PASS Information

Title	Observational Study Assessing Incidence of Osteosarcoma Among Forteo (teriparatide) Users by Linking State Cancer Registry Data to Large National Pharmacy Database Data [Observational Research Protocol, B3D-MC-GHBX Addendum 2.3(b)]
Version identifier of the final study report	1.0
Date of last version of the final study report	Not applicable
EU PAS register number	EUPAS18547
Active substance	Teriparatide (Calcium homeostasis, parathyroid hormones and analogues; 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:	Not applicable
Marketing authorisation holder(s)	Eli Lilly and Company, Indianapolis, IN
Joint PASS	No
Research question and objectives	The primary objective of study B3D-MC-GHBX (2.3b) was to estimate the incidence of osteosarcoma among patients who received treatment with teriparatide as compared to (1) an unexposed matched Osteoporosis comparator cohort and (2) an unexposed matched General Population comparator cohort using incidence rate ratios (IRRs) and 95% confidence intervals (CIs). The secondary objective was to characterize the teriparatide and unexposed matched comparator cohorts using demographic characteristics; select prescription medications dispensed during the baseline period; and duration of teriparatide use for the teriparatide-exposed cohorts.
Country(-ies) of study	United States
Author	PPD
Signature of principal investigator	Signature on file/see approval date below

Approval Date: 11-Oct-2018 GMT

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly and Company, Indianapolis, IN
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1. Abstract

Title: Observational Study Assessing Incidence of Osteosarcoma Among Forteo (teriparatide) Users by Linking State Cancer Registry Data to Large National Pharmacy Database Data [Study B3D-MC-GHBX 2.3(b)].

Rationale and background:

Teriparatide (Forteo®) is a recombinant human parathyroid hormone analogue indicated for increasing bone mass among postmenopausal women with osteoporosis (OP), men with primary or hypogonadal OP, and patients with glucocorticoid-induced OP. In clinical trials, teriparatide treatment was associated with increased bone mineral density and a decreased risk of fractures. In preclinical toxicology studies, dose-dependent increases in the incidence of osteosarcoma (OS), a malignant bone tumor, were reported in rats. Study B3D-MC-GHBX is a postmarketing study commitment to investigate any association between teriparatide and OS in humans. Study GHBX consists of 5 components: an ongoing retrospective United States (US) component (GHBX[b]), a completed European retrospective component in 5 Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) (GHBX[1]), an ongoing prospective US registry (GHBX[2.1]), and 2 completed addenda studies GHBX(2.2) and GHBX (2.3b).

Research question and objectives:

The primary objective of this study, GHBX 2.3(b), was to estimate the incidence of OS in patients who have received treatment with teriparatide over time as compared to a general population comparator cohort using an incidence rate ratio (IRR) and 95% confidence interval (CI). The secondary objective was to characterize the teriparatide and unexposed matched comparator cohorts using demographic characteristics; select prescription medications dispensed during the baseline period; duration of teriparatide use for the teriparatide-exposed cohorts, and; provider specialty.

Study design:

This population-based comparative cohort study of patients aged ≥18 years linked data from a US pharmacy dispensing database containing exposure details and data from 29 US state cancer registries (SCRs) to examine the relationship between teriparatide exposure and OS.

Setting: The study included US data during the study period 01 January 2005 - 31 December 2014.

Subjects and study size, including dropouts: The study population included patients age 18 years or older with at least one dispensed prescription for teriparatide or a non-teriparatide medication specifically indicated for OP (OP comparator) or a non-teriparatide medication (general population comparator). Patients were excluded from both comparator cohorts if they had ≥1 pharmacy dispensing for teriparatide between 01 September 2004 and 31 December 2014.

A total of 335,191 teriparatide patients (Teriparatide-OP) were matched with ≥1 unexposed OP patients and 379,283 teriparatide patients (Teriparatide-GP) were matched with ≥1 unexposed General Population patients. There were 637,387 patients in the unexposed OP cohort and 1,428,943 patients in the unexposed General Population cohort.

Variables and data sources: Study cohorts were selected using the IQVIA Longitudinal Prescription database (LRx), a commercial claims database where prescription dispensing and demographic data were obtained. LRx data were linked to osteosarcoma diagnosis data from the participating SCRs.

Results:

A total of 29 participating SCRs represented 65% of the US population aged ≥18 years and approximately 70% of all OS cases. The linkage found 3 cases of OS among the teriparatide-exposed patients (Teriparatide-OP and Teriparatide-GP); 6 cases in the unexposed OP cohort; and 9 cases in the unexposed General Population cohort.

The analysis adjusting for the coverage fraction, produced an IRR of 1.0 (95% CI 0.2, 4.5) for the OP matched cohorts and 1.3 (95% CI 0.2, 5.1) for the general population matched cohorts. The analysis restricted to participating cancer registries produced an IRR of 0.6 (95% CI 0.1, 3.6) for the OP matched cohorts and 0.8 (95% CI 0.1, 4.0) for the general population matched cohorts. These findings were similar in their respective sensitivity analyses due to the wide CIs of the incidence rates (IRs) and IRRs in the main analysis.

Discussion:

This study estimated IRRs to compare the IR of OS among Forteo treated patients (teriparatide-GP, teriparatide-OP) to two unexposed cohorts (OP, general population). A total of 3 cases of OS were identified among teriparatide-treated patients and the IRR when comparing teriparatide-treated patients to unexposed patients was less than 1 for the two main analyses. The findings from this study indicates that the rate of OS among Forteo-treated patients is consistent with what is expected in the background population. This study did not suggest an increased risk of OS among patients treated with teriparatide compared to an unexposed OP cohort or a general population cohort.

Marketing Authorisation Holder(s): Eli Lilly & Company

Names and affiliations of principal investigators: PPD of Eli Lilly & Company

2. List of abbreviations

Term	Definition
ADHD	Attention deficit hyperactivity disorder
AHFS	American Hospital Formulary Services
CI	Confidence interval
DC	District of Columbia
De-ID	De-identification
GHBX	Forteo Post-Approval Osteosarcoma Surveillance Study
GPI	Generic Product Identifier
ICD-O-3	International Classification of Diseases for Oncology, 3rd Edition
IR	Incidence rate
IRB	Institutional review board
IRR	Incidence rate ratio
LRx	Longitudinal Prescription database
mcg	Microgram
mg	Milligram
misc.	Miscellaneous
mL	Millilitre
MSA	Management Science Associates
NAACCR	North American Association of Central Cancer Registries
NDC	National drug code
NOS	Not otherwise specified
OP	Osteoporosis
OS	Osteosarcoma
PTH	Parathyroid hormone
PY	Person year

SAP	Statistical analysis plan
SCR	State Cancer Registry
SD	Standard deviation
SEER	National Cancer Institute's Surveillance, Epidemiology, and End Results
sFTP	Secure File Transfer Protocol
Teriparatide -GP	Teripratide (General Population-Matched)
Teriparatide -OP	Teriparitide (Osteoporosis-Matched)
US	United States of America

3. Investigators

Principal Investigator

PPD Eli Lilly and Company, GPS- Pharmacoepidemiology

Lead Investigator: IQVIA

PPD

4. Other responsible parties

Not applicable.

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	Not Applicable	3 March 2017	None
End of data collection	Not Applicable	19 March 2018	None
Registration in the EU PAS register	Not Applicable	Unknown	None
Final report of study results	Not Applicable	See Page 1	None

Abbreviation: PAS = post-authorization status.

6. Rationale and background

Forteo® (teriparatide), rhPTH (1-34), produced in E. coli using recombinant DNA technology, is identical to the 34 N-terminal amino acid sequence of endogenous human parathyroid hormone (PTH).

Teriparatide is administered subcutaneously into the thigh or abdominal wall at a recommended dose of 20-µg per day (Lilly product information). In clinical trials, teriparatide treatment was associated with increased bone mineral density and a decreased risk of fractures (Neer et al. 2001).

Forteo® was initially approved in 2002 in the United States (US) for the treatment of postmenopausal women with osteoporosis (OP) at high risk for bone fractures and for increasing bone mass in men with primary or hypogonadal OP who are at high risk for fracture. In 2009, the treatment indication was expanded to include treatment of men and women with glucocorticoid-induced OP who are at high risk for fracture.

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 (OS), a malignant tumor (Vahle et al. 2002; Forteo United States Package insert [USPI] 2012). 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). Studies have shown that the rat skeleton is more sensitive than monkey or human skeletons to the pharmacological effects of parathyroid hormone in the formation of new bone and osteosarcomas (Miller 2008).

In this study report, summarizing GHBX 2.3(b), IQVIA Longitudinal Prescription database (LRx), a commercial pharmacy claims database, identified teriparatide-treated patients and 2 unexposed comparison cohorts for persons aged 18 years or older and were linked with data from participating state cancer registries. GHBX 2.3(b) was conducted in parallel with the GHBX 2.2 study analyzing Medicare administrative claims data. This report details the findings from the completed GHBX 2.3(b) pharmacy claims study.

7. Research question and objectives

To estimate the incidence of osteosarcoma in patients who have received treatment with Forteo over time as compared to a general population comparator cohort using an incidence rate ratio (IRR) and 95% confidence interval (CI)

To characterize the Forteo user and comparator cohorts using the following:

- Demographic characteristics;
- Select prescription drugs dispensed during the baseline period;
- Duration of Forteo use for Forteo-treated cohort
- Provider specialty

8. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1 GHBX 2.3a	15 June 2016	Sections 3.1, 3.3 through 3.5, Figures 1, 2 and 3	Amendment (a); submitted to NDA 021318 (SN 0129)	Amended due to a change in the pharmacy database vendor
2 GHBX 2.3b	22 Nov2016	Sections 3.3.1, 3.3.2, 3.2.2.1, 3.3.4.2, Figures 1 and 2	Amendment (b) submitted to NDA 021318 (SN 0153)	Amended to add a new database

9. Research methods

9.1. Study design

This was an observational database study that utilized a matched cohort design to compare the incidence of OS among teriparatide-treated patients to the incidence of OS among patients not treated with teriparatide.

Patients in the US aged ≥18 years with a pharmacy dispensed prescription for teriparatide between January 2005 and December 2014 were identified using national drug codes (NDCs) (Table 1) in the IQVIA LRx, a commercial pharmacy database.

State cancer registry data containing OS diagnosis information from 29 participating state cancer registries (SCRs) were linked to study cohorts to determine whether the patients had been diagnosed with OS during the 10-year study period. Osteosarcoma was identified in SCR data using predefined oncology codes outlined in Section 9.4.2.

This study utilizes a population-based pharmacy claim database to increase the number of teriparatide-treated patients assessed and the PYs of observation. In addition to the sample size advantages, this approach has the added value of including comparator cohorts adding context to any findings.

9.2. Setting

This observational database study using a matched cohort design included patients in the US aged ≥18 years with a pharmacy-dispensed prescription for teriparatide captured in the IQVIA LRx database, a large US commercial outpatient pharmacy dispensing database, linked to cancer registry data. The study period was from 01 January 2005 through 31 December 2014 with a 4-month baseline period starting as early as 01 September 2004 (for patients who indexed on 01 January 2005).

The LRx database contains data on US retail prescriptions, US specialty and mail-order prescriptions, and prescriptions filled at long-term care facilities. See Section 9.5 for further details.

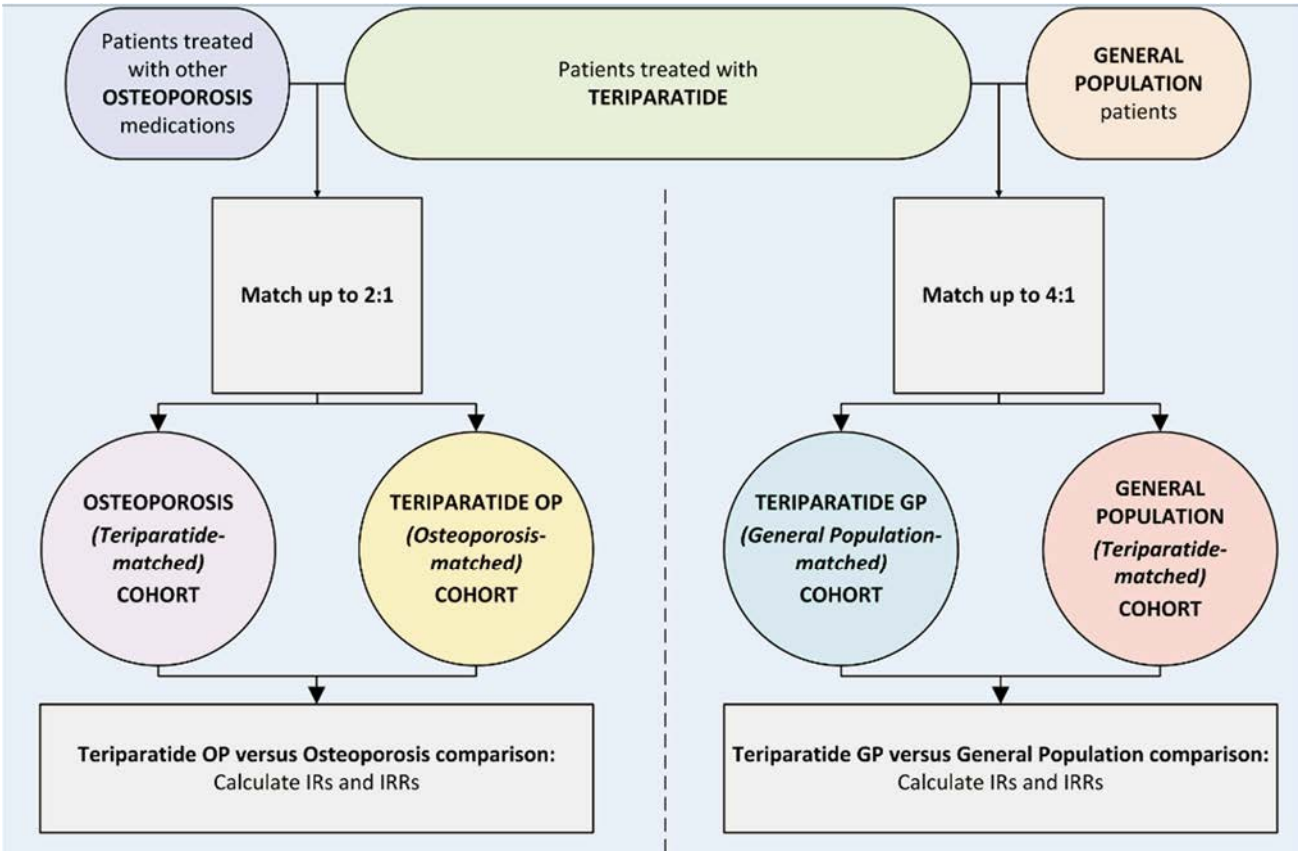
Individual institutional review board (IRB) approval was obtained from Quorum Review IRB for the study overall and from IRBs governing participating SCRs when applicable.

9.3. Subjects

Data from LRx were used to form 2 teriparatide-exposed cohorts matched to unexposed comparator cohorts using the matching criteria outlined in Section 9.3.2.1. The first teriparatide-exposed cohort (Teriparatide–OP) was formed by matching, up to 1:2, to OP patients not treated with teriparatide. The second teriparatide-exposed cohort (Teriparatide–GP) was formed by matching, up to 1:4, to General Population patients not treated with teriparatide. As a result, there was a total of 4 study cohorts (see Figure 1).

Study cohorts were generated using the universe of patients in LRx, therefore patients could have been included in both the Teriparatide-OP and the Teriparatide-GP cohorts. This approach

resulted in overlap of patients between the 2 teriparatide-exposed cohorts. Similarly, unexposed comparator patients could have been in both the OP and the General Population cohorts. See Section 9.7 for patient numbers included in the study cohorts.



Abbreviations: IR = incidence rate; IRR = incidence rate ratio.
Up to 2 patients treated with OP medications other than teriparatide were matched to 1 teriparatide-exposed patient and up to 4 general population patients were matched to 1 teriparatide-exposed patient.

Figure 1. Overview of study design.

9.3.1. Exposure cohorts

9.3.1.1. Teriparatide cohorts

Patients were eligible for inclusion in one or both of the final matched teriparatide cohorts if they had at least 1 dispensed prescription for teriparatide from an outpatient or long-term care facility pharmacy between 01 January 2005 and 30 December 2014 (see Table 1 for teriparatide NDCs). The first dispensing of teriparatide identified during this period was designated the teriparatide index date. Once a patient indexed on teriparatide they were considered exposed for the remaining duration of the study period (see Section 9.3.3 for more details). This study design included both prevalent and new users.

Table 1. NDCs Used to Identify Teriparatide-Exposed Patients

NDC	Drug	Dosage
00002-8971-01	Teriparatide (Recombinant)	750 µg / 3 mL injection
00002-8400-01	Teriparatide (Recombinant)	600 µg / 2.4 mL injection

Two NDCs associated with teriparatide were *not* included among the NDCs used to identify teriparatide-exposed patients for the following reasons: 00002-8400-99 was not commercially available during the study period and 54868-5406-00 represented a dose of 10 µg, which was deemed to be inappropriate for this analysis.

Teriparatide-exposed patients were not eligible for inclusion in teriparatide cohorts if they were <18 years of age during the year of the initial (index) teriparatide dispensing; resided outside the 50 US states and the District of Columbia (DC) during the study period; or were missing key matching variables such as sex, year of birth, or payer type on their index teriparatide prescription.

Residential status was determined by assessing patient and pharmacy 3-digit ZIP code(s) for all dispensings during the study period. This could have included 3-digit ZIP codes for US territories (e.g., Puerto Rico) and for US military bases that are not based in the US. Pharmacy 3-digit ZIP code was included to account for any missing data for patient 3-digit ZIP code.

Finally, teriparatide-exposed patients were excluded from teriparatide cohorts if they had a diagnosis of OS in the linked cancer registry data before their teriparatide index date.

9.3.1.2. Comparator cohorts

There were 2 independently matched comparator cohorts: an OP cohort and a General Population cohort. A patient could have been included in both matched comparator cohorts.

Patients were included in the OP cohort if they filled at least 1 prescription for a medication specifically indicated for OP, other than teriparatide (see Table 2 for details) from an outpatient pharmacy during the study period, met the matching criteria outlined in Section 9.3.2.1, and were selected to be matched (up to 2:1) to the teriparatide-exposed patients.

Table 2. Qualifying Osteoporosis Medications Used to Define the Osteoporosis Cohort

Drug class	Drug	Dose
Bisphosphonate	Fosamax (alendronate)	10 mg tablet, 70 mg tablet
	Actonel (risedronate)	5 mg tablet, 35 mg tablet, 150 mg tablet, 36 mg delayed release tablet
	Boniva (ibandronate)	150 mg tablet, 3 mg / 3mL injectable
	Reclast (zoledronic acid)	5 mg / 100 mL injectable
Biological	Prolia (denosumab)	60 mg / mL injection

Generic and marketed product names as well as combination therapy were included.

Patients were included in the final matched General Population cohort if they filled at least 1 prescription for any medication (other than teriparatide) from an outpatient pharmacy during the

study period, met the matching criteria outlined in Section 9.3.2.1, and were selected to be matched (up to 4:1) to teriparatide-exposed patients.

Patients were excluded from both comparator cohorts if they had ≥1 pharmacy dispensing for teriparatide in the commercial pharmacy database between 01 September 2004 and 31 December 2014 and did not meet the matching criteria outlined in Section 9.3.2.1.

A comparator patient was considered unexposed to teriparatide from cohort entry through the end of the study period (see Section 9.3.3 for more details).

Finally, matched comparator patients were excluded from the study analyses if they had a diagnosis of OS in the linked cancer registry data before their index date.

9.3.2. Matching

9.3.2.1. Matching criteria

Teriparatide-exposed patients were independently matched to up to 2 OP patients and up to 4 General Population patients, using the following variables:

1. Index date (Month and Year)

   A qualifying comparator medication must have been dispensed during the same month and year as the teriparatide-exposed patient's first dispensed teriparatide prescription during the study period. The comparator index date was set to be the same date as the index date of the matched teriparatide-exposed patient. This was done because a patient could have had multiple qualifying comparator prescriptions during the same index month and index year as their matched teriparatide-exposed patient.

2. Sex (male, female)
3. Age at index date

   Single ages up to 72 years old were used for matching. Due to privacy restrictions related to how age can be recorded in the LRx database matching on single ages past 72 years old wasn't possible. Patients aged ≥73 years old were matched with patients who were also ≥73 years old.

4. Patient or pharmacy 3-digit ZIP code

   The patient or pharmacy 3-digit ZIP code was used to identify geographical region. This included 3-digit ZIP codes for US territories (e.g., Puerto Rico) and for US military bases that are not based in the US. Pharmacy 3-digit ZIP code was used to account for any patients missing a 3-digit ZIP code.

5. Payer type

   This included third-party, Medicare, Medicaid, self-pay/cash. Payer type for teriparatide-treated patients included the payer for the index prescription dispensing. For comparator patients payer type was defined as the most frequent payer type during their index month.

6. Number of classes of medications dispensed during the 4 months prior to the index month.

This parameter served as a proxy for measuring overall health status and the presence of chronic comorbidities. Medication classes were based on the Generic Product Identifier (GPI) classification system at the 6-digit (sub-class) level (Wolters Cluwers Clinical Drug Information 2018). The GPI classification system groups drugs with similar pharmacologic, therapeutic, and/or chemical characteristics in a hierarchy based on a 14-digit GPI code. The number of classes were grouped into categories based on their distribution across all patients (0-2, 3-5, 6-8, ≥9 classes); these categories were then used as a matching variable.

9.3.2.2. Matching process

As outlined in the statistical analysis plan (SAP), selecting the matched unexposed comparator patients for each teriparatide-exposed cohort was performed sequentially for each calendar year of the study period after prioritizing final matches for the teriparatide-exposed patients with <2 pre-matched OP comparator patients and <4 pre-matched General Population comparator patients. Matching was conducted without replacement (i.e., a patient could have only been selected as a comparator once). All analyses were prespecified.

Starting 01 January 2005, every teriparatide index date was identified (i.e., the first dispensing of teriparatide for a given patient).

Osteoporosis Patients

For each calendar year of the study period, OP patients were selected for potential matching if they had ≥1 prescription dispensing for a qualifying osteoporosis medication (other than teriparatide; see Table 2) during the study year, were ≥18 years of age during the study year, and had a 3-digit ZIP code associated with any teriparatide-exposed patient indexing in the same study year. From the potential OP matches selected, for each calendar year of the study period, patients were then pre-matched to teriparatide-exposed patients on month of dispensing, sex, and age. A potential OP match could have been pre-matched with several teriparatide-exposed patients.

Final matching priority (using all matching criteria outlined in Section 9.3.2.1) was given to teriparatide-exposed patients who pre-matched to only 1 OP patient. Once those matches had been made, then, for each calendar year of the study period starting with 2005, the remaining pre-matched OP patients were randomly selected for final matching (up to 2:1) to teriparatide-exposed patients on month and year of dispensing, sex, age, payer type, and number of GPI medication classes.

General Population Patients

The General Population patients were selected for potential matching and were pre-matched similarly to the OP patients, but had ≥1 prescription dispensing for any product (including the qualifying OP medications listed in Table 2). A potential General Population match could have been pre-matched with several teriparatide-exposed patients. Due to the size of the commercial pharmacy database, a 10% random sample of pre-matched General Population patients were randomly selected for each calendar year of the study period for final random matching (up to 4:1) to teriparatide-exposed patients, with final matching priority given to teriparatide-exposed

patients who pre-matched to <4 General Population patients. The remaining pre-matched General Population patients were randomly selected for each calendar year of the study period starting with 2005 for final matching (up to 4:1) to teriparatide-exposed patients.

9.3.3. Person-time and censoring criteria

Person-time

For the primary analysis, person-time began on the day after the teriparatide or comparator index date; this assumed no induction and latency period between exposure and a diagnosis of pathologically-confirmed osteosarcoma recorded by the participating SCRs.

In a sensitivity analysis, person-time did not begin until 180 days (6-months) following the teriparatide index date to allow for a latency and induction period (see Section 9.9.4.1 for more details).

For both the primary analysis and the sensitivity analyses, person-time was accumulated until the earliest of the following:

- OS diagnosis date (per participating state cancer registry); or
- 31 December 2014 (end of follow-up).

The use of person-time in these analyses was to account for the variable length in follow-up, as opposed to changing exposure status. Once a patient indexed on teriparatide, they were considered exposed for the remaining duration of the study period or until diagnosis of OS. Similarly, once a patient was selected as a matched comparator, they were considered unexposed for the remaining duration of the study period. Any person-time that occurred prior to the teriparatide index date or prior to the comparator index date was not included. Mortality adjustments were included in a sensitivity analysis as described in Section 9.9.4.4.

9.4. Variables

9.4.1. Baseline variables and covariates

The baseline study variables and covariates are listed in Table 3.

Table 3. Baseline Study Variables and Covariates

Variable	Values	Reporting
Patient ID	Unique patient identifier	None
Exposure cohort	Teriparatide-OP Osteoporosis Teriparatide–GP General Population	Teriparatide-OP Osteoporosis Teriparatide–GP General Population
Index Medication (available for the teriparatide-exposed cohorts only)	National Drug Code (NDC) Generic name Dispensing dates Days' supply for each dispensing	Number of dispensings Days' supply per dispensed prescription Duration of exposure (months[a])
Age	Age at Index Date Age ≥18, ≥40, ≥65 Age 18-19, 5-year age groups to 69, 70-72, ≥73	Age ≥18, ≥40, ≥65 Age 18-19, 5-year age groups to 69, 70-72, ≥73
Sex	Female Male	Female Male
Geography	3-digit ZIP code State (including DC)	Census division[b] Census region
Payer type for index prescription dispensing[c]	Third-party Medicare Medicaid Self-Pay/Cash	Third-party Medicare Medicaid Self-Pay/Cash
Index Date[d]	Index Day (Month, and Year)	Index Month and Year in 6-month intervals
Medication use during the 4-month baseline period[e]	NDC codes mapped to generic name 2-digit (General Product Identifier) GPI classification	2-digit GPI medication classification
Count of medication classes during the 4-month baseline period[e]	NDC codes mapped to generic name 6-digit GPI classification Count of 6-digit GPI medication classes dispensed during the 4 months prior to the index Month[e]	0-2 3-5 6-8 ≥9

Table 3. Baseline study variables and covariates Cont'd

Variable	Values	Reporting
Specialty of prescribing provider[f]	Provider specialty	Provider specialty categories
Osteosarcoma diagnosis	International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) diagnosis codes specified in Table 4	Yes/No ICD-O-3 diagnosis codes
Pathological confirmation of osteosarcoma diagnosis	North American Association of Central Cancer Registries (NAACCR) variable "Diagnostic confirmation of osteosarcoma diagnosis" Evidence of pathologic confirmation was determined using the following NAACCR categories: "1 Positive histology;" "3 Positive histology PLUS - positive immunophenotyping AND/OR positive genetic studies (used only for hematopoietic and lymphoid neoplasms M-9590/3-9992/3);" and "4 Positive microscopic confirmation, method not specified." The following NAACCR categories did not meet the threshold for pathologic confirmation: "2 Positive cytology;" "5 Positive laboratory test/marker study;" "6 Direct visualization without microscopic confirmation;" "7 Radiography and/or other imaging techniques without microscopic confirmation;" "8 Clinical diagnosis only (other than 5, 6, or 7);" and "9 Unknown whether or not microscopically confirmed; death certificate only." Reported Yes/No	
Primary site of osteosarcoma	ICD-O-3 topographical codes C40-C41	ICD-O-3 topographical codes C40-C41

[a] A "month" was defined as 30.5 days.
[b] United States Census Bureau. Geographic Areas Reference Manual (GARM), Chapter 6. 1994.
[c] For the comparator patients, defined as most frequent payer type during their Index Month.
[d] For the comparator patients was set to be the same date as the index date of the matched teriparatide-exposed patient.
[e] Not including the index month.
[f] For comparator patients, defined as the specialty of the provider with the most claims during their Index Month.

9.4.2. Outcomes

Osteosarcoma cases were identified in the SCR data using 12 pre-defined International Classification of Diseases for Oncology, 3rd Edition, (ICD-O-3) codes (Table 4). Only patients with pathologically-confirmed cases of OS that were diagnosed after their index date were included in the study analyses. Date of OS diagnosis included either (1) month and year or (2) year only. For those OS cases with a month and year of diagnosis, the date of OS diagnosis was set to the last day of the month of that year. For those OS cases missing the month of diagnosis

(e.g., some states were unable to provide this information due to privacy concerns), the date of OS diagnosis was set to 31 December of that year.

Table 4. Osteosarcoma ICD-O-3 Diagnosis Codes

Code	Description
9180/3	Osteosarcoma NOS
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

Abbreviations: ICD-O-3 = International Classification of Diseases for Oncology, 3rd Edition
NOS = not otherwise specified.

9.5. Data sources

The IQVIA LRx database provided prescription medication dispensing data for this study and outcomes were obtained from participating SCRs.

9.5.1. Commercial pharmacy dispensing database – IQVIA Longitudinal Prescription (LRx) Database

The IQVIA LRx database consists of patient-level dispensed prescriptions that enable patient prescription-filling behavior to be tracked across time, payers, and pharmacies. Data contributors include retail chains and independent pharmacies, specialty, mail-order, and long-term care pharmacies. The LRx represents >85% of all US retail prescriptions, 40% to 75% of US specialty and mail-order prescriptions (depending on therapeutic area), and 71-83% of prescriptions filled at long-term care facilities (across therapeutic areas). Geographic coverage ranges from 57% in the Southwest to 70% to 80% in the Mid-Atlantic region. Drug exposure was obtained from the LRx database for the teriparatide-exposed and unexposed comparator study cohorts dating back to 01 September 2004. The LRx is an open database with no enrollment or eligibility data. All patients were assumed to have complete data for the duration of the study period (i.e., 01 January 2005 through 31 December 2014) and the 4-month baseline period, starting as early as 01 September 2004 for those patients who indexed on 01 January 2005.

9.5.2. Participating state cancer registries

State cancer registry data included demographic variables for linking and OS diagnosis information including diagnosis code (i.e., histology, as coded by ICD-O-3 codes), primary site, diagnostic confirmation, and month (when available) and year of OS diagnosis. Because commercial claims data lack detailed clinical diagnosis information for OS (i.e., do not have ICD-O-3 diagnosis codes), SCRs were deemed to be an appropriate source for identifying OS cases during the study period and providing OS diagnosis information.

All US SCRs were approached for participation in the study. Each SCR covered a certain proportion of the US population. The goal was to recruit enough SCRs so that at least 60% of the US population aged 18 years and older was potentially eligible for linkage with the LRx study cohorts. A total of 29 SCRs participated in the study, representing approximately 65% of the US population aged 18 years and older. Participating registry data included approximately 70% of all US OS cases aged 20 years and older during the study period (Table 5).

9.5.3. Data linkage

Study cohorts created using pharmacy dispensing data from the LRx database were linked to de-identified and encrypted OS data from the participating SCRs.

Each participating SCR created a data file containing all OS cases diagnosed in their state during the study period. The prepared data file included demographic variables for linking (i.e., first name, last name, date of birth, sex, street address, and ZIP code) and OS diagnosis codes, primary site, diagnostic confirmation, and date (year and month, when available) of OS diagnosis. The participating SCRs either installed the IQVIA de-identification and encryption software internally or provided the OS data files to the trusted third party data processor, Management Science Associates (MSA), for de-identification.

The linkage between study cohorts and SCR data included data from 01 January 2005 through 31 December 2014. However, exposure data from the LRx database began 01 September 2004 to allow for a 4-month baseline period for those patients who indexed on 01 January 2005. A deterministic data linkage method was used to match on demographic variables across the study cohorts and SCR data using encryption and de-identification technology. The data linkage rate was 89%. Study data extended only through 31 December 2014 due to the 9- to 18-month lag in data collection and availability after the close of the calendar year among participating SCRs.

The participating SCRs followed a standard process for preparing the data file, as described below in Section 9.5.3.1. The prepared data file was de-identified and encrypted and transferred using 1 of the 2 options described below in Section 9.5.3.2.

9.5.3.1. Data Linkage Step 1

The participating SCRs prepared a data file that included identified variables used for linking and additional variables used for study analysis. The following variables utilized for linkage were de-identified and encrypted into a patient token:

- Patient first and last name;

- Date of birth;
- Patient sex;
- Patient address 1 (patient's primary correspondence address 1); and
- Patient ZIP code (patient's primary correspondence ZIP code).

Variables utilized for the study analyses, which were not encrypted:

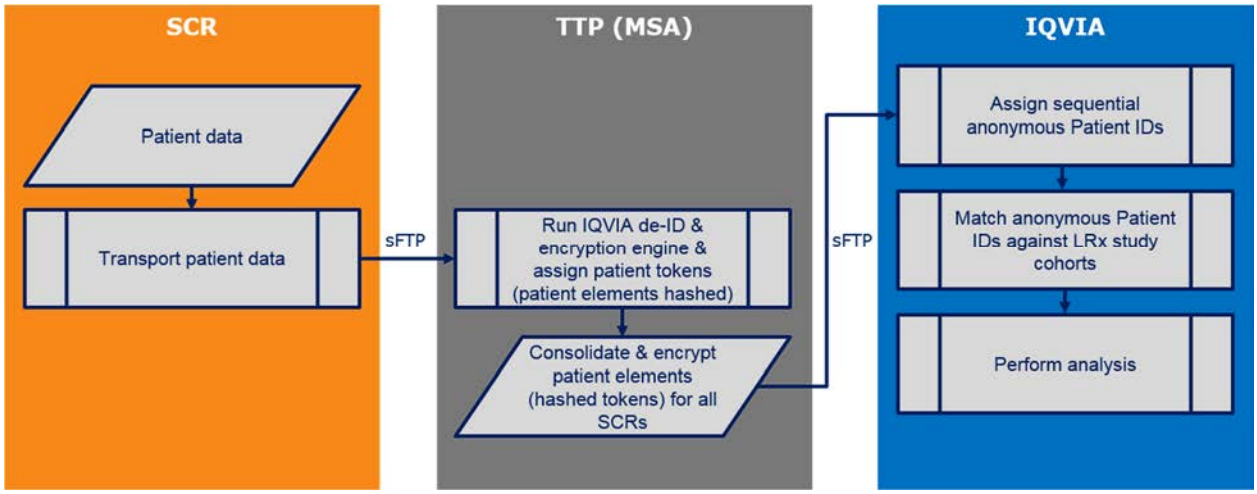
- OS ICD-O-3 diagnosis codes (Table 4);
- Primary site;
- Diagnostic confirmation of OS diagnosis; and
- OS diagnosis date (year and month, when available).

9.5.3.2. Data Linkage Step 2

The variables used for linkage were de-identified and encrypted patient tokens were created using one of the following methods:

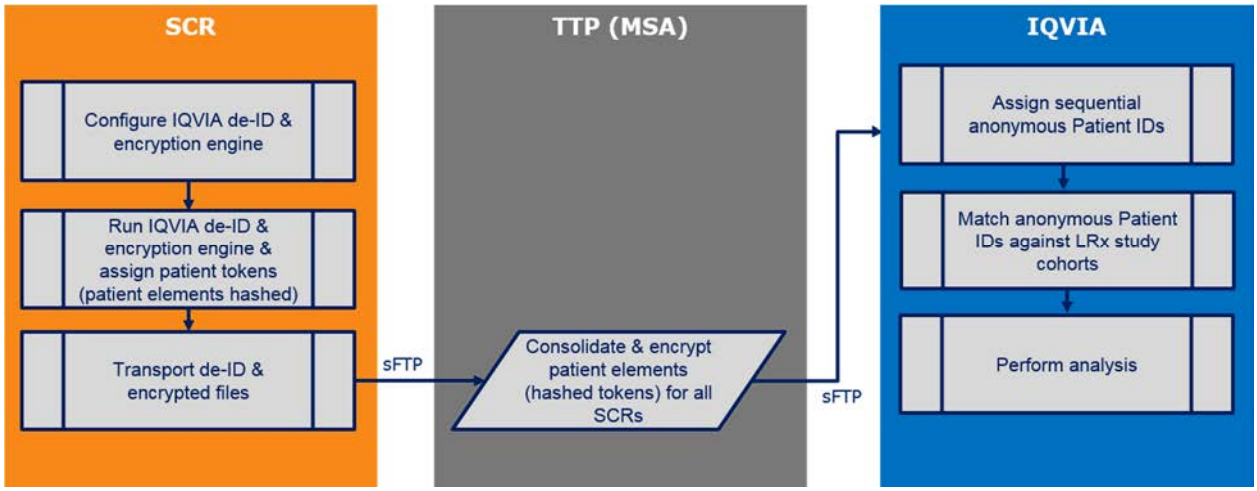
Option A (Figure 2): The SCR sent the file outlined in Step 1 to MSA for de-identification of the variables required for linkage and creation of encrypted patient tokens via the IQVIA encryption engine.

Option B (Figure 3): The SCR installed and ran the IQVIA de-identification and encryption engine locally and transferred the resulting encrypted patient tokens, along with the variables to be utilized for the study analyses, to MSA.



Abbreviations: de-ID = de-identification; LRx = IQVIA Longitudinal Prescription database; MSA = Management Science Associates; SCR = state cancer registry; sFTP = secure File Transfer Protocol; TTP = trusted-third party.

Figure 2. State cancer registry data transfer/linkage Option A - Encryption at MSA.



Abbreviations: de-ID = de-identification; LRx = IQVIA Longitudinal Prescription database; MSA = Management Science Associates; SCR = state cancer registry; sFTP = secure File Transfer Protocol; TTP = trusted-third party.

Figure 3. State cancer registry data transfer/linkage Option B - Encryption at the State Cancer Registry.

9.5.3.3. Data Linkage Step 3

MSA compiled data files from all participating SCRs and sent the encrypted patient tokens and the variables for the study analyses to the research team at IQVIA where they were linked to the study cohorts (i.e., the 2 teriparatide-exposed cohorts and the 2 matched comparator cohorts) created using the LRx database.

9.6. Bias

Patients were matched on possible confounding variables selected a priori (i.e., age, sex, 3-digit ZIP code, payer type, index month and year, and number of classes of medications dispensed during the 4-month baseline period).

A potential confounder, not matched on, was diagnosis of Paget's disease of the bone. It is not recommended that patients with a history of Paget's disease of the bone be treated with teriparatide; therefore, it was expected that Paget's disease of the bone would only be represented among the unexposed comparator cohorts. However, it is important to note that estimates for the prevalence of this rare outcome in the US are less than 4% (Cooper et al 2006). Also, the American Cancer Society notes that OS is 1 of the bone sarcomas that develop in 1% of people diagnosed with Paget's disease of the bone (ACS 2018). Therefore, it is unlikely that a potential difference in the prevalence of Paget's disease would have resulted in appreciable confounding. Additionally, history of radiation is not available in the IQVIA LRx database and could not be measured.

The literature has mixed reviews on other potential risk factors for OS. As such, we do not expect these other potential risk factors to have resulted in appreciable confounding. As stated by Savage and Mirabello in their 2011 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 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."

9.7. Study size

The LRx database included 429,486 patients with a dispensed prescription for teriparatide (See Table 1 for NDCs) between 01 January 2005 and 31 December 2014. Based on initial feasibility counts, it was expected that there would have been a match of up to 4 unexposed General Population patients to each teriparatide-exposed patient, for a total of approximately 1.8 million General Population comparator patients. The planned matching ratio for the unexposed OP patients was up to 2 unexposed OP patients to 1 teriparatide-exposed patient, for a total of approximately 900,000 OP comparator patients. The numbers of patients included in the 4 cohorts are described in Section 10.1.

9.8. Data transformation

No transformation of the data was performed.

Datasets and analytic programs were stored according to IQVIA procedures with access restricted to study personnel. IQVIA confidentiality agreements were signed by all employees and included data protection and strict prohibitions on reidentification attempts.

9.9. Statistical methods

9.9.1. Main summary measures

Primary analysis

The primary objective of the study was to estimate the IRR, IR and 95% CI of OS for patients aged 18 years or older with a prescription for teriparatide versus matched comparator cohorts with a prescription dispensing for a drug other than teriparatide. The OP comparator cohort had to have ≥1 dispensing for an OP medication.

For the primary analysis, the IRR and 95% CI for OS occurrence in teriparatide users and associated comparator cohort was estimated using exact conditional Poisson regression (Table 17). Primary estimates of the IR and the IRR assumed that there was no lag time for the induction and latency of OS to occur following the index date.

Analyses were conducted using SAS 9.3.

Descriptive statistics

For categorical variables, frequency distributions were reported. For ordinal variables, frequency distributions, means, standard deviations (SDs), minimums, 25th percentiles, medians, 75th

percentiles, and maximums were reported. For continuous variables, means, SDs, minimums, 25th percentiles, medians, 75th percentiles, and maximums were reported.

Descriptive statistics for all of the variables listed in Table 3 (unless otherwise specified) for the 4 cohorts are presented in Table 9, Table 15 and Table 16.

The IRs and 95% CIs of OS in the 4 cohorts and the IRRs and 95% CIs of OS, comparing each teriparatide-exposed cohort to their respective unexposed matched comparator cohort are presented in Table 17.

The IRs (and 95% CIs) and the IRRs (and 95% CIs) of OS from the sensitivity analyses are presented in Table 19, Table 21, Table 22, and Table 23, and Table 24.

9.9.2. Main statistical methods

9.9.2.1. Incidence of osteosarcoma

The IR of OS in each of the 2 teriparatide-exposed cohorts was estimated as the number of teriparatide-exposed patients with a diagnosis of OS that occurred after the teriparatide index date divided by the total number of PYs of follow-up among the teriparatide-exposed patients at risk.

The IR of OS in each of the unexposed matched comparator cohorts was estimated as the number of unexposed matched comparator patients with a diagnosis of OS that occurred after the Comparator Index Date divided by the total number of PYs of follow-up among the unexposed matched comparator patients at risk.

The IR was expressed as the number of OS cases per 1,000,000 PYs at risk and was estimated in 2 ways:

1. Using the total person-time of follow-up among patients at risk in each cohort adjusted for the coverage fraction (Section 9.9.2.2.1); and
2. Using the total person-time of follow-up among patients at risk in each cohort from states with participating SCRs (Section 9.9.2.2.1).

Since the number of cases of OS was expected to be very small, and to avoid the potential loss of information from matched sets without a case of OS, the IRR and corresponding 95% CIs of OS for teriparatide-exposed patients versus the unexposed matched comparator patients was estimated from the conditional distributions of the sufficient statistics for the parameters of a log-linear model. This analysis was implemented using SAS/STAT software and the methods of the GENMOD procedure for exact conditional Poisson regression using the EXACT statement. Also, because of the small number of cases expected, the model would only support a limited number of independent variables besides the exposure cohort indicator. Therefore, to determine which matching variables, if any, should have been included in the final model, the association between the OS outcome and each of the matching variables was assessed one at a time via exact Poisson regression models with the matching variable and the exposure cohort as main effects. Those matching variables which were associated with the outcome of OS then would have been included as main effects in the final model along with the exposure cohort.

No matching variables were associated with the outcome of OS; therefore, our final model only included an indicator for exposure cohort. The analysis data set consisted of 2 records for each matched set of patients: 1 record for the teriparatide-exposed patient and 1 for the unexposed matched comparator patient, in addition to the variables used to match patients, the total person-time of follow-up, and OS status. The model dependent variable was the number of OS cases; the model independent variable was an indicator for exposure cohort; and the offset was the person-time of follow-up among patients at risk in each cohort.

9.9.2.2. Adjustment for state cancer registry participation

All US SCRs were invited to participate and 29 agreed to participate in the study. As a result, the participating SCRs covered approximately 65% of the US population aged ≥18 years during the observation period. This was addressed by applying a coverage fraction and by limiting the analysis to data from participating states.

Using a coverage fraction that represented the number of OS cases captured in this study (based on SCR participation) divided by the total number of OS cases ≥20 years old expected in the US during the study period (Table 5). The expected number of OS cases in the US was estimated using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) for patients aged 20 years and older (as opposed to aged 18 years and older) because the SEER database uses 5-year age categories.

Calculation of IRs and IRRs using a cohort restricted to patients from states with participating state cancer registries.

9.9.2.2.1. Coverage fraction

The coverage fraction was defined as the proportion of OS cases represented by the participating SCRs. Determining the coverage fraction involved estimating the ratio of the number of OS cases age 18 years and older from the participating SCRs during 2005-2014 to the total number of OS cases age 20 years and older that were expected from both participating and non-participating SCRs during the same time period.

The total number of OScases expected in the US from 2005 to 2014 among adults age 20 years and older, defined by predetermined ICD-O-3 codes (Table 4), was estimated for each year of the study using SEER overall IR for OS as applied to the US Census Bureau's estimated population for the corresponding calendar year. Although the study included patients 18 years and older, SEER does not include data on patients age 18-19. The total number of expected cases for the study period was derived by summing the yearly estimates (Table 5). Person-time during follow-up was then adjusted for each study cohort by multiplying it by the coverage fraction and IRs and IRRs were estimated (Table 17).

Table 5. Determining the Coverage Fraction

	Expected number of cases ≥20 years old (US SEER)	Observed number of cases ≥18 years old (from participating state cancer registries)	Coverage fraction (Observed / Expected)
Total*	**6,076.40**	**4,242.00**	**0.70**

Abbreviations: SEER = National Cancer Institute's Surveillance, Epidemiology, and End Results; US = United States.

* The total coverage fraction (i.e., 70%) was used to adjust the person-time for all coverage fraction analyses.

9.9.2.2.2. Restricting to patients from states with participating cancer registries

The total person-time at risk was recalculated for each study cohort using the exposure information for only those patients with 3-digit ZIP codes from states with participating cancer registries and IRs and IRRs were estimated. The distribution of PYs by age and sex for patients in the 2 teriparatide-exposed cohorts and the 2 matched comparator cohorts among patients from states with participating cancer registries was compared descriptively to the distribution of PYs for patients from states with non-participating cancer registries to evaluate any potential differences based on limiting the analysis to only participating state registries (Table 17). Residential status was described in Section 9.3.1.

9.9.3. Missing values

All analyses were carried out on the data observed. No imputation of missing values was completed.

9.9.4. Sensitivity analyses

9.9.4.1. Implementing a 6-month lag

The primary analysis included estimates of the IR and the IRR which assumed that there was no lag time for the induction and latency of OS to occur following the index date. This may or may not be biologically plausible; therefore, a sensitivity analysis of the IR and the IRR was performed, allowing for a 6-month latency period following the index date. For this sensitivity analysis, follow-up time was recalculated to start at 6 months after the index date. This decreased the amount of person-time in all study cohorts and could have increased the IRs (depending on when cases of OS were reported relative to the revised index date). This approach should not have had as much of an impact on the IRR estimate since the adjustment was applied to all study cohorts (Table 19).

Teriparatide-exposed patients and their unexposed matched comparators who did not have at least 6 months of follow-up from their original index date, who had a diagnosis of OS prior to their revised index date and their unexposed matched comparators were excluded from this sensitivity analysis. Comparator patients who had a diagnosis of OS prior to their revised index date were excluded, as well. If their exclusion resulted in a teriparatide-exposed patient no longer having any matched comparators, then that teriparatide-exposed patient was also excluded

from the analyses (Table 18). The results showing the number of patients and the reasons they were excluded from the sensitivity analyses are described in Section 10.4.1.

9.9.4.2. Requiring 2 teriparatide prescriptions

For the primary estimates of the IR and the IRR, the index date for calculating person-time in the 2 teriparatide-exposed cohorts was based on the date of the first dispensed prescription for teriparatide. With a single dispensed prescription, it is always possible the patient did not use the medication of interest. However, the likelihood that the patient took the medication increases if the patient filled a second prescription. Consequently, a sensitivity analysis was performed with the teriparatide index date defined as the date of the second dispensed prescription for teriparatide. In this subset of teriparatide-exposed patients with ≥2 prescription dispensings for teriparatide, the original unexposed matched comparator patient(s) was retained if the unexposed matched comparator patient(s) had not been censored and had ≥1 prescription dispensing within the same calendar month and year of the second prescription dispensing for teriparatide. The revised index date for the unexposed matched comparator patients who met these requirements was then set to the revised teriparatide index date. If the original unexposed matched comparator patient(s) did not have a prescription dispensing within the same calendar month and year as the second teriparatide prescription dispensing, then the unexposed matched comparator patient(s) was excluded from the analyses. Teriparatide-exposed patients for whom there were no remaining unexposed matched comparator patients were excluded from the analyses (Table 20 and Table 21).

9.9.4.3. Differential mortality assumptions

For the primary estimates of the IR and the IRR, a sensitivity analysis that assumed up to 10% higher mortality for the 2 teriparatide-exposed cohorts was conducted since patients treated with teriparatide could be sicker given their disease progression (Table 22). This sensitivity analysis reduced the PYs of follow up for the teriparatide-exposed patients by assuming mortality rates of 2%, 4%, 6%, 8%, and 10%.

If a patient had an OS diagnosis date (per the participating SCR) that occurred after the mortality-adjusted end of follow-up, then person-time was accumulated until the date of the OS diagnosis and not truncated earlier.

9.9.4.4. Mortality adjustment

Due to the absence of mortality data in the LRx database and the resulting inability to censor patients at date of death, a mortality adjustment sensitivity analysis was planned. However, the planned mortality adjustment could not be implemented as originally conceived due to privacy restrictions related to how age was recorded in the LRx database. The planned methods and the revised approach for this sensitivity analysis are described below.

For the primary estimates of the IR and the IRR, follow-up was not assumed to continue to the end of the study period for all patients; instead, a proxy for date of death was derived from the Centers for Disease Control and Prevention's *United States Life Tables, 2010 (Arias et al. 2017),* which estimate life expectancy by age and sex (Table 6).

Planned Mortality Adjustment Sensitivity Analysis:

For all patients aged <80 years at their index date, the expected number of years of life remaining (per the life table) was greater than the entire 10-year study period. Thus, no mortality adjustment was needed for these patients and we planned to follow them until the first of the other censoring criteria (i.e., OS diagnosis or the end of follow-up).

However, for all patients aged ≥80 years at their index date, the expected number of years of life remaining (per the life table) was less than the entire 10-year study period and thus we planned to use the expected years of life remaining for 85-year-olds (per the life table) as a proxy for date of death. Therefore, person-time for patients aged ≥80 years at their index date was planned to accumulate to the earliest of either the other censoring criteria (i.e., OS diagnosis or the end of follow-up), or 5.8 years for men and 6.9 years for women.

If a patient whose follow-up was adjusted for mortality had an OS diagnosis date (per participating SCR) that occurred after the mortality-adjusted end of follow-up, then person-time was accumulated until the date of the OS diagnosis and not truncated earlier because there was definitive information that they were alive at least up until the date of the OS diagnosis (Table 24).

Revised Mortality Adjustment Sensitivity Analysis:

Due to restrictions related to how age was recorded, some patients aged 73-79 years, in addition to all patients aged ≥80 years, had their mortality adjusted as described above for patients aged ≥80 years at their index date. The revised approach resulted in a larger reduction of person-time in the study cohorts and an overestimation of the IR than had we been able to apply the mortality adjustment to only patients aged ≥80 years. Though an overestimation, this approach was used to inform the potential impact of mortality on the main analysis.

Table 6. Expectation of Life by Age and Sex: Centers for Disease Control and Prevention's United States Life Table, 2010

	All races and origins		
Age	**Total**	**Male**	**Female**
0	78.7	76.2	81.0
1	78.1	75.7	80.5
5	74.2	71.8	76.6
10	69.3	66.8	71.6
15	64.3	61.9	66.6
20	59.5	57.1	61.7
25	54.7	52.4	56.9
30	50.0	47.8	52.0
35	45.2	43.1	47.2
40	40.5	38.5	42.4

	All races and origins		
Age	**Total**	**Male**	**Female**
45	35.9	33.9	37.7
50	31.4	29.6	33.2
55	27.2	25.4	28.8
60	23.1	21.5	24.4
65	19.1	17.7	20.3
70	15.5	14.2	16.5
75	12.1	11.0	12.9
80	9.1	8.2	9.7
85	6.5	5.8	6.9
90	4.6	4.1	4.8
95	3.2	2.9	3.3
100	2.3	2.1	2.3

9.9.5. Amendments to the statistical analysis plan

An optional secondary objective was to assess the similarity of the teriparatide cohort and the comparator cohorts using medical claims for 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 available data

This optional secondary objective to assess the similarity of the teriparatide-exposed patients and the matched comparator patients using medical claims was not conducted after a feasibility assessment determined an anticipated low linkage rate between the commercial pharmacy database and the medical claims database as a result of the age distribution of the teriparatide-exposed patients, their matched comparators, and the under representation of patients aged 65 years or older in the medical claims database.

Initial estimates suggested that only approximately 4% of the teriparatide-exposed patients identified in the commercial pharmacy database could have been linked to enrollees with both medical and pharmacy coverage in PharMetrics Plus. However, for the planned sensitivity analysis, enrollees with medical coverage, regardless of pharmacy coverage, were eligible for linkage.

9.9.5.1. Version 1 (Approved 15 November 2016)

The following changes were made to B3D-MC-GHBX 2.3(b) Statistical Analysis Plan Version 1 in order to accurately reflect how the study cohorts were formed and how the analyses would be conducted given the constraints of the data source:

- Due to constraints encountered during matching, teriparatide exposed patients were not eligible to be selected as comparator patients prior to the teriparatide index date
- The GPI classification system at the 6-digit (sub-class) level was used instead of the American Hospital Formulary Services (AHFS) Pharmacologic Therapeutic Classification System for matching due to incomplete coding of the AHFS system in the LRx database
- Additional details regarding how the matching process occurred were added
- Because the SCRs did not provide the full date of the OS diagnosis (either because they provided the month and year or year only; or because it was missing), language was added describing how a date was assigned
- Testing of differences pre- vs. post-matching was not feasible due to the matching process and the size of the pre-matched comparator population
- Language addressing how to handle the calculation of person-time when a patient in the ≥80-year age group had an OS diagnosis date that occurred after the mortality-adjusted end of follow-up was added
- Testing of differences between the final teriparatide -exposed cohorts and the matched comparator cohorts was removed to align with Study B3D-MC-GHBX Addendum 2.2(a) Assessing the Incidence of Osteosarcoma Among Teriparatide Users Using Medicare Part D and State Cancer Registry Data
- Language describing a comparison of person-time under the 2 proposed adjustments to person-time for cancer registry participation was removed to align with Study B3D-MC-GHBX Addendum 2.2(a)
- Additional details regarding the 6-month lag period sensitivity analysis were added for clarity
- The sensitivity analysis requiring 2 teriparatide prescriptions was updated to align with Study B3D-MC-GHBX Addendum 2.2(a)

9.9.5.2. Version 2 (Approved 14 May 2018)

The following changes were made to B3D-MC-GHBX 2.3b Statistical Analysis Plan Version 2 in order to accurately reflect how the study cohorts were formed and how the analyses would be conducted given the constraints of the data source:

- Updated how age matching occurred (i.e., single age match by year up to 72 [vs. 84] years old) because of the inability to accurately identify the age of patients aged ≥73 years in the SAP

  - As a result, removed mortality adjustment for patients aged ≥80 years from main analysis and added it as a sensitivity analysis
  - Removed language addressing how to handle the calculation of person-time when a patient in the ≥80-year age group had an OS diagnosis date that occurred after the mortality-adjusted end of follow-up from the main analysis and added it to the sensitivity analysis that adjusts for mortality
- Updated the payer types to reflect data available in LRx
- Modified age reporting categories to reflect age groups based on available data
- Added attrition tables for 2 of the sensitivity analyses
- Removed reporting of age as a continuous variable
- Removed US Census geographic region
- Added a table; a sensitivity analysis that adjusted for mortality (as was originally planned for the main analysis)

9.10. Quality Control

At the study level, all aspects of the study from protocol development to the reporting of the results were conducted within the framework of the IQVIA Quality Management System. A Quality Control (QC) plan for the study was developed and executed, which included QC on the study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions, and study report.

Specific QC activities included:

- Checking the SCR data for content and structure upon receipt;
- For all data, performing a basic descriptive check to ensure that data quality was acceptable;
- Verifying that the study methods outlined in the SAP were followed;
- Verifying that the IRs and 95% CIs were estimated as described in the SAP;
- Verifying that the correct statistical models and SAS programming code were used to estimate the IRRs and 95% CIs;

10. Results

10.1. Participants

The LRx database included a total of 429,486 patients with ≥1 dispensed prescriptions for teriparatide from an outpatient pharmacy during the study period. Of those patients, 94.1% (n=404,130) were eligible for matching to unexposed study cohorts. Of the teriparatide-exposed patients eligible for matching, 82.9% (n=335,191) were matched with at least 1 unexposed OP comparator patient (Teriparatide-OP cohort) and 93.9% (n=379,283) were matched with at least 1 unexposed General Population comparator patient (Teriparatide-GP cohort). There were 329,166 teriparatide-exposed patients who were included in both the Teriparatide-OP cohort and the Teriparatide-GP cohort (Table 7).

When creating the OP cohort, a total of 14,623,365 patients had ≥1 dispensed prescriptions for an OP medication other than teriparatide during the study period. Of those patients, 4.4% (n=637,387) were matched with a teriparatide-exposed patient (Table 8).

When creating the general population cohort, a total of 511,902,649 patients had ≥1 dispensed prescription for a medication other than teriparatide during the study period and a 114,633,484 of these patients (22.4%) were "pre-matched" to a teriparatide-exposed patient. Due to the size of the LRx database, a random sample of the "pre-matched" was used to create the General Population cohort. Of the 26,096,396 patients randomly selected for final matching, 5.5% (n=1,428,943) were matched with a teriparatide-exposed patient. There were 44,570 patients included in both the Osteoporosis and the General Population cohorts (Table 8).

10.2. Descriptive data

The majority of patients in each the Teriparatide-OP and -GP cohorts were 65 years and older (70.5% and 66.9% respectively) The patients were mostly female (93.2% and 89.1%, respectively); and from the South (43.9% and 44.7%, respectively). The majority of patients either had a third-party payer type or Medicare on their index prescription (92.5% and 89.8%, respectively) (Table 9).

The most common provider specialty for patients treated were Family Medicine and Internal Medicine (17% and 25%, respectively). The most common class of prescriptions dispensed in the 4-month baseline period prior to the index month for both teriparatide-exposed cohorts was "Analgesics—opioid" (n=100,494 [42.3%] and n=122,417 [43.1%] for the Teriparatide-OP and -GP cohorts, respectively), followed by "Endocrine and metabolic agents" (n=92,010 [38.7%] and n=104,987 [36.9%], respectively) (Table 11).

The key differences for prescriptions dispensed during the baseline period for the Teriparatide-OP cohort was Analgesics-opiod, 42.3% compared to 20.4% for matched osteoporosis cohort. The proportion among the Teriparatide–GP was 43.1% compared to 25.2% among the General population controls. The most common class of prescriptions dispensed during the baseline period for the Osteoporosis cohort was "Endocrine and metabolic agents" (n=480,589 [84.0%], followed by "Antihyperlipidemics" (n=212,497 [37.1%]). The most common class of

prescriptions dispensed during the baseline period for the General Population cohort was "Antihypertensives" (n=483,978 [39.8%]), followed by "Antihyperlipidemics" (n=425,110 [35.0%]) (Table 11).

The distribution of unique GPI-6 medication classes was similar across each of the groupings (this was a matching criteria). The most common number of unique GPI-6 medication classes dispensed during the baseline period was 0-2 classes ,(> 35%), followed by ≥9 classes (>25%) (Table 11).

The mean number of teriparatide dispensings during the follow-up was 7.9 (SD: 8.0) and 7.8 (SD: 8.0) for the Teriparatide-OP and Teriparatide-GP cohorts, respectively, and the median number of dispensings was 5.0 and 4.0, respectively. The mean months' supply per dispensed teriparatide prescription during follow-up was 1.1 (SD: 0.6) for both teriparatide-exposed cohorts, and the median months' supply per dispensed prescription was 0.9 for both teriparatide-exposed cohorts (Table 15).

The mean duration of teriparatide exposure during follow-up was 8.4 (SD: 8.1) months and 8.2 (SD: 8.1) months for the Teriparatide-OP and Teriparatide-GP cohorts, respectively, and the median duration of exposure was 5.5 months and 4.9 months, respectively (Table 15).

10.3. Outcome data

Participating SCRs prepared files for all OS cases. A total of 4242 OS cases in patients ≥18 years old were identified by the participating SCRs during the study period (01 January 2005 - 31 December 2014). After linking the SCR data with the LRx study cohorts, a total of 18 OS cases were distributed among the study cohorts. Three of these cases were included in both the Teriparatide-OP and the -GP cohorts, 6 OS cases in the OP cohort and 9 OS cases in the General Population cohort (Table 16). None of the patients had >1 OS diagnosis.

One of the 3 teriparatide-exposed OS cases, and their matched comparator, was excluded from the analyses that were restricted to patients from states with participating SCRs because while the patient was diagnosed in a state with a participating SCR, they did not reside in a state with a participating SCR. This patient, and their matched comparator, was included in the analyses which adjusted for the coverage fraction.

10.4. Main results

The IR, IRR, and total person-time of observation following the index date for the study period from January 2005 through December 2014 are summarized in Table 12. The overall total number of PYs of follow-up was 2,095,082.3 for the Teriparatide-OP cohort; 4,016,476.1 for the OP cohort; 2,309,376.8 for the Teriparatide-GP cohort; and 8,740,332.2 for the General Population cohort (Table 17).

Coverage Fraction Analysis

This study included an adjustment for the coverage fraction of 70% which reduced the PYs of follow-up for each study cohort (Table 17).

For the OP matched cohort, the total number of PYs of follow-up adjusted for the coverage fraction was 1,462,597.9 for the Teriparatide-OP cohort; 2,803,942.1 for the OP cohort. After adjusting for the coverage fraction, the incidence of OS per 1,000,000 PYs, was 2.1 (95% CI: 0.4, 6.0) for the Teriparatide-OP cohort compared to 2.1 (95% CI: 0.8, 4.7) among the unexposed OP cohort. For this analysis the incidence rate ratio was 1.0 (95% CI: 0.2, 4.5).

For the general population matched cohort, the total number of PYs of follow-up adjusted for the coverage fraction was 1,612,199.0 for the Teriparatide-GP cohort; and 6,101,713.3 for the General Population cohort. After adjusting for the coverage fraction, the incidence of OS per 1,000,000 PYs, was 1.9 (95% CI: 0.4, 5.4) for the Teriparatide-GP cohort compared to 1.5 (95% CI: 0.7, 2.8) for the General Population cohort. For this analysis the incidence rate ratio was 1.3 (95% CI: 0.2, 5.1).

Restricting to Participating State Cancer Registries Analysis

This analysis was restricted to participating SCRs (Table 17).

For the OP matched cohort, the total number of PYs of follow-up was 1,218,635.0 for the Teriparatide-OP cohort; 2,333,294.6 for the OP cohort. Among patients from states with participating SCRs, the incidence of OS per 1,000,000 PYs, was 1.6 (95% CI: 0.2, 5.9) for the Teriparatide-OP cohort compared to 2.6 (95% CI: 0.9, 5.6) among the unexposed OP cohort. For this analysis the incidence rate ratio was 0.6 (95% CI: 0.1, 3.6).

For the general population matched cohort, the total number of PYs of follow-up adjusted for the coverage fraction was 1,340,952.7 for the Teriparatide-GP cohort; and 5,046,505.3 for the General Population cohort. Among patients from states with participating SCRs, the incidence of OS per 1,000,000 PYs, was 1.5 (95% CI: 0.2, 5.4) for the Teriparatide-GP cohort compared to 1.8 (95% CI: 0.8, 3.4) for the General Population cohort. For this analysis the IRR was 0.8 (95% CI: 0.1, 4.0).

10.4.1. Sensitivity analysis: Implementing a 6-month lag

After applying criteria for the 6-month lag sensitivity analysis, approximately 97% of each study cohort remained in the study. For the OP and General Population cohorts, 1 and 2 OS cases, respectively, were excluded from the sensitivity analysis for this reason (Table 18).

Coverage Fraction Analysis

After adjusting for the coverage fraction in this sensitivity analysis, the IRs (and 95% CIs) for the teriparatide-exposed cohorts, which did not lose any OS cases, were almost identical to those reported for the main analysis (Table 19).

For the OP matched cohort, the total number of PYs of follow-up adjusted for the coverage fraction was 1,460,916.5 for the Teriparatide-OP cohort; 2,800,904.7 for the OP cohort. After adjusting for the coverage fraction, the incidence of OS per 1,000,000 PYs, was 2.1 (95% CI: 0.4, 6.0) for the Teriparatide-OP cohort compared to 1.8 (95% CI: 0.6, 4.2) among the unexposed osteoporosis cohort. For this analysis the IRR was 1.2 (95% CI: 0.2, 5.9).

For the general population matched cohort, the total number of PYs of follow-up adjusted for the coverage fraction was 1,610,003.7 for the Teriparatide-GP cohort; and 6,093,587.0 for the General Population cohort. After adjusting for the coverage fraction, the incidence of OS per 1,000,000 PYs, was 1.9 (95% CI: 0.4, 5.5) for the Teriparatide-GP cohort compared to 1.2 (95% CI: 0.5, 2.4) for the General Population cohort. For this analysis the IRR was 1.6 (95% CI: 0.3, 7.1).

Restricting to Participating State Cancer Registries Analysis

Among patients from states with participating SCRs, the IRs (and 95% CIs) for the teriparatide-exposed cohorts, which did not lose any OS cases, were almost identical to those reported for the main analysis. For the 2 unexposed comparator groups, which both lost OS cases, the IRs (and 95% CIs) were slightly lower than those reported for the main analysis.

For the OP matched cohort, the total number of PYs of follow-up was 1,217,166.2 for the Teriparatide-OP cohort; 2,330,656.2 for the OP cohort. Among patients from states with participating SCRs, the incidence of OS per 1,000,000 PYs, was 1.6 (95% CI: 0.2, 5.9) for the Teriparatide-OP cohort compared to 2.2 (95% CI: 0.7, 5.0) among the unexposed OP cohort. For this analysis the incidence rate ratio was 0.8 (95% CI: 0.1, 4.7).

For the general population matched cohort, the total number of PYs of follow-up adjusted for the coverage fraction was 1,339,011.4 for the Teriparatide-GP cohort; and 5,039,011.4 for the General Population cohort. Among patients from states with participating SCRs, the incidence of OS per 1,000,000 PYs, was 1.5 (95% CI: 0.2, 5.4) for the Teriparatide-GP cohort compared to 1.4 (95% CI: 0.6, 2.9) for the General Population cohort. For this analysis the incidence rate ratio was 1.1 (95% CI: 0.1, 5.7).

10.4.2. Sensitivity analysis: Requiring 2 dispensed teriparatide prescriptions

Requiring 2 dispensed teriparatide prescriptions reduced the study cohorts. After this restriction was applied, approximately 59% of the Teriparatide-OP, 72% of the Teriparatide-GP, 46% of the OP, and 58% of the General Population cohorts remained.

Among the reasons for exclusion, approximately 25% of both teriparatide-exposed cohorts were excluded because they did not have at least 2 dispensed prescriptions for teriparatide. Approximately 16% of the Teriparatide-OP cohort and 3% of the Teriparatide-GP cohort were excluded because they no longer had at least 1 unexposed matched OP or General Population comparator patient, respectively.

Approximately 54% of the OP cohort and 42% of the General Population cohort were excluded because they did not have at least 1 dispensed prescription during the adjusted index month (Table 20).

Coverage Fraction Analysis for cohorts requiring 2 dispensed teriparatide prescriptions

After adjusting for the coverage fraction in this sensitivity analysis, the IRs (and 95% CIs) for the teriparatide-exposed cohorts, which both lost 2 OS cases, were lower than those reported for

the main analysis. For the 2 unexposed comparator groups, of which the OP (Teriparatide-matched) cohort lost 3 OS cases, the IRs (and 95% CIs) were slightly higher than those reported for the main analysis.

For the OP matched cohort, the total number of PYs of follow-up was 1,246,469.8 for the Teriparatide-OP cohort; 1,859,585.4 for the OP cohort. Among patients from states with participating SCRs, the incidence of OS per 1,000,000 PYs, was 1.4 (95% CI: 0.0, 7.7) for the Teriparatide-OP cohort compared to 2.8 (95% CI: 0.6, 8.1) among the unexposed OP cohort. For this analysis the incidence rate ratio was 0.5 (95% CI: 0.0, 6.2).

For the general population matched cohort, the total number of PYs of follow-up adjusted for the coverage fraction was 1,662,124.5 for the Teriparatide-GP cohort; and 4,990,963.3 for the General Population cohort. Among patients from states with participating SCRs, the incidence of OS per 1,000,000 PYs, was 1.0 (95% CI: 0.0, 5.8) for the Teriparatide-GP cohort compared to 3.1 (95% CI: 1.4, 5.9) for the General Population cohort. For this analysis the incidence rate ratio was 0.3 (95% CI: 0.0, 2.4) (Table 21).

Restricting to Participating State Cancer Registries Analysis

When restricting the analysis to only participating SCRs, the results were the same as for the coverage fraction analysis (Table 21).

10.4.3. Sensitivity analysis: Differential mortality assumptions

All patients, across all 4 study cohorts, were eligible for the sensitivity analysis applying differential mortality assumptions (0%, 2%, 4%, 6%, 8%, and 10%).

Coverage Fraction Analysis

After adjusting for the coverage fraction in this sensitivity analysis, as would be expected, the IRs (and 95% CIs) for both teriparatide-exposed cohorts increased slightly with the increasing differential mortality assumptions. For the Teriparatide-OP cohort, the IRs (and 95% CIs) of OS (per 1,000,000 PYs) ranged from 2.1 (95% CI: 0.4, 6.1) for the 2% mortality assumption to 2.3 (95% CI: 0.5, 6.7) for the 10% mortality assumption (Table 22) and for the Teriparatide (General Population-matched) cohort, the IRs (and 95% CIs) ranged from 1.9 (95% CI: 0.4, 5.5) for the 2% mortality assumption to 2.1 (95% CI: 0.4, 6.0) for the 10% mortality assumption (Table 23).

The IRRs (and 95% CIs) for both teriparatide-exposed cohorts also increased slightly with the increasing differential mortality assumptions. For the Teriparatide-OP cohort, the IRRs (and 95% CIs) comparing the incidence of OS in teriparatide-exposed patients to the incidence in OP patients who had not been exposed to teriparatide ranged from 1.0 (95% CI: 0.2, 4.6) for the 2% mortality assumption to 1.1 (95% CI: 0.2, 5.0) for the 10% mortality assumption (Table 22). For the Teriparatide-GP, the IRRs ranged from 1.3 (95% CI: 0.2, 5.2) for the 2% mortality assumption to 1.4 (95% CI: 0.2, 5.6) for the 10% mortality assumption (Table 23).

Restricting to Participating State Cancer Registries Analysis

Among patients from states with participating SCRs, as would be expected, the IRs (and 95% CIs) for both teriparatide-exposed cohorts increased slightly with the increasing differential mortality assumptions (Table 22). For the Teriparatide-OP cohort, the IRs (and 95% CIs) of OS (per 1,000,000 PYs) ranged from 1.7 (95% CI: 0.2, 6.0) for the 2% mortality assumption to 1.8 (95% CI: 0.2, 6.6) for the 10% mortality assumption and for the Teriparatide-GP cohort, the IRs (and 95% CIs) ranged from 1.5 (95% CI: 0.2, 5.5) for the 2% mortality assumption to 1.7 (95% CI: 0.2, 6.0) for the 10% mortality assumption (Table 23). QC - Confirmed increasing differential mortality assumptions. For the Teriparatide-OP cohort, the IRRs (and 95% CIs) comparing the incidence of OS in teriparatide-exposed patients to the incidence in OP patients who had not been exposed to teriparatide ranged from 0.7 (95% CI: 0.1, 3.6) for the 2% mortality assumption to 0.7 (95% CI: 0.1, 4.0) for the 10% mortality assumption (Table 22). For the Teriparatide-GP, the IRRs ranged from 0.9 (95% CI: 0.1, 4.1) for the 2% mortality assumption to 0.9 (95% CI: 0.1, 4.5) for the 10% mortality assumption (Table 23).

10.4.4. Sensitivity analysis: Mortality adjustment

All patients, across all 4 study cohorts, were eligible for the sensitivity analysis applying the mortality adjustment percentages of 0%, 2%, 4%, 6%, 8%, and 10%.

Coverage Fraction Analysis

For the OP matched cohort, the total number of PYs of follow-up adjusted for the coverage fraction was 1,365,916.5 for the Teriparatide-OP cohort; 2,612,240.8 for the OP cohort. After adjusting for the coverage fraction, the incidence of OS per 1,000,000 PYs, was 2.2 (95% CI: 0.4, 6.4) for the Teriparatide-OP cohort compared to 2.3 (95% CI: 0.8, 5.0) among the unexposed osteoporosis cohort. For this analysis the IRR was 1.0 (95% CI: 0.2, 4.5).

For the general population matched cohort, the total number of PYs of follow-up adjusted for the coverage fraction was 1,515,455.3 for the Teriparatide-GP cohort; and 5,717,762.90 for the General Population cohort. After adjusting for the coverage fraction, the incidence of OS per 1,000,000 PYs, was 1.6 (95% CI: 0.2, 5.7) for the Teriparatide-GP cohort compared to 1.9 (95% CI: 0.9, 3.6) for the General Population cohort. For this analysis the IRR was 1.3 (95% CI: 0.2, 5.04).

Restricting to Participating State Cancer Registries Analysis

Among patients from states with participating SCRs, the IRs (and 95% CIs) for the two teriparatide-treated cohorts and the two matched comparator cohorts, were slightly higher than those reported for the main analysis. Mortality adjustments resulted in IRRs that ranged from 0.8 (95% CI 0.1, 4.0) with a 0% mortality adjustment to 0.9 (95% CI 0.1, 4.5) for a 10% mortality adjustment (Table 24).

10.4.5. Prescriber specialty

The prescribers responsible for most of the prescriptions were “Internal medicine” with 25.4%, 37.3%, 24.8% and 31.4% for the teriparatide-OP, OP, Teriparatide-GP and general population

cohorts, respectively. This was followed by "family medicine" with 17.3%, 29.3%, 17.3% and 28.6%, respectively (Table 14).

10.5. Other analyses

There were no other analyses to report.

10.6. Adverse events/adverse reactions

There were no adverse events/adverse reactions to report.

11. Discussion

11.1. Key results

A total of 29 participating SCRs represented 65% of the US population aged ≥18 years and approximately 70% of all OS cases. There was a total of 18 cases of OS identified from the data linkages. A total of 3 cases of OS among the teriparatide-exposed patients (Teriparatide-OP and Teriparatide-GP); 6 cases in the unexposed OP cohort included; and 9 cases in the unexposed General Population cohort included. The mean duration of exposure to teriparatide during the 10-year study period was approximately 8 months for both teriparatide-exposed cohorts. The total number of PYs of follow-up adjusted for the coverage fraction was 1,462,597 for the Teriparatide-OP cohort; 2,803,942 for the Osteoporosis cohort; 1,612,199 for the Teriparatide GP cohort; and 6,101,713.3 for the General Population cohort. Study cohorts were predominantly 65 years or older and female.

The analysis adjusting for the coverage fraction, produced an IRR of 0.96 (95% CI 0.16, 4.49) for the OP matched cohort and 1.26 (95% CI 0.22, 5.06) for the general population matched cohorts. The analysis restricted to participating cancer registries produced an IRR of 0.64 (95% CI 0.06, 3.57) for the OP matched cohort and 0.84 (95% CI 0.09, 4.04) for the general population matched cohorts.

These findings were similar in their respective sensitivity analyses due to the wide CIs of the IRs and IRRs in the main analysis.

A previous study reported an IR of OS standardized to the age-sex distribution of patients receiving teriparatide that was higher than the current report (3.2 cases per 1,000,000 PYs) (Midkiff et al 2016). However, the published rate falls within the 95% CIs calculated in this study for both teriparatide-exposed cohorts. This same study also reported an IR of 2.5 cases (per 1,000,000 PYs) among adults aged 40 years and older (Midkiff et al 2016), which is similar to the IRs reported in this study for the OP and General Population cohorts.

This database study offered significant enhancements to the efforts for evaluating the risk of OS among teriparatide-treated patients. These enhancements included a linkage between LRx pharmacy dispensing data and cancer registry data which included not only teriparatide-exposed patients but also matched comparator patients. 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 LRx database is an open database; therefore, if a patient filled a prescription at a pharmacy that did not report to IQVIA (or reported inconsistently), those data were not captured, resulting in incomplete data and possible misclassification of exposure duration to teriparatide.

Additionally, it was possible that patients who filled a prescription for teriparatide did not actually take the medication, resulting in misclassification of teriparatide exposure.

Due to limitations associated with the LRx database, patients were matched on single ages up to 72 years old. Patients aged 73 years or older were matched with patients aged 73 years or older.

Additionally, there could have been imperfect matching on payer type because of payer type being extracted from the index prescription (for the teriparatide-exposed patients) or defined as the most frequent payer type during their index month (for the unexposed matched comparator patients).

These limitations of the LRx database could have resulted in residual confounding by age and/or payer type; however, when age and payer type were individually added to the model, along with exposure cohort, as main effects, they were not associated with the outcome.

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. 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 cohorts. This included an attempt to control for general health status through matching based on the number of unique therapeutic classes of medications dispensed during the 4 months prior to a patient's index date. The use of two different comparator cohorts also helps assess potential impact of unmeasured confounding. Furthermore, Forteo patients were not found to be "healthier" than either comparator populations.

Person-time was based on time from index date to the end of the study period or OS diagnosis. This approach could have over-estimated the true person-time at risk, artificially decreasing the incidence rates in all cohorts. Approximately a quarter of each cohort had four years or less to develop the condition after their index date. Given uncertainty around latency for OS, it is unknown if this is a sufficient amount of time to develop OS. Also, a mortality adjustment was conducted as a sensitivity analysis by applying a variable mortality rate which did not significantly impact the results.

The main study analysis required only one dispensing of teriparatide as patients which considered these patients as ever exposed. The mean duration of teriparatide exposure during the study period was approximately 8 months and the median duration of exposure was approximately 6 months.

Finally, the outcome was based on linkage with participating SCRs, which covered 65% of the US population and approximately 70% of all OS cases. Although all cases could not be included, the majority of cases in the US were included.

11.3. Interpretation

The findings from the main analysis, when adjusting for the coverage fraction, resulted in an IRR of approximately 1 with wide CIs. This would indicate no appreciable difference in IRs between the exposed and unexposed groups however the imprecision of the IRR estimates, as evidenced

by their wide 95% CIs, was likely related to the small number of OS cases observed. The findings from the sensitivity analyses were very similar. The findings from this study are consistent with what would be expected given the background rate of OS among adults aged18 years and older. The overall annual incidence estimated to be 2.7 cases per 1,000,000 population.

11.4. Generalizability

Large pharmacy claims databases, like the LRx database are representative of the general population and are often used to describe drug utilization patterns. This data source represents >85% of all US retail prescriptions, 40% to 75% of US specialty and mail-order prescriptions (depending on therapeutic area), and 71-83% of prescriptions filled at long-term care facilities (across therapeutic areas). As a result, findings can be applied to the broader population of patients treated with teriparatide in the US. Differences among patients from states with participating SCRs where not assessed; however, the majority (65%) of the population aged 18 years and older were included.

12. Other information

This database study, along with a separate study using Medicare data, was carried out to improve upon the design of the ongoing Forteo patient registry. These database studies, like the Forteo patient registry, link exposure data with cancer registry data in order to determine the proportion of teriparatide-treated patients that are diagnosed with OS. The database studies have improved our ability to capture a large number of patients to assess this rare disease. The Forteo patient registry was projected to observe 1.7 million person years over a maximum of 12 years. The Medicare study observed over 390,000 PY and the comparator cohort included over 1,500,000 over an 8 year observation window. The Medicare study did not identify an increase in risk of OS among patients treated with teriparatide. The Medicare study found zero OS cases among the teriparatide cohort. This commercial claims study included over 2,000,000 person years of follow-up among the teriparatide-treated cohorts, which varied depending on the applied analysis. The PY of follow-up among the comparator cohorts was two to four times that of the teriparatide-treated cohorts. In addition to improved capture of Forteo treated patients, the inclusion of comparator cohorts provide statistical comparisons among matched groups in addition to referencing published population based rates of OS.

Potential risk factors for OS are not well established as the etiology of OS in adults is not well established (Fletcher et al. 2002; 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). These factors were evaluated in complimentary studies evaluating the Medicare population and the population captured in the Truven database (a large US claims database). The Medicare study found that among risk factors relevant to developing OS, the teriparatide cohort and comparator cohort were similar with regard to radiation treatment and a history of Paget's disease of the bone. The findings for the Truven analysis were similar in that approximately 0.1% teriparatide-treated patients had a recorded history of Paget's disease of the bone for patients treated with teriparatide, the general population, and OP cohort.

13. Conclusion

This was a large, population-based study to assess the relationship between teriparatide use and OS using US prescription dispensing data linked with SCR data over a 10-year study period. The findings from this study, among over 330,000 Forteo treated patients, have not identified an increase in risk of OS among patients treated with teriparatide.

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15. Annex 1. List of standalone documents

Not applicable.

16. Annex 2. Additional information

16.1. Annex 2.1 Results Tables

16.1.1. Participants

Table 7. Study Attrition for the Teriparatide-Exposed Cohorts

	Excluded		Remaining	
	N	**%[a]**	**N**	**%[a]**
Teriparatide-exposed cohorts				
Patients with ≥1 dispensed prescription for teriparatide (NDC 00002-8971-01, 00002-8400-01) from an outpatient pharmacy between 1 January 2005 and 31 December 2014	—	—	429,486	100.0%
Exclude patients <18 years of age	2,362	0.5%	427,124	99.5%
Exclude patients not residing in the 50 US states or DC at any time during study period or missing patient and pharmacy 3-digit ZIP code on their index prescription for teriparatide	6,462	1.5%	420,662	97.9%
Exclude patients with data quality issues (e.g., missing/invalid sex, year of birth)	16,532	3.8%	404,130	94.1%
Exclude patients missing payer type on their index prescription for teriparatide **(teriparatide-exposed patient population eligible for matching)**	0	0.0%	**404,130**	**94.1%**
Teriparatide-OP cohort				
Teriparatide-exposed patients who matched to 1-2 Osteoporosis comparator patients	68,879	17.0%	335,251	83.0%
Exclude patients whose first dispensed prescription for teriparatide was on 31 December 2014	56	0.0%	335,195	82.9%
Exclude patients who no longer have ≥1 matched Osteoporosis patient because their matched comparator patient had ≥1 dispensed prescription for teriparatide between 1 September 2004 and 31 December 2004	3	0.0%	335,192	82.9%
Exclude patients with an osteosarcoma diagnosis that occurred prior to their Index Date	0	0.0%	335,192	82.9%
Exclude patients with an osteosarcoma diagnosis that was not pathologically-confirmed[b]	0	0.0%	335,192	82.9%
Exclude patients who no longer have ≥1 matched Osteoporosis comparator patient	1	0.0%	335,191	82.9%
Final Teriparatide-OP analytic sample	**68,939**	**17.1%**	**335,191**	**82.9%**

	Excluded		Remaining	
	N	%[a]	N	%[a]
Teriparatide-GP cohort				
Teriparatide-exposed patients who matched to 1-4 General Population comparator patients	24,779	6.1%	379,351	93.9%
Exclude patients whose first dispensed prescription for teriparatide was on 31 December 2014	66	0.0%	379,285	93.9%
Exclude patients who no longer have ≥1 matched General Population patient because their matched comparator patient had ≥1 dispensed prescription for teriparatide between 1 September 2004 and 31 December 2004	2	0.0%	379,283	93.9%
Exclude patients with an osteosarcoma diagnosis that occurred prior to their Index Date	0	0.0%	379,283	93.9%
Exclude patients with an osteosarcoma diagnosis that was not pathologically-confirmed[b]	0	0.0%	379,283	93.9%
Exclude patients who no longer have ≥1 matched General Population comparator patient	0	0.0%	379,283	93.9%
Final Teriparatide-GP analytic sample	**24,847**	**6.1%**	**379,283**	**93.9%**

[a] Denominator was the teriparatide-exposed patients eligible to match, not the initial base teriparatide-exposed population.
[b] Pathological confirmation of osteosarcoma diagnosis was determined using the NAACCR variable "Diagnostic confirmation of osteosarcoma diagnosis."

Evidence of pathologic confirmation was determined using the following NAACCR categories:
"1 Positive histology,"
"3 Positive histology PLUS - positive immunophenotyping AND/OR positive genetic studies (used only for hematopoietic and lymphoid neoplasms M-9590/3-9992/3)," and
"4 Positive microscopic confirmation, method not specified."

The following NAACCR categories did not meet the threshold for pathologic confirmation:
"2 Positive cytology,"
"5 Positive laboratory test/marker study,"
"6 Direct visualization without microscopic confirmation,"
"7 Radiography and/or other imaging techniques without microscopic confirmation,"
"8 Clinical diagnosis only (other than 5, 6, or 7)," and
"9 Unknown whether or not microscopically confirmed; death certificate only."

Note: Residential status was determined by assessing patient and pharmacy 3-digit ZIP code for all dispensings during the study period. If a patient or pharmacy 3-digit ZIP code was ever outside the 50 US states or DC, then the patient was excluded. Pharmacy 3-digit ZIP code was included due to the large proportion of patients missing a 3-digit ZIP code.
Note: Single ages up to 72 years old were used for matching. Patients aged ≥73 years old were matched with patients who were also ≥73 years old.

Note: N=329,166 teriparatide patients were included in both teriparatide-exposed cohorts.

US = United States

DC = District of Columbia

NAACCR = North American Association of Central Cancer Registries

Table 8. Study Attrition for the Unexposed Comparator Cohorts

	Excluded		Remaining	
	N	%	N	%
Osteoporosis cohort				
Patients with ≥1 dispensed prescription for a medication specifically indicated for osteoporosis (not including teriparatide) from an outpatient pharmacy between 1 January 2005 and 31 December 2014	—	—	14,623,365	100.0%
Exclude patients <18 years of age	21,249	0.1%	14,602,116	99.9%
Exclude patients not residing in the 50 US states or DC at any time during study period or missing patient and pharmacy 3-digit ZIP code	305,010	2.1%	14,297,106	97.8%
Exclude patients with data quality issues (e.g., missing/invalid sex, year of birth)	78,791	0.5%	14,218,315	97.2%
Pre-match to teriparatide-exposed patients on month of dispensing, sex, age, and 3-digit ZIP code by calendar year	5,816,601	39.8%	8,401,714	57.5%
Pre-match to teriparatide-exposed patients on payer type and number of unique GPI classes during the 4-month baseline period prior to the Index Month	4,572,531	31.3%	3,829,183	26.2%
Osteoporosis patients who matched to a teriparatide-exposed patient (limiting to up to 2 comparators per teriparatide-exposed patient)	3,191,555	21.8%	637,628	4.4%
Exclude patients with ≥1 dispensed prescription for teriparatide between 1 September 2004 and 31 December 2004	142	0.0%	637,486	4.4%
Exclude patients whose matched teriparatide-exposed patient had their index prescription for teriparatide on 31 December 2014	98	0.0%	637,388	4.4%
Exclude patients with an osteosarcoma diagnosis that occurred prior to their Index Date	1	0.0%	637,387	4.4%
Exclude patients with an osteosarcoma diagnosis that was not pathologically-confirmed[a]	0	0.0%	637,387	4.4%
Exclude patients who no longer have a matched teriparatide-exposed patient	0	0.0%	637,387	4.4%
Final Osteoporosis analytic sample	**13,985,978**	**95.6%**	**637,387**	**4.4%**

	Excluded		Remaining	
	N	%	N	%
General Population cohort				
Male or female patients ≥18 years old with ≥1 dispensed prescription for a medication other than teriparatide from an outpatient pharmacy during the same month and year of a Teriparatide Index Date, residing in the 50 US states or DC for the entire study period	—	—	511,902,649	100.0%
Pre-match to teriparatide-exposed patients on month of dispensing, sex, age, and 3-digit ZIP code by calendar year	397,269,165	77.6%	114,633,484	22.4%
Select a 10% random sample of pre-matched patients by calendar year	88,537,088	17.3%	26,096,396	5.1%
Pre-match to teriparatide-exposed patients on payer type and number unique GPI classes during the 4-month baseline period prior to the Index Month	17,417,709	3.4%	8,678,687	1.7%
General Population patients who matched to a teriparatide-exposed patient (limiting to up to 4 comparators per teriparatide-exposed patient)	7,249,343	1.4%	1,429,344	0.3%
Exclude patients with ≥1 dispensed prescription for teriparatide between 1 September 2004 and 31 December 2004	140	0.0%	1,429,204	0.3%
Exclude patients whose matched teriparatide-exposed patient had their index prescription for teriparatide on 31 December 2014	256	0.0%	1,428,948	0.3%
Exclude patients with an osteosarcoma diagnosis that occurred prior to their Index Date	3	0.0%	1,428,945	0.3%
Exclude patients with an osteosarcoma diagnosis that was not pathologically-confirmed[a]	2	0.0%	1,428,943	0.3%
Exclude patients who no longer have a matched teriparatide-exposed patient	0	0.0%	1,428,943	0.3%
Final General Population analytic sample	**510,473,706**	**99.7%**	**1,428,943**	**0.3%**

[a] Pathological confirmation of osteosarcoma diagnosis was determined using the NAACCR variable "Diagnostic confirmation of osteosarcoma diagnosis."

Evidence of pathologic confirmation was determined using the following NAACCR categories:
"1 Positive histology,"
"3 Positive histology PLUS - positive immunophenotyping AND/OR positive genetic studies (used only for hematopoietic and lymphoid neoplasms M-9590/3-9992/3)," and
"4 Positive microscopic confirmation, method not specified."

The following NAACCR categories did not meet the threshold for pathologic confirmation:
"2 Positive cytology,"
"5 Positive laboratory test/marker study,"
"6 Direct visualization without microscopic confirmation,"
"7 Radiography and/or other imaging techniques without microscopic confirmation,"
"8 Clinical diagnosis only (other than 5, 6, or 7)," and
"9 Unknown whether or not microscopically confirmed; death certificate only."

Note: Residential status was determined by assessing patient and pharmacy 3-digit ZIP code for all dispensings during the study period. If patient or pharmacy ZIP code was ever outside the 50 US states or DC, then the patient was excluded. Pharmacy 3-digit ZIP code was included due to the large proportion of patients missing a 3-digit ZIP code.
Note: Single ages up to 72 years old were used for matching. Patients aged ≥73 years old were matched with patients who were also ≥73 years old.
Note: N=44,570 comparator patients were included in both the Osteoporosis and General Population comparator cohorts.
US = United States
DC = District of Columbia
GPI = Generic Product Indicator
NAACCR = North American Association of Central Cancer Registries

16.1.2. Descriptive data

Table 9. Patient Demographics for the Teriparatide-Exposed and Unexposed Matched Comparator Cohorts

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Count of patients and percentage	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
N	335,191	100.0%	637,387	100.0%	379,283	100.0%	1,428,943	100.0%
Age (years)								
≥18	**335,191**	**100.0%**	**637,387**	**100.0%**	**379,283**	**100.0%**	**1,428,943**	**100.0%**
≥40	**333,964**	**99.6%**	**635,827**	**99.8%**	**373,183**	**98.4%**	**1,408,281**	**98.6%**
Male	22,518	6.7%	37,632	5.9%	39,541	10.4%	145,694	10.2%
Female	311,446	92.9%	598,195	93.9%	333,642	88.0%	1,262,587	88.4%
≥65	**236,295**	**70.5%**	**454,082**	**71.2%**	**253,826**	**66.9%**	**962,997**	**67.4%**
Male	16,642	5.0%	29,099	4.6%	25,055	6.6%	93,629	6.6%
Female	219,653	65.5%	424,983	66.7%	228,771	60.3%	869,368	60.8%
18-19	**30**	**0.0%**	**36**	**0.0%**	**176**	**0.0%**	**582**	**0.0%**
Male	PPD				46	0.0%	143	0.0%
Female					130	0.0%	439	0.0%
20-24	**86**	**0.0%**	**104**	**0.0%**	**676**	**0.2%**	**2,237**	**0.2%**
Male	PPD				204	0.1%	633	0.0%
Female					472	0.1%	1,604	0.1%

Count of patients and percentage	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
	N*	%	N*	%	N*	%	N*	%
25-29	**157**	**0.0%**	**182**	**0.0%**	**1,084**	**0.3%**	**3,651**	**0.3%**
Male	29	0.0%	31	0.0%	346	0.1%	1,105	0.1%
Female	128	0.0%	151	0.0%	738	0.2%	2,546	0.2%
30-34	**282**	**0.1%**	**351**	**0.1%**	**1,591**	**0.4%**	**5,363**	**0.4%**
Male	44	0.0%	46	0.0%	441	0.1%	1,393	0.1%
Female	238	0.1%	305	0.0%	1,150	0.3%	3,970	0.3%
35-39	**672**	**0.2%**	**887**	**0.1%**	**2,573**	**0.7%**	**8,829**	**0.6%**
Male	87	0.0%	100	0.0%	724	0.2%	2,372	0.2%
Female	585	0.2%	787	0.1%	1,849	0.5%	6,457	0.5%
40-44	**1,841**	**0.5%**	**2,757**	**0.4%**	**4,702**	**1.2%**	**16,585**	**1.2%**
Male	210	0.1%	247	0.0%	1,154	0.3%	3,889	0.3%
Female	1,631	0.5%	2,510	0.4%	3,548	0.9%	12,696	0.9%
45-49	**5,897**	**1.8%**	**9,944**	**1.6%**	**9,826**	**2.6%**	**35,548**	**2.5%**
Male	554	0.2%	734	0.1%	1,973	0.5%	6,804	0.5%
Female	5,343	1.6%	9,210	1.4%	7,853	2.1%	28,744	2.0%
50-54	**17,263**	**5.2%**	**31,567**	**5.0%**	**22,112**	**5.8%**	**82,553**	**5.8%**
Male	1,124	0.3%	1,564	0.2%	3,034	0.8%	10,899	0.8%
Female	16,139	4.8%	30,003	4.7%	19,078	5.0%	71,654	5.0%
55-59	**33,212**	**9.9%**	**62,795**	**9.9%**	**38,280**	**10.1%**	**144,287**	**10.1%**
Male	1,741	0.5%	2,585	0.4%	3,869	1.0%	14,123	1.0%
Female	31,471	9.4%	60,210	9.4%	34,411	9.1%	130,164	9.1%
60-64	**39,456**	**11.8%**	**74,682**	**11.7%**	**44,437**	**11.7%**	**166,311**	**11.6%**

Count of patients and percentage	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
	N*	%	N*	%	N*	%	N*	%
Male	2,247	0.7%	3,403	0.5%	4,456	1.2%	16,350	1.1%
Female	37,209	11.1%	71,279	11.2%	39,981	10.5%	149,961	10.5%
65-69	**44,142**	**13.2%**	**82,918**	**13.0%**	**49,301**	**13.0%**	**182,805**	**12.8%**
Male	2,284	0.7%	3,413	0.5%	4,732	1.2%	17,269	1.2%
Female	41,858	12.5%	79,505	12.5%	44,569	11.8%	165,536	11.6%
70-72	**27,132**	**8.1%**	**50,699**	**8.0%**	**30,455**	**8.0%**	**110,411**	**7.7%**
Male	1,383	0.4%	2,099	0.3%	2,953	0.8%	10,489	0.7%
Female	25,749	7.7%	48,600	7.6%	27,502	7.3%	99,922	7.0%
≥73	**165,021**	**49.2%**	**320,465**	**50.3%**	**174,070**	**45.9%**	**669,781**	**46.9%**
Male	12,975	3.9%	23,587	3.7%	17,370	4.6%	65,871	4.6%
Female	152,046	45.4%	296,878	46.6%	156,700	41.3%	603,910	42.3%
Total Sex								
Female	312,503	93.2%	599,568	94.1%	337,981	89.1%	1,277,603	89.4%
Male	22,688	6.8%	37,819	5.9%	41,302	10.9%	151,340	10.6%

* Frequency distributions for categorical and ordinal variables; means, standard deviations, minimums, 25th percentiles, medians, 75th percentiles, and maximums for ordinal and continuous variables.

Note: N=329,166 teriparatide-exposed patients were included in both teriparatide-exposed cohorts; N=44,570 unexposed matched comparator patients were included in both the OP and General Population comparator cohorts.

Note: Single ages up to 72 years old were used for matching. Patients aged ≥73 years old were matched with patients who were also ≥73 years old.

Table 10. Index Date for the Patients for the Teriparatide-Exposed and Unexposed Matched Comparator Cohorts

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
Index date[a]								
Jan-Jun 2005	32,548	9.7%	63,043	9.9%	34,747	9.2%	132,442	9.3%
Jul-Dec 2005	26,064	7.8%	50,733	8.0%	27,043	7.1%	104,545	7.3%
Jan-Jun 2006	24,804	7.4%	47,943	7.5%	26,209	6.9%	99,325	7.0%
Jul-Dec 2006	27,223	8.1%	52,500	8.2%	29,480	7.8%	112,086	7.8%
Jan-Jun 2007	25,919	7.7%	49,805	7.8%	28,441	7.5%	107,614	7.5%
Jul-Dec 2007	22,105	6.6%	42,292	6.6%	24,489	6.5%	92,364	6.5%
Jan-Jun 2008	21,254	6.3%	40,556	6.4%	24,032	6.3%	90,408	6.3%
Jul-Dec 2008	19,927	5.9%	37,896	5.9%	22,563	5.9%	84,675	5.9%
Jan-Jun 2009	19,782	5.9%	37,521	5.9%	22,976	6.1%	86,294	6.0%
Jul-Dec 2009	17,672	5.3%	33,506	5.3%	20,320	5.4%	76,179	5.3%
Jan-Jun 2010	12,839	3.8%	24,092	3.8%	15,169	4.0%	56,920	4.0%
Jul-Dec 2010	9,877	2.9%	18,650	2.9%	11,400	3.0%	42,405	3.0%
Jan-Jun 2011	9,720	2.9%	18,300	2.9%	11,362	3.0%	42,191	3.0%
Jul-Dec 2011	9,904	3.0%	18,493	2.9%	11,666	3.1%	43,557	3.0%
Jan-Jun 2012	9,150	2.7%	17,048	2.7%	10,948	2.9%	40,931	2.9%
Jul-Dec 2012	8,197	2.4%	15,158	2.4%	10,057	2.7%	37,447	2.6%
Jan-Jun 2013	9,578	2.9%	17,650	2.8%	11,823	3.1%	43,946	3.1%
Jul-Dec 2013	9,325	2.8%	17,151	2.7%	11,609	3.1%	43,229	3.0%
Jan-Jun 2014	9,195	2.7%	16,753	2.6%	11,808	3.1%	43,632	3.1%

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
Jul-Dec 2014	10,108	3.0%	18,297	2.9%	13,141	3.5%	48,753	3.4%

[a] For the comparator patients, defined as the Index Date of the matched teriparatide-exposed patient.

***** Frequency distributions for categorical and ordinal variables; means, standard deviations, minimums, 25th percentiles, medians, 75th percentiles, and maximums for ordinal and continuous variables

Note: N=329,166 teriparatide-exposed patients were included in both teriparatide-exposed cohorts; N=44,570 unexposed matched comparator patients were included in both the OP and General Population comparator cohorts.

Table 11. Patient Baseline Medication Use for the Teriparatide-Exposed and Unexposed Matched Comparator Cohorts

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
Prescriptions in the 4-month baseline period prior to the Index Month**								
ADHD/anti-narcolepsy/anti-obesity/anorexiants	4,218	1.8%	5,854	1.0%	5,507	1.9%	19,400	1.6%
Alternative medicines	151	0.1%	353	0.1%	203	0.1%	603	0.0%
Amebicides	0	0.0%	1	0.0%	1	0.0%	3	0.0%
Aminoglycosides	239	0.1%	340	0.1%	289	0.1%	985	0.1%
Analgesics - anti-inflammatory	44,624	18.8%	87,823	15.3%	53,454	18.8%	185,201	15.2%
Analgesics - nonnarcotic	9,263	3.9%	23,337	4.1%	10,945	3.9%	46,923	3.9%
Analgesics - opioid	100,494	42.3%	116,985	20.4%	122,417	43.1%	306,518	25.2%
Androgens-anabolic	1,124	0.5%	1,082	0.2%	2,128	0.7%	2,978	0.2%
Anorectal agents	2,757	1.2%	5,241	0.9%	3,256	1.1%	11,569	1.0%
Antacids	1,242	0.5%	2,568	0.4%	1,491	0.5%	4,904	0.4%
Anthelmintics	90	0.0%	138	0.0%	107	0.0%	366	0.0%
Anti-infective agents - misc.	18,041	7.6%	30,856	5.4%	22,127	7.8%	79,651	6.6%
Antianginal agents	9,732	4.1%	18,899	3.3%	11,074	3.9%	55,630	4.6%
Antianxiety agents	41,380	17.4%	65,044	11.4%	49,955	17.6%	178,531	14.7%
Antiarrhythmics	4,059	1.7%	6,624	1.2%	4,724	1.7%	17,418	1.4%
Antiasthmatic and bronchodilator agents	37,173	15.6%	65,826	11.5%	44,790	15.8%	148,065	12.2%
Anticoagulants	16,757	7.0%	28,761	5.0%	19,946	7.0%	73,425	6.0%

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
Anticonvulsants	36,800	15.5%	55,649	9.7%	45,973	16.2%	131,833	10.9%
Antidepressants	66,355	27.9%	121,143	21.2%	80,027	28.2%	287,836	23.7%
Antidiabetics	22,596	9.5%	62,409	10.9%	27,076	9.5%	205,574	16.9%
Antidiarrheals	3,784	1.6%	6,005	1.0%	4,525	1.6%	14,479	1.2%
Antidotes	52	0.0%	86	0.0%	78	0.0%	258	0.0%
Antiemetics	9,199	3.9%	15,045	2.6%	11,152	3.9%	38,107	3.1%
Antifungals	7,438	3.1%	11,543	2.0%	9,280	3.3%	32,931	2.7%
Antihistamines	22,548	9.5%	43,541	7.6%	26,746	9.4%	95,390	7.9%
Antihyperlipidemics	72,078	30.3%	212,497	37.1%	85,069	29.9%	425,110	35.0%
Antihypertensives	72,089	30.3%	195,134	34.1%	83,876	29.5%	483,978	39.8%
Antimalarials	8,308	3.5%	10,971	1.9%	9,889	3.5%	16,563	1.4%
Antimyasthenic agents	279	0.1%	388	0.1%	364	0.1%	713	0.1%
Antimycobacterial agents	347	0.1%	477	0.1%	435	0.2%	1,076	0.1%
Antineoplastics and adjunctive therapies	13,140	5.5%	27,897	4.9%	15,582	5.5%	38,295	3.2%
Antiparkinson agents	7,457	3.1%	12,206	2.1%	9,050	3.2%	26,728	2.2%
Antipsychotics/antimanic agents	8,180	3.4%	16,141	2.8%	10,206	3.6%	44,731	3.7%
Antiseptics & disinfectants	176	0.1%	245	0.0%	221	0.1%	648	0.1%
Antivirals	6,923	2.9%	12,952	2.3%	8,723	3.1%	30,209	2.5%
Assorted classes	3,083	1.3%	4,765	0.8%	4,193	1.5%	6,569	0.5%
Beta blockers	52,518	22.1%	127,161	22.2%	61,045	21.5%	321,007	26.4%
Biologicals misc.	1	0.0%	0	0.0%	1	0.0%	1	0.0%
Calcium channel blockers	36,875	15.5%	93,002	16.2%	42,414	14.9%	218,347	18.0%

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
Cardiotonics	5,975	2.5%	14,066	2.5%	6,641	2.3%	37,471	3.1%
Cardiovascular agents - misc.	1,673	0.7%	4,110	0.7%	2,474	0.9%	14,917	1.2%
Cephalosporins	16,038	6.7%	27,940	4.9%	19,502	6.9%	72,339	6.0%
Chemicals	550	0.2%	725	0.1%	689	0.2%	2,143	0.2%
Contraceptives	637	0.3%	1,860	0.3%	1,384	0.5%	13,615	1.1%
Corticosteroids	38,524	16.2%	52,896	9.2%	47,232	16.6%	108,514	8.9%
Cough/cold/allergy	18,121	7.6%	38,498	6.7%	21,465	7.6%	94,609	7.8%
Dermatologicals	44,169	18.6%	79,282	13.8%	53,051	18.7%	176,736	14.6%
Diagnostic products	8,883	3.7%	23,446	4.1%	10,754	3.8%	71,019	5.8%
Dietary products/dietary management products	2,428	1.0%	3,907	0.7%	2,890	1.0%	7,958	0.7%
Digestive aids	1,461	0.6%	1,605	0.3%	1,727	0.6%	2,968	0.2%
Diuretics	50,612	21.3%	121,292	21.2%	58,386	20.5%	311,587	25.7%
Endocrine and metabolic agents - misc.	92,010	38.7%	480,589	84.0%	104,987	36.9%	148,057	12.2%
Estrogens	12,878	5.4%	34,132	6.0%	14,989	5.3%	81,500	6.7%
Fluoroquinolones	31,502	13.2%	51,231	8.9%	37,143	13.1%	128,963	10.6%
Gastrointestinal agents - misc.	12,660	5.3%	16,142	2.8%	15,017	5.3%	38,352	3.2%
General anaesthetics	2	0.0%	0	0.0%	1	0.0%	1	0.0%
Genitourinary agents - misc.	6,612	2.8%	12,232	2.1%	8,958	3.2%	33,273	2.7%
Gout agents	3,681	1.5%	8,668	1.5%	4,521	1.6%	29,070	2.4%
Haematological agents - misc.	14,794	6.2%	30,953	5.4%	16,956	6.0%	76,166	6.3%

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
Hematopoietic agents	19,557	8.2%	30,419	5.3%	23,425	8.2%	57,726	4.8%
Hemostatics	14	0.0%	13	0.0%	18	0.0%	91	0.0%
Hypnotics	28,146	11.8%	45,646	8.0%	33,662	11.8%	107,489	8.8%
Laxatives	18,548	7.8%	30,410	5.3%	22,112	7.8%	62,720	5.2%
Local anaesthetics-parenteral	106	0.0%	104	0.0%	133	0.0%	345	0.0%
Macrolides	21,387	9.0%	41,172	7.2%	25,879	9.1%	103,501	8.5%
Medical devices	26,155	11.0%	18,561	3.2%	30,661	10.8%	58,555	4.8%
Migraine products	4,555	1.9%	8,097	1.4%	5,675	2.0%	16,381	1.3%
Minerals & electrolytes	27,353	11.5%	59,276	10.4%	32,211	11.3%	119,859	9.9%
Mouth/throat/dental agents	8,662	3.6%	12,359	2.2%	10,436	3.7%	26,467	2.2%
Multivitamins	3,406	1.4%	8,644	1.5%	4,106	1.4%	17,468	1.4%
Musculoskeletal therapy agents	28,301	11.9%	32,164	5.6%	35,769	12.6%	78,689	6.5%
Nasal agents - systemic and topical	20,023	8.4%	42,834	7.5%	24,015	8.5%	87,204	7.2%
Neuromuscular agents	48	0.0%	57	0.0%	60	0.0%	157	0.0%
Nutrients	83	0.0%	306	0.1%	122	0.0%	515	0.0%
Ophthalmic agents	30,983	13.0%	71,390	12.5%	35,620	12.5%	143,540	11.8%
Otic agents	2,521	1.1%	5,435	0.9%	3,014	1.1%	13,024	1.1%
Oxytocics	6	0.0%	13	0.0%	12	0.0%	55	0.0%
Passive immunizing agents	27	0.0%	23	0.0%	40	0.0%	66	0.0%
Penicillins	22,987	9.7%	45,782	8.0%	27,603	9.7%	111,452	9.2%
Pharmaceutical adjuvants	89	0.0%	132	0.0%	118	0.0%	400	0.0%
Progestins	1,880	0.8%	4,034	0.7%	2,258	0.8%	10,189	0.8%

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
Psychotherapeutic and neurological agents - misc.	10,894	4.6%	25,372	4.4%	12,782	4.5%	48,856	4.0%
Respiratory agents - misc.	26	0.0%	24	0.0%	42	0.0%	32	0.0%
Sulfonamides	4	0.0%	13	0.0%	6	0.0%	22	0.0%
Tetracyclines	7,209	3.0%	12,683	2.2%	9,043	3.2%	32,842	2.7%
Thyroid agents	50,250	21.1%	112,766	19.7%	58,238	20.5%	231,217	19.0%
Toxoids	114	0.0%	205	0.0%	154	0.1%	449	0.0%
Ulcer drugs	75,877	31.9%	127,166	22.2%	89,401	31.5%	282,670	23.3%
Urinary anti-infectives	8,404	3.5%	13,911	2.4%	9,793	3.4%	31,350	2.6%
Urinary antispasmodics	13,417	5.6%	30,160	5.3%	15,440	5.4%	51,844	4.3%
Vaccines	8,340	3.5%	18,396	3.2%	10,484	3.7%	36,711	3.0%
Vaginal products	9,667	4.1%	20,168	3.5%	11,280	4.0%	31,982	2.6%
Vasopressors	1,120	0.5%	1,636	0.3%	1,426	0.5%	3,931	0.3%
Vitamins	20,839	8.8%	21,877	3.8%	26,553	9.3%	31,852	2.6%

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
Number of unique GPI-6 medication classes in the 4-month baseline period prior to the Index Month**								
0-2	125,444	37.4%	238,210	37.4%	146,565	38.6%	560,727	39.2%
3-5	66,101	19.7%	126,800	19.9%	73,084	19.3%	278,517	19.5%
6-8	54,000	16.1%	102,658	16.1%	60,428	15.9%	225,132	15.8%
≥9	89,646	26.7%	169,719	26.6%	99,206	26.2%	364,567	25.5%

* Frequency distributions for categorical and ordinal variables; means, standard deviations, minimums, 25th percentiles, medians, 75th percentiles, and maximums for ordinal and continuous variables

** Not including the Index Month.

Note: N=329,166 teriparatide-exposed patients were included in both teriparatide-exposed cohorts; N=44,570 unexposed matched comparator patients were included in both the OP and General Population comparator cohorts.

GPI = Generic Product Identifier

ADHD = attention deficit hyperactivity disorder

Misc. = miscellaneous

Table 12. Patient Geographic Regions for the Teriparatide-Exposed and Unexposed Matched Comparator Cohorts

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
Subjects from states with participating state cancer registries								
Yes	195,276	58.3%	370,760	58.2%	221,059	58.3%	827,524	57.9%
US Census geographic division								
New England	9,367	2.8%	17,667	2.8%	10,849	2.9%	39,884	2.8%
Middle Atlantic	44,340	13.2%	85,439	13.4%	48,319	12.7%	184,828	12.9%
East North Central	55,559	16.6%	106,592	16.7%	60,161	15.9%	229,773	16.1%
West North Central	19,885	5.9%	37,083	5.8%	23,501	6.2%	85,196	6.0%
South Atlantic	74,051	22.1%	142,087	22.3%	81,986	21.6%	314,915	22.0%
East South Central	27,708	8.3%	51,561	8.1%	33,682	8.9%	124,049	8.7%
West South Central	45,349	13.5%	85,075	13.3%	53,702	14.2%	201,216	14.1%
Mountain	20,439	6.1%	38,762	6.1%	23,097	6.1%	85,684	6.0%
Pacific	38,493	11.5%	73,121	11.5%	43,986	11.6%	163,398	11.4%
US Census geographic region								
Northeast	53,707	16.0%	103,106	16.2%	59,168	15.6%	224,712	15.7%
Midwest	75,444	22.5%	143,675	22.5%	83,662	22.1%	314,969	22.0%
South	147,108	43.9%	278,723	43.7%	169,370	44.7%	640,180	44.8%
West	58,932	17.6%	111,883	17.6%	67,083	17.7%	249,082	17.4%

* Frequency distributions for categorical and ordinal variables; means, standard deviations, minimums, 25th percentiles, medians, 75th percentiles, and maximums for ordinal and continuous variables

Note: N=329,166 teriparatide-exposed patients were included in both teriparatide-exposed cohorts; N=44,570 unexposed matched comparator patients were included in both the OP and General Population comparator cohorts.

US = United States

Table 13. Payer Type for the Teriparatide-Exposed and Unexposed Matched Comparator Cohorts

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
Payer type[a]								
Third-party[b]	222,191	66.3%	425,724	66.8%	245,244	64.7%	948,390	66.4%
Medicare	87,832	26.2%	168,940	26.5%	95,243	25.1%	357,890	25.0%
Medicaid	7,272	2.2%	12,983	2.0%	9,614	2.5%	29,449	2.1%
Self-Pay/Cash	17,896	5.3%	29,740	4.7%	29,182	7.7%	93,214	6.5%

[a] For the comparator patients, defined as the most frequent payer type during their Index Month.

[b] "Third-party" consisted of several different payer types including, but not limited to, pharmacy benefit manager, employer, federal and state employee, preferred provider organization, health maintenance organization, non-Medicare seniors card, state assistance program, discount card program, Medicare discount card program, coupon/voucher program, managed Medicaid/Medicare supplement/Medigap/state assistance, Medicare Part D, unspecified plans, and unknown third-party.

***** Frequency distributions for categorical and ordinal variables; means, standard deviations, minimums, 25th percentiles, medians, 75th percentiles, and maximums for ordinal and continuous variables

Note: N=329,166 teriparatide-exposed patients were included in both teriparatide-exposed cohorts; N=44,570 unexposed matched comparator patients were included in both the OP and General Population comparator cohorts.

Table 14. Prescriber Specialty for the Teriparatide-Exposed and Unexposed Matched Comparator Cohorts

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
Prescriber specialty[a]								
Allergy and Immunology	340	0.1%	1,545	0.2%	393	0.1%	5,029	0.4%
Anaesthesiology	915	0.3%	977	0.2%	1,156	0.3%	5,200	0.4%
Colon and Rectal Surgery	16	0.0%	112	0.0%	19	0.0%	824	0.1%
Dermatology	153	0.0%	2,509	0.4%	172	0.0%	15,716	1.1%
Emergency Medicine	790	0.2%	2,683	0.4%	918	0.2%	17,518	1.2%
Family Medicine	58,003	17.3%	187,065	29.3%	65,723	17.3%	408,986	28.6%
Internal Medicine	85,283	25.4%	237,699	37.3%	93,983	24.8%	448,368	31.4%
Medical Genetics and Genomics	3	0.0%	24	0.0%	7	0.0%	30	0.0%
Neurological Surgery	1,062	0.3%	273	0.0%	1,372	0.4%	1,588	0.1%
Neurology	396	0.1%	3,986	0.6%	483	0.1%	15,391	1.1%
Nuclear Medicine	79	0.0%	47	0.0%	97	0.0%	124	0.0%
Obstetrics and Gynaecology	16,491	4.9%	43,299	6.8%	18,106	4.8%	39,116	2.7%
Ophthalmology	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Orthopaedic Surgery	12,284	3.7%	3,332	0.5%	14,778	3.9%	14,198	1.0%
Otolaryngology	87	0.0%	1,163	0.2%	103	0.0%	7,076	0.5%
Pathology	28	0.0%	164	0.0%	34	0.0%	460	0.0%
Paediatrics	432	0.1%	1,293	0.2%	534	0.1%	5,365	0.4%
Physical Medicine and Rehabilitation	2,213	0.7%	1,227	0.2%	2,642	0.7%	4,895	0.3%
Plastic Surgery	92	0.0%	410	0.1%	100	0.0%	2,136	0.1%
Preventive Medicine	92	0.0%	445	0.1%	101	0.0%	1,278	0.1%

	Teriparatide- Osteoporosis comparison				Teriparatide- General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients	**N***	**%**	**N***	**%**	**N***	**%**	**N***	**%**
Psychiatry	292	0.1%	5,479	0.9%	347	0.1%	25,559	1.8%
Radiology	605	0.2%	271	0.0%	732	0.2%	815	0.1%
Surgery (General Surgery)	659	0.2%	2,507	0.4%	789	0.2%	12,340	0.9%
Thoracic Surgery	51	0.0%	178	0.0%	53	0.0%	932	0.1%
Urology	134	0.0%	1,592	0.2%	149	0.0%	9,042	0.6%
Other/unknown	154,691	46.2%	139,107	21.8%	176,492	46.5%	386,957	27.1%

***** Frequency distributions for categorical and ordinal variables; means, standard deviations, minimums, 25th percentiles, medians, 75th percentiles, and maximums for ordinal and continuous variables

Note: N=329,166 teriparatide-exposed patients were included in both teriparatide-exposed cohorts; N=44,570 unexposed matched comparator patients were included in both the OP and General Population comparator cohorts.

[a] For the comparator patients, defined as the specialty of the provider with the most claims during their Index Month.

Table 15. Teriparatide Medication Use During Follow-up

	Teriparatide- Osteoporosis cohort	Teriparatide- General Population cohort
Total number of patients		
N	335,191	379,283
Teriparatide dispensings during follow-up		
Mean (SD)	7.9(8.0)	7.8(8.0)
Minimum	1.0	1.0
25th percentile	1.0	1.0
Median	5.0	4.0
75th percentile	12.0	12.0
Maximum	121.0	121.0
Months' supply per dispensed teriparatide prescription during follow-up[a]		
Mean (SD)	1.1(0.6)	1.1(0.6)
Minimum	0.0	0.0
25th percentile	0.9	0.9
Median	0.9	0.9
75th percentile	1.0	1.0
Maximum	3.0	3.0

	Teriparatide- Osteoporosis cohort	Teriparatide- General Population cohort
Duration of teriparatide exposure (months)[b]		
Mean (SD)	8.4(8.1)	8.2(8.1)
Minimum	0.0	0.0
25th percentile	1.8	1.8
Median	5.5	4.9
75th percentile	13.8	13.2
Maximum	114.9	119.0

[a] Months' supply for each dispensed teriparatide prescription during follow-up was calculated by dividing the days' supply of the dispensed teriparatide prescription by 30.5.
[b] For each teriparatide-exposed patient, the duration of exposure was calculated as the sum of the days' supply of all teriparatide dispensings during follow-up, without regard to overlap or gaps, divided by 30.5.

Note: There were N=11,435 prevalent patients in the Teriparatide-OP cohort and N=12,137 prevalent patients in the Teriparatide-GP cohort.

Abbreviation: SD = standard deviation.

16.1.3. Outcome data

Table 16. Osteosarcoma Case Information

	Teriparatide-Osteoporosis comparison				Teriparatide-General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
	N	%	N	%	N	%	N	%
Total number of patients								
N	335,191	100%	637,387	100%	379,283	100%	1,428,943	100%
Total number of patients with an osteosarcoma diagnosis								
N	3	100.0%	6	100.0%	3	100.0%	9	100.0%
Total number of patients with >1 osteosarcoma diagnosis								
N	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Diagnosis code								
9180/3: osteosarcoma NOS	1	33.3%	3	50.0%	1	33.3%	8	88.9%
9181/3: chondroblastic osteosarcoma	0	0.0%	1	16.7%	0	0.0%	0	0.0%
9182/3: fibroblastic osteosarcoma	0	0.0%	0	0.0%	0	0.0%	1	11.1%
9183/3: telangiectatic osteosarcoma	0	0.0%	0	0.0%	0	0.0%	0	0.0%
9184/3: osteosarcoma in Paget's disease of bone	0	0.0%	1	16.7%	0	0.0%	0	0.0%
9185/3: small cell osteosarcoma	0	0.0%	0	0.0%	0	0.0%	0	0.0%
9186/3: central osteosarcoma	1	33.3%	1	16.7%	1	33.3%	0	0.0%
9187/3: intraosseous well differentiated osteosarcoma	0	0.0%	0	0.0%	0	0.0%	0	0.0%
9192/3: parosteal osteosarcoma	1	33.3%	0	0.0%	1	33.3%	0	0.0%
9193/3: periosteal osteosarcoma	0	0.0%	0	0.0%	0	0.0%	0	0.0%
9194/3: high-grade surface osteosarcoma	0	0.0%	0	0.0%	0	0.0%	0	0.0%
9195/3: intracortical osteosarcoma	0	0.0%	0	0.0%	0	0.0%	0	0.0%

	Teriparatide-Osteoporosis comparison				Teriparatide-General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
	N	%	N	%	N	%	N	%
Diagnostic confirmation of osteosarcoma diagnosis[a]								
1 Positive histology	3	100.0%	6	100.0%	3	100.0%	9	100.0%
2 Positive cytology	0	0.0%	0	0.0%	0	0.0%	0	0.0%
3 Positive histology PLUS – positive immunophenotyping AND/OR positive genetic studies (used only for hematopoietic and lymphoid neoplasms M-9590/3-9992/3)	0	0.0%	0	0.0%	0	0.0%	0	0.0%
4 Positive microscopic confirmation, method not specified	0	0.0%	0	0.0%	0	0.0%	0	0.0%
5 Positive laboratory test/marker study	0	0.0%	0	0.0%	0	0.0%	0	0.0%
6 Direct visualization without microscopic confirmation	0	0.0%	0	0.0%	0	0.0%	0	0.0%
7 Radiography and/or other imaging techniques without microscopic confirmation	0	0.0%	0	0.0%	0	0.0%	0	0.0%
8 Clinical diagnosis only (other than 5, 6, or 7)	0	0.0%	0	0.0%	0	0.0%	0	0.0%
9 Unknown whether or not microscopically confirmed; death certificate only	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Primary site								
C40 Bones, joints, and articular cartilage of limbs	**2**	**66.7%**	**3**	**50.0%**	**2**	**66.7%**	**5**	**55.6%**
C40.0 Long bones of upper limb, scapula, and associated joints	0	0.0%	0	0.0%	0	0.0%	1	11.1%
C40.1 Short bones of upper limb and associated joints	0	0.0%	0	0.0%	0	0.0%	0	0.0%

	Teriparatide-Osteoporosis comparison				Teriparatide-General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
	N	%	N	%	N	%	N	%
C40.2 Long bones of lower limb and associated joints	2	66.7%	3	50.0%	2	66.7%	4	44.4%
C40.3 Short bones of lower limb and associated joints	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C40.8 Overlapping lesion of bones, joints, and articular cartilage of limbs	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C40.9 Bone of limb, NOS	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C41 Bones, joints, and articular cartilage of other and unspecified sites	**1**	**33.3%**	**2**	**33.3%**	**1**	**33.3%**	**2**	**22.2%**
C41.0 Bones of skull and face and associated joints	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C41.1 Mandible	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C41.2 Vertebral column	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C41.3 Rib, sternum, clavicle, and associated joints	1	33.3%	1	16.7%	1	33.3%	0	0.0%
C41.4 Pelvic bones, sacrum, coccyx, and associated joints	0	0.0%	1	16.7%	0	0.0%	2	22.2%
C41.8 Overlapping lesion of bones, joints, and articular cartilage	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C41.9 Bone, NOS	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C49 Other connective and soft tissue	**0**	**0.0%**	**1**	**16.7%**	**0**	**0.0%**	**2**	**22.2%**
C49.0 Connective and soft tissue of head, face, and neck	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C49.1 Connective and soft tissue of upper limb, including shoulder	0	0.0%	0	0.0%	0	0.0%	0	0.0%

	Teriparatide-Osteoporosis comparison				Teriparatide-General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
	N	%	N	%	N	%	N	%
C49.2 Connective and soft tissue of lower limb, including hip	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C49.3 Connective and soft tissue of thorax	0	0.0%	0	0.0%	0	0.0%	2	22.2%
C49.4 Connective and soft tissue of abdomen	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C49.5 Connective and soft tissue of pelvis	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C49.6 Connective and soft tissue of trunk, unspecified	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C49.8 Overlapping sites of connective and soft tissue	0	0.0%	0	0.0%	0	0.0%	0	0.0%
C49.9 Connective and soft tissue, unspecified	0	0.0%	1	16.7%	0	0.0%	0	0.0%

[a] Pathological confirmation of osteosarcoma diagnosis was determined using the NAACCR variable "Diagnostic confirmation of osteosarcoma diagnosis."

Evidence of pathologic confirmation was determined using the following NAACCR categories:

"1 Positive histology,"

"3 Positive histology PLUS – positive immunophenotyping AND/OR positive genetic studies (used only for hematopoietic and lymphoid neoplasms M-9590/3-9992/3)," and

"4 Positive microscopic confirmation, method not specified."

Note: The same 3 cases of osteosarcoma were identified in the Teriparatide-OP cohort as in the Teriparatide-GP cohort. However, the 6 osteosarcoma cases identified in the Osteoporosis cohort were different from the 9 osteosarcoma cases identified in the General Population cohort.

NOS = Not otherwise specified

NAACCR = North American Association of Central Cancer Registries.

16.1.4. Main results

Table 17. Incidence Rates and Incidence Rate Ratios: Main Analysis

	Teriparatide-Osteoporosis comparison		Teriparatide-General Population comparison	
	Teriparatide-OP cohort	**Osteoporosis cohort**	**Teriparatide-GP cohort**	**General Population cohort**
Total number of patients				
N	335,191	637,387	379,283	1,428,943
Total number of osteosarcoma cases				
N	3[a]	6	3[a]	9
Total person-years of follow-up				
Overall (age ≥18 years)	2,095,082.3	4,016,476.1	2,309,376.8	8,740,332.2
Males	139,866.6	237,093.4	238,266.5	877,321.6
Females	1,955,215.7	3,779,382.7	2,071,110.3	7,863,010.6
Age ≥40 years	2,086,513.4	4,005,334.0	2,273,138.5	8,617,075.7
Age ≥65 years	1,489,626.8	2,888,474.1	1,561,210.0	5,962,021.4
Total person-years of follow-up among patients from states with participating state cancer registries[a]				
Overall (age ≥18 years)	1,218,635.0	2,333,294.6	1,340,952.7	5,046,505.3
Males	84,376.3	142,748.6	144,427.0	526,923.1
Females	1,134,258.7	2,190,546.1	1,196,525.8	4,519,582.1
Age ≥40 years	1,213,322.5	2,326,334.2	1,318,403.4	4,971,129.8
Age ≥65 years	870,020.9	1,686,477.6	905,187.3	3,445,804.5
Total person-years of follow-up among patients from states *without* participating state cancer registries[a]				
Overall (age ≥18 years)	876,447.3	1,683,181.5	968,424.0	3,693,826.9
Males	55,490.3	94,344.9	93,839.6	350,398.5
Females	820,957.0	1,588,836.6	874,584.5	3,343,428.4
Age ≥40 years	873,190.9	1,678,999.8	954,735.1	3,645,945.8

	Teriparatide-Osteoporosis comparison				Teriparatide-General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Age ≥65 years	619,606.0		1,201,996.5		656,022.7		2,516,216.9	
Total person-years of follow-up adjusted for the coverage fraction[b]								
Overall (age ≥18 years)	1,462,597.9		2,803,942.1		1,612,199.0		6,101,713.3	
Males	97,642.3		165,517.3		166,336.2		612,467.0	
Females	1,364,955.6		2,638,424.8		1,445,862.8		5,489,246.3	
Age ≥40 years	1,456,615.9		2,796,163.7		1,586,900.7		6,015,666.7	
Age ≥65 years	1,039,923.4		2,016,472.7		1,089,896.3		4,162,146.8	
Incidence rate (per 1,000,000 person-years)								
Among patients from states with participating state cancer registries[a]	1.64		2.57		1.49		1.78	
(95% CI)	0.20	5.93	0.94	5.60	0.18	5.39	0.82	3.39
Adjusted for the coverage fraction	2.05		2.14		1.86		1.47	
(95% CI)	0.42	5.99	0.79	4.66	0.38	5.44	0.67	2.80
Incidence rate ratio								
Among patients from states with participating state cancer registries[a]	0.64		—		0.84		—	
(95% CI)	0.06	3.57	—	—	0.09	4.04	—	—
Adjusted for the coverage fraction	0.96		—		1.26		—	
(95% CI)	0.16	4.49	—	—	0.22	5.06	—	—

[a] 1 of the 3 teriparatide-exposed osteosarcoma cases (and unexposed matched comparator patient[s]) was excluded from the analysis restricting to patients from states with participating state cancer registries because the patient did not reside in a state with a participating state cancer registry; this patient was *diagnosed* in a state with a participating state cancer registry. This patient was included in the analysis adjusted for the coverage fraction.

[b] See Table 5 for calculation of the coverage fraction.

Abbreviation: CI = confidence interval.

Table 18. Study Attrition for the Teriparatide-Exposed and Unexposed Comparator Cohorts (Sensitivity Analysis: Implementing a 6-month Lag)

	Excluded		Remaining	
	N	%	N	%
Teriparatide-OP cohort				
Final Teriparatide-OP analytic sample (for the main analyses)	—	—	335,191	100.0%
Exclude patients who do not have >6 months of follow-up	9,912	3.0%	325,279	97.0%
Exclude patients with an osteosarcoma diagnosis occurring between their Index Date and their adjusted start of follow-up	0	0.0%	325,279	97.0%
Exclude patients who no longer have ≥1 matched Osteoporosis comparator patient	0	0.0%	325,279	97.0%
Final Teriparatide-OP analytic sample for Table 19	**9,912**	**3.0%**	**325,279**	**97.0%**
Teriparatide-GP cohort				
Final Teriparatide-GP analytic sample (for the main analyses)	—	—	379,283	100.0%
Exclude patients who do not have >6 months of follow-up	12,891	3.4%	366,392	96.6%
Exclude patients with an osteosarcoma diagnosis occurring between their Index Date and their adjusted start of follow-up	0	0.0%	366,392	96.6%
Exclude patients who no longer have ≥1 matched General Population comparator patient	0	0.0%	366,392	96.6%
Final Teriparatide-GP analytic sample for Table 19	**12,891**	**3.4%**	**366,392**	**96.6%**
Osteoporosis cohort				
Final Osteoporosis analytic sample (for the main analyses)	—	—	637,387	100.0%
Exclude patients who do not have >6 months of follow-up	17,953	2.8%	619,434	97.2%
Exclude patients with an osteosarcoma diagnosis occurring between their Index Date and their adjusted start of follow-up	1	0.0%	619,433	97.2%
Exclude patients who no longer have a matched teriparatide-exposed patient	0	0.0%	619,433	97.2%
Final Osteoporosis analytic sample for Table 19	**17,954**	**2.8%**	**619,433**	**97.2%**

	Excluded		Remaining	
	N	%	N	%
General Population cohort				
Final General Population analytic sample (for the main analyses)	—	—	1,428,943	100.0%
Exclude patients who do not have >6 months of follow-up	47,858	3.3%	1,381,085	96.7%
Exclude patients with an osteosarcoma diagnosis occurring between their Index Date and their adjusted start of follow-up	2	0.0%	1,381,083	96.7%
Exclude patients who no longer have a matched teriparatide-exposed patient	0	0.0%	1,381,083	96.7%
Final General Population analytic sample for Table 19	**47,860**	**3.3%**	**1,381,083**	**96.7%**

Table 19. Sensitivity Analysis: Incidence Rates and Incidence Rate Ratios – Implementing a 6-month Lag

	Teriparatide-Osteoporosis comparison				Teriparatide-General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients								
N	325,279		619,433		366,392		1,381,083	
Total number of osteosarcoma cases								
N	3[a]		5		3[a]		7	
Person-years of follow-up								
Total	2,092,673.8		4,012,125.2		2,306,232.2		8,728,691.8	
Among patients from states with participating state cancer registries[a]	1,217,166.2		2,330,656.1		1,339,011.4		5,039,398.4	
Adjusted for the coverage fraction	1,460,916.5		2,800,904.7		1,610,003.7		6,093,587.0	
Incidence rate (per 1,000,000 person-years)								
Among patients from states with participating state cancer registries[a]	1.64		2.15		1.49		1.39	
(95% CI)	0.20	5.94	0.70	5.01	0.18	5.40	0.56	2.86
Adjusted for the coverage fraction	2.05		1.79		1.86		1.15	
(95% CI)	0.42	6.00	0.58	4.17	0.38	5.45	0.46	2.37
Incidence rate ratio								
Among patients from states with participating state cancer registries[a]	0.77		—		1.08		—	
(95% CI)	0.07	4.68	—	—	0.11	5.65	—	—
Adjusted for the coverage fraction	1.15		—		1.62		—	
(95% CI)	0.18	5.91	—	—	0.27	7.11	—	—

[a] 1 of the 3 teriparatide-exposed osteosarcoma cases (and unexposed matched comparator patient[s]) was excluded from the analysis restricting to patients from states with participating state cancer registries because the patient did not reside in a state with a participating state cancer registry; this patient was *diagnosed* in a state with a participating state cancer registry. This patient was included in the analysis adjusted for the coverage fraction.

Abbreviation: CI = confidence interval.

Table 20. Study Attrition for the Teriparatide-Exposed and Unexposed Comparator Cohorts (Sensitivity Analysis: Requiring 2 Dispensed Teriparatide Prescriptions)

	Excluded		Remaining	
	N	%	N	%
Teriparatide-OP cohort				
Final Teriparatide-OP analytic sample (for the main analyses)	—	—	335,191	100.0%
Exclude patients who do not have ≥2 dispensed prescriptions for teriparatide	83,960	25.0%	251,231	75.0%
Exclude patients whose second dispensed prescription for teriparatide was on 31 December 2014	60	0.0%	251,181	74.9%
Exclude patients with an osteosarcoma diagnosis that occurred prior to their adjusted Index Date	0	0.0%	251,181	74.9%
Exclude patients who no longer have ≥1 matched Osteoporosis comparator patient	54,655	16.3%	196,526	58.6%
Final Teriparatide-OP analytic sample for Table 21	**138,675**	**41.4%**	**196,526**	**58.6%**
Teriparatide-GP cohort				
Final Teriparatide-GP analytic sample (for the main analyses)	—	—	379,283	100.0%
Exclude patients who do not have ≥2 dispensed prescriptions for teriparatide	97,125	25.6%	282,158	74.4%
Exclude patients whose second dispensed prescription for teriparatide was on 31 December 2014	60	0.0%	282,098	74.4%
Exclude patients with an osteosarcoma diagnosis that occurred prior to their adjusted Index Date	0	0.0%	282,098	74.4%
Exclude patients who no longer have ≥1 matched General Population comparator patient	9,882	2.6%	272,216	71.8%
Final Teriparatide-GP analytic sample for Table 21	**107,067**	**28.2%**	**272,216**	**71.8%**

	Excluded		Remaining	
	N	%	N	%
Osteoporosis cohort				
Final Osteoporosis analytic sample (for the main analyses)	—	—	637,387	100.0%
Exclude patients who do not have ≥1 dispensed prescription during their adjusted Index Month	346,653	54.4%	290,734	45.6%
Exclude patients with an osteosarcoma diagnosis that occurred prior to their adjusted Index Date	0	0.0%	290,734	45.6%
Exclude patients who no longer have a matched teriparatide-exposed patient	0	0.0%	290,734	45.6%
Final Osteoporosis analytic sample for Table 21	**346,653**	**54.4%**	**290,734**	**45.6%**
General Population cohort				
Final General Population analytic sample (for the main analyses)	—	—	1,428,943	100.0%
Exclude patients who do not have ≥1 dispensed prescription during their adjusted Index Month	605,485	42.4%	823,458	57.6%
Exclude patients with an osteosarcoma diagnosis that occurred prior to their adjusted Index Date	0	0.0%	823,458	57.6%
Exclude patients who no longer have a matched teriparatide-exposed patient	0	0.0%	823,458	57.6%
Final General Population analytic sample for Table 21	**605,485**	**42.4%**	**823,458**	**57.6%**

Table 21. Sensitivity Analysis: Incidence Rates and Incidence Rate Ratios – Requiring 2 Dispensed Teriparatide Prescriptions

	Teriparatide-Osteoporosis comparison				Teriparatide-General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Total number of patients								
N	196,526		290,734		272,216		823,458	
Total number of osteosarcoma cases								
N	1		3		1		9	
Person-years of follow-up								
Total	1,246,469.8		1,859,585.4		1,662,124.5		4,990,936.3	
Among patients from states with participating state cancer registries	723,694.7		1,077,194.8		962,779.1		2,894,663.8	
Adjusted for the coverage fraction	870,173.1		1,298,195.1		1,160,345.7		3,484,222.5	
Incidence rate (per 1,000,000 person-years)								
Among patients from states with participating state cancer registries	1.38		2.79		1.04		3.11	
(95% CI)	0.03	7.70	0.57	8.14	0.03	5.79	1.42	5.90
Adjusted for the coverage fraction	1.15		2.31		0.86		2.58	
(95% CI)	0.03	6.40	0.48	6.75	0.02	4.80	1.18	4.90
Incidence rate ratio								
Among patients from states with participating state cancer registries	0.50		—		0.33		—	
(95% CI)	0.01	6.18	—	—	0.01	2.41	—	—
Adjusted for the coverage fraction	0.50		—		0.33		—	
(95% CI)	0.01	6.19	—	—	0.01	2.41	—	—

Abbreviation: CI = confidence interval.

Table 22. Sensitivity Analysis: Incidence Rates and Incidence Rate Ratios – Differential Mortality Assumptions (Teriparatide-Exposed Patients Compared to Unexposed Osteoporosis Patients)

	Teriparatide-Osteoporosis comparison						
	Teriparatide 0%	Teriparatide 2%	Teriparatide 4%	Teriparatide 6%	Teriparatide 8%	Teriparatide 10%	Osteoporosis
Total number of patients							
N	335,191	335,191	335,191	335,191	335,191	335,191	637,387
Total number of osteosarcoma cases							
N	3[a]	3[a]	3[a]	3[a]	3[a]	3[a]	6
Person-years of follow-up							
Total	2,095,082.3	2,053,181.0	2,011,279.6	1,969,378.3	1,927,477.0	1,885,575.7	4,016,476.1
Among patients from states with participating state cancer registries[a]	1,218,635.0	1,194,262.6	1,169,890.1	1,145,517.7	1,121,145.2	1,096,772.8	2,333,294.6
Adjusted for the coverage fraction	1,462,597.9	1,433,346.2	1,404,094.4	1,374,842.7	1,345,591.0	1,316,339.2	2,803,942.1
Incidence rate (per 1,000,000 person-years)							
Among patients from states with participating state cancer registries[a]	1.64	1.67	1.71	1.75	1.78	1.82	2.57
(95% CI)	0.20, 5.93	0.20, 6.05	0.21, 6.18	0.21, 6.31	0.22, 6.44	0.22, 6.59	0.94, 5.60
Adjusted for the coverage fraction	2.05	2.09	2.14	2.18	2.23	2.28	2.14
(95% CI)	0.42, 5.99	0.43, 6.12	0.44, 6.24	0.45, 6.38	0.46, 6.52	0.47, 6.66	0.79, 4.66
Incidence rate ratio							
Among patients from states with participating state cancer registries[a]	0.64	0.65	0.66	0.68	0.69	0.71	—
(95% CI)	0.06, 3.57	0.06, 3.64	0.07, 3.72	0.07, 3.80	0.07, 3.88	0.07, 3.97	—
Adjusted for the coverage fraction	0.96	0.98	1.00	1.02	1.04	1.07	—
(95% CI)	0.16, 4.49	0.16, 4.58	0.16, 4.68	0.17, 4.77	0.17, 4.88	0.17, 4.99	—

[a] 1 of the 3 teriparatide-exposed osteosarcoma cases (and unexposed matched comparator patient[s]) was excluded from the analysis restricting to patients from states with participating state cancer registries because the patient did not reside in a state with a participating state cancer registry; this patient was diagnosed in a state with a participating state cancer registry. This patient was included in the analysis adjusted for the coverage fraction.

Abbreviation: CI = confidence interval.

Table 23. Sensitivity Analysis: Incidence Rates and Incidence Rate Ratios – Differential Mortality Assumptions (Teriparatide-Exposed Patients Compared to Unexposed General Population Patients)

	Teriparatide-General Population comparison						
	Teriparatide 0%	**Teriparatide 2%**	**Teriparatide 4%**	**Teriparatide 6%**	**Teriparatide 8%**	**Teriparatide 10%**	**General Population**
Total number of patients							
N	379,283	379,283	379,283	379,283	379,283	379,283	1,428,943
Total number of osteosarcoma cases							
N	3[a]	3[a]	3[a]	3[a]	3[a]	3[a]	9
Person-years of follow-up							
Total	2,309,376.8	2,263,189.6	2,217,002.4	2,170,815.2	2,124,627.9	2,078,440.7	8,740,332.2
Among patients from states with participating state cancer registries[a]	1,340,952.7	1,314,133.9	1,287,315.1	1,260,496.3	1,233,677.5	1,206,858.7	5,046,505.3
Adjusted for the coverage fraction	1,612,199.0	1,579,955.3	1,547,711.5	1,515,467.8	1,483,224.0	1,450,980.3	6,101,713.3
Incidence rate (per 1,000,000 person-years)							
Among patients from states with participating state cancer registries[a]	1.49	1.52	1.55	1.59	1.62	1.66	1.78
(95% CI)	0.18, 5.39	0.18, 5.50	0.19, 5.61	0.19, 5.73	0.20, 5.86	0.20, 5.99	0.82, 3.39
Adjusted for the coverage fraction	1.86	1.90	1.94	1.98	2.02	2.07	1.47
(95% CI)	0.38, 5.44	0.39, 5.55	0.40, 5.66	0.41, 5.79	0.42, 5.91	0.43, 6.04	0.67, 2.80
Incidence rate ratio							
Among patients from states with participating state cancer registries[a]	0.84	0.85	0.87	0.89	0.91	0.93	—
(95% CI)	0.09, 4.04	0.09, 4.12	0.09, 4.21	0.09, 4.30	0.10, 4.39	0.10, 4.49	—
Adjusted for the coverage fraction	1.26	1.29	1.31	1.34	1.37	1.40	—
(95% CI)	0.22, 5.06	0.22, 5.16	0.23, 5.27	0.23, 5.38	0.24, 5.49	0.24, 5.62	—

[a] 1 of the 3 teriparatide-exposed osteosarcoma cases (and unexposed matched comparator patient[s]) was excluded from the analysis restricting to patients from states with participating state cancer registries because the patient did not reside in a state with a participating state cancer registry; this patient was *diagnosed* in a state with a participating state cancer registry. This patient was included in the analysis adjusted for the coverage fraction.

Abbreviation: CI = confidence interval.

16.1.4.1. Sensitivity analysis: Mortality adjustment

Table 24. Sensitivity Analysis: Incidence Rates and Incidence Rate Ratios – Mortality Adjustment

	Teriparatide-Osteoporosis comparison		Teriparatide-General Population comparison	
	Teriparatide-OP cohort	**Osteoporosis cohort**	**Teriparatide-GP cohort**	**General Population cohort**
Total number of patients				
N	335,191	637,387	379,283	1,428,943
Total number of osteosarcoma cases				
N	3[a]	6	3[a]	9
Total person-years of follow-up				
Overall (age ≥18 years)	1,956,526.3	3,741,875.6	2,170,797.3	8,190,346.6
Males	122,794.0	204,533.6	219,128.6	801,798.2
Females	1,833,732.3	3,537,342.0	1,951,668.7	7,388,548.4
Age ≥40 years	1,947,957.4	3,730,733.6	2,134,559.0	8,067,090.1
Age ≥65 years	1,351,070.8	2,613,873.6	1,422,630.5	5,412,035.9
Total person-years of follow-up among patients from states with participating state cancer registries[a]				
Overall (age ≥18 years)	1,135,971.5	2,169,586.1	1,259,196.8	4,722,409.1
Males	73,770.2	122,536.3	132,466.5	479,755.6

	Teriparatide-Osteoporosis comparison				Teriparatide-General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Females	1,062,201.3		2,047,049.9		1,126,730.4		4,242,653.5	
Age ≥40 years	1,130,659.0		2,162,625.7		1,236,647.5		4,647,033.7	
Age ≥65 years	787,357.4		1,522,769.1		823,431.4		3,121,708.4	
Total person-years of follow-up among patients from states *without* participating state cancer registries[a]								
Overall (age ≥18 years)	820,554.8		1,572,289.5		911,600.4		3,467,937.5	
Males	49,023.8		81,997.3		86,662.1		322,042.5	
Females	771,531.0		1,490,292.2		824,938.4		3,145,894.9	
Age ≥40 years	817,298.4		1,568,107.8		897,911.5		3,420,056.4	
Age ≥65 years	563,713.5		1,091,104.5		599,199.1		2,290,327.5	
Total person-years of follow-up adjusted for the coverage fraction[b]								
Overall (age ≥18 years)	1,365,870.6		2,612,240.8		1,515,455.3		5,717,762.9	
Males	85,723.7		142,787.0		152,975.8		559,743.3	
Females	1,280,146.8		2,469,453.8		1,362,479.5		5,158,019.5	
Age ≥40 years	1,359,888.6		2,604,462.4		1,490,157.0		5,631,716.3	
Age ≥65 years	943,196.1		1,824,771.3		993,152.5		3,778,196.4	
Incidence rate (per 1,000,000 person-years)								
Among patients from states with participating state cancer registries[a]	1.76		2.77		1.59		1.91	
(95% CI)	0.21	6.36	1.01	6.02	0.19	5.74	0.87	3.62
Adjusted for the coverage fraction	2.20		2.30		1.98		1.57	
(95% CI)	0.45	6.42	0.84	5.00	0.41	5.79	0.72	2.99

	Teriparatide-Osteoporosis comparison				Teriparatide-General Population comparison			
	Teriparatide-OP cohort		Osteoporosis cohort		Teriparatide-GP cohort		General Population cohort	
Incidence rate ratio								
Among patients from states with participating state cancer registries[a]	0.64		—		0.83		—	
(95% CI)	0.06	3.56	—	—	0.09	4.03	—	—
Adjusted for the coverage fraction	0.96		—		1.26		—	
(95% CI)	0.15	4.48	—	—	0.22	5.04	—	—

[a] 1 of the 3 teriparatide-exposed osteosarcoma cases (and unexposed matched comparator patient[s]) was excluded from the analysis restricting to patients from states with participating state cancer registries because the patient did not reside in a state with a participating state cancer registry; this patient was *diagnosed* in a state with a participating state cancer registry. This patient was included in the analysis adjusted for the coverage fraction.

[b] See Table 5 for calculation of the coverage fraction.

Abbreviation: CI = confidence interval.

17. Annex 3.
Forteo Cohort Characterization Study: Truven Marketscan Database (2017-5865)

PASS Information

Title	Forteo Cohort Characterization Study: Truven Marketscan Database (2017-5865)
Version identifier of the final study report	1.0
Date of last version of the final study report	Not applicable
EU PAS register number	Not applicable
Active substance	Teriparatide (Calcium homeostasis, parathyroid hormones and analogues; 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:	Not applicable
Marketing authorisation holder(s)	Eli Lilly and Company, Indianapolis, IN
Joint PASS	No
Research question and objectives	The primary objective was to characterize teriparatide treated patients and matched controls with the Truven Marketscan database using demographic characteristics, duration of teriparatide use among the teriparatide treated cohort, provider specialty, and important comorbidities. Secondary objective was to assess the similarity of the teriparatide cohort and the comparator cohorts during the baseline period for number of inpatient and outpatient visits within the prior 4 months and select prescription drugs dispensed during the baseline period.
Country of study	United States
Author	PPD
Signature of principal investigator	Signature on file

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

Forteo Cohort Characterization Study: Truven Marketscan Database.

Keywords

Epidemiology; teriparatide, Forteo, surveillance, parathyroid hormone.

Rationale and background

Forteo® (teriparatide) was initially approved in 2002 in the United States (US) and is indicated for the treatment of postmenopausal women with osteoporosis at high risk for bone fractures; and for increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; and, the treatment of men and women with glucocorticoid-induced osteoporosis at high risk for fracture.

This database study adds to the scientific information generated to date by using a commercial pharmacy claims database to characterize teriparatide-treated patients. Large pharmacy claims data can be representative and are often used to describe drug utilization patterns for the general population, including special populations like the elderly, which is a population more likely to be treated with teriparatide (Schneeweiss and Avorn 2005; Bradley et al. 2007). Claims databases include an accurate record of dispensing dates, and are not biased by knowledge of the study outcome, which allows for an inclusive picture of the use of certain drugs in a population and its dynamics, making this the gold standard for drug exposure information (Schneeweiss and Avorn 2005).

Research question and objectives

This descriptive study commencedin the US to evaluate the demographic characteristics of teriparatide-treated patients and osteoporosis patients not treated with teriparatide. The primary objective was to characterize teriparatide-treated patients and matched controls with the Truven Marketscan database using demographic characteristics, duration of teriparatide use among the teriparatide-treated cohort, provider specialty for Forteo-treated cohort, and important comorbidities. Secondary objective was to assess the similarity of the teriparatide cohort and the comparator cohorts during the baseline period for number of inpatient and outpatient visits within the prior 4 months and select prescription drugs dispensed during the baseline period.

Study design

This is a population based descriptive study which obtained drug exposure data from dispensed pharmacy claims using Truven Marketscan data. Diagnoses are categorized using the Agency for Healthcare Research and Quality (AHRQ), multi-level Clinical Classifications Software diagnosis categories.

Setting

This observational descriptive database study used a US claims database which includes data on over 230 million de-identified patients, covering a large portion of the US population. The included patients in the US aged ≥18 years with pharmacy claims from 01 January 2004 through 01 October 2015. All available data before the index date were used to evaluate patient characteristics among the teriparatide-treated and comparator cohorts.

Subjects and study size, including dropouts

The study sample included 37,468 patients in the teriparatide cohort, 125,788 in the general population cohort, and 65,661 in the osteoporosis cohort.

Variables and data sources

The Truven Marketscan database commercial pharmacy claims were used to identify teriparatide-treated patients and matched unexposed patients. Demographic variables included age, sex, and zip code. Additional variables of interest included payer type and therapeutic drug class.

Results

The majority of subjects were female (89%) and the mean age was 67 years. Over 75% of the teriparatide-treated cohort were using 3 or more classes of drugs during the 4 month baseline period while only 44% of the general population cohort and 64% of the osteoporosis cohort were on 3 or more classes of drugs during the same time period. Among the teriparatide-treated cohort, the mean treatment duration is 8 months and the median was 9 months. History of radiation use was 0.6% among the Forteo cohort and the general population cohort, and higher (1.17%) among the osteoporosis cohort. Forteo patients were found to have a higher prevalence of Paget's as compared to the general population (0.07% vs. 0.03%), but lower than the osteoporosis cohort (0.12%).

Discussion

The demographic characteristics of this teriparatide-treated study sample mirror that of study populations seen in the GHBX surveillance studies. The majority of patients treated with teriparatide are female and the mean age is over age 65. It is recommended that patients with a history of Paget's disease not be treated with teriparatide. As a result, the expectation was that some representation of Paget's disease of the bone would be present only in the comparator population, however overall less than 1% of Paget's was present in each study cohort. For patients of similar age and gender distributions, a higher proportion was also treated with corticosteroids, using 3 or more classes of drugs, and had a higher proportion of inpatient and outpatient visits. Findings from this analysis show the health status of the Forteo treated population was worse than the comparator cohorts.

Marketing Authorisation Holder(s): Eli Lilly and Company, Indianapolis, IN

Names and affiliations of principal investigators: PPD

2. List of abbreviations

Term	Definition
AHFS	American Hospital Formulary Services
AHRQ	Agency for Healthcare Research and Quality
CNS	Central nervous system
IRB	institutional review board
MAH	Marketing authorisation holder
US	United States

3. Investigators

Not applicable.

4. Other responsible parties

Not applicable.

5. Milestones

Not applicable

6. Rationale and background

Forteo (teriparatide) was initially approved in 2002 in the US and is indicated for the treatment of postmenopausal women with osteoporosis at high risk for bone fractures; and for increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; and, the treatment of men and women with glucocorticoid-induced osteoporosis at high risk for fracture.

This database study adds to the scientific information generated to date by using a commercial pharmacy claims database to characterize teriparatide-treated patients. Large pharmacy claims data can be representative and are often used to describe drug utilization patterns for the general population, including special populations like the elderly, which is a population more likely to be treated with teriparatide (Schneeweiss and Avorn 2005; Bradley et al. 2007). Claims databases include an accurate record of dispensing dates, and are not biased by knowledge of the study outcome, which allows for an inclusive picture of the use of certain drugs in a population and its dynamics.

7. Research question and objectives

Primary Objective

To characterize teriparatide-treated patients and matched controls with the Truven Marketscan database using the following:

- Demographic characteristics
- Duration of teriparatide use for teriparatide-treated cohort
- Provider specialty for teriparatide-treated cohort
- Comorbidities, including:
    - History of radiation treatment
    - History of fracture
    - History of cancer
    - History of Paget's disease of the bone

Secondary Objectives

To assess the similarity of the teriparatide cohort and the comparator cohorts for the following factors measured during the baseline period:

- Number of inpatient and outpatient visits within the prior 4 months
- Select prescription drugs dispensed during the baseline period

8. Amendments and updates

There are no amendments / updates.

9. Research methods

9.1. Study design

This study used a population-based cohort from secondary data to characterize teriparatide-treated patients. Exposure was ascertained from prescription drug claims using the Truven Marketscan database.

9.2. Setting

Thisobservational descriptive database study used a US claims database which includes data on over 230 million de-identified patients, covering a large portion of the US population. The included patients in the US aged ≥18 years with pharmacy claims from 01 January 2004 through 01 October 2015. All available data before the index date were used to evaluate patient characteristics among the teriparatide-treated and comparator cohorts.

9.3. Subjects

Teriparatide-Treated Patients: Patients treated with teriparatide were identified in the Truven Marketscan database using dispensed prescriptions of teriparatide identified by NDCs (See Table 1.) One or more dispensed prescriptions of teriparatide during the study period qualified patients as teriparatide -exposed. This study design included both prevalent and new users.

Matched Comparators: Teriparatide-treated patients were described as well as 2 matched comparator cohorts. The 2 comparator cohorts were defined as follows:

General population: This group included patients with a dispensed prescription for any other medication, other than teriparatide. For each teriparatide user, a target of 4 comparators was selected. The comparator cohort was defined as general population pharmaceutical users.

The general population comparator group was identified as persons with at least 1 dispensed prescription for any product other than teriparatide during the same month and year as the identified teriparatide user. A target of 4 controls to 1 teriparatide-treated patient match was targeted for this group.

Osteoporosis population: This group included patients with a dispensed prescription, other than teriparatide, for treatment of osteoporosis. The osteoporosis comparator group was identified as persons with at least 1 dispensed prescription for any osteoporosis treatment other than teriparatide during the same month and year as the identified teriparatide user. A smaller number of available patients were expected in this population and a target of 2 controls to 1 teriparatide-treated patient match was targeted for this group.

The comparator cohorts did not have a teriparatide prescription filled during the study period. This group was matched at baseline to teriparatide-treated patients during the same month as the index period on age group (5-year age categories), sex, geography (ZIP code), payer type, and count of select unique dispensed prescriptions during the same month/year as teriparatide grouped by therapeutic class. Patients were grouped in 5-year age categories up to age 80, where all patients aged 80 and older were combined (See Table 4).

9.3.1. National Drug Codes

Table 1. Teriparatide National Drug Codes (NDC)

11 Digit NDC Code	Product Description	Labeler
00002-8971-01	Teriparatide (Recombinant) Inj 750 MCG/3ML	Eli Lilly & Company
00002-8400-01	Teriparatide (Recombinant) Inj 600 MCG/2.4ML	Eli Lilly & Company

Table 2. Medications Used to Define the Osteoporosis Cohort

Drug class	Drug	Dose
Bisphosphonate	Fosamax (alendronate)	10 mg tablet, 70 mg tablet
	Actonel (risedronate)	5 mg tablet, 35 mg tablet, 150 mg tablet, 36 mg delayed release tablet
	Boniva (ibandronate)	150 mg tablet, 3 mg/3mL injectable
	Reclast (zoledronic acid)	5 mg/100 mL injectable
Biological	Prolia (denosumab)	60 mg/mL injection

9.4. Variables

The variables collected during the time period are listed below.

Table 3. Study Variables

Variable	Source	Definition
Cohort: Teriparatide-Exposed and Unexposed comparators	Commercial pharmacy claims	Patients treated with teriparatide (Exposed): • Patients aged ≥18 years with dispensed prescription of teriparatide during the study period (first observed defined the index date) (for NDC list see Table 1.) Teriparatide cohort drug utilization • Date of prescription fill, days of supply, quantity dispensed, dosage form and strength General Population Comparator: • Patients aged ≥18 years with a dispensed prescription other than teriparatide during same month/year as the matched exposed Osteoporosis Population Comparator: • Patients aged ≥18 years with a dispensed prescription for treatment of osteoporosis other than teriparatide during same month/year as the matched exposed
Baseline Characteristics:	Commercial pharmacy claims	Tables are reported stratified for the teriparatide-exposed and the comparator cohort. Baseline characteristics included: Age • Overlapping age groups (18+ ; 40+; and 65+) • Mutually exclusive age groups (18-19, then 5-year intervals thereafter, ending with 80+) Sex: • % Female; % unknown if ≥5% Geography • Zip code. Depending on the numbers, findings were reported on a state or higher level (Census Division or Region level). Payer type • Commercial plans, Medicare, Medicaid, other third parties Dates • Month and year of cohort entry, dispensed prescription for both teriparatide users and the matched cohort • Selected prescription drugs dispensed during the baseline period. National drug codes collapsed to drug class groups Therapeutic class • Count of unique dispensed prescriptions during the same month/year as teriparatide grouped by therapeutic class

9.5. Data sources

Patients treated with teriparatide were identified in the Truven Marketscan database using dispensed prescriptions of teriparatide identified by NDCs (See Table 1). The Truven

Marketscan database included data on over 230 million de-identified patients, covering a large portion of the US population. The core datasets included commercial claims and encounters and Medicare supplemental databases.

9.6. Bias

This study used Truven Marketscan data to assign exposure status. Pharmacy claims data are not captured for research purposes, but for billing. An exact matched cohort design was used to minimize bias and address confounding. This study is qualitative in nature, therefore controlling for confounding is not necessary.

9.7. Study size

All available data during the study period was used. This is a descriptive study therefore sample size was not predetermined.

9.8. Data transformation

No data transformation was performed.

9.9. Statistical methods

9.9.1. Main summary measures

The focus of this study is to describe patients exposed to teriparatide versus comparators unexposed to teriparatide.

9.9.2. Main statistical methods

Proportions were used to describe study variables.

9.9.3. Missing values

Patients with missing information on the pharmacy claims on variables used for matching were dropped during the cohort selection process, with the possible exception of sex. If matching could not be achieved for a particular matching variable, that variable was dropped from the matching process. If fewer than 5% of the teriparatide-exposed cohort was described as having an unknown sex, these patients were dropped prior to matching. If ≥5% of teriparatide-exposed had an unknown sex, these patients were retained and matched to comparators with an unknown sex. Patients were eliminated or reported as unknown from any descriptive reporting where required data fields were missing. The teriparatide-exposed cohort with missing or invalid days' supply and quantity dispensed values on 1 or more teriparatide-dispensed prescription claims between index and the earlier of end of study period were not included in assessment of cumulative teriparatide exposure.

9.9.4. Sensitivity analyses

None performed for this descriptive analysis.

9.9.5. Amendments to the statistical analysis plan

None.

9.10. Quality Control

All information about this observational study and individual subject medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. Publications may result from this study.

10. Results

10.1. Participants

The total study included three cohorts, the teriparatide-treated patients, general population cohort not treated with teriparatide, and an osteoporosis cohort not treated with teriparatide. The teriparatide cohort included over 37 000 teriparatide-treated patients, the general population cohort included over 125 000 patients and the osteoporosis cohort included over 65 000 patients (See Table 4).

10.2. Descriptive data

The general population cohort and osteoporosis cohort were matched to the teriparatide-treated cohort on age, gender so these characteristics were similar across groups. The majority of subjects were female (89%) and the mean age was 67 years (Table 4). The use of corticosteroids among teriparatide-treated patients was approximately 25% compared to only 10% among the general population controls and 19% among the osteoporosis cohort (Table 5). Of the three study cohorts, the teriparatide-treated cohort showed the highest proportion of central nervous system (CNS) drug use (69%) followed by the osteoporosis cohort (55%) and the general population cohort (39%) (Table 5).

10.3. Main results

The number of unique therapeutic classes of medications dispensed based on the prescriptions claims during the 4 months prior to index was 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. Over 75% of the teriparatide-treated cohort were using 3 or more classes of drugs during the 4 month baseline period while only 44% of the general population cohort and 64% of the osteoporosis cohort were on 3 or more classes of drugs during the same time period (Table 6).

Among the teriparatide-treated cohort, the mean treatment duration is 8 months and the median was 9 months (Table 7). The most common treating physician type was internal medicine and the majority of patients were treated in acute care hospitals (Table 7).

Of the risk factors associated with osteosarcoma 0.07%, 0.03%, and 0.12% had a recorded history of Paget's disease of the bone for patients treated with teriparatide, the general population, and osteoporosis cohort respectively (Table 8).

The proportion of patients with a history of fracture was 30.76%, 3.49%, and 10.53% for patients treated with teriparatide, the general population, and osteoporosis cohort respectively (Table 8).

The proportion of patients with a history of cancer was 18.54%, 13.41%, and 18.92% for patients treated with teriparatide, the general population, and osteoporosis cohort respectively (Table 8).

The proportion of patients with greater than 2 inpatient and outpatient visits was highest among teriparatide treated patients (13.37% inpatient, 95.84% outpatient). The proportion of patients

with greater than 2 inpatient visits was 4.00% and 7.31% in the general population, and osteoporosis cohort respectively. The proportion of patients with greater than 2 outpatient visits was 68.00% and 87.96% the general population, and osteoporosis cohort respectively (Table 8).

10.4. Adverse events/adverse reactions

Not applicable.

11. Discussion

11.1. Key results

The demographic characteristics of this teriparatide-treated study sample mirror that of study populations seen in the GHBX surveillance studies. The majority of patients treated with teriparatide are female and the mean age is over age 65.

Corticosteroid use was higher among the teriparatide cohort (24.51%) than the comparator cohorts (10.07% general population, 19.26% Osteoporosis).

Notably, the use of medications during the baseline period in most of the unique therapeutic classes was higher in the teriparatide cohort than the comparator cohorts. Osteoporosis drugs other than teriparatide were more frequently dispensed in the teriparatide cohort (30.06%) than the general population cohort (9.66%), and the osteoporosis cohort (2.19%).

History of radiation use was 0.6% among the Forteo cohort and the general population cohort and higher (1.17%) among the osteoporosis cohort. History of cancer was approximately 19% for both the Forteo treated cohort and the osteoporosis cohort, and 13% among the general population cohort.

The proportion of patients with greater than 2 inpatient and outpatient visits was highest among teriparatide-treated patients (13.37% inpatient, 95.84% outpatient) and lowest in the general population cohort (4% inpatient, 68% outpatient).

It is recommended that patients with a history of Paget's disease not be treated with teriparatide. As a result the expectation was that some representation of Paget's disease of the bone would be present only in the comparator population, however overall less than 0.2% of Paget's was present in each study cohort and Forteo patients were found to have a higher prevalence of Paget's as compared to the general population (0.07% vs. 0.03%) but lower than the osteoporosis cohort (0.12%).

11.2. Limitations

This is a descriptive study using claims data. The data used in this analysis lacked information on prior health history. Although no statistical comparisons were made, 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.

Misclassification could have resulted if patients were not categorized correctly with regard to exposure. The limitations of claims-based analysis include lack of detailed clinical information resulting in potential misclassification. Here exposures are identified based on a billing claim for a prescription and no information confirming the patient took the medication. In addition, there was the potential for misclassification of the exposure in the comparator cohort if a comparator

had a gap in enrolment during which he or she received a dispensing for teriparatide. Given the out of pocket cost the impact is likely low.

In general, there are few established risk factors for osteosarcoma. Age and sex were balanced between groups due to matching.

History of radiation therapy is described based on available data however this may not be complete capture of all prior radiation therapy. Cancer outcomes among patients treated with radiation therapy can take as long as 10 years for solid tumors to develop. Leukemia, the cancer with the shortest expected latency post radiation exposure, can take approximately 7 years to develop (Hall 2000).

11.3. Interpretation

Findings from this descriptive analysis confirm that the health status of patients treated with teriparatide is worse than the general population and patients treated for osteoporosis with medications other than teriparatide. For patients of similar age and gender distributions, a higher proportion were also treated with corticosteroids, using 3 or more classes of drugs, and higher proportion of inpatient and outpatient visits.

11.4. Generalizability

This population based study included patients aged 18 years and older identified in the Truven Marketscan database using dispensed prescriptions. Study results are representative of insured patients with prescription benefits.

12. Other information

None.

13. Conclusion

This descriptive analysis is used to further understand the characteristics of the Forteo treated population as well as patients with similar demographics not treated with Forteo. The majority of the Truven population of teriparatide patients were on up to 5 unique therapeutic classes of medication within the 4 months before index (Forteo 67%, General population 89%, osteoporosis cohort 80%). This descriptive analysis observed a history of Paget's disease of the bone in 0.07%, 0.03%, and 0.12% for the Forteo cohort, general population cohort, and the osteoporosis cohort respectively. History of radiation use was low across study cohorts with , 0.6% among the Forteo treated cohort and the general population cohort and 1.2% in the osteoporosis cohort. The proportion of patients with greater than 2 inpatient and outpatient visits was highest among teriparatide treated patients (13.37% inpatient, 95.84% outpatient). The low proportion of patients with risk factors associated with osteosarcoma are important findings and these data provide additional information to put into context findings from the main analyses for GHBX 2.2 and GHBX 2.3. Findings from this analysis show the health status of the Forteo treated population is worse than the comparator cohorts.

14. References

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Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol*. 2005;58(4):323-337.

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Annex 1. List of standalone documents

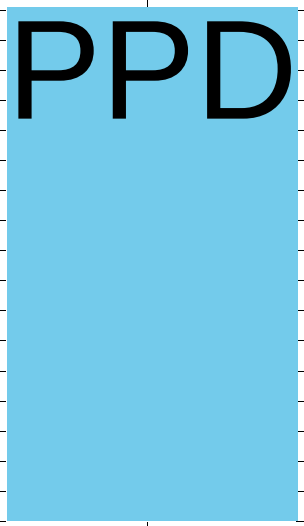
Not applicable.

Annex 2. List of standalone documents

See below tables.

Table 4. Cohort Characteristics at Baseline: Age and Sex Distribution

		Teriparatide COHORT[a]		GENERAL COHORT		OSTEOPOROSIS COHORT	
Total		37,468		125,788		65,661	
		N	%	N	%	N	%
Sex, n(%)							
	Male	4,154	11.09	14,812	11.78	6,390	9.73
	Female	33,311	88.91	110,976	88.22	59,224	90.20
Age (Years) on Index Date							
	Mean (SD)	67.24 (12.14)		67.52 (12.19)		67.19 (11.31)	
Age Group (Years) on Index Date, n(%)							
18-19							
	Male			25	0.02	-	0.00
	Female			20	0.02	-	0.00
20-24							
	Male			69	0.05	-	0.00
	Female			98	0.08	2	0.00
25-29							
	Male			97	0.08	2	0.00
	Female			124	0.10	10	0.02
30-34							
	Male			106	0.08	2	0.00
	Female			244	0.19	50	0.08
35-39							
	Male			177	0.14	18	0.03
	Female			533	0.42	156	0.24
40-44							
	Male			395	0.31	81	0.12
	Female			1,152	0.92	527	0.80
45-49							



	Male			712	0.57	204	0.31
	Female			3,011	2.39	1,579	2.40
50-54							
	Male			1,157	0.91	501	0.76
	Female			8,806	7.00	5,089	7.75
55-59							
	Male			1,611	1.28	814	1.24
	Female			17,386	13.82	9,863	15.02
60-64							
	Male			2,334	1.86	1,262	1.92
	Female			20,746	16.49	11,905	18.13
65-69							
	Male			1,142	0.91	516	0.79
	Female			9,684	7.70	5,234	7.97
70-74							
	Male			1,725	1.37	764	1.16
	Female			13,163	10.46	6,894	10.50
75-79							
	Male			1,991	1.58	933	1.42
	Female			14,293	11.36	7,716	11.75
80+							
	Male			3,271	2.60	1,293	1.97
	Female			21,716	17.26	10,199	15.53
Lookback Period							
Mean (SD)		121.08 (76.92)		117.91 (79.18)		108.47 (71.73)	

[a] Teriparatide Cohort - This includes Teriparatide patients who matched with either General Matched Cohort or Osteoporosis Matched Cohort, or both.

Table 5. Use of Corticosteroid or Other Osteoporosis Drugs Prior to the Index Date

	FORTEO COHORT		GENERAL COHORT		OSTEOPOROSIS COHORT	
Total(N)	37,468		125,788		65,661	
	N	%	N	%	N	%
Use of Corticosteroid drugs prior to the index date	9,185	24.51	12,669	10.0717	12,648	19.26
Dispensing among those with at least 1 corticosteroid						
dispensing:	14,014		25,302		34,307	
Mean (SD) dispensing per patient	3.38 (3.60)		2.24 (2.35)		3.39 (3.43)	
Duration of Corticosteroid exposure (months), Mean (SD)	3.57 (5.06)		1.72 (3.02)		3.33 (4.54)	
Use of Other Osteoporosis drugs prior to the index date	11,264	30.06	12,157	9.66	1,437	2.19
Dispensing among those with at least 1 osteoporosis						
dispensing	3,545		20,852		65,622	
Mean (SD) dispensing per patient	3.07 (2.76)		4.81 (3.40)		4.41 (3.49)	
Duration of Osteoporosis drug exposure (months), Mean (SD)	5.23 (3.72)		8.18 (4.02)		6.82 (4.70)	
Medication by AHFS Therapeutic Class within 4 Months prior to index date, n(%)*						
ASH, Benzodiazepines	6,501	17.35	10,724	8.53	8,104	12.34
Anesthetics, Local	15	0.04	22	0.02	10	0.02
Anti-Infective Agents	16,278	43.45	30,266	24.06	24,060	36.64
Antihistamines & Comb.	3,583	9.56	5,673	4.51	4,904	7.47
Antineoplastic Agents	2,274	6.07	3,184	2.53	3,823	5.82
Antituss/Expector/Mucolytic	1,896	5.06	3,867	3.07	3,088	4.70
Autonomic Drugs	11,344	30.28	15,801	12.56	13,562	20.65
Blood Derivatives	5	0.01	2	0.00	5	0.01
Blood Form/Coagul Agents	4,890	13.05	9,854	7.83	6,966	10.61
Caloric/Nutrition/Dietary Misc	65	0.17	73	0.06	58	0.09
Cardiovascular Agents	22,348	59.65	74,580	59.29	40,112	61.09
Central Nervous System	25,826	68.93	49,308	39.20	36,318	55.31

Contraceptive Cream/Foam/Devic	-	0.00	1	0.00	-	0.00
Dental Agents	230	0.61	384	0.31	244	0.37
Devices & Non-Drug Items	3,541	9.45	1,935	1.54	1,151	1.75
Diagnostic Agents	4,192	11.19	3,670	2.92	2,354	3.59
Electrolytic, Caloric, Water	8,926	23.82	25,315	20.13	14,830	22.59
Enzyme Prep, Topical S/MM, NEC	74	0.20	109	0.09	58	0.09
Enzymes	-	0.00	-	0.00	-	0.00
Eye, Ear, Nose Throat	2,187	5.84	6,252	4.97	3,662	5.58
Gastrointestinal Drugs	14,222	37.96	22,934	18.23	18,150	27.64
Gold Compounds	8	0.02	6	0.00	2	0.00
Heavy Metal Antagonists	7	0.02	8	0.01	13	0.02
Hormones & Synthetic Subst	20,842	55.63	48,317	38.41	31,356	47.75
Immunosuppressants	1,732	4.62	791	0.63	1,344	2.05
Mast Cell Stabilizers, NEC	19	0.05	21	0.02	29	0.04
Oxytocics	2	0.01	1	0.00	4	0.01
Roentgenography, NEC	2	0.01	8	0.01	12	0.02
Serums, Toxoids, Vaccines	370	0.99	718	0.57	727	1.11
Skin & Mucous Membrane	8,357	22.30	13,580	10.80	10,725	16.33
Smooth Muscle Relaxants	2,484	6.63	4,357	3.46	3,409	5.19
Vitamins & Comb	6,044	16.13	4,444	3.53	4,423	6.74

Table 6. Count of Unique AHFS Therapeutic Classes within 4 months prior to index date, n (%)

	FORTEO COHORT		GENERAL COHORT		OSTEOPOROSIS COHORT	
	N	%	N	%	N	%
0 Classes	1,669	4.45	13,900	11.05	5,270	8.03
1 - 2 Classes	7,283	19.44	56,326	44.78	18,214	27.74
3 - 5 Classes	15,967	42.62	41,830	33.25	29,248	44.54
6 - 8 Classes	10,020	26.74	12,169	9.67	11,308	17.22
9 - 11 Classes	2,329	6.22	1,497	1.19	1,559	2.37
12 - 15 Classes	199	0.53	66	0.05	62	0.09
> 15 Classes	1	0.00	-	0.0000	-	0.0000

Table 7. Duration of Treatment and Provider Specialty Among Forteo Cohort

	FORTEO COHORT	
	N	%
Duration of Treatment (Months)[a]		
Mean (SD)	8.36 (4.66)	
Median	9.33	
Treating Physician/Provider Specialty, n(%)		
Abdominal Surgery	64	0.17
Acupuncturist	123	0.33
Acute Care Hospital	25,352	67.66
Allergy & Immunology	1,153	3.08
Ambulatory Surgery Centers	3,341	8.92
Anesthesiology	8,377	22.36
Birthing Center	15	0.04
Cardiothoracic Surgery	113	0.30
Cardiovascular Dis/Cardiology	9,908	26.44
Cardiovascular Surgery	419	1.12
Case Manager	6	0.02
Chemical Depend Treatment Ctr	19	0.05
Child Psychiatry	8	0.02
Chiropractor/DCM	2,164	5.78
Colon & Rectal Surgery	285	0.76
Continuing Care Retirement Com	1	0.00
Convalescent Care Facility	15	0.04
Critical Care Medicine	351	0.94
Day/Night Care Center	1	0.00
Dental Specialist	362	0.97
Dental Technician	11	0.03

Dentist - MD & DDS (NEC)	117	0.31
Dermatologic Surgery	1	0.00
Dermatology	8,231	21.97
Dietitian	57	0.15
Emergency Medicine	6,493	17.33
Endocrinology & Metabolism	5,103	13.62
Extended Care Facility	1,324	3.53
Family Practice	18,438	49.21
Gastroenterology	6,382	17.03
Genetics	18	0.05
Geriatric Hospital	1	0.00
Geriatric Medicine	301	0.80
Head and Neck Surgery	9	0.02
Health Educator/Agency	10	0.03
Hearing Labs	574	1.53
Hematology	1,198	3.20
Home Health Organiz/Agency	1,697	4.53
Hospice Facility	527	1.41
Hospitalist	108	0.29
Imaging Center	3,292	8.79
Infectious Disease	807	2.15
Intermediate Care Facility	6	0.02
Internal Medicine (NEC)	19,536	52.14
Laboratory	13,251	35.37
Longterm Care (NEC)	12	0.03
Medical Doctor - MD (NEC)	4,800	12.81
Medical Technician	320	0.85
Mental Health Facilities	81	0.22
Mental Health/Chemical Dep NEC	19	0.05
Mental Hlth/Chem Dep Day Care	4	0.01
Midwife	39	0.10
MultiSpecialty Physician Group	3,488	9.31
N/A	1,443	3.85
Neonatal-Perinatal Medicine	43	0.11
Nephrology	1,153	3.08
Neurological Surgery	1,603	4.28
Neurology	4,358	11.63
Nuclear Medicine	497	1.33
Nurse Practitioner	2,253	6.01
Nursing Services	1,368	3.65
Obstetrics & Gynecology	7,273	19.41
Oncology	1,330	3.55
Ophthalmology	11,067	29.54
Optician	50	0.13
Optometrist	3,324	8.87

Orthopaedic Surgery	10,547	28.15
Osteopathic Medicine	186	0.50
Other Facility (NEC)	5,143	13.73
Otolaryngology	3,813	10.18
Pain Mgmt/Pain Medicine	1,258	3.36
Palliative Medicine	3	0.01
Pathology	9,050	24.15
Pediatric Allergy & Immunology	32	0.09
Pediatric Anesthesiology	1	0.00
Pediatric Cardiology	13	0.03
Pediatric Critical Care Med	1	0.00
Pediatric Emergency Medicine	6	0.02
Pediatric Endocrinology	15	0.04
Pediatric Gastroenterology	2	0.01
Pediatric Hematology-Oncology	7	0.02
Pediatric Infectious Diseases	2	0.01
Pediatric Nephrology	3	0.01
Pediatric Ophthalmology	16	0.04
Pediatric Orthopaedics	25	0.07
Pediatric Otolaryngology	14	0.04
Pediatric Pathology	4	0.01
Pediatric Pulmonology	9	0.02
Pediatric Radiology	17	0.05
Pediatric Rheumatology	10	0.03
Pediatric Specialist (NEC)	36	0.10
Pediatric Surgery	19	0.05
Pediatric Urology	7	0.02
Pediatrician (NEC)	480	1.28
Pharmacist	103	0.27
Pharmacy	978	2.61
Physical Medicine & Rehab	2,821	7.53
Physician Assistant	1,723	4.60
Plastic/Maxillofacial Surgery	761	2.03
Podiatry	5,533	14.77
Preventative Medicine	129	0.34
Proctology	73	0.19
Psychiatric Nurse	41	0.11
Psychiatry	1,977	5.28
Psychologist	855	2.28
Public Health Agency	104	0.28
Pulmonary Disease	3,545	9.46
Radiology	22,297	59.51
Rehabilitation Facilities	499	1.33
Renal Dialysis Therapy	87	0.23
Residential Treatment Center	19	0.05

Rheumatology	5,998	16.01
Special Care Facility (NEC)	76	0.20
Spiritual Healers	1	0.00
Sports Medicine (Pediatrics)	5	0.01
Supply Center	8,295	22.14
Surgeon (NEC)	4,043	10.79
Surgical Critical Care	23	0.06
Therapists (Alternative)	36	0.10
Therapists (Supportive)	729	1.95
Therapy (Physical)	445	1.19
Thoracic Surgery	449	1.20
Transplant Surgery	1	0.00
Transportation	3,692	9.85
Traumatic Surgery	7	0.02
Treatment Center	35	0.09
Urgent Care Facility	1,101	2.94
Urology	3,149	8.40
Vision Center	79	0.21

[a] 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.

Table 8. Cohort Characteristics at Baseline: Health Status

	FORTEO COHORT		GENERAL COHORT		OSTEOPOROSIS COHORT	
	37,468		125,788		65,661	
Risk Factors, n (%)	N	%	N	%	N	%
Radiation Use	218	0.58	751	0.60	769	1.17
History of Paget's Disease of the bone	26	0.07	40	0.03	77	0.12
Health Status Proxies						
History of Fracture, n (%)[a]	11,527	30.76	4,386	3.49	6,914	10.53
History of Cancer, n (%)	6,946	18.54	16,873	13.41	12,425	18.92
Number of Inpatients in the 4 months prior to Index Date						
0	32,410	86.50	120,703	95.96	60,803	92.60
1	19	0.05	32	0.03	25	0.04
2	30	0.08	26	0.02	35	0.05
>2	5,009	13.37	5,027	4.00	4,798	7.31
Number of Outpatient visits in the 4 months prior to Index Date						
0	818	2.18	25,377	20.17	4,490	6.84
1	311	0.83	7,742	6.15	1,652	2.52
2	428	1.14	7,139	5.68	1,766	2.69
>2	35,911	95.84	85,530	68.00	57,753	87.96

[a] In the table shells document, this says Vertebral or hip Fracture, but in the original Study protocol, it says Fracture (therefore, all fracture types were included in Aetion study earlier during pilot- Same has been done here i.e. all fractures).