1. Observational Research Protocol B3D-MC-GHBX Addendum 2.2(a)

Assessing the Incidence of Osteosarcoma Among Teriparatide Users Using Medicare Part D and State Cancer Registry Data

Teriparatide (LY333334)

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Observational Research Protocol Electronically Signed and Approved by Lilly on date provided below.

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List of Abbreviations

Term	Definition
AES	Advanced encryption standard
AHFS	American Hospital Formulary Services
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
FDA	Food and Drug Administration
GDIT	General Dynamics Information Technology
HCPCS	Healthcare Common Procedure Coding System
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-O-3	International Classification of Diseases for Oncology, Third Edition
ID	Identification
IRR	Incidence rate ratio
ISPE	International Society for Pharmacoepidemiology
NDC	National Drug Code
NOS	Not otherwise specified
NSA	National Security Agency
PTH	Parathyroid hormone
RTI-HS	RTI Health Solutions
SEER	National Cancer Institute's Surveillance, Epidemiology, and End Results
SSN	Social Security Number
US	United States

3. Observational Research Protocol

3.1. Rationale

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

Teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. Teriparatide is administered as a subcutaneous injection into the thigh or abdominal wall with a recommended dosage of 20 μg once a day. In clinical studies, patients with osteoporosis treated for up to 2 years with teriparatide demonstrated increases in bone mineral density and a significant decrease in the incidence of fractures compared with the placebo group. Compared with the placebo group, the teriparatide 20-μg/day group experienced a 65% reduction in the proportion of patients with new vertebral fractures (Neer et al. 2001). Across clinical studies, treatment with teriparatide was well tolerated. No cases of osteosarcoma were reported during clinical trials or in a 5-year posttreatment follow-up study that included 7 long-term teriparatide clinical trials and very few spontaneous cases of osteosarcoma have been in reported in patients who were treated with Forteo.

In rats, in one 2-year (near-lifetime) toxicology study in which doses were administered at levels that produced systemic exposures 3 to 60 times greater than that of a 20-μg dose in humans, teriparatide caused increases in bone mass and a dose-dependent increase in the incidence of osteosarcoma, a malignant tumor (Forteo USPI 2012, Vahle et al. 2002). A subsequent rat study conducted to determine the effect of duration of treatment and age at initiation of treatment found that the bone neoplastic response in rats was dependent on both dose and duration of treatment. The study established a "no-effect" dose of 5 μg/kg when initiated at 6 months of age and continued for a duration of either 6 months or 20 months (Vahle et al. 2004). In a long-term study of cynomolgus monkeys (spanning 18 months of treatment plus 3 years of follow-up observation), no bone tumors were detected by radiographic or histological evaluation (Vahle et al. 2008). Studies have shown that the rat skeleton is more sensitive than monkey or human skeletons to the pharmacological effects of PTH in the formation of new bone and osteosarcomas s (Miller 2008).

Little is known about the etiology of osteosarcoma in adult humans (Unni and Dahlin 1996; Fletcher et al. 2002). It has been observed in association with Paget's disease of the bone and after radiation treatment to the bones (Unni and Dahlin 1996; Grimer et al. 2003). In addition, rare inherited disorders, including Li-Fraumeni syndrome (p53 mutation) and retinoblastoma (pRb loss) are associated with increased rates of osteosarcoma (Savage and Mirabello 2011). Other potential risk factors, including injury or infection at the tumor site and metallic implants

at the tumor site, have been suggested (Unni and Dahlin 1996). 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's disease of the bone. However, the majority of osteosarcoma cases occur in the absence of these risk factors. Numerous studies of growth and other genetic risk factors have been conducted but strong data on risk for apparently sporadic osteosarcoma are limited" (Savage and Mirabello 2011).

At the time of drug approval in the US (2002), because of the preclinical findings, the Food and Drug Administration (FDA) requested a case-finding safety surveillance study to evaluate a potential association between Forteo and adult osteosarcoma in humans. In this study, patients are identified through more than 25 participating state, regional, or local cancer registries and exposure is ascertained through telephone interview with patients or patient proxies. Interim results of the first 7 years of the study, presenting descriptive data on the first 549 patients with osteosarcoma who had a completed telephone interview to ascertain exposure, have been published (Andrews et al. 2012). At the time the FDA approved the new indication for use in the treatment of men and women with glucocorticoid-induced osteoporosis in the US (2009), the FDA requested a prospective voluntary registry of patients treated with Forteo as a second method to complement the ongoing retrospective US component of the study. Exposure is ascertained by self-report for patients who voluntarily enroll in the Forteo Patient Registry, and information from these patients is linked with 41 participating state cancer registries to ascertain incidence of osteosarcoma (Kellier et al. 2014). The objective of the Forteo Patient Registry study is to estimate the incidence of osteosarcoma in patients who have received treatment with Forteo. To achieve this objective, the registry target is to observe 1.7 million patient-years within the study population. Based on current enrollment estimates/projections, the registry will need to at least continue through 2024 to meet this objective.

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

The availability of Medicare Part D prescription drug data for persons aged 65 years and older, which were not available at the time the first 2 studies were initiated, affords an opportunity to supplement the existing studies in 2 ways: (1) exposure data from Medicare Part D enables the capture of information on duration of Forteo use, which is not collected in the Forteo Patient Registry, and (2) a concurrent comparison group of Forteo nonusers is possible. The Medicare linkage study described in this protocol couples the accurate case ascertainment and classification performed by cancer registries with capture of the large majority of Forteo users, most of whom are over 65 years of age and are covered by Medicare Part D. This effort will increase access to a larger number of Forteo users.

At least annually, an existing advisory board provides a comprehensive review of study data, spontaneous reports, and any relevant information in the published literature on Forteo treatment and osteosarcoma in humans, to advise whether there is a possible signal of increased risk, and to recommend additional follow-up activities. The results of the Medicare linkage study will be included in the advisory board review. Because of the diverse and accumulating nature of the evidence reviewed by the board, a qualitative assessment of the results is preferred to an a priori statistical rule for signal detection or confirmation.

RTI Health Solutions (RTI-HS), a business unit of RTI International, will provide scientific oversight for the Medicare linkage study and serves as the main contact for registry recruitment.

This protocol represents 1 of 2 database studies, which will be incorporated into the ongoing GHBX osteosarcoma surveillance program with an aim to address enrollment targets and increase person-years of observation beyond what has been achieved in the Study GHBX(2). After assessing the findings from this database linkage study and overall progress of the GHBX surveillance program, Lilly will consult with the FDA to decide whether the strength of the evidence is sufficient or an additional linkage in the future is required.

3.2. Objectives

3.2.1. Primary Objective

- To estimate the incidence rate ratio (IRR) and 95% confidence interval (CI) of osteosarcoma for patients aged 65 years or older with a prescription claim for Forteo versus a cohort of matched comparators.

3.2.2. Secondary Objectives

- To describe the characteristics of each cohort, including the following factors:
    - Demographics
    - Baseline and prior use of other medications, including the number of unique pharmacologic therapeutic classes within the previous 4 months
    - Baseline and prior use of other osteoporosis medications
    - Baseline and prior use of glucocorticoids

  For the Forteo cohort:

    - Duration of use of Forteo
    - Specialty of the provider, if available
- To assess the similarity of the Forteo cohort and the comparator cohort using Medicare Parts A, B, and D for a subset of the patients according to the following factors measured during the baseline period:
    - History of radiation treatment
    - History of fracture
    - History of cancer

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

3.3. Research Design

This population-based cohort study will utilize secondary data to compare the incidence of osteosarcoma among Forteo users aged 65 years and older with the incidence of osteosarcoma among nonusers aged 65 years and older. Exposure will be ascertained from prescription drug claims, and outcome will be ascertained through linkage with state cancer registries. Forteo users will be matched to nonusers based on demographic and baseline characteristics.

The index date for Forteo users will be defined as the first date the patient has a claim for Forteo after a 4-month look-back period. This study design will include both prevalent and new users. Patients will be eligible to be selected as comparators if they had received a prescription for a drug other than Forteo within the same calendar month as the index date of the Forteo user. The index date for each matched comparator will be set to equal the date of his or her qualifying prescription closest to the index date of the Forteo user.

The look-back time—all available data before the index date (a minimum of 4 months)—will be used to evaluate patient characteristics among the Forteo and comparator cohorts and the potential for confounding (with the exception of counts of the therapeutic classes of medications or inpatient/outpatient visits, which will be restricted to the past 4 months). The follow-up time, which begins the day after the index date, will be used to evaluate the incidence of osteosarcoma.

Sensitivity analyses using a data-driven approach are planned and will be prompted by the number of identified osteosarcoma cases (e.g., if there are few to no cases, there is likely little need for sensitivity analyses) and/or a qualitative assessment (for example, assessment of patient comorbidities). If needed, these proposed secondary sensitivity analyses will provide another dimension to the study and will add to the robustness of the overall interpretation of study findings.

3.3.1. Study Type

This cohort study will compare the incidence of osteosarcoma among Forteo users aged 65 years and older with the incidence of osteosarcoma among nonusers aged 65 years and older selected from the Medicare Part D general population, matched to Forteo users on demographic and comorbidity indicators. Exposure will be ascertained from prescription drug claims, and outcome will be ascertained through linkage with state cancer registries.

A cohort design allows for direct estimation of the incidence of the cancer outcome in patients with a Forteo dispensing and allows for a comparison to a group of patients without a Forteo dispensing. Ascertaining exposure via prescription claims removes the possibility of recall bias and provides more information relating to duration of use than self-report. Ascertaining outcome through cancer registries minimizes the possibility of misclassification of the cancer diagnosis given that *International Classification of Diseases for Oncology, Third Edition* (ICD-O-3) codes used by cancer registries are more specific than *International Classification of Diseases, 9th*

Revision (ICD-9) or *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes in claims data.

3.3.2. Data Source

3.3.2.1. Exposure Data Source

This study will identify Forteo users and comparators using Medicare Part D data.

Medicare is a federally sponsored health insurance program in the US that offers health coverage to 47 million people, including 39 million people aged 65 years or older and 8 million nonelderly people with a permanent disability (Cubanski et al. 2010). Most adults become eligible for Medicare when they reach 65 years of age, although younger adults can qualify if they are permanently disabled. Medicare beneficiaries make up approximately 15% of the total US population and constitute more than 98% of the US population aged 65 years or older (Research Data Assistance Center 2013).

Medicare consists of Part A, which is hospitalization insurance; Part B, which covers physician services and outpatient care; and Part D, which is outpatient prescription drug coverage. Parts B and D are optional, and enrollees must pay a monthly premium for this coverage. Part D coverage has been available since 2006 and is purchased by beneficiaries through private insurance companies approved by Medicare. As of 2014, about 69% of the US population aged 65 years and older enrolled in Medicare (32.9 million enrolled in Part D of 47.6 million Medicare beneficiaries) were also enrolled in Medicare Part D (CMS 2016).

Using Medicare Part D claims data as the data source to identify exposure is particularly relevant because most Forteo users are over 65 years of age. The mean age of a cohort of Forteo users in Medicare Part D was 73.4 years (Hazel-Fernandez et al. 2013). Therefore, using Medicare Part D as a data source is appropriate to capture a significant proportion of patients taking Forteo. An additional benefit of using this data source is the accumulation of a large number of patients and their corresponding person-time, which is necessary due to the rarity of osteosarcoma.

However, using Medicare data for research purposes does have limitations. One limitation is the lag time in data availability. Data are available for research approximately 2 years following the close of a calendar year. For example, for a study conducted in 2016, data would be available through the end of 2014. In addition, the data are claims-based information, which is assembled for reimbursement purposes and not specifically for research purposes. The limitations of claims-based analyses have been described elsewhere (Crystal et al. 2007; Crystal et al. 2010), but include lack of detailed clinical information and potential misclassification given that exposure is identified based on a claim for a prescription and there is no information that confirms whether or not the patient actually used the medication. Based on market research data, 70% of new patients refill their Forteo prescription at least once, and 64% refill their prescription to cover at least 90 days. Therefore, the potential for exposure misclassification is likely to be minimal.

3.3.2.2. Outcome Data Source

The outcome of interest—osteosarcoma—will be identified using state cancer registry data, which is the most accurate and complete population-based source of cancer outcomes, including osteosarcomas. Cancer registries collect detailed clinical information for various cancers including the tumor site, type, and stage of cancer at the time of diagnosis (extent of disease) and the cancer treatment that patients receive during the first 6 months following diagnosis (i.e., the first course of therapy). Physicians, hospitals, therapeutic radiation facilities, freestanding surgical centers, and pathology laboratories are required by law to report all cancers to their central statewide cancer registry. Participation by cancer registries is vital for the identification (ID) of primary osteosarcoma because registries confirm the actual diagnosis based on histopathology records. In addition, they code individual cases using ICD-O-3 codes, which are more precise and accurate than ICD-9 or ICD-10 codes, which do not distinguish between primary osteosarcoma and other tumors with bone metastases.

Using cancer registry data does have limitations. Primarily, there is delay between the diagnosis of a case and when the case is reported to the central cancer registry. This lag time can be 2 years or more. Nonetheless, the majority of US cancer registries capture 90% or more of all incident cases of cancer in their catchment area and therefore are considered population-based reporting systems. A registry's ability to capture a large proportion of the incident cases occurring each year through active surveillance is also rated by the North American Association of Central Cancer Registries.

3.3.2.3. Mortality Data Source

The Medicare Master Beneficiary Summary File will be linked to the Medicare Part D data file to identify whether patients die during the follow-up period to allow for appropriate censoring. The Medicare Master Beneficiary Summary File includes beneficiary unique ID, state and county codes, zip code, date of birth, date of death, sex, race, age, monthly entitlement indicators (A/B/D), reasons for entitlement, and monthly managed care indicators (yes/no). As of 2006, it also includes variables specific to enrollment in Medicare Part D.

3.3.2.4. Data Linkage

The study cohort identified in Medicare Part D will be linked to state cancer registries. Information on all Forteo users and all comparators will be linked to participating state cancer registry data by Medicare's trusted independent third-party organization (currently, this company is General Dynamics Information Technology [GDIT]). A deterministic data linkage (i.e., exact match) will be conducted between the Medicare Part D beneficiaries selected for the study cohorts and patients diagnosed with osteosarcoma in the cancer registry data. GDIT will perform the linkage in 1 of 2 ways, depending on each cancer registry's ability to release personally identifiable information. GDIT will link using either (1) the 9-digit Social Security Number (SSN) or (2) at least 3 of the following 4 variables: the last 4 digits of the SSN, last name, date of birth, and sex (zip code and state will also be used to clarify possible matches). Given that deterministic data linkage utilizing SSN alone is highly effective, finding approximately 98% of all true matches (Simon et al. 2005), the preferred option is to have cancer registries send SSNs to GDIT for linkage. However, given known local restrictions at some

individual state cancer registries regarding the release of SSN to external parties and to facilitate participation by as many registries as possible, the secondary linkage option has been included. Deterministic data linkages using variables other than SSN have been shown to capture approximately 70% to 80% of people expected to be in both databases when using a deterministic match approach similar to the one that will be utilized by GDIT (Grannis et al. 2002, Rotermann et al. 2015). If any matches are found during the linkage, tumor-related variables will be requested from the cancer registry. The tumor-related information will be used to establish the date of diagnosis to confirm that a linked patient was exposed to Forteo prior to the cancer diagnosis. Additionally, information on the cancer site and morphology will be used to ensure that the patient meets the study case definition for osteosarcoma.

A follow-up linkage, if required, will be a replication of the first linkage methods and inclusion/exclusion criteria.

3.3.3. Study Populations

The study cohorts will be selected from people enrolled in Medicare Part D. The Forteo (exposed) cohort will comprise patients with a health insurance claim for an outpatient medication dispensing of Forteo. These patients will be individually matched to patients from the general population of Medicare Part D patients with similar demographic and baseline characteristics and with a prescription for a medication other than Forteo (comparator cohort). For each Forteo user, a target of 4 comparators will be selected. The following characteristics will be used to match patients: 5-year age category; sex; 2- or 3-digit zip code; calendar month of qualifying prescription; and, based on prescription claims, the number of unique therapeutic classes of medications dispensed during the prior 4 months (see Section 3.4.2).

Patients will be eligible for inclusion in 1 of the study cohorts once they meet all of the following inclusion criteria in the order below:

- Are aged 65 years or older
- Have at least 4 months of enrollment prior to first dispensing of Forteo in the exposed cohort (e.g., the index date) or the corresponding index date for the comparator cohort
- Had 1 or more prescriptions for Forteo during the study period OR are a member of the Medicare Part D general population

At the time of the index date for a patient starting Forteo, all other eligible comparators will be eligible to serve as a matched comparator regardless of whether they initiate Forteo in the future. A minimum look-back period of 4 months prior to the index date will be required to assess differences between the Forteo users and comparators using available medication as a proxy to control for unmeasured confounding.

No exclusion criteria are applicable to this study.

3.3.4. Time Periods

The study period to identify exposure for the primary analysis is January 2007 through December 2014. Exposure and outcome will be assessed concurrently during the study period,

under the assumption that there is no induction and latency period between Forteo exposure and the development of clinically detectable osteosarcoma (see Section 3.4.5 for a discussion of a sensitivity analysis that incorporates a lag period).

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

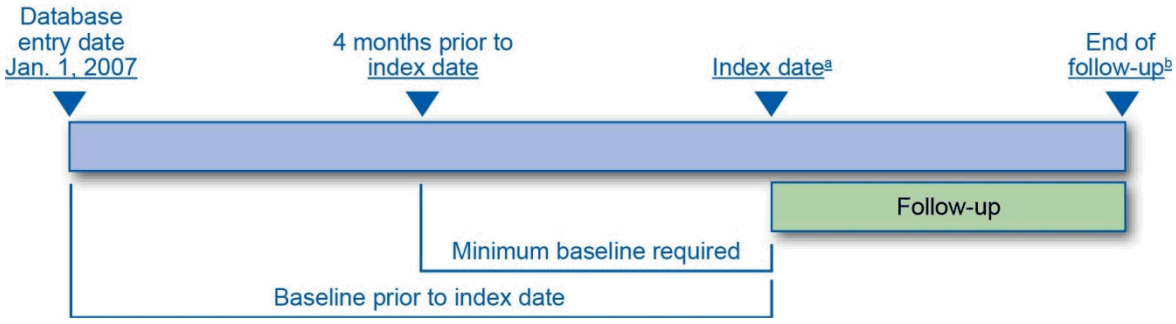

Figure 1. Forteo Medicare linkage study design.

[a] Date of Forteo prescription for the exposed cohort, or date of prescription closest to the Forteo prescription for the comparator cohort.
[b] Osteosarcoma diagnosis, death, or study period end.

The index date for Forteo users occurs on the earliest date that the patient meets all of the following:

- Four months of continuous enrollment in Medicare Part D
- Has a claim for Forteo

The index date for matched comparators occurs on the earliest date that the patient meets all of the following:

- Four months of continuous enrollment in Medicare Part D
- A non-Forteo prescription within the same calendar month as the index date of the exposed patient

If the comparator has multiple prescriptions that meet these criteria, the prescription date closest to the index date of the matched Forteo user will be used as the index date for the comparator.

Follow-up for each Forteo user begins on the day after the index date and ends at the earliest of any of the following:

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

Follow-up for each comparator begins on the day after the index date and ends when they experience the earliest of any of the following:

- Date of diagnosis with osteosarcoma
- Date of death
- End of study period
- Date of a claim for Forteo, at which time the patient's person-time in the comparator cohort will be censored and the patient's subsequent person-time will be counted in the Forteo cohort

The rationale for censoring the person-time if a comparator starts Forteo is to ensure that the study is not subject to immortal person-time bias (Suissa 2007). At the time of the index date for a patient starting Forteo, all other patients without Forteo use during the minimum 4-month look-back period should be eligible to serve as a matched comparator regardless of what happens to comparators in the future. If a comparator does start on Forteo, his or her person-time subsequent to starting Forteo is counted with the Forteo cohort. Allowing Forteo use to be a time-varying exposure reduces bias and maximizes the pool of patients that can be selected into the Forteo cohort at any given point in time.

Person-time will be calculated for Forteo users and nonusers, and an incidence rate ratio for the occurrence of osteosarcoma will be calculated to compare the 2 cohorts.

A follow-up linkage, if required, will extend the study period from January 2007 through December of the year 2 years prior to the date of the linkage.

3.3.5. Variables (Including Exposures and Outcomes)

3.3.5.1. Exposure

For this Medicare linkage study, the study medication of interest among eligible patients using health insurance claims for prescription dispensings in Medicare Part D data will be identified. Forteo use will be defined as the date of the first dispensing in the data source during the study period. Forteo will be identified by its National Drug Code (NDC) number. Forteo use will also be classified as incident or prevalent exposure based on whether the patient had a prescription during the look-back period. Dispensings of all other medication types will be used to identify a matched comparator cohort (i.e., any patient with Medicare Part D coverage during the study period without a dispensing for Forteo).

The following NDC numbers will be used to identify Forteo:

- 00002-8971-01 (3 mL)
- 00002-8400-01 (2.4 mL)

If additional NDC numbers become available during the study period, these will be included.

3.3.5.2. Outcome

Outcomes to be ascertained, through linkage with cancer registries, will be pathologically confirmed cases of osteosarcoma newly reported any time after the patient had a validated claim for Forteo.

The following ICD-O-3 codes will be used by state cancer registries to identify cases of osteosarcoma:

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

3.3.5.3. Baseline Characteristics Used to Match Forteo Users to Comparators

Due to the nature of the Medicare Part D data, the type and number of baseline characteristics that we can use to match Forteo users to comparators will be limited. Baseline characteristics will be measured during the look-back period and will involve prescription use other than Forteo. Quantifying the number of unique therapeutic classes of medications dispensed based on the prescriptions claims during the prior 4 months will be used as a proxy for measuring overall health status and the presence of other chronic comorbidities. American Hospital Formulary Services (AHFS) codes to group prescriptions into therapeutic classes will be used. An assessment of several different prescription-based scores showed that the number of distinct prescriptions based on AHFS codes was a good predictor of future physician visits and mortality (Schneeweiss et al. 2001).

3.3.5.4. Additional Characteristics to Be Described during Baseline

The use of other osteoporosis drugs and use of glucocorticoids in both the Forteo cohort and the comparator cohort during all available look-back time will be described. As described in Section 3.4.5, a data-driven sensitivity analysis from Medicare Parts A, B, and D, using a more extensive set of baseline variables and a longer look-back period, will be conducted, provided the number of patients is sufficient to support this analysis.

3.3.5.5. Characteristics to Be Described during the Follow-Up Period

Other characteristics during the period between the index date and the end of follow-up will be described. Following the index date, the number of dispensings, days' supply and duration of exposure (e.g., by months) will be summarized for each cohort for the index medication and for glucocorticoids. For both the exposed and unexposed cohorts, the number of deaths occurring

during the follow-up period, as well as identified risk factors for osteosarcoma, will be characterized.

Table 1 presents the study variables and operational definitions.

Table 1. Variables and Definitions

Variable	Source	Definition
Exposure:		
Forteo	Pharmacy claims file	All outpatient dispensings (any dosage or formulation) during the study period identified using the NDC
Baseline matching characteristics:		
Number of unique therapeutic classes of medications	Pharmacy claims file	Count of relevant therapeutic classes during the 4 months prior to the index date, using the AHFS class-to-NDC mapping to classify compounds
Age or Age category Sex 2- or 3-digit zip code Calendar month of qualifying prescription	Master Beneficiary Summary File	
Baseline characteristics:		
Presence of osteoporosis drugs other than Forteo	NDC from pharmacy claims file	At least 1 osteoporosis drug other than Forteo dispensed in the look-back period, based on AHFS therapeutic class
Presence of corticosteroid drugs	NDC from pharmacy claims file	At least 1 corticosteroid dispensing during the look-back period
Characteristics during follow-up:		
Number of Forteo dispensings and duration of use	NDC from pharmacy claims file	Index exposure (any dosage or formulation) and subsequent exposures during follow-up identified using the NDC for Forteo and AHFS code for other osteoporosis medications (excluding Forteo)
Number of other osteoporosis medications and duration of use	NDC from pharmacy claims file	
Mortality	Master Beneficiary Summary File	Date of death and count of deaths occurring during follow-up
Outcomes:		
Osteosarcoma	State cancer registry files	Pathologically confirmed cases of osteosarcoma identified using ICD-O-3 oncology codes

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

3.4. Plan of Analysis

The primary objective of the study is to estimate the IRR and 95% CI of osteosarcoma for patients aged 65 years or older with a prescription claim for Forteo versus a matched comparison

cohort with a prescription claim for a drug other than Forteo. The study uses Medicare Part D prescription drug data to identify the cohort of patients aged 65 years or older who have a claim for Forteo and a cohort of nonusers matched to the Forteo users by age, sex, 2- or 3-digit zip code, calendar month of the qualifying prescription, and number of unique therapeutic classes of medications dispensed during the prior 4 months. The outcome of osteosarcoma will be ascertained by linkage of the Medicare Part D study files to the data files from state cancer registries.

After assessing the findings from this database linkage and the overall progress of the GHBX surveillance program, Lilly will consult with the FDA to decide whether the strength of the evidence is sufficient or if an additional linkage in the future is required. For the primary analysis of each linkage, the IRR and 95% CI for osteosarcoma occurrence in Forteo users and nonusers will be estimated using exact conditional Poisson regression.

Secondary objectives include analyses to describe the demographics and baseline characteristics of the Forteo and comparator cohorts and an assessment of the comparability of the Forteo users with the comparators for a subset of patients using information from the Medicare Parts A, B, and D data sets.

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

3.4.1. Methods

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

Although all US state cancer registries will be invited to participate, it is anticipated that not all registries will agree to participate due to resource constraints or other local restrictions related to use of state cancer registry data; therefore, it is expected that the participating state cancer registries will cover a fraction of the US population during the observation period. This incomplete capture of cases due to registries not participating in the study will be addressed in the following ways: (1) by estimating a *coverage fraction* that represents the percentage of osteosarcoma cases captured in this study (based on cancer registry participation) divided by the total number of osteosarcoma cases expected, (2) by recalculating the person-time at risk using the exposure information for only those patients from the states with participating registries and comparing it with the proposed person-time calculation using the coverage fraction to see if they differ in a meaningful way, and (3) by repeating the IRR analysis using only the cases from participating registries and the person-time at risk from the states with participating registries for comparison with the IRR analysis using the coverage fraction.

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

$$f = \frac{\text{number of cases reported by the participating registries from 2007-2014}}{\text{total number of osteosarcoma cases expected in the US during 2007-2014}}$$

The total number of osteosarcoma cases expected in the US will be estimated for the age group of interest for each year of the study using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) overall incidence rate for osteosarcoma (using the study case definition of 12 ICD-O-3 histology codes) as applied to the US Census Bureau's estimated population for the corresponding calendar year. The total number of expected cases will be derived by summing the yearly estimates. Subsequent to determining the estimated coverage fraction, the person-time of observation for individuals at risk in both cohorts will be adjusted accordingly by multiplying it by the coverage fraction. For the purposes of describing the analysis method and the statistical power calculation, a 60% coverage fraction (0.60) was assumed.

The observation period for the linkage to cancer registries will start in January 2007 and end in December 2014. A follow-up linkage, if required, will extend the study period from January 2007 through a date to be determined prior to the date of the linkage. The person-time of each patient will be calculated as the duration of time between the day after the index date until the patient experiences osteosarcoma, death, or the end of the follow-up period, multiplied by the coverage fraction. If a patient in the comparator cohort receives a prescription for Forteo during the observation period, the person-time will be censored from the comparator cohort on the date of the prescription for Forteo, and subsequent person-time will be counted in the Forteo cohort. The impact of nonparticipating state cancer registries will be assessed by comparing the distributions of person-years by age and sex of individuals in both cohorts for nonparticipating states with those from participating states to see if they differ in a meaningful way. Patients with a registry-identified diagnosis of osteosarcoma occurring prior to the index date will be excluded from the cohort. If the patient is in the Forteo cohort, both that patient and the matched comparators will be excluded. If the patient is in the comparator cohort, only that patient will be excluded from the cohort.

Within each cohort, the incidence rate of osteosarcoma will be calculated as the number of cases of osteosarcoma reported during the observation period divided by the total person-time of observation among individuals at risk. Incidence rates will be reported as point estimates (in cases per 1 million person-years) and 95% CIs.

Since the matching process (see Sections 3.3.3 and 3.4.2) produces many matched sets with small numbers of patients in each matched set, and the number of cases of osteosarcoma is expected to be small, the IRR and corresponding 95% CI will be estimated using exact

conditional Poisson regression. For supportive purposes, the incidence rate difference and corresponding 95% CI will also be provided.

Demographic and baseline characteristics will be summarized separately for the Forteo and comparator cohorts using descriptive statistics. Categorical variables will be summarized by frequencies and percentages, and continuous variables will be summarized by means and standard deviations or medians and interquartile ranges. The following variables will be summarized for the Forteo and comparator cohorts: age, sex, state, enrollment reference year, year of cohort entry, and total person-time of observation. Variables describing other prescription use during the baseline period and follow-up (including the number of unique therapeutic classes of medications dispensed, use of other osteoporosis drugs, and use of glucocorticoids) will also be summarized. Duration of use of Forteo and classification of Forteo exposure (i.e., incident or prevalent) will be measured for Forteo users. For all cases of osteosarcoma identified during the study, a data listing describing the key details about the case (e.g., time from index date to diagnosis, duration of Forteo use, age-range of individual) will be provided, consistent with the Centers for Medicare and Medicaid Services (CMS) and cancer registry policies on disclosure of results.

3.4.2. Bias Adjustment

Bias in selection of the comparator cohort to control for potentially confounding effects will be addressed by matching the patients based on available demographic and baseline characteristics. Comparators will be selected to be individually matched to Forteo patients on 5-year age categories (unless the number of patients in 5-year age groups over 84 years is too sparse, then patients aged 85 years or older will be combined together), sex, 2- or 3-digit zip code, month and year of cohort entry, and number of unique therapeutic class of medications dispensed using prescription claims in the prior 4 months. For each Forteo user, a target of 4 comparators will be selected. The selection of 4 comparators for each Forteo user was chosen for statistical power considerations (see Section 3.4.5.1) and to optimize the efficiency of the IRR estimate. If there are difficulties in matching comparators to Forteo users for a particular matching variable, that variable will be dropped from the matching process and controlled for in the IRR analysis.

3.4.3. Scope of Inference

The target population for which inference is to be made is the elderly population aged 65 years and older in the US. The study population will include patients aged 65 years and older who are enrolled in Medicare Part D during the study period. Medicare Part D covers about 60% of the US population aged 65 years or older, and therefore is an appropriate population to address the scope of inference for the study.

3.4.4. Missing Data

It is anticipated that few variables will have notable missing values, as validated claims data from Medicare Part D will be provided on our behalf by the CMS. Consequently, all analyses will be conducted on the observed data available; there will be no imputation of missing values. However, it is possible that sex may be unknown. If this occurs in less than 5% of patients in the

database prior to matching, then these patients will be excluded. If sex is unknown in 5% or more of patients, then these patients will be dropped from the analysis. Patients will be included in all analyses to the extent possible with respect to their available data.

3.4.5. Robustness

The following sensitivity analyses will be performed to determine the robustness of the primary analysis.

3.4.5.1. Similarity of Forteo Users to Comparators Using Medicare Parts A and B

The similarity of the Forteo cohort and the matched comparison cohort among a subset of patients who are also represented in Medicare databases for Parts A and B will be assessed. Demographics, baseline characteristics, and total follow-up time will be summarized for the Forteo and the comparator cohorts using descriptive statistics. Other factors that will be assessed were chosen because they may increase the risk of osteosarcoma (Savage and Mirabello 2011) or are a proxy for overall health status. The presence of each condition will be measured during the look-back period, which will include all available look-back time. Table 2 and Table 3 list the factors that will be compared between cohorts and the codes that will be used to assess each condition.

Table 2. Characteristics That Will Be Assessed for a Subset of Patients with Medicare Parts A, B, and D: Risk factors

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

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

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

Table 3. Characteristics That Will Be Assessed for a Subset of Patients with Medicare Parts A, B, and D: Possible proxies for health status

Condition	ICD-9-CM Code[a]	CPT/HCPCS Code
History of fracture (includes vertebral and hip fracture)	805.xx, 806.xx, 808.xx	N/A
History of cancer	140.xx – 209.xx	N/A
Number of inpatient and outpatient visits in the past 4 months	N/A	N/A
Summary measure of chronic comorbidities (e.g., Charlson Index)	Codes listed elsewhere (Quan et al. 2005)	

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

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

Each factor will be summarized separately for the Forteo and comparator cohorts using descriptive statistics. Categorical variables will be summarized by frequencies and percentages, and continuous variables will be summarized by means and standard deviations or medians and interquartile ranges.

3.4.5.2. Implementing a 6-Month Lag Period

The primary estimate of the IRR (95% CI) assumes that there is no lag time for the induction and latency of osteosarcoma to occur following the index date, which may or may not be biologically plausible. Therefore, a data-driven sensitivity analysis to estimate the IRR (95% CI) will be performed, allowing for a 6-month latency period following the index date. For this analysis, follow-up time will be recalculated starting at 6 months after the index date rather than starting the day after the index date. This will decrease the amount of person-time in both cohorts and could increase the incidence rates in both cohorts (depending on when cases of osteosarcoma were reported relative to the revised index date), but it should not have as much of an impact on the IRR estimate since the adjustment will be applied to both the Forteo and comparator cohorts.

3.4.5.3. Requiring 2 Forteo Prescriptions

For the primary estimate of the IRR, the index date for calculating person-time in the Forteo cohort is based on the date of the first prescription claim for Forteo. A single dispensed prescription does not necessarily mean the patient took the medicine; however, the likelihood that the patient took the medicine increases if the patient filled a second prescription. Consequently, a sensitivity analysis will be performed with the index date starting on the date of the second prescription claim for Forteo. This will decrease the amount of person-time in the Forteo cohort, which could increase the incidence rate (depending on when cases of osteosarcoma were reported relative to the revised index date), as well as the IRR estimate, since the adjustment will be applied only to the Forteo cohort.

3.4.5.4. Incidence Rate Ratio Estimation among Patients Covered by Medicare Parts A, B, and D Using Propensity Score Methods

An analysis using a longer minimum 6-month look-back period can be conducted using a data-driven sensitivity analysis, on those patients enrolled in Medicare Part D from the primary analysis who are also enrolled in Medicare Parts A and B, providing the number of patients is sufficient to support this analysis. This will allow for a more comprehensive strategy to control for confounding; however, restricting this analysis to patients with Medicare Parts A and B will reduce the available number of patients by approximately one-third from the primary analysis. This is because only about two-thirds of beneficiaries with Medicare Part D are also enrolled in Parts A and B fee-for-service plans (CMS 2013). Therefore, instead of matching patients on only 5 demographic and baseline characteristics variables to control confounding, a propensity score will be estimated and used as the stratification factor in a propensity score-stratified analysis to estimate the IRR (95% CI) to control for confounding in the comparison between Forteo users and nonusers.

Propensity scores will be estimated after the Forteo use/nonuse cohorts are selected and after frequency matching by age categories of up to 10 nonusers for each Forteo user. The propensity score for each subject is the predicted probability of being assigned to a particular treatment conditional on a set of observed covariates (D'Agostino 1998; Perkins et al. 2000; Braitman and Rosenbaum 2002). Grouping patients into subclassifications based on their propensity score should produce similar distributions of covariates within that subclass if the propensity scores are relatively constant within the subclass, thus controlling for the effects of the observed covariates (Perkins et al. 2000).

Propensity scores will be estimated by fitting a multivariate logistic regression model with Forteo use or nonuse as the dependent variable and potential confounders or variables associated with osteosarcoma as independent variables during all available look-back time (e.g., the baseline characteristics in Table 1 and the additional characteristics in Table 2). The propensity score distributions for Forteo users and nonusers will be visually examined to assess the magnitude of overlap between the distributions, and patients with nonoverlapping propensity scores in the tails of the distribution or patients with extreme values of the propensity score will be excluded—this process is known as "trimming."

The *trimmed* cohort will be divided into 10 mutually exclusive strata defined by deciles of the propensity score (or, if necessary, into 5 mutually exclusive strata defined by quintiles). Balance among the covariates between the exposure cohorts will be checked by comparing the covariate distributions between the exposure cohorts within each propensity score stratum by creating a table with the frequency distribution of each covariate within each propensity score stratum. If substantial imbalance remains after the propensity score stratification, the logistic regression model will be refined by including additional interaction terms, and the process will be repeated (Perkins et al. 2000; Braitman and Rosenbaum 2002).

The common IRR and 95% CI will be estimated using Mantel-Haenszel methods as described in *Modern Epidemiology, Third Edition* (Rothman et al. 2008).

3.4.6. Study Size and Power Considerations

The estimated background rate for the incidence of osteosarcoma in the US population aged 65 years and older is 3.9 cases per million per year (SEER 2013). The estimated person-time of

follow-up for Forteo users was determined from Medicare Part D data where 141,565 patients had at least 1 claim for Forteo in Medicare Part D from 2007-2012, for an average of 23,594 new Forteo users each year. Using the average of 23,594 new Forteo users each year (and assuming that half of these appear during the first year of entry for each year of the follow-up period), a 5% per year mortality rate, a 60% participation rate for the state cancer registries, and a 4:1 ratio of person-time in the comparator cohort compared with the Forteo cohort, it is estimated that there will be a total of 397,792 person-years of follow-up in the Forteo cohort and 1,591,168 person-years of follow-up in the comparator cohort for the analysis.

For the assumptions provided above, and assuming that the incidence of osteosarcoma follows a Poisson distribution, Table 4 shows the estimated power to detect an increase in the incidence rate for multiples of 3, 4, and 5 times the background rate under a null hypothesis that the true Forteo-to-comparator IRR is 1.0 using methods for the variance-stabilized test of the ratio of 2 Poisson means.

Table 4. Power Estimates

Observation Period	Person-Years in Forteo Cohort	Person-Years in Comparator Cohort	X Times Background Rate	Power if Osteosarcoma Incidence Rate in Forteo Users Is X Times Background Rate (%)
2007-2014	397,792	1,591,168	3	51
			4	70
			5	81

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

3.5. Other Aspects

3.5.1. Data Linkage Process

All cancer registries in the US will be invited to participate in the study; however, it is anticipated that not all will be able or willing to participate due to lack of resources and/or regulations that prohibit some registries from sending identifiable data to third parties. Cancer registries must be able to prepare and send a file with patient-identifiable information of osteosarcoma patients identified during the study period, to the CMS trusted third party to conduct the linkage. Registries will follow a standard process for preparing the linkage file, so files sent to the third party will be in the same data format.

The file sent to Medicare's trusted third party (currently, GDIT) will also contain a unique, study-specific cancer registry patient ID (different from the registry's standard unique patient ID). This unique identifier will be in the format of state initial followed by a 4-digit number. For example, records from North Carolina would be in the format "NC0001, NC0002, etc." RTI-HS will use this project-specific ID to de-duplicate matches found in both the Medicare data and a similar study using commercial data.

Under contract to CMS, GDIT performs all of the linkages of external research data sets to data sets within CMS's Chronic Conditions Warehouse. GDIT will complete the deterministic linkage based on either the full 9-digit SSN or by using at least 3 of the following 4 variables: the last 4 digits of the SSN, last name, date of birth, and sex (zip code and state will also be used to clarify possible matches). GDIT will then provide the study-specific registry ID and Medicare beneficiary unique ID to RTI-HS, which will then contact the state cancer registry to request and obtain the tumor-specific information for a linked patient.

3.5.2. Data Security

Prior to sending their data to Medicare's trusted third party, the registries must encrypt the data with an advanced encryption standard (AES) of at least a 256-bit encryption algorithm. This is a block cipher adopted as an encryption standard by the US government. The National Security Agency (NSA) has deemed the use of 256-bit AES encryption algorithm as secure enough for US government top secret information. Data sent to GDIT by the cancer registries via physical media (CD/flash drive) are destroyed once per quarter via a data destroyer; until that time, the media are stored in a secured cabinet.

The study-specific unique identifier provided by the state cancer registries will not allow linkage to data from the Osteosarcoma Surveillance Study or Forteo Patient Registry via the real cancer registry patient identifier supplied to RTI-HS for those studies by some states. At no time will RTI-HS or the study sponsor have personally identifiable information for Medicare Part D patients linked with cancer registry data.

3.5.3. Quality Control

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

3.5.4. Protection of Human Subjects

As with all research at RTI International that involves human subjects or data on human subjects, RTI-HS will request review of the protocol by the RTI International institutional review board (IRB).

For use of Medicare data, the CMS requires that an IRB review and approval be obtained before use of Medicare data for research can be approved. This protocol will be reviewed by the RTI International IRB before applying to use Medicare data, and will undergo a continuing IRB review at least once per year.

Under the Privacy Rule (45 CFR 164.512), CMS may disclose protected health information for research without documentation of individual authorization only if an IRB or a CMS Privacy

Board has approved a waiver of research. Such a waiver must be provided to CMS. Data requests for research-identifiable data must be reviewed by the CMS Privacy Board to ensure that any study subject's privacy is protected and the need for identifiable data is justified.

Additionally, ethics committee approvals will be obtained at each participating registry consistent with the requirements at each site.

Details regarding matches, including age (if <90 years), sex, year of exposure, and year of diagnosis, will be reported if the number of matches allows, based on confidentiality restrictions imposed by the data sources contributing data for analysis to this study. If there are cell sizes that would allow individual re-identification from the data, strata will be collapsed to achieve cell sizes that comply with governing data use regulations. Reports will comply with CMS and individual cancer registry requirements as detailed in the data use agreements.

3.5.5. Limitations

Due to the nature of the prescription data source and the rarity of osteosarcoma, it will be difficult to control for many confounding variables. All potential confounding variables for which data are available will be 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 will be made based on the number of unique therapeutic classes of medications dispensed during the prior 4 months. Finally, differences between the Forteo users and nonusers will be assessed in a subset of patients with an expanded data set.

In a sensitivity analysis using data from Medicare Parts A, B, and D, we will be able to control for more potential confounders. This unmeasured confounding could be addressed through propensity score calibration using information on the additional variables measured in Medicare Parts A and B. This propensity score calibration combines propensity scores with regression calibration to address confounding by variables unobserved in 1 subset of the study data by using information that is observed in another subset of the study data (Stürmer et al. 2007). This calibration would result in an improved estimate of the IRR and associated CI. Obtaining a regression-calibrated, propensity score-adjusted estimate of the IRR and associated CI would involve creating an initial propensity score from the variables used for matching (5-year age category, sex, 2- or 3-digit zip code, calendar month of qualifying prescription, and number of unique prescription claims by therapeutic class during the prior 4 months); creating a second propensity score based on the additional variables available in Medicare Parts A, B, and D; and then applying regression calibration to the first propensity score to obtain the improved propensity score value. The resulting regression-calibrated propensity score would be used as the stratification factor in a stratified analysis to estimate the IRR (95% CI) for the comparison between Forteo users and nonusers.

Misclassification bias can result if patients are not categorized correctly with regard to exposure or outcome. In this study, there is the potential for misclassification of the exposure, specifically for the comparator cohort. This could happen if a comparator has a gap in enrollment, during which he or she receives a dispensing for Forteo. Although patients can lose Medicare Part D coverage, out-of-pocket payment for Forteo will most likely be uncommon due to the high cost

of the drug. There is also potential for misclassification of outcome if the matching algorithm is unsuccessful, and this would be more likely for registries that are unable to send the full SSN to external researchers; however, there is no expectation that the misclassification would be differential between the exposed and unexposed cohorts.

In general, there are few established risk factors for osteosarcoma. Age and sex will be balanced between groups by virtue of the matching. Race could be a confounding factor to the extent it is unknown and turns out to be unbalanced in the present design. However, according to the American Cancer Society (ACS [WWW]), African Americans have only a slightly higher incidence of osteosarcoma than Caucasians; consequently, confounding is not expected to be appreciable. Paget's disease of the bone is a potential confounder. It is not recommended that patients with a history of Paget's disease be treated with Forteo; it is expected that some representation of Paget's disease of the bone will be present only in the comparator population. It is important to note that estimates of prevalence in the US for this rare condition are less than 4% (Cooper et al. 2006); therefore, it should not result in appreciable confounding. It is also acknowledged that history of radiation therapy may differ between study cohorts; however, the data are insufficient to capture this information (e.g., a 4- to 6-month look-back period or even longer is not sufficient to measure all prior radiation therapy). Related cancer outcomes among patients treated with radiation therapy can take as long as 10 years or more for solid tumors to develop. Leukemia, the cancer with the shortest expected latency post-radiation exposure, can take at least 5 to 7 years to develop (Hall 2000). Research is mixed on other risk factors, and they are not expected to result in appreciable confounding.

3.6. Management and Reporting of Adverse Events

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

3.7. Product Complaints

Not applicable.

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Attachment 1. Observational Research Protocol B3D-MC-GHBX Addendum 2.2(a) Summary: Assessing the Incidence of Osteosarcoma Among Teriparatide Users Using Medicare Part D and State Cancer Registry Data

Observational Research Protocol B3D-MC-GHBX Addendum 2.2 (Assessing the Incidence of Osteosarcoma Among Teriparatide Users Using Medicare Part D and State Cancer Registry Data) has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Medicare's trusted independent third party for data linkage has changed from Buccaneer to General Dynamics Information Technology (GDIT). Mention of Buccaneer has been revised to GDIT throughout the protocol.
- Added additional description of data linkage (Section 3.3.2.4) and data security (Section 3.5.2) and appropriate references.
- Added a List of Abbreviations
- Minor typographical and grammatical revisions and clarifications not affecting content made throughout the document.