosumab /any bisphosphonate), if trimming results in 0 events of AFF in either exposure group, the above methods will apply.

As noted in section 11.6.5.2.6, subjects will be followed from the index date (ie, treatment initiation) until the first of the following: date of a given outcome, death, treatment discontinuation or switching (the minimum of: end of study medication plus 60 days or start of different OP medication), disenrollment (defined as >60 day gap in enrollment), first diagnosis of Paget's disease or cancer (excluding non-melanoma skin cancer) as described in the 20090522 study, treatment with chemotherapy, hormonal therapy or radiation therapy for cancer, or end of

available data in database. This will be carried through for these additional AFF analyses recommended by FDA.

13.10.5.7.2.6.7 Other Sensitivity Analysis – Quantitative Bias Analysis

We will also conduct a Quantitative Bias Analysis to assess the extent of unmeasured confounding that would be required to refute the observed difference in outcome incidence between initiators of denosumab and zoledronic acid exposure groups at 1 year. **For outcomes in which the 1-year RR between denosumab and zoledronic acid shows no observed difference (95% confidence interval of the RR includes 1.0) or the RR and 95% confidence intervals are favored towards denosumab (RR and 95% CI are <1.0), the E-value method (Vanderweele, 2017) will be used to evaluate how susceptible these outcomes are to the influence of unmeasured or residual confounding.**

13.10.5.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

As describe in the main 20090522 study.

13.10.5.8 Limitations of the Research Methods

13.10.5.8.1 Internal Validity of Study Design

13.10.5.8.1.1 Measurement Error(s)/Misclassification(s)

We required a minimum of 455 days of continuous enrollment to provide a minimum washout period. In addition, we used all data available pre-index date to identify the naive user cohort. However, without lifetime treatment data, our naive user cohort could also include subjects who re-initiate medication after a gap of greater than 455 day.

As with any pharmacoepidemiologic study conducted using health claims data, there is a possibility of misclassification and measurement error. Presence of a diagnosis code on a medical claim is not positive presence of disease, as the diagnosis may be incorrectly coded or included as a rule-out criterion rather than indicating actual disease. We do not anticipate misclassification to be differential on the basis of osteoporosis treatment. As mentioned in Section 13.10.13.10.5.3.4, validated algorithms have been used to define most of the outcomes to minimize misclassification of these variables.

As noted in Section 13.10.13.10.3.3, it was recommended that 2 events, osteonecrosis of the jaw and atypical femur fracture, not be included in the comparative analysis. The rarity of these events can result in lack of power and precision that has the potential to obscure a positive safety association. The osteonecrosis of the jaw algorithm used in the 20090522 study was developed to optimize sensitivity and has a low positive

predictive value (probability that subjects identified using the algorithm truly have the event) in US databases. The resulting misclassification can bias the results in either direction (Fox et al, 2005). To address this, uncertainty around bias due to misclassification from the resultant low positive predictive value will be assessed by varying our assumptions around the osteonecrosis of the jaw algorithm definition (Section 13.10.13.10.5.7.2.6.5) and recalculating the adjusted relative risks. In addition, in a sensitivity analysis, we will apply a correction for the margin of error introduced by the low PPV

13.10.5.8.1.2 Information Bias

We will be ascertaining information for all subjects using the same methods (extracting information from administrative claims) so we expect that misclassification will not be differential on the basis of osteoporosis treatment.

13.10.5.8.1.3 Selection Bias

Denosumab and zoledronic acid have different dosing intervals which could contribute to subjects being censored. Selection bias may be a concern if there is significant loss to follow-up. As noted in Section 13.10.13.10.5.7.2.2 (missing data) we will compare follow-up post-index date to examine significant differences between the two treatment groups. If we encounter potential survivor bias with varying lengths of follow-up, we are also conducting an ITT analysis (see Section 13.10.13.10.5.7.2.6.4). This limitation may be more pronounced in the oral bisphosphonate comparison

13.10.5.8.1.4 Confounding

To address confounding, we are estimating the cumulative risk of each outcome using inverse-probability of treatment and censoring weighted estimation functions. We also plan to conduct subgroup analyses of subjects with a recent fracture and with no renal disease for further control of confounding. We also added negative control outcomes to indicate the presence of unmeasured or residual confounding.

Active comparator arms with similar indications and use patterns have been reported to enhance the validity of real-world evidence (Franklin et al, 2020) (Lund et al, 2015). However, actively controlled studies have the potential drawback in that the comparator might not be a neutral comparator (Cummings and Mcculloch, 2020). Past literature has suggested that zoledronic acid reduces the risk of cancer which would favor the analysis away from Denosumab (Reid et al, 2020).

Confounding by indication or channeling bias (Lobo et al. 2006) is particularly worrisome, as newer medications can be prescribed preferentially to older, sicker patients. As discussed in Section 13.10.13.10.5.1 Study Design, we used information from previous studies that assessed unmeasured confounding in adjusted comparisons of osteoporosis medications using negative control outcomes to select the zoledronic acid active comparator that would reduce confounding. Introduction of bias is anticipated with the inclusion of the oral bisphosphonate comparators. Previous studies have shown that patients treated with Prolia in the United States data systems were older, had a higher baseline prevalence of fragility fracture, renal impairment, vitamin D deficiency and Charlson Comorbidity Index score >3+ than the women in the BP cohorts (YR 10 ORSR) supporting an unfavorable bias toward Prolia.

13.10.5.8.2 External Validity of Study Design

We expect impact from selection bias to be minimal. In 2019 The Medicare system had medical coverage for approximately 61.5 million beneficiaries, of which approximately 53 million (86.1%) were age 65 or older, 38.6 million (62.7%) were in original Medicare plan and remaining were enrolled in Medicare Advantage or other healthcare plans, approximately 45.8 million (74.5%) had part D prescription drug coverage. Among those with part D drug coverage and 39.1 million (85.3%) were age 65 or older, 25.6 million (55.8%) had stand-alone part D coverage and remaining had Medicare Advantage prescription drug coverage. According to 2020 US census there were 54 million adults age 65 or older indicating that at least 98% of US adults aged 65 or older have Medicare coverage. This study requires a minimum of 455 days of continuous enrollment for eligibility. We use a 455-day look-back period to evaluate baseline characteristics and prior treatment. We also require that subjects be enrolled in traditional Fee for Service Plan and not on Medicare advantage or other private healthcare plan. Selection bias may occur if the subjects who do not have 455 days of continuous insurance coverage before the index date are systematically different from those who do have continuous coverage or if subjects who are enrolled in Medicare advantage plans are systematically different than those in Medicare Fee for Service plans. Similar bias can also occur if the subjects who are 65 years or older but do not have Medicare coverage because they are in active workforce and have employer provided healthcare. Therefore, the population included in the analyses may be slightly different from the total population of patients.

13.10.6 References

- Aalen O. Nonparametric Estimation of Partial Transition Probabilities in Multiple Decrement Models. *Ann Stat.* 1978;6:534–545.
- Brenner H, Gefeller O. Use of the positive predictive value to correct for disease misclassification in epidemiologic studies. *American journal of epidemiology.* 1993;138:1007-1015.
- Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. *American journal of epidemiology.* 2006;163:1149-1156.
- Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis-2020 Update Executive Summary. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists.* 2020.
- Choi NK, Solomon DH, Tsacogianis TN, Landon JE, Song HJ, Kim SC. Comparative Safety and Effectiveness of Denosumab Versus Zoledronic Acid in Patients With Osteoporosis: A Cohort Study. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2017;32:611-617.
- Cummings SR, Mcculloch C. Explanations for the difference in rates of cardiovascular events in a trial of alendronate and romosozumab. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2020.
- Ehrenstein V, Heide-Jorgensen U, Schiodt M, et al. Osteonecrosis of the jaw among patients with cancer treated with denosumab or zoledronic acid: Results of a regulator-mandated cohort postauthorization safety study in Denmark, Norway, and Sweden. *Cancer.* 2021.
- Fox MP, Lash TL, Greenland S. A method to automate probabilistic sensitivity analyses of misclassified binary variables. *International journal of epidemiology.* 2005;34:1370-1376.
- Franklin JM, Patorno E, Desai RJ, et al. Emulating Randomized Clinical Trials with Nonrandomized Real-World Evidence Studies: First Results from the RCT DUPLICATE Initiative. *Circulation.* 2020.
- Lash TL, Fox MP, Fink AK. Misclassification. In: *Applying Quantitative Bias Analysis to Epidemiologic Data.* 2009:117-150.
- Lewiecki EM. Bisphosphonates for the treatment of osteoporosis: insights for clinicians. *Ther Adv Chronic Dis.* 2010;1:115-128.
- Lin TC, Yang CY, Kao Yang YH, Lin SJ. Incidence and risk of osteonecrosis of the jaw among the Taiwan osteoporosis population. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2014;25:1503-1511.
- Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep.* 2015;2:221-228.

- Magder LS, Hughes JP. Logistic regression when the outcome is measured with uncertainty. *American journal of epidemiology.* 1997;146:195-203.
- Mcgrath LJ, Spangler L, Curtis JR, et al. Using negative control outcomes to assess the comparability of treatment groups among women with osteoporosis in the United States. *Pharmacoepidemiology and drug safety.* 2020;29:854-863.
- Mills, L. A., S. A. Aitken and A. Simpson (2017). "The risk of non-union per fracture: current myths and revised figures from a population of over 4 million adults." Acta Orthop 88(4): 434-439.
- Newcomer SR, Xu S, Kulldorff M, Daley MF, Fireman B, Glanz JM. A primer on quantitative bias analysis with positive predictive values in research using electronic health data. *Journal of the American Medical Informatics Association : JAMIA.* 2019;26:1664-1674.
- Ozenne BMH, Scheike TH, Staerk L, Gerds TA. On the estimation of average treatment effects with right-censored time to event outcome and competing risks. *Biom J.* 2020;62:751-763.
- Reid IR, Horne AM, Mihov B, et al. Effects of Zoledronate on Cancer, Cardiac Events, and Mortality in Osteopenic Older Women. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2020;35:20-27.
- Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. *Biometrics.* 2000;56:779-788.
- Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology.* 2000;11:550-560.
- Schiodt M, Vadhan-Raj S, Chambers MS, et al. A multicenter case registry study on medication-related osteonecrosis of the jaw in patients with advanced cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2018;26:1905-1915.
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Research CFBEA. Guidance for Industry and FDA Staff Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data. 2013.
- **VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Annals of Internal Medicine.* 2017; 167: 268-274.**
- Westreich, D. and S. R. Cole (2010). "Invited commentary: positivity in practice." Am J Epidemiol 171(6): 674-677; discussion 678-681.
- Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value Health.* 2010;13:273-277.
- Zura, R., J. T. Watson, T. Einhorn, S. Mehta, G. J. Della Rocca, Z. Xiong, Z. Wang, J. Jones and R. G. Steen (2017). "An inception cohort analysis to predict nonunion in tibia and 17 other fracture locations." Injury 48(6): 1194-1203.

13.10.7 Appendices

13.10.7.1 Gating Comparative Observational Analyses

General description of Gating for comparative safety studies: activities by study role and stage of analysis (Adaptable by study)

Version 24 June 2020

Gating in Comparative Analyses

Purpose: Decisions about study design or analysis should not be informed by knowledge of how such decisions might affect study results. Protocol and SAP authors attempt to pre-specify all statistical analysis plans in sufficient detail to minimize ambiguity about how the results will be obtained. However, often data will need to be examined to inform key aspects of the study design or analysis; and in other cases, issues discovered during analysis might require certain deviations from the planned design or analysis.

To avoid biasing point estimates and standard errors for the primary comparative analysis, the individuals making these decisions will be isolated – through their assigned roles and responsibilities in each analysis stage – from knowledge about how these decisions might affect outcomes. Based on data supplied to them by the analysts, investigators will make decisions about model specifications, determination of adequate covariate balance and analytic sample sizes, and decisions to proceed with subgroup analyses. The results supplied by the analyst should not provide any direct information about how such decisions might affect results.

The gating procedures described below – or similar procedures employed by external collaborators – are required for comparative safety or effectiveness studies that will be reported to a Health Authority.

	Stage 0 Dataset preparation	**Stage 1** Characteristics of cohorts and covariate balancing	**Stage 2** Incidence of outcomes overall and by treatment group	**Stage 3** Comparative analyses between treatment groups**	**Stage 4** Results dissemination
Primary programmer	Builds cohort according to SAP. Randomly assigns character to treatment groups. Delivers blinded (±) cohort with **no outcome data** to Analyst.	No involvement	Delivers blinded (±) cohort **with outcome data included** to Analyst.	No involvement	**Unblinds** treatment group identities.
Analyst	No involvement	Receives treatment-blinded (±) data set with **no outcome data.** Conducts descriptive analyses and propensity score building, weighting, balance diagnostics. Manages analytic QC of each stage.	Receives treatment-blinded (±) data set with **outcome data.** Conducts descriptive outcome analyses.	Conducts comparative analyses.	Replaces blinding characters with treatment identities in all tables.
Analytic advisor	No involvement	Makes and records decisions on variable inclusion and parameteriz-ation in propensity score models. This is an iterative process with Analyst(s). After QC, determines which results will be submitted for gatekeeper review.	Reviews outcome results and proposes the outcomes that should move forward or be discarded, based on sample sizes and event numbers.	Reviews comparative results and ensures completeness, given approved SAP and gate approvals.	No involvement
Gatekeeper		**Gate 1** Covariates are balanced between treatment groups.* Reviews final PS model diagnostics and balance assessments. Grants access to stage 2 for each cohort or subgroup that meet balance criteria.	**Gate 2** Analytic sample size and number of outcome events are adequate.* Reviews final sample sizes and event numbers. Grants access to stage 3 for each cohort or subgroup with sufficient size.	**Gate 3** All analyses are complete.*** Reviews final results and gives approval for unblinding.	

* If subgroup analyses are planned, each subgroup must be assessed at the gate separately. Subgroups may be discarded if the Analytic Advisors and Gatekeepers determine the criteria cannot be met. The full cohort analyses can proceed without discarded subgroups having passed the gate. Discarded subgroups cannot re-enter the analytic process if this risks later-stage analyses of non-discarded groups informing (biasing) analytic decisions for earlier-stage discarded subgroups.

** All cohorts and subgroups must have been assessed for Gate 2 and either passed or be discarded before any comparative analyses are initiated.

*** If subgroups are still present, Gate 3 cannot be passed until all subgroup analyses are complete.

13.10.7.2 Variables Considered During Creation of Propensity Score

Characteristic
Demographic and Other Patient Characteristics
Race/ethnicity
Age
Geographic region
Calendar year of index date
Seasonality (quarter) of index date
Fragility fracture history
Number of fractures
Fragility fracture history (hip, closed)
Fragility fracture history (distal radius/ulna)
Fragility fracture history (humerus-closed)
Fragility fracture history (other femur closed)
Fragility fracture history (pelvis-closed)
Fragility fracture history (distal radius/ulna – other)
Fragility fracture history (spine, closed pathologic; other)
Charlson comorbidity index score
Usage of healthcare facilities
Number of physician office visits per patient during the 15-month baseline period
Number of emergency room visits per patient during the 15-month baseline period
Days of hospitalization per patient during the 15-month baseline period
Duration of hospitalization or nursing facility stay

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Footnotes defined on the last page of this table

Risk Factors
Diseases - Chronic
HIV/AIDS
Kidney disease (CKD)
Type I diabetes
Type II diabetes
Inflammatory bowel disease
Psoriasis
Rheumatic fever
Dermatologic adverse events
Asthma
Atopy
Allergic rhinitis
Allergic conjunctivitis
Allergic rash/allergic skin eruption
Eczema
Positive skin allergy history
Liver cirrhosis
Overweight /obesity
Chronic lung disease2
Lupus
Rheumatoid arthritis
Ankylosing spondylitis
Multiple sclerosis
Peripheral vascular disease
Colorectal polyps
Ulcerative colitis
Crohn’s disease
Familial adenomatous polyposis
Polycystic ovarian syndrome

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Footnotes defined on the last page of this table

Diseases - Other
Hypocalcemia
Hypoparathyroidism
Kyphosis
Osteoarthritis
Vitamin D deficiency
Malnutrition
Anorexia
Hypoalbuminemia
Hypersensitivity
Drug allergies
Serious infection
Severe neutropenia
Decubitus ulcer
Gallstones
Biliary disease / Choledocholithiasis
Hyperlipidemia
Hypertriglyceridemia
Medications
Number of Medications
Anticoagulants
Estrogen (hormone replacement therapy)
Selective Estrogen Receptor Modulator
Duration of prior zoledronic acid (days)[b]
Duration of prior Denosumab use (days)[b]
Duration of prior Oral BP use (days)b
Parathyroid hormone
Corticosteroid (oral or injectable)
Proton pump inhibitor
Anti-diabetics
Immunosuppressant drugs
Tamoxifen
Opiates use
Anti-platelet drug
Use of nonsteroidal anti-inflammatory drugs

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Footnotes defined on the last page of this table

Antibiotics (within 2 weeks before index date)
Sulfonamides
Penicillin
Cephalosporins
Others
Thyroidectomy
Inflammatory or infectious dental disease
Periodontal and dental abscesses
Gingival bleeding, calculus
Dental fistula
Osteomyelitis in the jaw
Recent dental extraction
Oral surgical interventions
Endodontic/periodontal bone surgery
Periapical surgery
Root canal treatment
Dental implants
Use of dentures
Tooth loss
Tobacco use disorders
Disorders related to sun exposure
Family history of cancers
Exposure to radiation
Alcohol abuse
Post endoscopic retrograde cholangiopancreatography
Substance abuse (illicit drug injection)

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[a] Among patients with > 1 visit.
[b] Analysis restricted to patients with fracture healing complications and AFF