ORIGINAL REPORT

Design and methods of a postmarketing pharmacoepidemiology study assessing long-term safety of Prolia® (denosumab) for the treatment of postmenopausal osteoporosis[‡]

Fei Xue[1]*, Haijun Ma[2], Catherine Stehman-Breen[3], Christine Haller[4], Leonid Katz[3], Rachel B. Wagman[3], and Cathy W. Critchlow[1] for the Denosumab Global Safety Assessment Team[†]

[1] *Center for Observational Research, Amgen Inc., Thousand Oaks, CA, USA*
[2] *Global Safety Biostatistics, Amgen Inc., Thousand Oaks, CA, USA*
[3] *Global Development, Amgen Inc., Thousand Oaks, CA, USA*
[4] *Global Safety, Amgen Inc., Thousand Oaks, CA, USA*

ABSTRACT

Purpose To describe the rationale and methods for a prospective, open-cohort study assessing the long-term safety of Prolia® for treatment of postmenopausal osteoporosis (PMO) in postmarketing settings.

Methods Data will be derived from United States Medicare, United Healthcare, and Nordic (Denmark, Sweden, Norway) national registries. Observation will begin on the date of first Prolia® regulatory approval (May 26, 2010) and continue for 10 years. Women with PMO will be identified by postmenopausal age, osteoporosis diagnosis, osteoporotic fracture, or osteoporosis treatment. Exposure to Prolia® and bisphosphonates will be updated during follow-up; exposure cohorts will be defined based on patient-years during which patients are on- or post-treatment. Nine adverse events (AEs) will be assessed based on diagnosis codes: osteonecrosis of the jaw (ONJ), atypical femoral fracture (AFF), fracture healing complications, hypocalcemia, infection, dermatologic AEs, acute pancreatitis, hypersensitivity, and new primary malignancy. Medical review will confirm selected potential cases of ONJ and AFF. Incidence rates (IRs) of AEs will be described overall and for exposure cohorts; multivariate Cox proportional hazard regression models will compare IRs of AEs across exposure cohorts. Utilization patterns of Prolia® for approved, and unapproved indications will be described.

Conclusion This study is based on comprehensive preliminary research and considers methodological challenges specific to the study population. The integrated data systems used in this regulatory committed program can serve as a powerful data resource to assess diverse and rare AEs over time. © 2013 Amgen Inc. Pharmacoepidemiology and Drug Safety published by John Wiley & Sons, Ltd.

KEY WORDS—postmenopausal osteoporosis; Prolia® (denosumab); postmarketing drug safety; pharmacovigilance; database; pharmacoepidemiology methods; pharmacoepidemiology

INTRODUCTION

Osteoporosis is a skeletal disorder characterized by low bone mass, bone tissue deterioration, disruption of bone architecture, and compromised bone strength, predisposing those affected to increased fracture risk.[1] Postmenopausal women are at particularly high risk with an estimated one in two women aged ≥50 years developing an osteoporotic fracture in her lifetime.[2] Such fractures, particularly hip fractures, are debilitating and can lead to diminished quality of life, disability, and death.[1] Worldwide prevalence of osteoporosis is approximately 200 million,[3] which will likely increase due to longer life expectancy and aging populations.

Denosumab (Amgen Inc., Thousand Oaks, CA, USA) is a fully human monoclonal antibody to RANK ligand (RANKL) that inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength.[4] Prolia® (denosumab 60 mg subcutaneously every six months) is approved in the United States (US), Canada,

---

*Correspondence to: Fei Xue, One Amgen Center Drive, MS 24-2-C, Thousand Oaks, CA 91320, USA. E-mail: fxue@amgen.com
[†] Elizabeth Delzell, Jeffrey R. Curtis (University of Alabama at Birmingham, AL, USA); David Dore, Florence Wang (OptumInsight, Boston, MA, USA); Henrik Toft Sorensen, Lars Pedersen, Vera Ehrenstein (Arhus University, Denmark)
[‡] Methods of the current study have been presented as a poster at the International Conference of Pharmacoepidemiology, August 2011, Chicago, USA

European Union, and other countries for the treatment of postmenopausal osteoporosis (PMO) in women at high or increased risk for fracture. Although several agents are approved for treatment and/or prevention of osteoporosis, Prolia® represents a novel approach with its targeted inhibition of RANKL.[4]

In 2007, the Food and Drug Administration (FDA) Amendment Act granted the FDA new authority to strengthen safety programs for marketed drugs. In this new regulatory environment, there is intense interest in pharmacoepidemiologic studies using large healthcare databases. During review of the Prolia® Marketing Authorization Application, regulatory authorities raised potential or theoretical safety considerations based on mechanism of action, biological plausibility, clinical trial evidence, and/or findings from studies of other antiresorptive agents (potential 'class' effects).

Amgen Inc. therefore proactively developed a comprehensive risk management plan with FDA input. Here we describe the design of one component of this plan: a prospective, multi-national, 10-year, open-cohort study using existing data systems to assess the long-term safety of Prolia® for the treatment of PMO. Study objectives are to (i) describe characteristics of women with PMO; (ii) estimate incidence rates (IRs) of specific adverse events (AEs) among women with PMO; (iii) compare IRs of specific AEs among women treated with Prolia® versus a bisphosphonate (the most commonly used osteoporosis medication); and (iv) describe Prolia® utilization patterns for approved and unapproved indications.

DESIGN AND RESEARCH PLAN

This prospective cohort study is based on data accumulated over 10 years following the date of first regulatory approval for Prolia®, May 26, 2010. Data sources include US Medicare, United Healthcare, and national healthcare registries from Denmark, Sweden, and Norway ('Nordic national registries').

Data sources

Data system selection was based on several considerations: the number of expected Prolia® users had to be large enough to enable informative analyses of rare events; available diagnosis, procedure, and medication codes needed to reliably identify women with PMO, medication exposures, comorbidities, and specific AEs; long-term follow-up had to be sufficient to minimize potential selection bias from subject attrition and detect AEs with long induction or latency periods; access to medical charts was preferred to verify AE

occurrence; and study populations had to be representative of the source populations. Thus, data systems were chosen to complement each system's strengths and limitations. Investigators from each system obtained approval from their respective Internal Review Board or Ethics Committee.

US Medicare is a nationally representative, population-based, federal health plan primarily for Americans ≥65 years of age. A large number of women at high risk of osteoporotic fracture would be expected. Patient information is documented from initial enrollment until death or subsequent loss of full Medicare coverage. Loss to follow-up is low, though data may be incomplete for beneficiaries switching from fee-for-service coverage to Medicare Advantage. Medical records can be retrieved from consenting beneficiaries or providers to confirm specific AEs. Approximately 20.6 million women receive pharmacy benefits through Medicare D which can be linked to institutional (Part A) and non-institutional (Part B) claims. As the largest data system, Medicare will provide >80% of the total study sample size. The time lag for data availability is approximately 24 months. Prolia® is covered mainly by Medicare Part B rather than Part D, allowing reimbursement for drug administered according to the US label.

United Healthcare is an operating division of UnitedHealth Group, the largest private health carrier in the US.[5] Administrative databases include claims submitted by health care professionals for covered services, and patient enrollment and provider data. Data are relatively complete for billable medical transactions paid by United Healthcare; claims paid by Medicare for patients with Medicare supplemental coverage are not available. Pharmacy claims data are available within six weeks of claim submission, and 95% of paid medical claims are collected and adjudicated within six to nine months, the shortest time lag between data collection and availability among the three study data systems. Prolia® is covered under medical benefit with varying co-pays governed by medical policies consistent with the US product label.

Medical care in Denmark, Sweden, and Norway is provided as part of national health systems. These national healthcare registries, through a system of interlinked databases, collect a broad spectrum of data on all citizens beginning at birth including medical records, hospitalizations, prescriptions, laboratory and pathology results, electronic radiographs, death certificates, and socioeconomic data. Data are collected until death or emigration, providing virtually complete follow-up. The time lag for data availability is approximately 24 months. In each country, Prolia® is prescribed

for postmenopausal women with documented osteoporosis after first trying generic medication.

Patient selection criteria

Women with PMO between May 26, 2010 and May 25, 2020 will be identified according to the following algorithm: postmenopausal age (≥65 years in US Medicare or ≥55 years in other data systems) and diagnostic codes indicating osteoporosis or osteoporotic fracture and/or medication codes indicating PMO treatment.

The validity of diagnosis codes and treatment codes to identify women with osteoporosis were explored by Lix et al.[6], in which sensitivity of a similar algorithm was approximately 70–80% and specificity was approximately 70%. Diagnostic codes are International Classification of Disease (ICD) codes (ICD-9-CM for US Medicare and United Healthcare; ICD-10 for the Nordic national registries). Medication codes include drug codes (National Drug Codes [NDC] in the US; treatment or Anatomical Therapeutic Chemical classifications [ATC] codes in Nordic national registries) and procedure codes (Healthcare Common Procedure Coding System [HCPCS] in the US).

Women must be continuously enrolled for ≥12 months in the insurance claims data systems. In Medicare, patients must be enrolled in Parts A, B, and D but not Medicare Advantage; patients must have complete pharmacy and medical coverage in United Healthcare. The patient's study index date is the date when both the PMO algorithm and 12-month continuous enrollment criterion are satisfied. To eliminate patients who might receive osteoporosis medications for other indications, women diagnosed with Paget's disease of the bone or malignancy (excluding non-melanoma skin cancer) or who received chemotherapy, hormonal therapy, or radiation therapy for cancer 12-months before the index date (study baseline period) will be excluded. The exclusion of prevalent cancer patients minimizes potential confounding by malignancy and potentially increases the specificity of identifying Prolia®-treated patients by avoiding inclusion of XGEVA®-treated patients (denosumab 120 mg subcutaneously every four weeks), indicated for the prevention of skeletal-related events in patients with bone metastases.

Exposure assessment and cohorts

Prolia® and bisphosphonate (oral or intravenous [IV]) exposure will be identified based on medication codes. Before assignment of denosumab-specific HCPCS codes (C9272: injection denosumab 1 mg, assigned October 1, 2010; J0897: injection denosumab 1 mg, assigned January 1, 2012), nonspecific HCPCS codes (J3490:

drugs unclassified injection; J3590: unclassified biologic) were used by providers seeking reimbursement. These nonspecific codes will be used along with diagnostic codes, costs, and units administered associated with claims to identify Prolia® exposure before the adoption of specific codes. There was no delay in assigning denosumab-specific NDC, ATC, or treatment codes.

Bisphosphonate treatment will be assessed by codes indicating prescription of branded oral bisphosphonates (alendronate [Fosamax®], risedronate [Actonel®], ibandronate [Boniva®/Bonviva®]); generic bisphosphonates (alendronate and etidronate); and IV bisphosphonates (ibandronate and zoledronate [Reclast®/Aclasta®]). Separate assessment of exposure to oral versus IV bisphosphonates will be performed in US Medicare, United Healthcare, and Norwegian registries where these treatments can be distinguished. To avoid including patients receiving bisphosphonate for conditions such as Paget's disease of the bone or cancer, patients receiving bisphosphonates with dosages indicated for those conditions will be excluded. Other osteoporosis medications will be assessed by codes indicating prescription of calcitonin, teriparatide, or raloxifene.

Exposure cohorts are defined based on accumulated person-years (PYs) of Prolia® or bisphosphonate (oral or IV) exposure.

On-treatment and post-treatment periods

Patients will be considered on-treatment for medication if time between the current and subsequent medication administration or prescription fill/refill is less than or equal to the medication days supplied plus 60 days. Otherwise, on-treatment periods will stop at the end of days supplied plus 60 days. The post-treatment period is defined as the time immediately following the on-treatment period until the earliest of end of follow-up or new prescription of the same medication.

Patient follow-up

Follow-up begins at a patient's index date and continues until the earliest of disenrollment from the data system; death; diagnosis of Paget's disease of the bone or malignancy (excluding non-melanoma skin cancer); treatment with chemotherapy, hormonal therapy, or radiation therapy for cancer; or end of study. When assessing AE incidence, patients will be censored at occurrence of the corresponding AE. For events that may recur (infection, dermatologic AEs, hypersensitivity, and hypocalcemia), repeated occurrences will also be assessed. Follow-up time will be divided into mutually exclusive on- or post-treatment periods within Prolia® only, bisphosphonate only (oral and/or IV), and both

Prolia®- and bisphosphonate-exposure cohorts. A patient who discontinues and reinitiates treatment or changes medication over time will contribute multiple segments of PYs to the same or different exposure cohorts.

Time at risk for AEs of interest

Time at risk for specific AEs within exposure cohorts will be defined based on putative relationships between Prolia® and/or bisphosphonate exposure and specific AEs. Time at risk will be defined as the on-treatment period for some AEs and as the on-treatment plus post-treatment period for other AEs. Post-treatment period lengths are based on an etiologically relevant period for the specific exposure and AE. Figure 1 shows an example of classification of time at risk for a patient receiving one bisphosphonate dose before one Prolia® dose.

Outcome assessment

AEs of interest were based on clinical study findings or theoretical concerns suggested by Prolia's® mechanism of action. AEs (and specific subtypes) include: osteonecrosis of the jaw (ONJ); atypical femoral fracture (AFF)[7] leading to hospitalization; fracture healing complications; hypocalcemia leading to hospitalization or ER visit; infection (subtype: skin infection) leading to hospitalization, ER visit, or administration of parenteral anti-infective medication; dermatologic AEs (subtype: bullous dermatoses) leading to hospitalization or ER visit; hypersensitivity (subtype: anaphylactic hypersensitivity) leading to hospitalization or ER visit; new primary malignancy (excluding non-melanoma skin cancer); and acute pancreatitis leading to hospitalization. For all AEs, occurrence of incident events will be assessed. As infection, dermatologic AEs, hypersensitivity, and hypocalcemia may recur, repeated occurrences will also be assessed.

AEs will be identified using case ascertainment algorithms incorporating diagnosis codes and, for some AEs, medication codes. Comprehensive literature reviews provided important information concerning development, validation, and use of algorithms ascertaining AEs in the same or similar data systems as those in our study: ONJ,[8] AFF,[9] serious infections,[10–12] dermatological AEs,[13,14] hypersensitivity,[15] malignancy,[16,17] and pancreatitis.[18–20] For example, the positive predictive value of the ascertainment algorithm for serious infection was >80%.[10–12] At the time of study design, algorithm validation results were not available for AFF or hypocalcemia
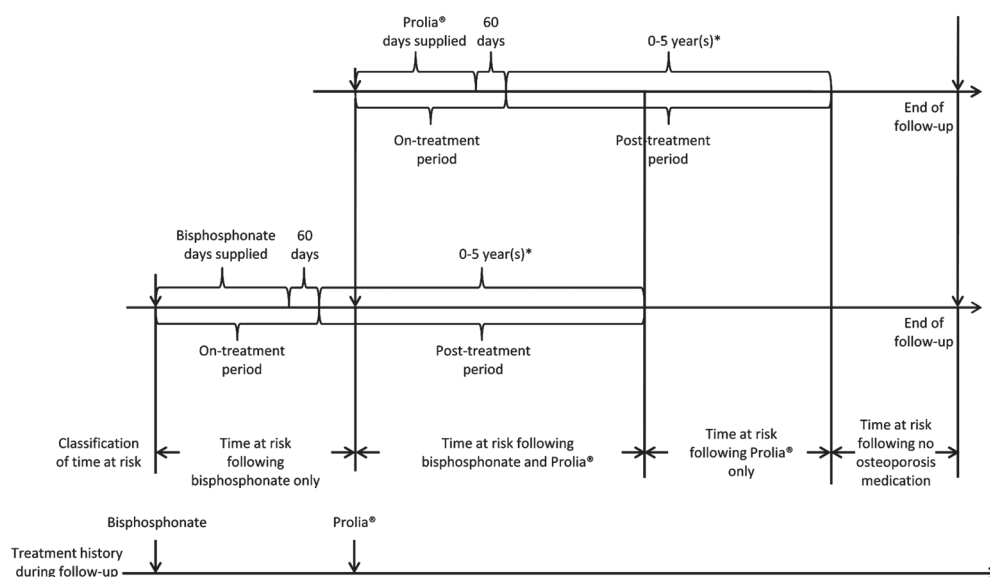
*For all adverse events, analyses will be conducted based on time at risk defined by on-treatment period only, without accounting for post-treatment period. Additionally, time at risk will include up through the first year of the post-treatment period for osteonecrosis of the jaw, atypical femoral fracture, and fracture healing complications, and up to the first 5 years of the post-treatment period for new primary malignancy.

Figure 1. Example of the classification of time at risk based on the on-treatment and post-treatment period for a patient receiving one dose of a bisphosphonate before receiving one dose of Prolia®

and were not well described for ONJ and fracture healing complications. Also, compared with the comprehensive list of conditions included in our definition of dermatologic events and hypersensitivity, validation results were available for only a small subset of severe conditions, such as erythema multiforme[13,14] and anaphylactic shock.[15] Ongoing research is focusing on the development or refinement of ascertainment algorithms where gaps in the literature exist. Because of limitations of ICD-based algorithms identifying true cases of ONJ and AFF, all cases of Prolia®-exposed, and a sample of bisphosphonate-exposed patients with diagnoses suggestive of ONJ and AFF for whom medical records can be retrieved will be confirmed by medical record or radiograph review where feasible (Medicare, Central and North Denmark Regions, and Sweden for ONJ; Central and North Denmark Regions for AFF).

Covariate assessment

Covariates to be considered include demographics, osteoporosis severity reflected by fragility fracture or use of osteoporosis medications, overall health status (e.g. Charlson comorbidity index), health seeking behaviors (e.g. health resource utilization), and AE-specific risk factors. Covariates will be assessed during the 12-month study baseline period and re-evaluated as time-dependent covariates during the 12-month period before entry to each exposure cohort (exposure cohort baseline period). Once identified, chronic conditions (e.g. renal failure, diabetes) will be considered present throughout the remaining study follow-up period.

Statistical considerations

Study size. The estimated PYs of Prolia® exposure were calculated based on the expected number of women with PMO and the proportion of Prolia® users among them. It was assumed that 50% of PMO women would receive osteoporosis medication[21,22] with 5% (2.5% in the year after launch) being treated with Prolia® after stabilization of Prolia® uptake. Assuming that the number of women with PMO remains stable over time, the overall PYs of Prolia® exposure was estimated to be 575 462 during 10 years post-approval including 475 000 from Medicare; 19 712 from United Healthcare; 21 850 from Denmark; 37 050 from Sweden; and 21 850 from Norway.

Using Fisher's two-sided exact test with α = 0.05,[23] and based on a ratio of 10:1 between comparator- and Prolia®-exposed cohorts, analyses in Medicare will have over 90% power to detect a relative risk of ≥2 for AEs with a background IR of ≥7 per 100 000 PYs including all AEs except ONJ and AFF. Medicare-based analyses will have appreciable power to detect moderately elevated relative risks for rarer AEs (e.g. >80% power to detect a relative risk of ≥4 for ONJ [1 per 100 000 PYs]).[24] United Healthcare-based analyses, which have the smallest sample size, will have >90% power to detect a relative risk of ≥2 for AEs with a background IR of ≥130 per 100 000 PYs including fracture healing complications, infection, dermatologic AEs, pancreatitis, hypersensitivity, and malignancy.

Description of patients with PMO. Patient characteristics, including AE risk factors assessed over the study baseline period, will be described for PMO women overall and by osteoporosis treatment received on the patient's study index date (no treatment or treatment with Prolia® or bisphosphonate). PYs of follow-up in women with PMO overall and in each exposure cohort will be described by covariates assessed both during the study baseline period and each exposure cohort baseline period.

Estimation of AE IRs and event rates. The IR and 95% confidence interval for each AE will be calculated for PMO women overall and for each exposure cohort.

To avoid inclusion of potentially prevalent cases of ONJ, AFF, fracture healing complications, new primary malignancy and acute pancreatitis, patients diagnosed with the same or similar condition (e.g. pancreatic disease when assessing pancreatitis) during the study baseline period will be excluded when estimating the corresponding IR.

For each AE, IR and event rate analyses will be conducted based on time at risk defined by the on-treatment period (Prolia® only, bisphosphonates only, and both Prolia® and bisphosphonates). For events which may recur (e.g. infection, dermatologic AEs, hypersensitivity, and hypocalcemia), time at risk is not censored at first AE occurrence, and event rates will be assessed over all occurrences of that AE. For selected AEs, additional analyses will be conducted based on time at risk including the on-treatment period through the first year (i.e. ONJ, AFFs, and fracture healing complications) or five years (i.e. new primary malignancy) of the post-treatment period (Table 1).

Analyses stratified by cumulative doses of prior bisphosphonate treatments will be conducted to explore the effect of long-term bisphosphonate exposure on the risk of ONJ, AFF, fracture healing complication, and new primary malignancy.

Table 1. Analyses for estimating or comparing rates of adverse events of interest

Adverse events of interest	Time at risk defined by:		Event type		Exclude prevalent cases	Sub-group analyses
	On-treatment period only	On- and post-treatment periods	First event	First and subsequent events		
Osteonecrosis of the jaw	X	X (+ up to 1 year post-tx)	X		X	
Atypical femoral fracture	X	X (+ up to 1 year post-tx)	X		X	
Fracture healing complications	X	X (+ up to 1 year post-tx)	X		X	
Hypocalcemia	X		X	X		
Infection	X		X	X		Skin infection
Dermatologic adverse events	X		X	X		Bullous dermatoses, erythematous events
Acute pancreatitis	X		X		X (Pancreatic diseases)	
Hypersensitivity	X		X	X		Anaphylactic hypersensitivity
New primary malignancy	X	X (+ up to 5 year post-tx)	X		X	

tx = treatment

Comparison of AE IRs. Multivariate Cox proportional hazard regression models will be used to estimate IR ratios for all AEs comparing the Prolia® exposure cohort with a comparable bisphosphonate exposure cohort, adjusting for potential confounders assessed during the study baseline period and updated during the exposure cohort baseline periods. Anderson–Gill or Poisson regression models will be used to estimate adjusted AE event rates for which multiple occurrences are allowed. Similar to estimation of IRs, the comparison of AE IRs will follow the same specifications related to time at risk, event type, exclusion of prevalent cases, and sub-group analyses (Table 1).

Description of Prolia® utilization patterns for PMO. Descriptive statistics will be used to characterize frequency of Prolia® administration, length of utilization, and the proportion of treated women who initiate therapy, discontinue therapy, or switch to another osteoporosis medication.

Sensitivity analyses. Robustness of effect estimates will be assessed in sensitivity analyses varying length of time at risk and length of study baseline period. To better understand the risk of dermatologic AEs, hypersensitivity, and hypocalcemia associated with denosumab treatment initiation, the monthly cumulative IRs in the first six months following initial treatment will be calculated.

Analysis of Prolia® utilization patterns for unapproved indications. Analyses describing the utilization pattern of Prolia® (denosumab 60 mg subcutaneously every six months) for unapproved indications will be performed at the patient and administration level among all patients receiving Prolia® without applying other study eligibility criteria.

Prolia® administrations will be classified as an approved or unapproved indication per the label based on patients' age and gender, Prolia® dose and intervals between doses, and received diagnosis. The frequency and proportion of Prolia® treatment for unapproved indications will be summarized. Prolia® utilization for unapproved indications will be described with respect to demographics, clinical characteristics, and the potential indication.

Reporting of results. Interim analyses will be performed annually to describe patient accrual, patient characteristics, Prolia® utilization patterns, and rates of specific AEs. A final analysis addressing all objectives for all AEs will be performed following the 10 year data collection period. Analyses assessing the effect of Prolia® on common events may be conducted before end of study if data are sufficient to permit adequate statistical power. All analyses will be conducted independently in each data system by data system investigators according to a common protocol and statistical analysis plan adapted to leverage the unique features of each data system. A meta-analysis based on study-level summary statistics may be considered if significant heterogeneity of study results across data systems is not observed.

DISCUSSION

Several design, methodological, and analytical issues were considered due to challenges specific to the study population and exposures and outcomes of interest. First, use of administrative data was more feasible than a prospective registry due to the need for a large population to assess rare AEs. Second, identification of PMO, an under-diagnosed and under-treated condition,[1] was based on both diagnosis of osteoporosis/

osteoporotic fracture and receipt of osteoporosis medications. Since both Prolia® and zoledronate are indicated for other conditions, excluding patients who could have been treated for other indications was necessary. Third, because physician preference for Prolia® versus another osteoporosis medication may be affected by factors such as patient age and comorbidities or duration and severity of osteoporosis, confounding by indication must be accounted for in both study design and analysis. Fourth, because a large proportion of new Prolia® users may have been previously treated with a bisphosphonate, a new-user design[25] which mitigates biases associated with previous treatments, if adopted, will be based on a very small number of patients. Also, patients with osteoporosis tend to switch treatments over time, so an open-cohort design combined with an 'as treated' analysis was selected to account for time-varying medication exposure. Finally, to facilitate analyses of outcomes with various lengths of induction or latency periods, time at risk could either be limited to on-treatment periods or could include both on- and post-treatment periods. Despite comprehensive feasibility assessments conducted to inform study design, emerging challenges are anticipated over the 10-year study period due to changes in data availability, number of patients receiving Prolia®, physician practice patterns, coding practices and systems, and evolving epidemiological and statistical methodologies. Therefore, study protocol and statistical plan amendments may be necessary.

Our study has several limitations. First, in these administrative data systems, study exposure, outcomes, and covariates are based on diagnosis, medication, and procedure codes, which may not reliably identify the intended variables. For instance, drug dispensations during hospitalization may not be fully captured. To reduce potential misclassification, ongoing research will validate and may refine study algorithms. Second, as potential confounding variables such as anthropometric factors, life style factors, and clinical measures of disease severity may not be captured, residual confounding may be present. Third, results from feasibility assessments suggested variations in the prevalence of baseline covariates and AE IRs across data systems that are likely due to differences in patient populations and data capture methodology. However, since analyses will be performed within each data system, such differences are not expected to bias effect estimates. Fourth, since our approach adjusts for time-varying covariates in an as-treated analysis, time-varying confounding is possible if an updated variable is influenced by previous treatments and confounds the association between subsequent treatment and an AE. This possibility will be carefully evaluated and use of methods such as marginal structural modeling may address this issue. Finally, modification of analytic plans or additional approaches such as new data linkages or ancillary studies may need to be considered given possible changes in the external environment or emergence of new safety signals over the 10-year study period. Ensuring transparency between the study sponsor, study investigators, and regulatory agencies will be crucial to obtaining study results that accurately characterize the long-term safety of Prolia® when used in clinical practice settings.

We posit that this study, within the context of the Prolia® postmarketing risk assessment program, is appropriate to assess long-term Prolia® safety. The integrated data systems used in this regulatory committed pharmacovigilance program can serve as a powerful data resource to assess diverse and rare AEs over time.

CONFLICT OF INTEREST

Authors are employees of Amgen Inc. and may hold stock/stock options of Amgen Inc.

KEY POINTS

- Although several agents have been approved by regulatory agencies for the treatment and/or prevention of osteoporosis, Prolia® (denosumab) represents a novel approach to the treatment of bone loss with its targeted inhibition of RANK ligand.
- A comprehensive pharmacovigilance plan for denosumab was developed with input from FDA commensurate to mechanism of action, biological plausibility, clinical trial evidence, and/or findings from studies of other antiresorptive agents (potential 'class' effects).
- This is a prospective multi-national, 10-year, open-cohort study using existing data systems to assess the long-term safety of denosumab for the treatment of postmenopausal osteoporosis (PMO).
- This study employs a rigorous methodology to identify women with PMO and assess adverse events (AEs) of interest associated with the use of denosumab for treatment of PMO within the context of a postmarketing pharmacoepidemiology study.
- The integrated data systems used in this regulatory-committed pharmacovigilance program can serve as a powerful data resource to assess diverse and rare AEs over time.

ACKNOWLEDGEMENTS

REFERENCES

1. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. National Osteoporosis Foundation: Washington, DC, 2010.
2. NIH Consensus Development Panel on Osteoporosis Prevention. Diagnosis, and Therapy, March 7–29, 2000: highlights of the conference. *South Med J* 2001; **94**(6): 569–573.
3. Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. *Bone* 2006; **38**(2S1): S4-S9.
4. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature* 2003; **423**(6937): 337–342.
5. Trefis Team. UnitedHealth Group is worth $70 on health insurance enrollments growth. *Forbes* 2010 http://www.forbes.com/sites/greatspeculations/2012/10/29/unitedhealth-group-is-worth-70-on-health-insurance-enrollments-growth/' (last accessed 10/01/2013).
6. Lix LM, Yogendran MS, Leslie WD, *et al.* Using multiple data features improved the validity of osteoporosis case ascertainment from administrative databases. *J Clin Epidemiol* 2008; **61**(12): 1250–1260.
7. Neviaser 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.
8. Tennis P, Zavras A, Laskarides C, Tan H. Predictive value of ICD and CPT codes for identifying osteonecrosis of the jaw (ONJ). *Pharmacoepidemiol Drug Saf* 2009; **18**(S1): S153–S154.
9. Narongroeknawin P, Patkar NM, Shakoory B, *et al.* Validation of diagnostic codes for subtrochanteric, diaphyseal, and atypical femoral fractures using administrative claims data. *J Clin Densitom* 2012; **15**(1): 92–102.
10. 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**(3): 321–327.
11. 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**(4): 397–409.
12. Thomsen RW, Schoonen WM, Farkas DK, *et al.* Risk for hospital contact with infection in patients with splenectomy: a population-based cohort study. *Ann Intern Med* 2009; **151**(8): 546–555.
13. Chan HL, Stern RS, Arndt KA, *et al.* The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol* 1990; **126**(1): 43–47.
14. Strom BL, Carson JL, Halpern AC, *et al.* Using a claims database to investigate drug-induced Stevens-Johnson syndrome. *Stat Med* 1991; **10**(4): 565–576.
15. Johannes CB, Ziyadeh N, Seeger JD, *et al.* Incidence of allergic reactions associated with antibacterial use in a large, managed care organisation. *Drug Saf* 2007; **30**(8): 705–713.
16. 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.
17. 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.
18. 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**(4): 1019–1027.
19. Eland IA, Sturkenboom MJ, Wilson JH, Stricker BH. Incidence and mortality of acute pancreatitis between 1985 and 1995. *Scand J Gastroenterol* 2000; **35**(10): 1110–1116.
20. 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**(12): 1461–1465.
21. 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* 2003; **163**(18): 2165–2172.
22. 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* 2003; **85-A**(12): 2294–2302.
23. Agresti A 1990 Categorical Data Analysis. Wiley: New York.
24. Sambrook P, Olver I, Goss A. Bisphosphonates and osteonecrosis of the jaw. *Aust Fam Physician* 2006; **35**(10): 801–803.
25. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003; **158**(9): 915–920.