PASS Information

Title	Assessing the Incidence of Osteosarcoma Among Teriparatide Users Using Medicare Part D and State Cancer Registry Data [Study B3D-MC-GHBX Addendum 2.2(a)]
Version identifier of the final study report	1.1
Date of version	**25Apr2018**
EU PAS register number	EUPAS 18117
Active substance	Teriparatide (Calcium homeostasis, parathyroid hormones and analogs; ATC code, H05AA02)
Medicinal product(s):	FORTEO 20 micrograms/80 microliters solution for injection in prefilled pen
Product reference:	EU/1/03/247/001-002
Procedure number:	
Marketing authorization holder(s)	Eli Lilly and Company, Indianapolis, IN
Joint PASS	No
Research question and objectives	Study B3D-MC-GHBX Addendum 2.2(a) was initiated post approval/launch in the United States of America (US). The study commenced in 2014 in the US to evaluate a potential association between teriparatide and adult osteosarcoma in humans. The primary objective was to estimate the incidence rate ratio and 95% confidence interval of osteosarcoma among patients aged 65 years or older with a prescription claim for Forteo versus a cohort of matched comparators in Medicare Part D prescription claim data. The secondary objective was to describe characteristics of each cohort and assess the similarity of certain factors within the two cohorts measured during a baseline period using Medicare Parts A, B, and D for a subset of the patients. This report presents the findings from following patients during an 8-year time period for the occurrence of osteosarcoma.
Country(-ies) of study	United States
Author	PPD RTI Health Solutions PPD
Signature of principal investigator	PPD Signature on file/see approval date below

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly and Company, Indianapolis, IN
MAH contact person	Lilly Global Patient Safety Pharmacoepidemiologist

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1. Abstract

Title: Assessing the Incidence of Osteosarcoma Among Teriparatide Users Using Medicare Part D and State Cancer Registry Data [Study B3D-MC-GHBX Addendum 2.2(a)]

Keywords: osteosarcoma; epidemiology; teriparatide, surveillance; parathyroid hormone (PTH)

Rationale and background: Teriparatide is identical to the 34 N-terminal amino acid sequence of endogenous human parathyroid hormone that stimulates new bone formation. Teriparatide is indicated in adults for the treatment of osteoporosis in postmenopausal women and in men at increased risk for fracture, and for men and women who are at increased risk for fracture due to osteoporosis associated with sustained systemic glucocorticoid therapy. In clinical studies in postmenopausal women, teriparatide significantly reduced the incidence of vertebral and nonvertebral fractures, except hip fractures. Teriparatide caused dose-dependent increases in the incidence of osteosarcoma in rats during preclinical testing. Studies have shown that the rat skeleton is more sensitive to the pharmacological effects of parathyroid hormone in formation of new bone and osteosarcoma than monkey or human skeletons. Study GHBX includes five components: case-finding surveillance in Europe (completed in 2014) and the United States (US), a Forteo Patient Registry in the US, and two population-based observational cohort studies. The population-based cohort studies were designed to identify patients with teriparatide treatment and a comparator group and determine the incidence of osteosarcoma.

Research question and objectives: Study B3D-MC-GHBX Addendum 2.2(a) commenced in 2014 in the US to evaluate a potential association between teriparatide and adult osteosarcoma in humans. The primary objective was to estimate the incidence rate ratio and 95% confidence interval of osteosarcoma among patients aged 65 years or older with a prescription claim for teriparatide in Medicare Part D data versus a cohort of matched comparators. The secondary objective was to describe characteristics of each cohort and assess the similarity of certain factors within the two cohorts measured during a baseline period using Medicare Parts A, B, and D for a subset of the patients. This report presents the findings from following patients during an 8-year time period for the occurrence of osteosarcoma.

Study design: Population-based comparative cohort study. Exposure details and matching variables were obtained from prescription claims. Outcomes were obtained through linkage with state cancer registries. Patients were followed from their index date to date of osteosarcoma diagnosis, death, or end of study period, whichever came first.

Setting: The study takes place in the US.

Subjects and study size, including dropouts: Patients were identified in Medicare Part D prescription claims data. Patients were eligible if they were aged 65 years or older and enrolled in Medicare Part D with at least 4 months of continuous enrollment prior to the index date and had at least one prescription for teriparatide (exposed) or had a non-teriparatide prescription (comparator) within the same calendar month and year as the index date of the exposed patient. Patients were followed from 01 January 2007 until death, a diagnosis of osteosarcoma, or the end of the study period (31 December 2014).

Variables and data sources: Prescription treatments, including teriparatide, were determined based on Medicare Part D; Demographic information was determined based on the Medicare Master Beneficiary Summary File; medical history information used in a subcohort analysis was determined based on Medicare Parts A and B; osteosarcoma diagnosis information was obtained from state cancer registry files.

Results: There were 153,316 patients in the teriparatide and 613,247 patients in the comparator cohort. The study cohort was predominantly female (91%), and 59% were aged 75 years or older on the index date. Corticosteroid use was higher among the teriparatide cohort than the comparator cohort both during the baseline period (39% vs. 31%) and during follow-up (45% vs. 36%). The majority (79%) of teriparatide exposures in the cohort were incident exposures based on the available look-back period. On average, patients in the teriparatide cohort were treated for 10 months.

A total of 26 cancer registries submitted 811 cases of osteosarcoma for linkage against the study cohort, which represented 68% of all osteosarcoma cases occurring during the study period. A total of 1,895,715 person-years (397,000 person-years in teriparatide cohort; 1,498,715 in the comparator cohort) were observed, after adjusting for the 68% coverage fraction.

There were no cases of osteosarcoma observed in the teriparatide cohort (IR, 0.0; 95% confidence interval [CI], 0.0 to 9.3), and fewer than 11 cases observed in the comparator cohort. As a condition of the Medicare data use agreement, in order to protect patient privacy, non-zero cell counts less than 11 cannot be disclosed; thus, the exact number of cases cannot be reported since it is more than zero but less than 11. In addition, the incidence rate in the comparator group cannot be reported, but the confidence interval (95% CI, 1.5 to 8.7) indicates it is similar to what would be expected in the general US population aged 65 years or older given the estimated background incidence rate of osteosarcoma and the person-years observed in this cohort. The incidence rate ratio was 0.0 (95% CI, 0.0 to 3.2), and the incidence rate difference per million person-years was -4.5 (95% CI, -8.2 to -0.8).

D**iscussion:** No cases were observed in the teriparatide cohort, and the incidence in the comparator cohort was consistent with the background rate among adults age 65 and older. Given the rarity of osteosarcoma (3.9 cases per million patients per year in adults aged 65 years or older) and the 1,895,715 person-years of observation among both cohorts in this study, only 7 cases would have been expected. These findings are consistent with other published study findings (Andrews et al., 2012; Midkiff, 2014).

The results of this comparative study (IRR, 0.0; 95% CI, 0.0 to 3.2) support the interpretation that the incidence of osteosarcoma among teriparatide-treated patients aged 65 years or older in the US ranges from 0 to 3.2 times the incidence of osteosarcoma in US patients aged 65 years or older treated with other medications. Given the low rates of osteosarcoma, this range of effects is inconsistent with a large absolute increase in risk for osteosarcoma.

Marketing authorization holder(s): Eli Lilly & Co.

Names and affiliations of principal investigators: PPD of RTI Health Solutions

2. List of abbreviations

Term	Definition
AHFS	American Hospital Formulary Services
ATC	Anatomical Therapeutic Chemical
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMS	Center for Medicare and Medicaid Services
CPT	Current Procedural Terminology
GDIT	General Dynamics Information Technology
HCPCS	Healthcare Common Procedure Coding System
ICD-10	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
ICD-10-CM	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification*
ICD-9	*International Statistical Classification of Diseases and Related Health Problems, 9th Revision*
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
ICD-O-3	International Classification of Diseases for Oncology, Third Edition
ID	identification
IR	incidence rate
IRB	institutional review board
IRR	incidence rate ratio
ISPE	International Society for Pharmacoepidemiology
MBSF	Medicare Master Beneficiary Summary File
NDC	National Drug Code
NOS	not otherwise specified
PTH	parathyroid hormone
ResDAC	Research Data Assistant Center

RTI-HS	RTI Health Solutions, a business unit of RTI International
SAP	statistical analysis plan
SEER	Surveillance, Epidemiology, and End Results Program
SSN	Social Security number
US	United States
VRDC	Virtual Research Data Center

3. Investigators

Principal Investigator	Country	Institutional Affiliation
PPD	United States	RTI Health Solutions, PPD

4. Other responsible parties

Not applicable.

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	Not applicable	06 October 2016	None
End of data collection	Not applicable	15 September 2017	None
Final report of study results	Not applicable	05 December 2017	None

6. Rationale and background

Forteo® (teriparatide), rhPTH(1-34), produced in *E. coli* using recombinant DNA technology, is identical to the 34N-terminal amino acid sequence of endogenous human parathyroid hormone (PTH). Teriparatide was initially approved in 2002 in the United States (US) for adults for the treatment of postmenopausal women with osteoporosis at high risk for bone fractures and for increasing bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. In 2009, the treatment indication was expanded to include treatment of men and women with glucocorticoid-induced osteoporosis who are at high risk for fracture.

Teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. Teriparatide is administered as a subcutaneous injection into the thigh or abdominal wall with a recommended dosage of 20 µg once a day. In clinical studies, patients with osteoporosis treated for up to 2 years with teriparatide demonstrated increases in bone mineral density and a significant decrease in the incidence of fractures compared with the placebo group. Compared with the placebo group, the teriparatide 20-µg/day group experienced a 65% reduction in the proportion of patients with new vertebral fractures (Neer et al., 2001). Across clinical studies, treatment with teriparatide was well tolerated. No cases of osteosarcoma were reported during clinical trials or in a 5-year posttreatment follow-up study that included seven long-term teriparatide clinical trials, and very few spontaneous cases of osteosarcoma have been in reported in patients who were treated with teriparatide. Moreover, other ongoing noninterventional studies have yielded frequencies of teriparatide-exposed cases of osteosarcoma that are consistent with the background frequency in the general population similar in age to the teriparatide patients (Andrews et al., 2012; Kellier et al., 2014).

In rats, in one 2-year (near-lifetime) toxicology study in which doses were administered at levels that produced systemic exposures 3 to 60 times greater than that of a 20-µg dose in humans, teriparatide caused increases in bone mass and a dose-dependent increase in the incidence of osteosarcoma, a malignant tumor (Eli Lilly and Company; Vahle et al., 2002). A subsequent rat study conducted to determine the effect of duration of treatment and age at initiation of treatment found that the bone neoplastic response in rats was dependent on both dose and duration of treatment. The study established a “no-effect” dose of 5 µg/kg when initiated at 6 months of age and continued for a duration of either 6 months or 20 months (Vahle et al., 2004). In a long-term study of cynomolgus monkeys (spanning 18 months of treatment plus 3 years of follow-up observation), no bone tumors were detected by radiographic or histological evaluation (Vahle et al., 2008). Research has shown that the rat skeleton is more sensitive than monkey or human skeletons to the pharmacological effects of PTH in the formation of new bone and osteosarcomas (Miller, 2008).

Little is known about the etiology of osteosarcoma in adult humans (Fletcher et al., 2002; Unni and Dahlin, 1996). Potential risk factors for osteosarcoma, including injury or infection at the tumor site and metallic implants at the tumor site, have been suggested (Unni and Dahlin, 1996). Osteosarcoma has been observed in association with Paget’s disease of the bone and after

radiation treatment to the bones (Grimer et al., 2003; Unni and Dahlin, 1996). However, as stated by Savage and Mirabello (2011) in their published review article "Using Epidemiology and Genomics to Understand Osteosarcoma Etiology," "There are a limited number of proven risk factors associated with osteosarcoma. It occurs more frequently after therapeutic radiation for a different cancer, in individuals with certain cancer predisposition syndromes, and in those with Paget's disease of the bone. However, the majority of osteosarcoma cases occur in the absence of these risk factors. Numerous studies of growth and other genetic risk factors have been conducted but strong data on risk for apparently sporadic osteosarcoma are limited."

In an attempt to understand osteosarcoma etiology, Savage and Mirabello (2011) also described some extremely rare disorders such as Li-Fraumeni syndrome (p53 mutation) and retinoblastoma (pRb loss) that are not common causes of osteosarcoma but are associated with increased rates of osteosarcoma.

Osteosarcoma in humans is a primary malignant bone tumor (a sarcoma in which the neoplastic cells produce osseous matrix) with an incidence rate that varies in adults from 1.7 per million in those aged 25 to 59 years to 4.2 per million for those aged 60 years or older (Mirabello et al., 2009). Given the very rare outcome and infrequent exposure to teriparatide, large study sizes are needed to detect a small increase in risk (i.e., less than a 3- or 4-fold increased risk) with adequate statistical power.

In this study, Medicare Part D prescription drug data for persons aged 65 years or older were used to identify patients exposed to teriparatide and a comparison cohort; measure exposure to teriparatide and other medications; and follow patients until death, end of the available follow-up data, or diagnosis of osteosarcoma as recorded in participating cancer registries. A companion study is ongoing using a large national pharmacy database linked with cancer registry data. This report details the findings from the completed Medicare linkage study.

7. Research question and objectives

The primary objectives of this study were to (1) estimate the incidence rate ratio (IRR) and 95% confidence internal (CI) of osteosarcoma for patients aged 65 years or older with a prescription claim for teriparatide versus a cohort of matched comparators and (2) describe the characteristics of each cohort, including the following factors:

- Demographics
- Baseline and prior use of other medications, including the number of unique pharmacologic therapeutic classes within the previous 4 months
- Baseline and prior use of other osteoporosis medications
- Baseline and prior use of glucocorticoids

For the teriparatide cohort:

- Duration of use of teriparatide
- Specialty of the provider, if available

To assess the similarity of the teriparatide cohort and the comparator cohort using Medicare Parts A, B, and D for a subset of the patients according to the following factors measured during the baseline period:

- History of radiation treatment
- History of fracture
- History of cancer
- History of Paget's disease of the bone
- Number of inpatient and outpatient visits within the prior 4 months
- History of chronic comorbid conditions using all available data

8. Amendments and updates

Not applicable.

9. Research methods

9.1. Study design

This study used a population-based cohort from secondary data to compare the incidence of osteosarcoma among teriparatide users aged 65 years or older with the incidence of osteosarcoma among nonusers aged 65 years or older. Exposure was ascertained from prescription drug claims, and the outcome was ascertained through linkage with state cancer registries. Teriparatide users were matched to nonusers based on demographic and baseline characteristics.

9.2. Subjects

9.2.1. Study population

The study cohorts were selected from people enrolled in Medicare Part D. The teriparatide (exposed) cohort comprised patients with a Medicare claim for an outpatient medication dispensing of teriparatide. These patients were individually matched to patients from the general population of Medicare Part D patients with similar demographic and baseline characteristics and with a prescription for a medication other than teriparatide (comparator cohort) in the same calendar month. Patients were eligible for inclusion in one of the study cohorts after meeting *all* of the following inclusion criteria, in the order below:

- Were aged 65 years or older
- Had at least 4 months of Medicare enrollment prior to the first dispensing of teriparatide in the exposed cohort (e.g., the index date) or the corresponding index date for the comparator cohort
- Had one or more prescriptions for teriparatide during the study period OR were a member of the Medicare Part D general population and had a prescription filled during the same month as the matched teriparatide patient

Patients were excluded from the study cohorts if *any* of the following criteria was met:

- Had inconsistently coded values for sex across Medicare enrollment years
- Had recorded dates of birth that varied in month and/or year of birth across enrollment years
- Had a gap of one or more years' worth of Medicare enrollment data in between two other Medicare enrollment records, after the 65th birthday
- Was not a resident of the 50 US states or District of Columbia
- Died before the start of the study period, 01 January 2007
- Was older than 103 years of age at the start of the study period

For each teriparatide user, up to four comparators were selected. Patients were matched on *all* of the following characteristics:

- Age in single years up to age 85 years and an age category for those aged 85 years or older

- Sex
- Three-digit zip code during the index year
- A filled prescription (of any medication) during the calendar year and month of the qualifying prescription of the teriparatide user
- Based on prescription claims, the category of the number of unique therapeutic classes of medications dispensed during the 4 months prior to the index date

The index date for the comparators was set to the same index date of the matched teriparatide user. A minimum look-back period of 4 months before the index date was required to assess differences between the teriparatide users and comparators. Other prior medications (grouped into therapeutic classes) were used as a proxy for comorbidity to control for unmeasured confounding. At the time of the index date for a patient starting teriparatide, all other beneficiaries were eligible to serve as a matched comparator unless they had a prescription claim for teriparatide in all available Medicare Part D data during the study period and before. From the full set of available matched comparators for each teriparatide-treated patient in the study cohort, up to four were chosen using simple random sampling without replacement. After assignment, if any of the teriparatide-treated patients had fewer than four comparators, then available comparators were searched again using 5-year age categories (instead of single-year age categories) for patients up to age 85 years.

9.2.2. Time period

The study period to identify exposure for the primary analysis was January 2007 through December 2014. Follow-up began on the index date, under the assumption that there was no induction or latency period between teriparatide exposure and the development of clinically detectable osteosarcoma, and ended at the diagnosis of osteosarcoma, death, or end of the study period.

Figure 1 shows the study design, including how person-time was calculated for each patient.

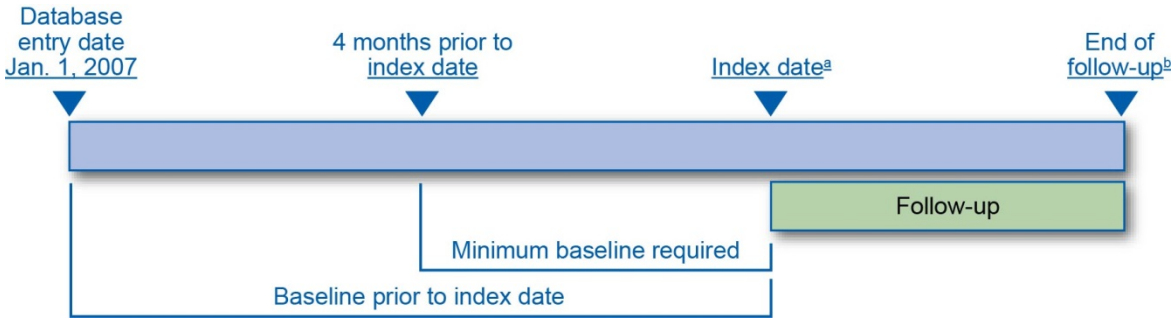

Figure 1. Forteo Medicare linkage study design

[a] Date of teriparatide prescription for the exposed and comparator cohort.
[b] Osteosarcoma diagnosis, death, or end of study period.

For all final matched sets, each comparator was assigned the same index date as the teriparatide-exposed patient to whom he or she was matched.

Follow-up for each teriparatide user and comparator began on the index date and ended on the earliest of any of the following:

- Date of diagnosis with osteosarcoma
- Date of death
- End of study period

9.3. Setting

The study setting is the prescription claims data in US Medicare Part D, which in 2014 covered over 40 million Medicare beneficiaries (70%) in the US (CMS, 2016) linked with comprehensive, population-based, state cancer registries. The study period, assessing exposure and outcome concurrently, was from 01 January 2007 to 31 December 2014. RTI Health Solutions (RTI-HS) acted as the principal investigator and coordinating center for the study.

The study was approved by the RTI International institutional review board (IRB) under a Federal-wide Assurance in the US. In addition, a research application was submitted to the Research Data Assistant Center (ResDAC) and reviewed by the Center for Medicare and Medicaid Services (CMS) Privacy Board, who approved access to the Medicare beneficiary-level research identifiable files for analysis. To restrict privacy, data files were accessed by RTI-HS analysts through the Virtual Research Data Center (VRDC). Analysis output tables generated in the VRDC virtual desktop environment underwent a privacy screening by General Dynamics Information Technology (GDIT). In addition, RTI-HS analysts were bound by the data use agreement, which stipulated that, "No cell (e.g., admittances, discharges, patients, services) 10 or less may be displayed. Also, no use of percentages or other mathematical formulas may be used if they result in the display of a cell 10 or less."

Cancer registries at all 50 US states and the District of Columbia were invited to participate in the study. RTI-HS enrolled the interested registries by submitting research applications (e.g., local data use committee, IRB) to obtain the necessary research approvals.

9.4. Variables

9.4.1. Exposure

Teriparatide was identified by its National Drug Code (NDC). The following NDC numbers were used to identify teriparatide:

- 00002-8971-01 (3 mL)
- 00002-8400-01 (2.4 mL)
- 00002-8400-99 (2.4 mL)
- 54868-5406-00 (3 mL)

Teriparatide use began at the date of the first dispensing in Medicare Part D claims data during the study period for which the patient met the study inclusion criteria. Teriparatide use was classified as incident or prevalent exposure based on whether the patient had a teriparatide prescription during the look-back period. Dispensings of all other medication types were used to

identify a matched comparator cohort (i.e., any patient with Medicare Part D coverage during the study period without a dispensing for teriparatide).

9.4.2. Outcome

The primary outcome of incident osteosarcoma was ascertained through linkage with cancer registries. Osteosarcoma was defined as pathologically confirmed and newly reported any time after the index date. The following ICD-O-3[*] codes were used by state cancer registries to identify cases of osteosarcoma in adults aged 65 years or older at the time of diagnosis during the study period:

- 9180/3 Osteosarcoma NOS (not otherwise specified)
- 9181/3 Chondroblastic osteosarcoma
- 9182/3 Fibroblastic osteosarcoma
- 9183/3 Telangiectatic osteosarcoma
- 9184/3 Osteosarcoma in Paget's disease of bone
- 9185/3 Small cell osteosarcoma
- 9186/3 Central osteosarcoma
- 9187/3 Intraosseous well differentiated osteosarcoma
- 9192/3 Parosteal osteosarcoma
- 9193/3 Periosteal osteosarcoma
- 9194/3 High-grade surface osteosarcoma
- 9195/3 Intracortical osteosarcoma

9.4.3. Baseline characteristics used for matching

Due to the nature of the Medicare Part D data, which includes prescription claims only, the type and number of baseline characteristics available to match teriparatide users to comparators was limited. Baseline characteristics used at the index date for matching were age, sex, 3-digit zip code, and calendar year and month of teriparatide use. The number of unique therapeutic classes of medications dispensed based on the prescriptions claims during the prior 4 months was also used as a matching variable and served as a proxy for measuring overall health status and the presence of other chronic comorbidities. American Hospital Formulary Services (AHFS) codes were used to group prescriptions into therapeutic classes, and then categories were created based on the total number of therapeutic classes.

9.4.4. Additional characteristics described during baseline

The use of other osteoporosis drugs and of glucocorticoids in both the teriparatide and comparator cohorts during all available look-back time was described.

9.4.5. Characteristics described during the follow-up period

Other characteristics during the period between the index date and the end of follow-up were described. The number of dispensings, days' supply, and duration of exposure were summarized

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[*] ICD-O-3 = *International Classification of Diseases for Oncology, Third Edition.*

for teriparatide users. Days' supply was obtained from each teriparatide prescription in the Medicare Part D data. Duration of exposure was calculated beginning on the index date, and for each teriparatide user, the duration of exposure was calculated as the sum of the days' supply of all teriparatide dispensings during follow-up, without regard to overlaps or gaps, and truncated at the end of the study period. For both the exposed and unexposed cohorts, the number of deaths occurring during the follow-up period, as well as identified risk factors for osteosarcoma, were characterized. Time at risk started at the index date and ended at the diagnosis of osteosarcoma, death, or end of study period.

Table 1 presents the study variables and operational definitions.

Table 1. Variables and definitions

Variable	Source	Definition
Exposure:		
Teriparatide	Pharmacy claims file	All outpatient dispensings (any dosage or formulation) during the study period identified using the NDC
Baseline matching characteristics:		
Category of the number of unique therapeutic classes of medications	Pharmacy claims file	Category-relevant therapeutic classes of medications dispensed during the 4 months prior to the index date, using AHFS class-to-NDC mapping to classify compounds, and the total number of medication classes
Single-year age category up to age 85 years; 85+ years thereafter	Master Beneficiary Summary File	
Sex		
Three-digit zip code		
Calendar month and year of qualifying prescription		
Baseline characteristics:		
Presence of osteoporosis drugs other than teriparatide	NDC from pharmacy claims file	At least one osteoporosis drug other than teriparatide dispensed in the look-back period, based on AHFS therapeutic class
Presence of corticosteroid drugs	NDC from pharmacy claims file	At least one corticosteroid dispensing during the look-back period
Characteristics during follow-up:		
Number of teriparatide dispensings and duration of use	NDC from pharmacy claims file	Index exposure (any dosage or formulation) and subsequent exposures during follow-up identified using the NDC for teriparatide and AHFS code for other osteoporosis medications (excluding teriparatide)
Number of other osteoporosis medications and duration of use	NDC from pharmacy claims file	
Mortality	Master Beneficiary Summary File	Date of death and count of deaths occurring during follow-up

Variable	Source	Definition
Outcomes: Osteosarcoma	State cancer registry files	Pathologically confirmed cases of osteosarcoma identified using ICD-O-3 oncology codes, and date of diagnosis

AHFS = American Hospital Formulary Services; ICD-O-3 = *International Classification of Diseases for Oncology, Third Edition*; NDC = National Drug Code.

9.5. Data sources

9.5.1. Exposure data source

This study identified subjects using Medicare Part D claims data in the US. Medicare is a federally sponsored health insurance program in the US that offers health coverage to 47 million people, including 39 million people aged 65 years or older and 8 million nonelderly people with permanent disability (Cubanski et al., 2010). Medicare beneficiaries make up approximately 15% of the total US population and constitute more than 98% of the US population aged 65 years or older (Research Data Assistance Center, 2013). Medicare consists of Part A, which is hospitalization insurance; Part B, which covers physician services and outpatient care; and Part D, which is outpatient prescription drug coverage. Parts B and D are optional, and enrollees must pay a monthly premium for this coverage. Part D coverage has been available since 2006 and is purchased by beneficiaries through private insurance companies approved by Medicare. As of 2014, about 69% of the US population aged 65 years or older and enrolled in Medicare (47.6 million) were also enrolled in Medicare Part D (32.9 million) (CMS, 2016). Using Medicare Part D claims data as the data source to identify exposure is particularly relevant because most teriparatide users are over 65 years of age. The mean age of a cohort of teriparatide users in Medicare Part D was 73 years (Hazel-Fernandez et al., 2013). Medicare data are available for research approximately 2 years following the close of a calendar year. For example, for a study conducted in 2016, data would be available through the end of 2014.

9.5.2. Outcome data source

The outcome of interest—osteosarcoma—was identified using state cancer registry data. Cancer registries collect detailed clinical information for all cancers excluding non-melanoma skin cancers. Data include the tumor site, type, and stage of cancer (extent of disease) at the time of diagnosis and the cancer treatment that patients received during the first 6 months following diagnosis (i.e., the first course of therapy). Physicians, hospitals, therapeutic radiation facilities, freestanding surgical centers, and pathology laboratories are required by law to report all cancers to their central statewide cancer registry. Data are coded using ICD-O-3 codes.

9.5.3. Mortality data source

The Medicare Master Beneficiary Summary File (MBSF) was linked to the Medicare Part D data file to identify whether patients died during the follow-up period to allow for appropriate censoring. The occurrence and date of death were included, but the cause of death was not available in the MBSF; therefore, only total mortality could be characterized during follow-up.

The MBSF included beneficiary unique identification (ID), state and county codes, zip code, date of birth, date of death, sex, race, age, monthly entitlement indicators (A/B/D), reasons for entitlement, and monthly managed care indicators (yes/no). Since 2006, it includes variables specific to enrollment in Medicare Part D.

9.5.4. Data linkage

The study cohort identified in Medicare Part D by RTI-HS was linked to participating state cancer registries by Medicare's trusted independent third-party organization GDIT. A deterministic data linkage (i.e., exact match) was conducted between the Medicare Part D beneficiaries selected for the study cohorts and patients diagnosed with osteosarcoma in the cancer registry data. RTI-HS did not have access to personally identifying information for the study cohort and submitted the encrypted beneficiary ID for individuals in the study cohort to GDIT for linkage. GDIT linked using either (1) the 9-digit Social Security number (SSN) or (2) at least three of the following four variables: the last four digits of the SSN, last name, date of birth, and sex (zip code and state were used to clarify possible matches). Given that deterministic data linkage utilizing SSN alone is highly effective, finding approximately 98% of all true matches (Simon et al., 2005), the preferred option was to have cancer registries send SSNs to GDIT for linkage. However, given known local restrictions at some individual state cancer registries regarding the release of SSN to external parties and to facilitate participation by as many registries as possible, a secondary linkage option was included. Deterministic data linkages similar to the one utilized by GDIT, using variables other than SSN, have been shown to capture approximately 70% to 80% of people expected to be in both databases (Grannis et al., 2002; Rotermann et al., 2015). When matches were found during the linkage, the encrypted beneficiary ID was returned to RTI-HS, who then requested tumor-related variables from the cancer registry. Cancer registries were blinded to the exposure status of patients that matched, and GDIT was not provided with cancer diagnosis information for patients with osteosarcoma submitted by the cancer registries. The tumor-related information was used to establish the date of diagnosis to confirm that a linked patient was exposed to teriparatide prior to the cancer diagnosis. Additionally, information on the cancer site and morphology was used to ensure that the patient met the study case definition for osteosarcoma.

9.6. Bias

Bias in selection of the comparator cohort to control for potentially confounding effects was addressed by matching the patients based on available demographic and baseline characteristics. Comparators were selected to be individually matched to teriparatide patients on age, sex, 3-digit zip code at the time of the index date, month and year of cohort entry, and category for the number of unique therapeutic classes of medications dispensed using prescription claims in the prior 4 months. Age was matched using single-year age categories up to age 85 years, and then patients aged 85 years or older were be combined into one category. For each teriparatide user, a target of four comparators was set. If four comparators could not be found for a teriparatide user, then the age categories were widened to 5-year age intervals up to age 85 years. In addition, for a subset of patients with Medicare Part A and B coverage, additional outpatient and inpatient data were used to compare characteristics at baseline.

9.7. Study size

The estimated background rate for the incidence of osteosarcoma in the US population aged 65 years or older is 3.9 cases per million per year (SEER, 2013). The estimated person-time of follow-up for teriparatide users was determined from Medicare Part D data where 141,565 patients had at least one claim for teriparatide in Medicare Part D from 2007-2012, for an average of 23,594 new teriparatide users each year (CMS-CCW, 2014). Using the average of 23,594 new teriparatide users each year (and assuming that half of these appear during the first year of entry for each year of the follow-up period), a 5% per year mortality rate, a 60% coverage fraction achieved by participating state cancer registries, and a 4:1 ratio of person-time in the comparator cohort compared with the teriparatide cohort, follow-up time was estimated to be a total of 397,792 person-years in the teriparatide cohort and 1,591,168 person-years in the comparator cohort for the analysis.

For the assumptions provided above, and assuming that the incidence of osteosarcoma follows a Poisson distribution, Table 2 shows the estimated power to detect an increase in the incidence rate for multiples of three, four, and five times the comparator rate, under a null hypothesis that the teriparatide-to-comparator IRR is 1.0, using methods for the variance-stabilized test of the ratio of two Poisson means.

Table 2. Power estimates

Observation period	Person-years in teriparatide cohort	Person-years in comparator cohort	X times the comparator rate	Power if osteosarcoma incidence rate in teriparatide users is x times comparator rate (%)
2007-2014	397,792	1,591,168	3	51
			4	70
			5	81

In summary, the Medicare linkage study was estimated to be able to detect a 4- or 5-fold increase over the incidence rate of osteosarcoma in the comparator cohort.

9.8. Data transformation

None.

9.9. Statistical methods

9.9.1. Main summary measures

The primary objective of the study was to estimate the IRR and 95% CI of osteosarcoma for patients aged 65 years or older with a prescription claim for teriparatide versus a matched comparison cohort with a prescription claim for a drug other than teriparatide. For the primary analysis, the IRR and 95% CI for osteosarcoma occurrence in teriparatide users and nonusers was estimated using exact conditional Poisson regression. For the primary analysis, it was assumed that there was not an induction or latency period between teriparatide exposure and the development of clinically detectable osteosarcoma. Secondary objectives included analyses to describe the demographics and baseline characteristics of the teriparatide and comparator cohorts

and an assessment of the comparability of the teriparatide users with the comparators for a subset of patients using information from the Medicare Parts A, B, and D data sets.

All data analyses and derivations from the original data files to analysis-ready variables were performed using SAS software version 9.3 or higher (Cary, North Carolina, US: SAS Institute Inc.; 2002-2010).

9.9.2. Main statistical methods

The primary endpoint in the study was an estimate of the IRR and 95% CI of osteosarcoma for patients aged 65 years or older with a prescription claim for teriparatide versus a matched comparator cohort with a prescription claim for a drug other than teriparatide. The IRR of osteosarcoma was calculated as the ratio of the incidence rate of osteosarcoma in teriparatide users to the incidence rate in the comparator cohort. The incidence rate of osteosarcoma among teriparatide users and comparators was estimated by the number of cases of osteosarcoma captured by the participating state cancer registries during the observation period divided by the total person-time of observation among individuals at risk.

Although all US state cancer registries were invited to participate, not all registries were able to participate due to resource constraints or other local restrictions related to use of state cancer registry data; therefore, the participating state cancer registries covered a fraction of the osteosarcoma cases occurring in the US population during the observation period. This incomplete capture of cases due to registries not participating in the study was addressed in the following ways: (1) by applying a coverage fraction that represents the percentage of osteosarcoma cases captured in this study (based on cancer registry participation) to the total person-time observed and (2) by recalculating the person-time at risk using the exposure information for only those patients from the states with participating registries and comparing it with the proposed person-time calculation using the coverage fraction to see if patients in these states differ in a meaningful way from patients in states with nonparticipating registries.

Determining the coverage fraction involved estimating the ratio of osteosarcoma cases from the participating registries to the total number of osteosarcoma cases over the age of 65 years expected from both participating and nonparticipating registries throughout the US. The coverage fraction (f) that represents the percentage of osteosarcoma cases captured in this cohort study was calculated from counts of osteosarcoma cases reported by the participating registries from 2007 to 2014, divided by the total number of osteosarcoma cases occurring in the US over the same 8-year period:

> f = number of cases reported by the participating registries from 2007-2014 divided by the total number of osteosarcoma cases occurring in the US during 2007-2014

The total number of osteosarcoma cases occurring in the US was obtained for the age group of interest for each year of the study using the Centers for Disease Control and Prevention's (CDC's) National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program overall combined incidence count for

osteosarcoma (using the study case definition of 12 ICD-O-3 histology codes). The total number of cases was calculated by summing the reported yearly incidence counts. Subsequent to determining the estimated coverage fraction, the person-time of observation for individuals at risk in both cohorts was adjusted accordingly by multiplying it by the coverage fraction. For the purposes of describing the analysis method and the statistical power calculation in the protocol, a 60% coverage fraction (0.60) was assumed.

The observation period for the linkage to cancer registries started 01 January 2007 and ended 31 December 2014. The person-time of each patient was calculated as the duration of time between the index date until the patient experienced osteosarcoma, death, or the end of the follow-up period, multiplied by the coverage fraction. The impact of nonparticipating state cancer registries was assessed by comparing the distributions of person-years by age and sex of individuals in both cohorts for nonparticipating states with those from participating states to see if they differed in a meaningful way. Patients with a registry-identified diagnosis of osteosarcoma occurring before the index date were excluded from the cohort. If such a patient was in the teriparatide cohort, both that patient and the matched comparators were excluded. If the patient was in the comparator cohort, only that patient was excluded from the cohort.

Incidence rates were reported as point estimates (in cases per 1 million person-years) and 95% CIs. Since the matching process (see Sections 9.2.1 and 9.6) produced many matched sets with small numbers of patients in each matched set, and the number of cases of osteosarcoma was expected to be small, the IRR and corresponding 95% CI were estimated using exact conditional Poisson regression. For supportive purposes, the incidence rate difference and corresponding 95% CI were also provided.

Demographic and baseline characteristics were summarized separately for the teriparatide and comparator cohorts using descriptive statistics. Categorical variables were summarized by frequencies and percentages, and continuous variables were summarized by means and standard deviations or medians and interquartile ranges. The following variables were summarized for the teriparatide and comparator cohorts: age, sex, census region, enrollment reference year, year of cohort entry, and total person-time of observation. Variables describing other prescription use during the baseline period and follow-up (including the therapeutic classes of the medications dispensed and the category of the number of unique therapeutic classes of medications dispensed, use of other osteoporosis drugs, and use of glucocorticoids) were also summarized. Duration of use of teriparatide and classification of teriparatide exposure (i.e., incident or prevalent) were measured for teriparatide users.

9.9.3. Missing values

It was anticipated that few variables would have notable missing values, as Medicare Part D consists of validated claims data. Consequently, all analyses were planned to be conducted on the observed data available; there was no imputation of missing values.

9.9.4. Sensitivity analyses

The similarity of the teriparatide cohort and the matched comparison cohort among a subset of patients who are also represented in Medicare databases for Parts A and B was assessed to determine the robustness of the primary analysis. Demographics, baseline characteristics, and total follow-up time were summarized for the teriparatide and the comparator cohorts using descriptive statistics. Other factors were also assessed if they were suspected of increasing the risk of osteosarcoma (Savage and Mirabello, 2011) or were a proxy for overall health status. The presence of each condition was measured during the look-back period, which included all available look-back time. Table 3 and Table 4 list the factors that were compared between cohorts and the codes that were used to assess each condition.

Table 3. Characteristics that were assessed for a subset of patients with Medicare Parts A, B, and D: risk factors

Condition	ICD-9-CM code[a]	CPT/HCPCS code
Radiation use		77371-3, 77401-9, 77411-4, 77416, 77418, 77422, 77423, 77432, 77470, 77750, 77761-3, 77776-8, 77781-4, 77789
History of Paget's disease of the bone	731.0	N/A

CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; ICD-10-CM = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification*; N/A = not applicable.

[a] ICD-9-CM codes were mapped to ICD-10-CM codes when necessary.

Table 4. Characteristics that were be assessed for a subset of patients with Medicare Parts A, B, and D: possible proxies for health status

Condition or characteristic	ICD-9-CM code[a]	CPT/HCPCS code
History of fracture (includes vertebral and hip/pelvic fracture)	733.14, 733.15, 733.96, 733.97, 733.98, 805.xx, 806.xx, 808.xx, 820.00, 820.01, 820.02, 820.03, 820.09, 820.10, 820.11, 820.12, 820.13, 820.19, 820.20, 820.21, 820.22, 820.30, 820.31, 820.32, 820.8x, 820.9x	N/A
History of cancer	140.xx – 209.xx, V10.xx	N/A
Number of inpatient and outpatient visits in the past 4 months	N/A	N/A
Summary measure of chronic comorbidities (e.g., Charlson Index)	Codes listed elsewhere (Quan et al., 2005)	

CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; ICD-10-CM = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification*; N/A = not applicable.

Each factor was summarized separately for the teriparatide and comparator cohorts using descriptive statistics. Categorical variables were summarized by frequencies and percentages,

and continuous variables were summarized by means and standard deviations or medians and interquartile ranges.

9.9.5. Amendments to the protocol or statistical analysis plan

Table 5 presents changes implemented in the final analysis that were different from the approved protocol and statistical analysis plan.

Table 5. Summary of Amendments

Document/section	Change Implemented	Reason
Protocol 3.3.3	Beneficiaries without prescription claim for teriparatide in all available Medicare Part D data were allowed to serve as a matched comparator	Simplify comparator cohort selection criteria
Protocol 3.3.3	Revised exclusion criteria for study cohorts	Address data inconsistencies
Protocol 3.3.4	Index date for comparator set to index date of teriparatide patient	Streamline index date assignment for comparator
Protocol 3.3.5.1	Added NDC codes to identify teriparatide prescriptions	To identify additional teriparatide NDC numbers in claims data
SAP 5.5	Added codes for history of fracture	Add more vertebral and hip/pelvic fracture codes
SAP 5.5	Added codes for history of cancer	Add more ICD-9 codes

ICD-9 = *International Classification of Diseases, 9th Revision;* NDC = National Drug Code; SAP = statistical analysis plan.

9.10. Quality control

This study was conducted in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Epidemiology Practices (ISPE, 2007) and applicable regulatory requirements. Experienced US-based RTI-HS programmers performed all analyses involving the Medicare data. To ensure the integrity and quality of the study results, RTI-HS followed the programming validation life cycle process for all analyses. This includes quality-checking programs, logs, and output for accuracy according to relevant standard operating procedures. All programs were independently reviewed by a second programmer/analyst.

10. Results

10.1. Participants

An initial data extract prepared by GDIT included 39,936,596 unique Medicare beneficiaries, aged 65 years or older. These were beneficiaries in Medicare Part D that had a prescription for teriparatide with a date of service from 2007 through 2014 and eligible comparators that could potentially be matched to a teriparatide user based on month and year of the prescription, sex, 5-year age categories, and the first two digits of the zip code. Once all inclusion and exclusion criteria were applied, the final study cohort included a total of 153,316 patients with a prescription for teriparatide, to whom 613,247 comparators were matched (Annex 2, Table 1) based on age, sex, year and month of qualifying prescription, 3-digit zip code, and the number of classes of medications prescribed during the 4 months before the index date. During the follow-up period, the teriparatide cohort had 585,955 person-years of observation and the matched comparator cohort had 2,212,036 person-years (Annex 2, Table 6).

For the sensitivity analyses conducted in the subcohort with Medicare Parts A, B, and D (see Section 9.9.4), 105,794 patients were treated with teriparatide, to whom 297,509 comparators were matched (Annex 2, Table 7). The subcohort had 513,073 person-years of observation during the period of follow-up and the matched comparator cohort had 1,924,912 person-years of follow-up (Annex 2, Table 8).

10.1.1. Baseline characteristics

The study cohort was predominantly female (91%), and 59% were aged 75 years or older on the index date (Annex 2, Table 1). Over 65% of patients in the study cohort were from states with a participating cancer registry. Nearly 70% of patients were on six or more unique therapeutic classes of medications within the 4 months before the index date.

The majority of patients (71%) enrolled in Medicare Part D during 2006 (the first year enrollment was available). Half of the cohort members entered the study cohort during the first 3 years of the 8-year study period. A minimum of 4 months of look-back before the index date was required, but the mean length of the look-back period in the study cohort was 38 months.

Before the index date, a higher percentage of teriparatide users had a dispensing of a corticosteroid drug (39%) than did the comparators (31%). Osteoporosis drugs other than teriparatide were more frequently dispensed in the teriparatide cohort (60%) than the comparator cohort (27%). Cardiovascular drugs were more frequently dispensed in the comparator cohort (83%) than the teriparatide cohort (73%).

10.1.2. Teriparatide exposure during follow-up

Among the teriparatide cohort, 120,302 patients (79%) had an incident exposure to teriparatide during the study period (Annex 2, Table 2). Teriparatide was dispensed on average nine times during the follow-up period, and the average duration of exposure was approximately 10 months.

10.1.3. Concomitant medication use during follow-up

Similar to the baseline period, the use of corticosteroids remained higher among the teriparatide cohort (45%) than the comparator cohort (36%) during follow-up. The same was true for use of osteoporosis medications excluding teriparatide, where use among the teriparatide cohort was 41% versus 23% in the comparator cohort (Annex 2, Table 4). Notably, the use of medications during follow-up in most of the unique therapeutic classes was higher in the teriparatide cohort than the comparator cohort except for cardiovascular drugs and electrolytic, caloric, and water balance treatments, where use was higher in the comparator cohort.

10.1.4. Person-time of observation and deaths during follow-up

The mean person-years of observation did not vary appreciably by whether or not the patient was from a state with a participating cancer registry (Annex 2, Table 3). Females consistently had a higher mean person-years of observation in every age category than males (Annex 2, Table 3). A total of 227,296 deaths occurred among both cohorts combined after the index date. Overall, 28% of the teriparatide cohort (42,180 of 153,316) and 30% of the comparator cohort (185,116 of 613,247) died during the study period.

10.2. Outcome data

None of the 153,316 patients in the teriparatide cohort matched a case of osteosarcoma submitted for linkage by participating state cancer registries (Annex 2, Table 6). The exact number cannot be reported, but there were fewer than 11 and greater than zero patients in the comparator cohort of 613,247 patients that matched a case of osteosarcoma submitted by the cancer registries (Annex 2, Table 6).

A total of 27 cancer registries agreed to participate in the study, and the necessary local data use committee and IRB approvals were obtained. One of the cancer registries was excluded from the analysis because the variables submitted by the registry for linkage were insufficient (due to local privacy restrictions) and not consistent with the study protocol. From the 26 cancer registries included in the analysis, a total of 811 cases of osteosarcoma diagnosed from 2007 through 2014 were submitted to GDIT for linkage against the teriparatide-treated and comparator study cohorts (Annex 2, Table 5).

A total of 19 cancer registries submitted variables to GDIT for the primary linkage method (9-digit SSN), and 7 cancer registries submitted an alternative combination of variables to GDIT for linkage. The overall match rate was 92%; 95% (461 of 485) using the primary linkage method and 87% (219 of 252) using an alternative method.[*]

10.3. Main results

The incidence rate, incidence rate ratio, and total person-time of observation following the index date for the study period from 01 January 2007 to 31 December 2014 are summarized in

[*] Michigan and Oklahoma were excluded from the match rate calculation because they provided additional cases for linkage to mask the identity of subjects submitted who were aged 65 years or older.

Annex 2, Table 6. The primary adjustment to the person-time of observation was made by applying the coverage fraction. During the study period, 1,197 case of osteosarcoma were diagnosed in the US (SEER, 2017). Therefore, the percentage of incident cases covered by participating state cancer registries was 68% (811 of 1,197) (Annex 2, Table 5). Applying this adjustment resulted in 397,000 person-years of observation in the teriparatide cohort and 1,498,715 person-years of observation in the comparator cohort (Annex 2, Table 6).

No cases of osteosarcoma were observed in the teriparatide cohort (incidence rate [IR], 0.0; 95% CI, 0.0 to 9.3), and the incidence rate in the comparator cohort is not reportable due to small numbers, but the 95% CI (1.5 to 8.7 per million person-years) indicates that the rate is similar to what would be expected in the general US population aged 65 years or older, given the estimated background incidence rate of osteosarcoma and the person-years observed in this cohort (Annex 2, Table 6). The IRR was 0 (95% CI, 0.0 to 3.2), and the incidence rate difference per million person-years was -4.5 (95% CI, -8.2 to -0.8) (Annex 2, Table 6).

10.4. Other analyses

As described in Section 9.9.4, a sensitivity analysis was performed to assess the similarity of the teriparatide cohort and the matched comparator cohort among a subset of patients with Medicare Parts A, B, and D to determine the robustness of the primary analysis. The variables assessed were conditions suspected of increasing the risk of osteosarcoma or proxies for overall health status. The presence of the condition was assessed during all available look-back time, which may have gone as far back as 01 January 1999.

Patients in the teriparatide subcohort were similar to those in the comparator subcohort at baseline with respect to sex, age distribution, year of Medicare enrollment and year of cohort entry, length of look-back period, and the percentage of patients that were from states with a participating registry (Annex 2, Table 7). Similar to the primary study cohorts, use of corticosteroids was higher in the teriparatide subcohort, and the percentage of patients in the teriparatide cohort that used osteoporosis medications (59%) was more than double that of the comparator subcohort (26%) (Annex 2, Table 7). Cardiovascular drug use and electrolytic, caloric, and water balance treatments were higher among the comparator subcohort than the teriparatide subcohort.

Among risk factors relevant to developing osteosarcoma, the teriparatide subcohort and comparator subcohort were similar with regard to radiation treatment and a history of Paget's disease of the bone (Annex 2, Table 7).

When comparing variables used as proxies for health status, the proportion of patients with a vertebral or hip/pelvic fracture in the teriparatide subcohort (23%) was nearly triple that of the percentage of patients with a fracture in the comparator subcohort (8%). There were more inpatient and outpatient visits among the teriparatide cohort. However, the mean Charlson comorbidity index was nearly the same for the two groups (Annex 2, Table 7).

10.5. Adverse events/adverse reactions

During the course of this observational research, information pertaining to adverse reactions was not discovered as the study did not involve identifiable patient data associated with a Lilly drug. Data in this study were analyzed in aggregate only. Study data sets did not include safety measures, and there was no medical chart review or review of free-text data fields.

11. Discussion

11.1. Key results

There were no cases of osteosarcoma among teriparatide-treated patients in the study cohort. Fewer than 11 and greater than zero patients in the matched comparator group developed osteosarcoma during the study period (consistent with the background rate of 3.9 cases per million per year in adults aged 65 years or older). A total of 1,895,715 person-years were observed among the teriparatide cohort and comparator cohort combined, adjusted for the coverage fraction (Annex 2, Table 6). The IRR was 0.0 (95% CI, 0.0 to 3.2) (Annex 2, Table 6).

Because Medicare Part D enrollees may not necessarily be a representative sample of all Medicare beneficiaries, a sensitivity analysis was undertaken on a subset of the study cohort to evaluate any differences between the teriparatide cohort and the comparator cohort, using a broader set of claims information (Medicare Part A & B). The findings from the sensitivity analysis did not alter the study findings. Thus, the findings from the primary analysis of Medicare Part D enrollees would appear to apply to the larger Medicare population (parts A and B), aged 65 years or older in the US. These findings are consistent with other efforts to determine the extent, if any, of an increased risk associated with teriparatide treatment in humans (Andrews et al., 2012; Midkiff, 2014).

This cohort design allowed for direct estimation of the incidence of osteosarcoma in patients with a teriparatide dispensing and allowed for a comparison to a group of patients without a teriparatide dispensing. Use of the Medicare Part D prescription claim data linked with cancer registry data, and use of a comparator group matched on baseline demographic characteristics, were important advantages over prior noninterventional studies included in the ongoing surveillance program (Andrews et al., 2012; Kellier et al., 2014). The ability to characterize exposure more completely and precisely using prescription data for a large group of patients was also an advantage over prior studies that relied on self-report or medical record review. Ascertaining outcome through cancer registries reduced the possibility of misclassification of the cancer diagnosis given that ICD-O-3 codes used by cancer registries are more specific than ICD-9 or ICD-10 codes in claims data.

11.2. Limitations

The possibility that residual confounding affected the findings of this study cannot be ruled out due to the nature of the prescription data source and the rarity of osteosarcoma. The prescription data used for the primary analysis lacked information on prior health history. However, all potential confounding variables for which data were available were accounted for to the extent possible, primarily through the use of matching when selecting the comparator population. In addition, an attempt to control for general health status through matching was made based on the categorized number of unique therapeutic classes of medications dispensed during the prior 4 months. Differences between the teriparatide users and nonusers was assessed in a subset of patients where health status could be assessed through a more diverse set of proxy variables.

In a sensitivity analysis using data from Medicare Parts A, B, and D, we were able to evaluate additional variables for the possibility that there were more potential confounders. Given the similarity between the teriparatide subcohort and comparator subcohort, and the lack of osteosarcoma cases in the teriparatide cohort, additional adjustments that had been planned were unnecessary.

Misclassification bias could have resulted if patients were not categorized correctly with regard to exposure or outcome. The limitations of claims-based analyses have been described elsewhere (Crystal et al., 2007; Crystal et al., 2010), but include lack of detailed clinical information and potential misclassification given that exposure is identified based on a claim for a prescription and there is no information that confirms whether the patient actually used the medication. In addition, there was the potential for misclassification of the exposure in the comparator cohort if a comparator had a gap in enrollment during which he or she received a dispensing for teriparatide. Although patients can lose Medicare Part D coverage, out-of-pocket payment for teriparatide was likely uncommon due to the high cost of the drug.

A bias akin to immortal time bias could have resulted from our excluding future users of teriparatide from the comparator group, as this approach excluded patients based on future information. The excluded person-time could be "immune" to osteosarcoma, because had osteosarcoma occurred among these patients, it might have diminished the probability of receiving teriparatide (Suissa, 2008). Owing to the very large number of comparators available for matching and because none of the teriparatide-treated patients had an osteosarcoma diagnosis occurring before their index date, this source of bias would have had at most a very small effect.

There was also potential for misclassification of the outcome if the matching algorithm was unsuccessful. This was more likely for registries that were unable to send the full SSN to GDIT for linkage; however, regardless of the method chosen, a high percentage of cases submitted by cancer registries were uniquely matched against a person in the Medicare database. Further, we did not anticipate that differential misclassification between the exposed and unexposed cohorts would occur.

There was a potential for bias due to missing data because not all registries were able to participate. One state (containing approximately 8% of the US population aged 65 years or older) had to be excluded because it could not provide the full set of linking variables due to privacy restrictions. We attempted to account for these missing data by using a coverage fraction for decrementing the patient-years of observation.

In general, there are few established risk factors for osteosarcoma. Age and sex could not be evaluated as confounders because they were balanced between groups due to matching. Paget's disease of the bone could have been a potential confounder; however, in the subcohort analysis, it was not markedly different between groups. Because it is recommended that patients with a history of Paget's disease not be treated with teriparatide; it is expected that some representation of Paget's disease of the bone would be present only in the comparator population. It is important to note that estimates of prevalence in the US for this rare condition are less than 4% (Cooper et al., 2006); therefore, it should not result in appreciable confounding. It is also

acknowledged that history of radiation therapy may differ between study cohorts; however, the data are insufficient to capture this information (e.g., a 4- to 6-month look-back period or even longer is not sufficient to measure all prior radiation therapy). Related cancer outcomes among patients treated with radiation therapy can take as long as 10 years or more for solid tumors to develop. Leukemia, the cancer with the shortest expected latency post radiation exposure, can take at least 5 to 7 years to develop (Hall, 2000). Research on other risk factors is mixed, and they are not expected to result in appreciable confounding.

11.3. Interpretation

No cases were observed in the teriparatide cohort (397,000 person-years). Given the rarity of osteosarcoma (3.9 cases per million patients per year in adults aged 65 years or older), and the 1,895,715 person-years of observation among both cohorts in this study, seven cases would have been expected.

The results of this comparative study (IRR, 0.0; 95% CI, 0.0 to 3.2) support the interpretation that the incidence of osteosarcoma among teriparatide-treated patients aged 65 years or older in the US ranges from 0 to 3.2 times the incidence of osteosarcoma in US patients aged 65 years or older treated with other medications.

11.4. Generalizability

The target population for which inference is applicable is the elderly population aged 65 years or older in the US. The study population included patients aged 65 years or older who were enrolled in Medicare Part D during the study period. Medicare Part D covered about 60% of the US population aged 65 years or older, and therefore was an appropriate population to address the scope of inference for the study.

12. Other information

None.

13. Conclusion

The results of this comparative study (IRR, 0.0; 95% CI, 0.0 to 3.2) support the interpretation that the incidence of osteosarcoma among teriparatide-treated patients aged 65 years or older in the US ranges from 0 to 3.2 times the incidence of osteosarcoma in US patients aged 65 years or older treated with other medications.

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15. Annex 1. List of standalone documents

Not applicable.

16. Annex 2. Results tables

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Table 1.
Cohort Characteristics at Baseline
Primary Study Population

Category or Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
Sex, n (%)		
Male	13,426 (8.8)	53,699 (8.8)
Female	139,890 (91.2)	559,548 (91.2)
Age (years) on index date		
Mean (SD)	76.9 (7.64)	77.0 (7.85)
Age group (years) on index date, n (%)[a]		
65-69	32,250 (21.0)	128,997 (21.0)
Male	2,823 (8.8)	11,292 (8.8)
Female	29,427 (91.2)	117,705 (91.2)
70-74	31,048 (20.3)	124,191 (20.3)
Male	2,821 (9.1)	11,284 (9.1)
Female	28,227 (90.9)	112,907 (90.9)
75-79	32,686 (21.3)	130,740 (21.3)
Male	2,849 (8.7)	11,394 (8.7)
Female	29,837 (91.3)	119,346 (91.3)
80-84	29,555 (19.3)	118,216 (19.3)

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

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Table 1.
Cohort Characteristics at Baseline
Primary Study Population

Category or Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
Male	2,508 (8.5)	10,030 (8.5)
Female	27,047 (91.5)	108,186 (91.5)
≥ 85	27,777 (18.1)	111,103 (18.1)
Male	2,425 (8.7)	9,699 (8.7)
Female	25,352 (91.3)	101,404 (91.3)
Medicare Part D enrollment year, n (%)		
2006	110,237 (71.9)	437,051 (71.3)
2007	9,958 (6.5)	38,807 (6.3)
2008	7,112 (4.6)	29,467 (4.8)
2009	5,242 (3.4)	23,703 (3.9)
2010	4,441 (2.9)	19,733 (3.2)
2011	4,502 (2.9)	19,513 (3.2)
2012	4,023 (2.6)	17,723 (2.9)
2013	6,344 (4.1)	23,405 (3.8)
2014	1,457 (1.0)	3,845 (0.6)
Calendar year of cohort entry, n (%)		

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

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Table 1.
Cohort Characteristics at Baseline
Primary Study Population

Category or Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
2007	40,063 (26.1)	160,247 (26.1)
2008	19,198 (12.5)	76,789 (12.5)
2009	17,933 (11.7)	71,731 (11.7)
2010	13,802 (9.0)	55,206 (9.0)
2011	14,029 (9.2)	56,116 (9.2)
2012	14,540 (9.5)	58,156 (9.5)
2013	17,541 (11.4)	70,162 (11.4)
2014	16,210 (10.6)	64,840 (10.6)
Length of look-back period (months)		
Mean (SD)	38.2 (28.69)	38.0 (27.65)
Subjects from states with participating cancer registries, n (%)	100,033 (65.2)	400,119 (65.2)
US census region, n (%)[b]		
Northeast	25,675 (16.7)	102,697 (16.7)
Subjects from states with participating cancer registries	14,647 (57.0)	58,583 (57.0)
Subjects from states without participating cancer registries	11,028 (43.0)	44,114 (43.0)
Midwest	29,695 (19.4)	118,773 (19.4)

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

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Table 1.
Cohort Characteristics at Baseline
Primary Study Population

Category or Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
Subjects from states with participating cancer registries	24,998 (84.2)	99,988 (84.2)
Subjects from states without participating cancer registries	4,697 (15.8)	18,785 (15.8)
South	66,400 (43.3)	265,598 (43.3)
Subjects from states with participating cancer registries	35,218 (53.0)	140,871 (53.0)
Subjects from states without participating cancer registries	31,182 (47.0)	124,727 (47.0)
West	31,546 (20.6)	126,179 (20.6)
Subjects from states with participating cancer registries	25,170 (79.8)	100,677 (79.8)
Subjects from states without participating cancer registries	6,376 (20.2)	25,502 (20.2)
Use of corticosteroid drugs prior to the index date, n (%)	58,953 (38.5)	186,924 (30.5)
Use of other osteoporosis drugs prior to the index date, n (%)	92,632 (60.4)	162,905 (26.6)
Medications by AHFS therapeutic class within the 4 months prior to the index date, n (%)		
Antihistamine drugs	6,758 (4.4)	26,353 (4.3)
Anti-infective agents	69,434 (45.3)	280,925 (45.8)
Antineoplastic agents	10,732 (7.0)	29,034 (4.7)
Autonomic drugs	47,648 (31.1)	167,263 (27.3)
Blood derivatives	0 (0.0)	n < 11

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

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Table 1.
Cohort Characteristics at Baseline
Primary Study Population

Category or Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
Blood formation, coagulation, and thrombosis agents	27,958 (18.2)	122,156 (19.9)
Cardiovascular drugs	112,092 (73.1)	508,567 (82.9)
Central nervous system agents	109,903 (71.7)	392,259 (64.0)
Diagnostic agents	139 (0.1)	2,210 (0.4)
Electrolytic, caloric, and water balance	56,889 (37.1)	303,711 (49.5)
Enzymes	409 (0.3)	2,274 (0.4)
Respiratory tract agents	8,567 (5.6)	28,263 (4.6)
Eye, ear, nose, and throat (EENT) preparations	38,452 (25.1)	162,231 (26.5)
Gastrointestinal drugs	74,206 (48.4)	265,962 (43.4)
Gold compounds	18 (0.0)	n < 11
Heavy metal antagonists	45 (0.0)	59 (0.0)
Hormones and synthetic substitutes	82,052 (53.5)	336,900 (54.9)
Local anesthetics	1,302 (0.8)	6,094 (1.0)
Oxytocics	0 (0.0)	0 (0.0)
Serums, toxoids, and vaccines	2,209 (1.4)	7,113 (1.2)
Skin and mucous membrane agents	40,572 (26.5)	148,909 (24.3)

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

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Table 1.
Cohort Characteristics at Baseline
Primary Study Population

Category or Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
Smooth muscle relaxants	12,621 (8.2)	45,692 (7.5)
Vitamins	3,735 (2.4)	9,982 (1.6)
Miscellaneous therapeutic agents	53,507 (34.9)	132,440 (21.6)
Unclassified	0 (0.0)	0 (0.0)
Number of unique AHFS therapeutic classes within the 4 months prior to the index date, n (%)		
0-2 classes	14,442 (9.4)	57,767 (9.4)
3-5 classes	32,311 (21.1)	129,244 (21.1)
6-8 classes	37,512 (24.5)	150,047 (24.5)
9-11 classes	30,431 (19.8)	121,722 (19.8)
12-15 classes	24,141 (15.7)	96,563 (15.7)
> 15 classes	14,479 (9.4)	57,904 (9.4)

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

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Table 2.
Extent of Teriparatide Exposure
Primary Study Population

Category or Statistic	Teriparatide Cohort (N = 153,316)
Type of exposure[a], n (%)	
Incident	120,302 (78.5)
Prevalent	33,014 (21.5)
Number of dispensings	
Mean (SD)	9.4 (8.43)
Average days' supply per dispensing episode[b]	
Mean (SD)	33.3 (14.91)
Duration of exposure (months)[c]	
Mean (SD)	9.5 (8.21)

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
CMS = Centers for Medicare and Medicaid Services; SD = standard deviation.
[a] If the patient did not have a previous prescription for teriparatide prior to the index date, the exposure was classified as incident; if the patient had a previous prescription for teriparatide prior to the index date, the exposure was classified as prevalent.
[b] For each teriparatide user, the per episode average was calculated using all dispensings of teriparatide during follow-up.
[c] For each teriparatide user, the duration of exposure was calculated as the sum of the days' supply of all teriparatide dispensings during follow-up, without regard to overlaps or gaps.

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Table 3.
Distribution of Person-Years by Patient Characteristics at the Index Date
Primary Study Population

	Subjects from States with Participating Cancer Registries[a]		Subjects from States Without Participating Cancer Registries[a]	
Characteristic	**Teriparatide Cohort**	**Comparator Cohort**	**Teriparatide Cohort**	**Comparator Cohort**
All Patients	N = 100,033	N = 400,119	N = 53,283	N = 213,128
Mean (SD)	3.8 (2.48)	3.6 (2.50)	3.9 (2.49)	3.7 (2.53)
Females	n = 90,689	n = 362,746	n = 49,201	n = 196,802
Mean (SD)	3.9 (2.49)	3.6 (2.52)	4.0 (2.49)	3.7 (2.54)
Aged 65-69 years	n = 19,029	n = 76,114	n = 10,398	n = 41,591
Mean (SD)	4.0 (2.52)	4.0 (2.53)	4.1 (2.52)	4.1 (2.53)
Aged 70-74 years	n = 18,309	n = 73,234	n = 9,918	n = 39,673
Mean (SD)	4.1 (2.55)	4.0 (2.56)	4.2 (2.55)	4.1 (2.57)
Aged 75-79 years	n = 19,484	n = 77,930	n = 10,353	n = 41,416
Mean (SD)	4.1 (2.53)	3.9 (2.54)	4.3 (2.52)	4.0 (2.55)
Aged 80-84 years	n = 17,283	n = 69,132	n = 9,764	n = 39,054
Mean (SD)	3.8 (2.43)	3.6 (2.46)	3.9 (2.43)	3.8 (2.47)
Aged ≥ 85 years	n = 16,584	n = 66,336	n = 8,768	n = 35,068
Mean (SD)	3.2 (2.26)	2.4 (2.13)	3.2 (2.28)	2.5 (2.19)

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] 26 state cancer registries participated.

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Table 3.
Distribution of Person-Years by Patient Characteristics at the Index Date
Primary Study Population

	Subjects from States with Participating Cancer Registries[a]		Subjects from States Without Participating Cancer Registries[a]	
Characteristic	**Teriparatide Cohort**	**Comparator Cohort**	**Teriparatide Cohort**	**Comparator Cohort**
Males	n = 9,344	n = 37,373	n = 4,082	n = 16,326
Mean (SD)	3.1 (2.27)	3.1 (2.32)	3.1 (2.29)	3.2 (2.37)
Aged 65-69 years	n = 1,911	n = 7,644	n = 912	n = 3,648
Mean (SD)	3.4 (2.31)	3.6 (2.37)	3.4 (2.36)	3.6 (2.44)
Aged 70-74 years	n = 1,949	n = 7,796	n = 872	n = 3,488
Mean (SD)	3.4 (2.39)	3.4 (2.40)	3.3 (2.38)	3.5 (2.46)
Aged 75-79 years	n = 2,006	n = 8,022	n = 843	n = 3,372
Mean (SD)	3.3 (2.29)	3.3 (2.35)	3.2 (2.31)	3.3 (2.41)
Aged 80-84 years	n = 1,755	n = 7,020	n = 753	n = 3,010
Mean (SD)	3.0 (2.24)	3.0 (2.28)	3.0 (2.23)	3.1 (2.27)
Aged ≥ 85 years	n = 1,723	n = 6,891	n = 702	n = 2,808
Mean (SD)	2.4 (1.93)	2.3 (1.93)	2.4 (2.00)	2.3 (2.00)

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] 26 state cancer registries participated.

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Table 4.
Cohort Characteristics During Follow-up
Primary Study Population

Category or Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
Use of corticosteroid drugs, n (%)	68,348 (44.6)	220,591 (36.0)
Among those with at least 1 corticosteroid dispensing:		
Number of dispensings per patient		
Mean (SD)	7.7 (12.91)	4.9 (8.90)
Duration of exposure (months)[a]		
Mean (SD)	7.0 (14.37)	3.6 (9.57)
Use of other osteopososis drugs, n (%)	62,616 (40.8)	139,984 (22.8)
Among those with at least 1 other osteoporosis drug dispensing:		
Number of dispensings per patient		
Mean (SD)	14.4 (17.16)	15.6 (17.60)
Duration of exposure (months)[a]		
Mean (SD)	18.6 (19.41)	20.2 (20.10)
Medications by AHFS therapeutic class, n (%)		
Antihistamine drugs	16,404 (10.7)	54,167 (8.8)
Anti-infective agents	133,581 (87.1)	502,006 (81.9)
Antineoplastic agents	24,973 (16.3)	66,401 (10.8)

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation.
[a] For each patient, the duration of exposure was calculated as the sum of the days' supply of all dispensings of the medication of interest during follow-up, without regard to overlaps or gaps.

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Table 4.
Cohort Characteristics During Follow-up
Primary Study Population

Category or Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
Autonomic drugs	90,945 (59.3)	317,113 (51.7)
Blood derivatives	n < 11	n < 11
Blood formation, coagulation, and thrombosis agents	50,750 (33.1)	200,044 (32.6)
Cardiovascular drugs	131,191 (85.6)	548,074 (89.4)
Central nervous system agents	138,267 (90.2)	524,750 (85.6)
Diagnostic agents	444 (0.3)	5,043 (0.8)
Electrolytic, caloric, and water balance	91,338 (59.6)	400,776 (65.4)
Enzymes	4,608 (3.0)	15,716 (2.6)
Respiratory tract agents	18,954 (12.4)	55,747 (9.1)
Eye, ear, nose, and throat (EENT) preparations	97,026 (63.3)	348,122 (56.8)
Gastrointestinal drugs	120,292 (78.5)	434,154 (70.8)
Gold compounds	20 (0.0)	15 (0.0)
Heavy metal antagonists	75 (0.0)	153 (0.0)
Hormones and synthetic substitutes	114,393 (74.6)	441,357 (72.0)
Local anesthetics	10,937 (7.1)	33,686 (5.5)
Oxytocics	n < 11	n < 11

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation.
[a] For each patient, the duration of exposure was calculated as the sum of the days' supply of all dispensings of the medication of interest during follow-up, without regard to overlaps or gaps.

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Table 4.
Cohort Characteristics During Follow-up
Primary Study Population

Category or Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
Serums, toxoids, and vaccines	22,386 (14.6)	70,473 (11.5)
Skin and mucous membrane agents	103,756 (67.7)	358,596 (58.5)
Smooth muscle relaxants	27,786 (18.1)	88,290 (14.4)
Vitamins	7,733 (5.0)	22,988 (3.7)
Miscellaneous therapeutic agents	76,531 (49.9)	213,086 (34.7)
Unclassified	220 (0.1)	513 (0.1)

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation.
[a] For each patient, the duration of exposure was calculated as the sum of the days' supply of all dispensings of the medication of interest during follow-up, without regard to overlaps or gaps.

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Table 5.
Calculation of Coverage Fraction and Number of Cases of Osteosarcoma Submitted by Participating Registries by US Census Region

Total number of osteosarcoma cases reported by participating registries, n	811
Total number of osteosarcoma cases expected[a], n_T	1,197
Coverage fraction, n / n_T	0.68
Osteosarcoma Cases Submitted by Participating Registries by US census region, n (%)	
Northeast	100 (12.3)
Midwest	267 (32.9)
South	251 (30.9)
West	193 (23.8)

US = United States
[a] The number of expected cases was taken to be the total number of osteosarcoma cases occurring in the US during 2007-2014 for adults aged ≥ 65 (using the study case definition of 12 ICD-O-3 histology codes) from the combined public use data file of the CDC's National Program of Cancer Registries and the National Cancer Institute's SEER program (Data: SEER*Stat Database: NPCR and SEER Incidence – Public Use Data – 2001-2014).

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Table 6.
Incidence Rates of Osteosarcoma, Incidence Rate Ratio, and Incidence Rate Difference
Primary Study Population

Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
Number of matched osteosarcoma cases by linkage to the participating cancer registries, n	0	n < 11
Total person-time of observation (years), P_T	585,955	2,212,036
Adjusted for the coverage fraction (P_T x 0.68)	397,000	1,498,715
Among patients from only the states with participating cancer registries[a]	378,631	1,426,199
Incidence rates per 1,000,000 person-years (n / P_T x 1,000,000)		
Adjusted for the coverage fraction	0.00	Suppressed
(95% CI)	(0.00, 9.29)	(1.47, 8.71)
Among patients from only the states with participating cancer registries[a]	0.00	Suppressed
(95% CI)	(0.00, 9.74)	(1.54, 9.16)
Incidence rate ratio		
Adjusted for the coverage fraction	0.00	
(95% CI)	(0.00, 3.21)	

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
CI = confidence interval.
[a] 100,033 patients in the teriparatide cohort and 400,119 patients in the comparator cohort were from states with participating cancer registries.

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Table 6.
Incidence Rates of Osteosarcoma, Incidence Rate Ratio, and Incidence Rate Difference
Primary Study Population

Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
Among patients from only the states with participating cancer registries[a]	0.00	
(95% CI)	(0.00, 3.20)	
Incidence rate difference per 1,000,000 person-years		
Adjusted for the coverage fraction	-4.49	
(95% CI)	(-8.16, -0.82)	
Among patients from only the states with participating cancer registries[a]	-4.71	
(95% CI)	(-8.56, -0.86)	

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
CI = confidence interval.
[a] 100,033 patients in the teriparatide cohort and 400,119 patients in the comparator cohort were from states with participating cancer registries.

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Table 7.
Sensitivity Analysis: Cohort Characteristics at Baseline
Subset Study Population With Medicare Parts A, B and D

Category or Statistic	Teriparatide Cohort (N = 105,794)	Comparator Cohort (N = 297,509)
Sex, n (%)		
Male	9,129 (8.6)	24,662 (8.3)
Female	96,665 (91.4)	272,847 (91.7)
Age (years) on index date		
Mean (SD)	77.3 (7.72)	77.7 (8.03)
Age group (years) on index date, n (%)[a]		
65-69	20,947 (19.8)	56,176 (18.9)
Male	1,893 (9.0)	5,023 (8.9)
Female	19,054 (91.0)	51,153 (91.1)
70-74	20,646 (19.5)	56,043 (18.8)
Male	1,882 (9.1)	4,982 (8.9)
Female	18,764 (90.9)	51,061 (91.1)
75-79	22,205 (21.0)	61,927 (20.8)
Male	1,888 (8.5)	5,123 (8.3)
Female	20,317 (91.5)	56,804 (91.7)
80-84	21,092 (19.9)	60,526 (20.3)

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AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

Table 7.
Sensitivity Analysis: Cohort Characteristics at Baseline
Subset Study Population With Medicare Parts A, B and D

Category or Statistic	Teriparatide Cohort (N = 105,794)	Comparator Cohort (N = 297,509)
Male	1,709 (8.1)	4,659 (7.7)
Female	19,383 (91.9)	55,867 (92.3)
≥ 85	20,904 (19.8)	62,837 (21.1)
Male	1,757 (8.4)	4,875 (7.8)
Female	19,147 (91.6)	57,962 (92.2)
Medicare Part D enrollment year, n (%)		
2006	78,759 (74.4)	222,788 (74.9)
2007	6,560 (6.2)	17,590 (5.9)
2008	4,057 (3.8)	11,393 (3.8)
2009	2,966 (2.8)	9,189 (3.1)
2010	2,544 (2.4)	7,584 (2.5)
2011	2,541 (2.4)	7,482 (2.5)
2012	2,769 (2.6)	8,126 (2.7)
2013	4,647 (4.4)	11,704 (3.9)
2014	951 (0.9)	1,653 (0.6)
Calendar year of cohort entry, n (%)		

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[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

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Table 7.
Sensitivity Analysis: Cohort Characteristics at Baseline
Subset Study Population With Medicare Parts A, B and D

Category or Statistic	Teriparatide Cohort (N = 105,794)	Comparator Cohort (N = 297,509)
2007	30,987 (29.3)	95,320 (32.0)
2008	13,441 (12.7)	38,191 (12.8)
2009	12,087 (11.4)	32,972 (11.1)
2010	9,130 (8.6)	24,891 (8.4)
2011	9,074 (8.6)	24,113 (8.1)
2012	9,324 (8.8)	24,833 (8.3)
2013	11,530 (10.9)	30,583 (10.3)
2014	10,221 (9.7)	26,606 (8.9)
Length of look-back period (months)		
Mean (SD)	36.9 (28.25)	35.4 (26.90)
Subjects from states with participating cancer registries, n (%)	68,134 (64.4)	191,002 (64.2)
US census region, n (%)[b]		
Northeast	16,858 (15.9)	47,510 (16.0)
Subjects from states with participating cancer registries	9,820 (58.3)	27,619 (58.1)
Subjects from states without participating cancer registries	7,038 (41.7)	19,891 (41.9)
Midwest	20,228 (19.1)	60,865 (20.5)

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AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

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Table 7.
Sensitivity Analysis: Cohort Characteristics at Baseline
Subset Study Population With Medicare Parts A, B and D

Category or Statistic	Teriparatide Cohort (N = 105,794)	Comparator Cohort (N = 297,509)
Subjects from states with participating cancer registries	16,286 (80.5)	47,719 (78.4)
Subjects from states without participating cancer registries	3,942 (19.5)	13,146 (21.6)
South	50,143 (47.4)	146,492 (49.2)
Subjects from states with participating cancer registries	27,155 (54.2)	82,392 (56.2)
Subjects from states without participating cancer registries	22,988 (45.8)	64,100 (43.8)
West	18,565 (17.5)	42,642 (14.3)
Subjects from states with participating cancer registries	14,873 (80.1)	33,272 (78.0)
Subjects from states without participating cancer registries	3,692 (19.9)	9,370 (22.0)
Use of corticosteroid drugs prior to the index date, n (%)	40,841 (38.6)	91,026 (30.6)
Use of other osteoporosis drugs prior to the index date, n (%)	62,549 (59.1)	78,652 (26.4)
Medications by AHFS therapeutic class within the 4 months prior to the index date, n (%)		
Antihistamine drugs	5,198 (4.9)	14,970 (5.0)
Anti-infective agents	49,827 (47.1)	145,844 (49.0)
Antineoplastic agents	7,683 (7.3)	15,330 (5.2)
Autonomic drugs	34,267 (32.4)	88,182 (29.6)
Blood derivatives	0 (0.0)	n < 11

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AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

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Table 7.
Sensitivity Analysis: Cohort Characteristics at Baseline
Subset Study Population With Medicare Parts A, B and D

Category or Statistic	Teriparatide Cohort (N = 105,794)	Comparator Cohort (N = 297,509)
Blood formation, coagulation, and thrombosis agents	20,481 (19.4)	65,649 (22.1)
Cardiovascular drugs	78,657 (74.3)	249,518 (83.9)
Central nervous system agents	77,473 (73.2)	198,733 (66.8)
Diagnostic agents	114 (0.1)	1,290 (0.4)
Electrolytic, caloric, and water balance	41,015 (38.8)	155,028 (52.1)
Enzymes	309 (0.3)	1,311 (0.4)
Respiratory tract agents	6,302 (6.0)	14,931 (5.0)
Eye, ear, nose, and throat (EENT) preparations	27,687 (26.2)	81,886 (27.5)
Gastrointestinal drugs	52,906 (50.0)	136,276 (45.8)
Gold compounds	n < 11	n < 11
Heavy metal antagonists	33 (0.0)	30 (0.0)
Hormones and synthetic substitutes	57,809 (54.6)	168,155 (56.5)
Local anesthetics	988 (0.9)	3,489 (1.2)
Oxytocics	0 (0.0)	0 (0.0)
Serums, toxoids, and vaccines	1,268 (1.2)	2,576 (0.9)
Skin and mucous membrane agents	29,268 (27.7)	77,145 (25.9)

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AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

Table 7.
Sensitivity Analysis: Cohort Characteristics at Baseline
Subset Study Population With Medicare Parts A, B and D

Category or Statistic	Teriparatide Cohort (N = 105,794)	Comparator Cohort (N = 297,509)
Smooth muscle relaxants	9,176 (8.7)	24,579 (8.3)
Vitamins	2,335 (2.2)	4,237 (1.4)
Miscellaneous therapeutic agents	36,503 (34.5)	65,436 (22.0)
Unclassified	0 (0.0)	0 (0.0)
Number of unique AHFS therapeutic classes within the 4 months prior to the index date, n (%)		
0-2 classes	8,812 (8.3)	23,209 (7.8)
3-5 classes	20,824 (19.7)	56,619 (19.0)
6-8 classes	25,592 (24.2)	71,175 (23.9)
9-11 classes	21,531 (20.4)	60,925 (20.5)
12-15 classes	17,757 (16.8)	51,679 (17.4)
> 15 classes	11,278 (10.7)	33,902 (11.4)
Risk factors, n (%)		
Radiation use	3,061 (2.9)	12,891 (4.3)
History of Paget's disease of the bone	630 (0.6)	1,241 (0.4)
Health status proxies		
History of vertebral or hip/pelvic fracture, n (%)	24,683 (23.3)	24,162 (8.1)

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AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

Table 7.
Sensitivity Analysis: Cohort Characteristics at Baseline
Subset Study Population With Medicare Parts A, B and D

Category or Statistic	Teriparatide Cohort (N = 105,794)	Comparator Cohort (N = 297,509)
History of cancer, n (%)	37,356 (35.3)	101,575 (34.1)
Number of inpatient and outpatient visits in the 4 months prior to the index date		
0	27,467 (26.0)	106,033 (35.6)
1	19,078 (18.0)	59,619 (20.0)
2	14,631 (13.8)	38,383 (12.9)
≥ 3	44,618 (42.2)	93,474 (31.4)
Charlson comorbidity index		
Mean (SD)	3.8 (3.25)	3.8 (3.31)

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
AHFS = American Hospital Formulary Services; CMS = Centers for Medicare and Medicaid Services; SD = standard deviation; US = United States.
[a] Percentages for gender were calculated using the number of patients in the age subgroup as the denominator.
[b] Percentages for states with and without participating cancer registries were calculated using the number of patients in the region subgroup as the denominator.

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Table 8.
Sensitivity Analysis: Incidence Rates of Osteosarcoma, Incidence Rate Ratio, and Incidence Rate Difference
Primary Study Population With a 6-Month Latency Period

Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
Number of subjects with < 6 months of follow-up	11,337	59,944
Number of matched osteosarcoma cases by linkage to the participating cancer registries, n	0	n < 11
Total person-time of observation (years), P_T	513,073	1,924,912
Adjusted for the coverage fraction (P_T x 0.68)	347,621	1,304,180
Among patients from only the states with participating cancer registries[a]	331,089	1,238,794
Incidence rates per 1,000,000 person-years (n / P_T x 1,000,000)		
Adjusted for the coverage fraction	0.00	Suppressed
(95% CI)	(0.00, 10.61)	(1.69, 10.01)
Among patients from only the states with participating cancer registries[a]	0.00	Suppressed
(95% CI)	(0.00, 11.14)	(1.78, 10.54)

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
CI = confidence interval.
[a] 100,033 patients in the teriparatide cohort and 400,119 patients in the comparator cohort were from states with participating cancer registries.

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Table 8.
Sensitivity Analysis: Incidence Rates of Osteosarcoma, Incidence Rate Ratio, and Incidence Rate Difference Primary Study Population With a 6-Month Latency Period

Statistic	Teriparatide Cohort (N = 153,316)	Comparator Cohort (N = 613,247)
Incidence rate ratio		
Adjusted for the coverage fraction	0.00	
(95% CI)	(0.00, 3.19)	
Among patients from only the states with participating cancer registries[a]	0.00	
(95% CI)	(0.00, 3.18)	
Incidence rate difference per 1,000,000 person-years		
Adjusted for the coverage fraction	-5.28	
(95% CI)	(-9.61, -0.95)	
Among patients from only the states with participating cancer registries[a]	-5.54	
(95% CI)	(-10.09, -0.99)	

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
CI = confidence interval.
[a] 100,033 patients in the teriparatide cohort and 400,119 patients in the comparator cohort were from states with participating cancer registries.

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Table 9.
Sensitivity Analysis: Incidence Rates of Osteosarcoma, Incidence Rate Ratio, and Incidence Rate Difference
Primary Study Population Requiring Two Teriparatide Prescriptions

Statistic	Teriparatide Cohort (N = 126,020)	Comparator Cohort (N = 433,485)
Number of matched osteosarcoma cases by linkage to the participating cancer registries, n	0	n < 11
Total person-time of observation (years), P_T	482,580	1,564,106
Adjusted for the coverage fraction (P_T x 0.68)	326,961	1,059,724
Among patients from only the states with participating cancer registries[a]	311,887	1,003,189
Incidence rates per 1,000,000 person-years (n / P_T x 1,000,000)		
Adjusted for the coverage fraction	0.00	Suppressed
(95% CI)	(0.00, 11.28)	(1.53, 11.01)
Among patients from only the states with participating cancer registries[a]	0.00	Suppressed
(95% CI)	(0.00, 11.83)	(1.62, 11.63)
Incidence rate ratio		
Adjusted for the coverage fraction	0.00	
(95% CI)	(0.00, 3.54)	

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
CI = confidence interval.
[a] 82,297 patients in the teriparatide cohort and 282,007 patients in the comparator cohort were from states with participating cancer registries.

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Table 9.
Sensitivity Analysis: Incidence Rates of Osteosarcoma, Incidence Rate Ratio, and Incidence Rate Difference
Primary Study Population Requiring Two Teriparatide Prescriptions

Statistic	Teriparatide Cohort (N = 126,020)	Comparator Cohort (N = 433,485)
Among patients from only the states with participating cancer registries[a]	0.00	
(95% CI)	(0.00, 3.51)	
Incidence rate difference per 1,000,000 person-years		
Adjusted for the coverage fraction	-5.97	
(95% CI)	(-11.74, -0.20)	
Among patients from only the states with participating cancer registries[a]	-6.27	
(95% CI)	(-12.33, -0.21)	

Note: Frequency counts not equal to zero and < 11 are suppressed per CMS privacy policy.
CI = confidence interval.
[a] 82,297 patients in the teriparatide cohort and 282,007 patients in the comparator cohort were from states with participating cancer registries.