1. Observational Research Protocol B3D-MC-GHBX Addendum 2.3(b)

Observational Study Assessing Incidence of Osteosarcoma Among Forteo (teriparatide) Users by Linking State Cancer Registry Data to Large National Pharmacy Database Data

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List of Abbreviations

Term	Definition
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
HIPAA	Health Insurance Portability and Accountability Act
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 revision
IMS	IMS Health
IRR	Incidence rate ratio
LRx	IMS longitudinal prescription database
MSA	Metropolitan Statistical Area
NDC	National Drug Code
US	United States

3. Observational Research Protocol

3.1. Rationale

Forteo (teriparatide) was initially approved in 2002 in the United States (US) 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.

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 (Vahle et al. 2002; Forteo 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).

Osteosarcoma has rarely been reported in people who have received treatment with Forteo. It is not known if patients who are treated with Forteo have a higher risk of osteosarcoma; however, there have been spontaneous reports of osteosarcoma in Forteo-treated patients.

In 2009, a prospective US Forteo Patient Registry study addendum (Study GHBX[2]), was added as a component of the Forteo Post-Approval Osteosarcoma Surveillance Study (GHBX). This study addendum included a prospective voluntary registry of patients treated with Forteo to complement the US and European retrospective components of the GHBX study. The Forteo Patient Registry is a voluntary prospective cohort study with a 1-time registration of consenting adult patients (aged ≥18 years) living in the US who have received treatment with Forteo. Data from the registered patients are linked to participating state cancer registry data to ascertain any new confirmed cases of osteosarcoma. 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 continue at least through 2024 to meet this objective.

The 2 retrospective components of the GHBX studies include a US case finding study as well as a case finding study in the European Union. The US case finding study is ongoing. The European component of the GHBX surveillance studies was a 10-year safety surveillance study to evaluate a potential association between Forteo and adult osteosarcoma in humans. The study

included 5 Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) with national registries and used a case-series design to identify incident cases of osteosarcoma from participating cancer registries. This study completed in 2014 and found that none of the patients diagnosed with osteosarcoma in the study had prior Forteo exposure.

This database study will add to the scientific information generated to date by using a commercial pharmacy claims database to identify Forteo-treated patients and linking with data from participating state cancer registries. This database study analyzing outpatient pharmacy claims will be conducted in parallel with a second database study analyzing Medicare data. Analysis of each of these data sources will be conducted independently using harmonized protocols and customized statistical analysis plans based on the unique features of each data source. It is expected that the 2 aforementioned data sources will serve as a more efficient approach (versus the existing model involving voluntary patient recruitment) in identifying patients exposed to Forteo, and for subsequent linkage to the US cancer registries. As a result, we anticipate achieving our stated objective (estimating the incidence of osteosarcoma among Forteo users) sooner than the currently estimated Forteo Patient Registry 2024 timeframe.

Claims databases provide longitudinal data capture, which is useful in assessing rare events such as osteosarcoma, given the need for a large population, and allows for more precision and increased accuracy to assess this potential risk (Schneeweiss and Avorn 2005). 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 Forteo (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).

At least annually, an existing advisory board provides a comprehensive review of GHBX study data, spontaneous reports, and any relevant information in the published literature on Forteo treatment and osteosarcoma in humans, in order to advise whether there is a possible signal of increased risk and to recommend additional follow-up activities. The progress and results of the database linkage studies will be included in the advisory board review.

Following assessment of the findings from the linkage and the overall progress of the GHBX surveillance program in 2016, Lilly will consult with the regulators, where appropriate, to decide whether the strength of the evidence is sufficient or whether a further linkage is required.

3.2. Objectives

3.2.1. Primary Objective(s)

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).

3.2.2. Secondary Objective(s)

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

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

3.2.2.1. Optional Secondary Objective

To assess the similarity of the Forteo 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

3.3. Research Design

This cohort study will estimate the incidence rate and IRR for osteosarcoma among adult patients aged ≥18 years treated with Forteo compared to an untreated population. Drug exposure data will be obtained from dispensed pharmacy claims and osteosarcoma diagnosis information will be obtained from state cancer registry files. Study cohorts created in the commercial claims database will be linked to state cancer registry data to assess whether or not they have been diagnosed with osteosarcoma using predefined oncology codes.

3.3.1. Study Type

This is an observational database study using a matched cohort design. The study cohorts will include patients aged ≥18 years with a pharmacy-dispensed prescription of Forteo compared to 2 unexposed cohorts. The first unexposed cohort will include any patients not treated with Forteo. The second will include any patients treated with osteoporosis medications other than Forteo. Each Forteo user will be matched to a target of 2 patients from the unexposed osteoporosis cohort and 4 patients from the unexposed general population cohort on demographic variables, payer type, time of entry into the cohort (month and year), and a count of therapeutic classes dispensed.

This study will link the commercial pharmacy claims database (IMS longitudinal prescription [LRx] database) containing drug exposure information to state cancer registry databases containing osteosarcoma diagnosis information. In addition, an optional sensitivity analysis has been planned which links commercial medical claims database (IMS PharMetrics database) to evaluate baseline patient characteristics.

3.3.2. Data Sources

IMS Longitudinal Prescription (LRx) Data

The IMS Health (IMS) longitudinal prescription database (LRx) 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 captures prescriptions purchased through all methods of payment (for example, cash, Medicaid, third party). Currently, the database contains data for over 220 million unique de-identified patients and 1 million physicians. Data are consistently robust across all regions of the country, ranging from 57% coverage in the Southwest to 70% to 80% in the Mid-Atlantic region. The LRx represents >85% of all US retail prescriptions and 40% to 75% of US specialty and mail-order prescriptions (depending on therapeutic area). The IMS documents the saturation of pharmacies in LRx at the state and the Metropolitan Statistical Area (MSA) level; these internal IMS data can be used to estimate data completeness. The LRx data are available from 2005.

The database includes de-identified patient-level longitudinal data such as age, sex, zip codes, dispensed drug (through National Drug Code [NDC]), molecule, form, strength, quantity, and days' supply. All data are Health Insurance Portability and Accountability Act (HIPAA) compliant to protect patient privacy.

There are limitations to using pharmacy claims data for research purposes. Claims data are generated primarily for reimbursement purposes and not research. One such limitation is potential misclassification given that exposure is identified based on a claim for a dispensed prescription without 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. In addition, LRx is an open source claims database with data contributed by pharmacies, not health plans. As such, the completeness of data capture is contingent upon the consistency of data contributions from pharmacies.

The patient counts for Forteo from LRx are as follows:

- IMS Longitudinal Prescription (LRx) Data (January 2005 to January 2016): 477,140 patients, with approximately 23,000 patients with a prescription filled in 2015.

State Cancer Registry Databases

State cancer registry databases will be used to identify osteosarcoma cases diagnosed in the US during the years of observation. The variables of interest include demographic variables for matching and osteosarcoma diagnosis codes (See Table 1 in Attachment 1), month and year of diagnoses, and other clinical and pathological information. (See Section 3.5.2 for additional variables needed for linkage prior to analysis.) All US state cancer registries will be contacted with the target to recruit at least 25 state registries for participation in linkages. Results from an initial feasibility survey sent to 41 state cancer registries suggest that at least 60% are willing and able to participate in this effort. The recruitment and coordination with state registries will be handled within a parallel research study, under the facilitation of RTI Health Solutions.

Because of the lack of detailed, clinical diagnosis information in claims data, which use International Classification of Diseases diagnosis codes (ICD-9 and ICD-10), state cancer registries are deemed the appropriate source for osteosarcoma diagnosis information using International Classification of Diseases for Oncology, Third revision, (ICD-O-3) codes. State cancer registry data include information on cancer histology, stage at diagnosis, tumor grade, and date of diagnosis.

IMS PharMetrics Plus™ Database

The IMS PharMetrics Plus™ database is the largest claims database of integrated medical claims in the US. The aggregated IMS PharMetrics Plus database comprises adjudicated claims for more than 150 million unique enrollees across the US. Enrollees with both medical and pharmacy coverage represent 100 million lives. Data are available from 2006 onwards; with a typical 4-month lag due to claims adjudication. PharMetrics Plus includes a diverse representation of geography, employers, payers, providers, and therapy areas, with the majority of 3-digit zip codes in the US covered and reported. Patients in the PharMetrics Plus database are similar to the national, commercially insured population in terms of age and sex for individuals aged 65 and under. Although there is representation of individuals aged 65+, this is an underrepresentation relative to the overall US population. The 65 and older population will be assessed in a parallel study using Medicare claims.

PharMetrics Plus contains:

- Inpatient and outpatient diagnoses (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes; International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM] codes).
- Inpatient and outpatient procedures (Current Procedural Terminology, 4th Edition, Healthcare Common Procedure Coding System, and ICD-9-CM codes),other data elements including dates of service, demographic variables (for example, age, sex, and geographic region), and start and stop dates of health plan enrollment.

Data contributions are subjected to a series of quality checks to ensure a standardized format and to minimize error rates. All data are HIPAA compliant to protect patient privacy. PharMetrics Plus data used for this study will be limited to medical claims to assess baseline patient characteristics for a sensitivity analysis.

The linkage rate between the LRx database and PharMetrics Plus for this patient population is expected to be very low due to the age distribution of Forteo users and the underrepresentation of the 65 and older patient population. In addition, PharMetrics Plus data are available from 2006 forward. Initial estimates suggest 4% of Forteo users in LRx can be linked to enrollees with both medical and pharmacy coverage in PharMetrics Plus. However, enrollees with medical coverage, regardless of pharmacy coverage, will be eligible for linkage. This data source has been included as an optional sensitivity analysis.

3.3.3. Study Populations

Patient eligibility for inclusion in the study cohorts

Forteo-treated Patients:

- This group includes patients with at least 1 prescription for Forteo.

Matched Comparators:

- General population: This group includes patients with a dispensed prescription for any other medication, other than Forteo.
- Osteoporosis population: This group includes patients with a dispensed prescription, other than Forteo, for treatment of osteoporosis.

3.3.3.1. Forteo-Treated Patients

Patients treated with Forteo will be identified in the pharmacy claims database using dispensed prescriptions of Forteo identified by NDCs (See Table 2 in Attachment 1). This design improves the accuracy of drug exposure information by eliminating recall bias. One or more dispensed prescriptions of Forteo during the study period will qualify patients as Forteo-exposed. This study design will include both prevalent and new users. 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. Given the limited use of Forteo, this would be expected to rarely occur.

3.3.3.2. Matched Comparators

Forteo-treated patients will be compared to 2 matched comparator cohorts. The general population control will be included in the main analysis and the osteoporosis population will be included as a sensitivity analysis. The 2 comparator cohorts will be defined as follows:

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

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

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

The comparator cohorts will not have a Forteo prescription filled during the time they contribute as unexposed to Forteo. This group will be matched at baseline to Forteo-treated patients during

the same month as the index period on age group (5-year age categories), sex, geography (zip code), payer type (commercial plans, Medicare, Medicaid, other third parties, and self-pay/cash payments), and count of select unique dispensed prescriptions during the same month/year as Forteo grouped by therapeutic class. Patients will be grouped in 5-year age categories up to age 80, where all patients aged 80 and older will be combined.

At the time of the index date for a patient treated with Forteo, comparators will be eligible to serve as a matched comparator regardless of whether they initiate Forteo in the future.

3.3.4. Time Periods

This study will include linkages between commercial pharmacy claims data and state cancer registry data. A linkage is expected to occur late in 2016 or early in 2017 and will include data from 01 January 2005 through December 2 years prior to the linkage year.

An IRR will be estimated assessing osteosarcoma among patients treated with Forteo compared to a general population control group and an osteoporosis-treated control group. Possible differential mortality between the cohorts will be considered in a sensitivity IRR analysis.

The outcome, osteosarcoma, will be identified using 12 identified ICD-O-3 codes in state cancer registry data (See Table 1 in Attachment 1). These codes are currently used for the prospective US Forteo Patient Registry (GHBX [2]).

3.3.4.1. 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 sensitivity analysis of the IRR (95% CI) will be performed, allowing for a 6-month latency period following the index date, if there are enough available patients. For this sensitivity 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.

3.3.4.2. Linkage

The linkage will include a cohort of Forteo users and matched comparators with qualifying dispensed pharmacy claims from 01 January 2005 through December 2 years prior to the linkage year. A deterministic data linkage method will be used to match on demographic variables across the commercial claims study cohorts and cancer registry data. The state cancer registry data will extend through December 2 years prior to the linkage year to account for the 9- to 18-month lag in data collection and reporting among state cancer registries in the year of the linkage. The index date will be the date of the earliest identified dispensed prescription for Forteo and the comparators will have a dispensed prescription during the same calendar month and year.

For optional sensitivity analyses, an attempt will be made to link all study cohorts to the PharMetrics Plus database for ascertainment of medical claims representing baseline patient characteristics. The linkage rate between the LRx database and PharMetrics Plus for this patient population is expected to be very low due to the age distribution of Forteo users and the underrepresentation of the 65 and older patient population.

Analysis will be conducted looking at 2 time periods. The first time period will include all exposure and outcome data from 01 January 2005 through December 2 years prior to the linkage year. This second time period will include a baseline look-back period of at least 3 months prior to the cohort entry date and will include the 6-month lag time. The baseline period will be used to identify descriptive characteristics used for matching for each cohort.

The risk detection window will be the period of time after the index date up until the linkage completion date. Person-time will be calculated for Forteo-treated population and comparator cohorts, and an IRR for the occurrence of osteosarcoma will be calculated to compare the 2 cohorts.

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

3.3.5. Variables (Including Exposures and Outcomes)

Table 1 presents the study variables and operational definitions.

Table 1. Variables and Definitions

Variable	Source	Definition
Cohort: Forteo-Exposed and Unexposed comparators	Commercial pharmacy claims	Patients treated with Forteo (Exposed): • Patients aged ≥18 years with dispensed prescription of Forteo during the cohort entry window (first observed will define the index date) (for National Drug Code [NDC] list see Table 2 in Attachment 1) Forteo 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 Forteo 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 Forteo during same month/year as the matched exposed
Baseline Characteristics:	Commercial pharmacy claims and state cancer registry files	Tables will be reported stratified for the Forteo-exposed and the comparator cohort. Baseline characteristics will include: 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 will be reported on a state or higher level (Census Division or Region level). Payer type • Commercial plans, Medicare, Medicaid, other third parties (for example, military), and self-pay/cash payments Dates • Month and year of cohort entry, dispensed prescription for both Forteo users and the matched cohort • Select 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 Forteo grouped by therapeutic class
Outcomes: Osteosarcoma diagnosis	State cancer registry	12 ICD-O-3 codes reported in Table 1 in Attachment 1

3.4. Plan of Analysis

This is an exact-matched cohort design to compare the incidence of osteosarcoma among a Forteo-exposed cohort to unexposed cohorts matched at baseline. Forteo-treated patients will be matched during the same month/year as the index period using age group (5-year age categories), sex, geography (zip code), payer type (Medicare, Medicaid, commercial plans, other third

parties, and self-pay/cash payments), and count of unique dispensed prescriptions grouped by therapeutic class to the unexposed cohort during the same month/year.

Matching criteria may be adjusted if the matching ratio cannot be achieved. If matching cannot be achieved for a particular matching variable, that variable will be dropped from the matching process and controlled for in the IRR analysis (if deemed necessary).

Baseline characteristics will be measured during the look-back period and will involve prescription use other than Forteo. Quantifying the number of unique prescriptions grouped by therapeutic class during the baseline period will be used as a proxy for measuring overall health status and the presence of other chronic comorbidities.

Evaluation of the standardized mean difference between the samples' characteristics postmatching (target of <10% for good balance) will be employed. If matching was determined based on these criteria to not be well-balanced, then a logistic regression analysis could be conducted to further adjust for potential bias of characteristics and provide an estimated proportion of patients that develop osteosarcoma.

Baseline characteristics will be reported in total and stratified by reporting age categories. The number and percent of patients along with descriptive statistics (mean, standard deviation, median, 25th and 75th percentiles) will be reported for continuous data. Categorical variables (for example, payer type) will report the number and percent of patients.

Matched pairs will be statistically compared between the Forteo-exposed and the comparator cohorts pre- and postmatching. Pearson's chi-square tests, using Yate's correction for 2x2 tables, will be conducted for categorical variables and Welch Two Sample 2-sided t-tests for differences in means, assuming unequal variances. Statistical analyses will be conducted using SAS® and/or the Comprehensive R Network® using a statistical significance level of 0.05. Counts of less than 5 will be reported as "N<5" within study results.

Incidence will be estimated in the Forteo-exposed cohort as well as in the unexposed/comparator cohorts. An IRR and 95% CI will be estimated to compare the incidence of osteosarcoma among Forteo-exposed with the incidence of osteosarcoma in the matched comparator cohorts. If after the linkage there is a match, cases will be described.

Data-driven sensitivity analyses are planned. The need for data-driven sensitivity analyses will be driven by the number of identified osteosarcoma cases (for example, 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 characteristics). 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.

3.4.1. Methods

Incidence rate and IRR for osteosarcoma will be estimated among Forteo users versus matched comparator cohorts. 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. The following describe components of the IRR:

1) Incidence of osteosarcoma among the Forteo cohort will be estimated as the number of Forteo-exposed with a diagnosis of osteosarcoma during the study period divided by total person-years of follow-up where follow-up among Forteo-exposed is adjusted for mortality.
2) Incidence of osteosarcoma among the comparator cohorts will be estimated as the number of matched comparators with a diagnosis of osteosarcoma during the study period divided by the total person-years of follow-up among matched comparators where follow-up is adjusted for mortality.
3) An IRR will be estimated as the incidence of osteosarcoma among the Forteo cohort divided by incidence of osteosarcoma among the matched comparators adjusted for mortality.

Health outcomes vary by age, and subsequently the effect of the populations' age distributions will be taken into account as mortality generally increases with age. Since mortality files will not be used, mortality adjustments using Centers for Disease Control and Prevention published rates will be applied to estimate appropriate time to censor each patient's person-years. A sensitivity analysis that includes assumptions about differential mortality between the cohorts will be conducted. This will be done by assuming up to 10% higher mortality for the Forteo cohort and by calculating the percent differential mortality that would be necessary for the IRR to be statistically significantly elevated.

All US state cancer registries will be invited to participate; however, it is expected that not all state registries will participate. As a result, the participating state cancer registries will cover only a percentage of the US population aged ≥18 years during the observation period. This will be addressed in 2 ways: 1) calculation of incidence rates and IRRs using a cohort restricted to patients in states with participating registries; 2) using 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. This will involve a recalculation of 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 repeating the IRR analysis for comparison with the IRR analysis not using the coverage fraction.

The observation period, or the time at risk, will be defined as the time postentry into the study cohort. Person-time will be calculated from the start of the observation period until the end of the study period, the linkage date, which will then be mortality adjusted and multiplied by the coverage fraction based on the participating registries. For patients with an osteosarcoma diagnosis, the observation period will begin the day after the index date and will end at the date of osteosarcoma diagnosis rather than the linkage date.

Cohorts will be selected prior to linking to registry data. If a Forteo-exposed patient is identified as having a registry identified diagnosis of osteosarcoma prior to the index date, this patient as well as their matched comparators will be removed from the study. If a Forteo-matched comparator is identified as having a registry identified diagnosis of osteosarcoma prior to the

index date, the comparator alone will be dropped from the analysis and a substitute comparator will be selected.

Descriptive characteristics will be reported for both the Forteo-exposed and comparator cohorts (See Table 1). Among the Forteo cohort, drug utilization patterns will be reported including the number of dispensed prescriptions, mean days of supply, dosage form and strength. Baseline characteristics will be reported in total and stratified by reporting age categories. The number and percent of patients along with descriptive statistics (mean, standard deviation, median, 25th and 75th percentiles) will be reported for continuous data. Categorical variables (for example, payer type) will report the number and percent of patients. Baseline characteristics reported in Table 1 will be summarized for both cohorts.

Two time periods are included with variable look-back windows for assessment of osteosarcoma diagnosis postcohort entry using a data-driven approach. Additionally, 2 comparator cohorts will be established and analyzed. The analysis will be conducted using the following scenarios:

- Primary time period: Using the full 10 years of data available for Forteo exposure and the matched cohort. This will be January 2005 through December 2 years prior to the linkage. State cancer registry data will be linked to all data during this window. This approach assesses all available data and provides a more comprehensive analysis.
- Secondary time period: Using a data-driven approach, a sensitivity analysis will be conducted. This sensitivity analysis will include a variable look-back window where the exposed cohort will only be included when at least a 3-month look-back period is available prior to the index date to describe baseline characteristics.

Findings from these analyses will be described and compared.

3.4.2. Bias Adjustment

This study will use commercial pharmacy claims data to assign exposure status and will use state cancer registry data to identify a diagnosis of osteosarcoma. Pharmacy claims data are not captured for research purposes, but for billing. State cancer registries, however, collect data in part for public health purposes including monitoring of cancer trends. An exact matched cohort design will be used to minimize bias and address confounding.

A confounding factor is an independent risk factor for osteosarcoma that is associated with Forteo exposure. There are, however, few established risk factors for osteosarcoma. Age and sex will be balanced between groups by virtue of the matching. 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, so we would expect some representation of Paget's disease of the bone only in the comparator population. It is important to note that in the US estimates for the prevalence of this rare outcome are less than 4% (Cooper et al. 2006); therefore, it should not result in appreciable confounding. It is also acknowledged that history of radiation may differ between study cohorts; however, claims data are insufficient to capture this information (for example, a 4- to 6-month look-back period or even longer is not sufficient to measure 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 postradiation exposure, can take at least 5 to 7 years to develop (Hall 2000). Research is mixed on other risk factors, and we do not expect them to result 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'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."

Since comparators and Forteo-exposed will be matched on geography, there is no reason to believe that either cohort will have a disproportionate probability of aligning to nonparticipating states.

3.4.3. Scope of Inference

The findings from this study should be considered as complementary to others with proper consideration given to various differences in geographic distribution, payer types, comparator population selection, and matching techniques. Currently the IMS database contains data for over 220 million unique de-identified patients and 1 million physicians. Data are consistently robust across all regions of the country, ranging from 57% coverage in the Southwest to 70% to 80% in the Mid-Atlantic region. The LRx represents >85% of all US retail prescriptions and 40% to 75% of US specialty and mail-order prescriptions (depending on therapeutic area). IMS documents the saturation of pharmacies in LRx at the state and the MSA level. These internal IMS data can be used to estimate data completeness. Of note, there is potential overlap with the parallel study (Study GHBX Addendum 2.2) being conducted covering the 65-and-older Medicare population.

Limitations of the pharmacy data include a potential for Forteo drug exposure misclassification: 1) for patients who received Forteo from pharmacies outside of the coverage area or from pharmacies with inconsistent data contributions to LRx (that is, underreporting) and, 2) assuming dispensed Forteo prescriptions were truly administered to patients (that is, over-reporting or overestimation).

3.4.4. Subgroups

There are no planned subgroup analyses. The focus of this study is to evaluate patients exposed to Forteo versus comparators unexposed to Forteo.

3.4.5. Multiplicity

Multiplicity is not a concern given incidence rates and IRRs will be estimated at planned linkages.

The study described in this protocol and a parallel postauthorization database study are assessing the risk of osteosarcoma independently and are using 2 independent data sources. Given the size

and scale of both data sources it is likely there will be overlap of patients in the commercial claims database and the Medicare database among patients aged 65 and older. This is not a concern as each study will assess their data and interpret the findings independently. After completion of the analysis, the findings from each study will be qualitatively compared for the population aged 65 years and older.

3.4.6. Missing Data

Patients with missing information in the pharmacy claims on variables used for matching will be dropped during the cohort selection process, with the possible exception of sex. If matching cannot be achieved for a particular matching variable, that variable will be dropped from the matching process and controlled for in the IRR analysis (if deemed necessary). If fewer than 5% of the Forteo-exposed cohort are described as having an unknown sex, these patients will be dropped prior to matching to limit bias introduced from potentially mismatching patients on a risk factor (males have higher incidence and females may develop osteosarcoma at younger ages than do males [ACS 2014]). If ≥5% of Forteo-exposed has an unknown sex, these patients will be retained and matched to comparators with an unknown sex.

Patients will be eliminated or reported as unknown from any descriptive reporting where required data fields are missing, but will remain in the primary analysis. The Forteo-exposed cohort with missing or invalid days' supply and quantity dispensed values on 1 or more Forteo-dispensed prescription claims between index and the earlier of end of study period or date on which osteosarcoma is detected will not be included in assessment of cumulative Forteo exposure.

3.4.7. Robustness

The currently proposed approach using a large commercial pharmacy claims database will improve our ability to assess the incidence of the rare condition of osteosarcoma. This approach, which adds comparator arms to provide a background rate, is a viable approach to help place the rate for the Forteo user group into context.

3.4.8. Sample Size and Power Considerations

It is anticipated that there will be approximately 477,140 total unique patients treated with Forteo. An attrition table will be reported for each cohort comparison and time period showing the number of patients remaining after each inclusion criterion.

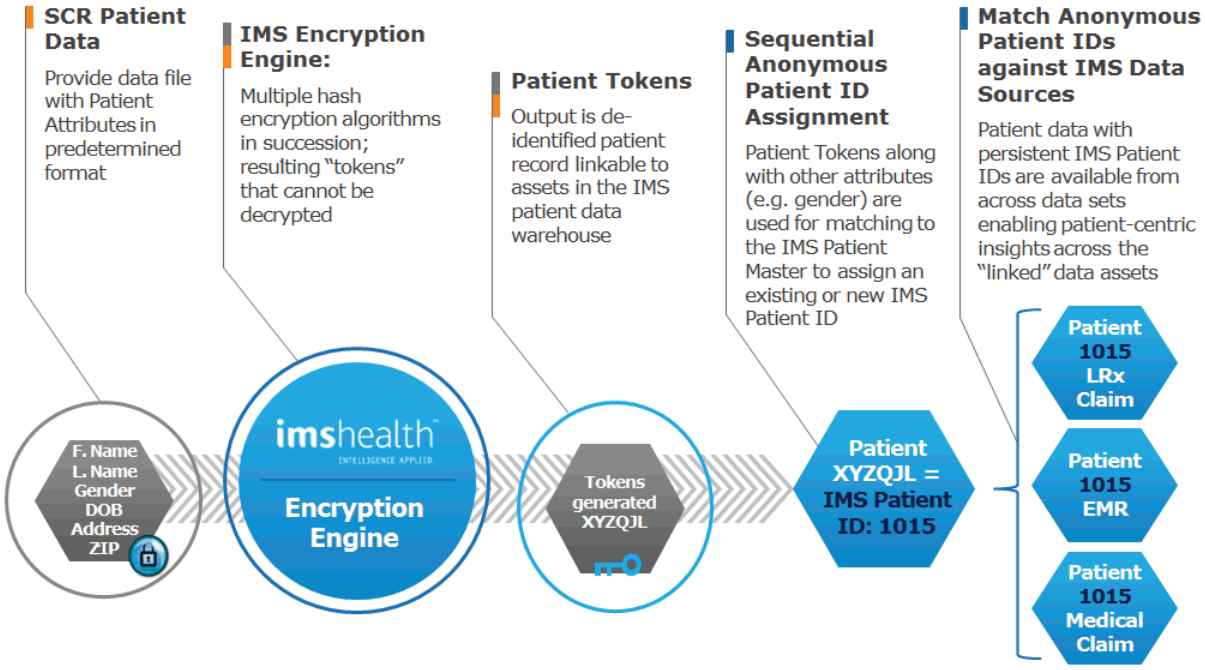
3.5. Other Relevant Information

3.5.1. Database Linkage Process

All state cancer registries in the US will be invited to participate in the study, which will involve preparation of a dataset of patients diagnosed with osteosarcoma during the study period for de-identification and subsequent use in the specified analyses.

It is anticipated that not all cancer registries will be able or willing to participate due to lack of resources and/or regulations that prohibit them from sending identifiable data to third parties.

The exposure data identifying patients treated with Forteo and matched unexposed comparators will be selected from IMS LRx data. This study will use the standard IMS de-identification and linkage process. This process is certified as HIPAA compliant and is depicted in Figure 1 below.



Abbreviations: DOB = date of birth; EMR = electronic medical record; ID = identification; LRx = IMS longitudinal prescription database; SCR = state cancer registry.

Figure 1. IMS de-identification and linkage process.

Database processing and transfer procedures are described in Section 3.5.2 below.

3.5.2. Database Processing and Transfer

Participating state cancer registries will transfer data using 1 of the 2 options described and depicted below. The following steps describe the cancer registry data transfer process:

Step 1

Prepare a file with a minimum the following variables:

Variables utilized for linkage:

- Patient First and Last Name
- Birth Date
- Patient Gender
- Patient Address 1 (Patient's primary correspondence address 1)
- Patient Zip Code (Patient's primary correspondence zip code)

Variables utilized for study analyses:

- Osteosarcoma diagnosis codes (See Table 1 in Attachment 1)
- Month and year of osteosarcoma diagnosis
- Pathological confirmation for osteosarcoma

Registries will be asked to follow a standard process for preparing the linkage file, although files sent to the third party can be in different layouts as long as all data elements are represented and the format/layout agreed with the third party a priori.

Step 2

De-identify the file using IMS encryption engine using one of the following options:

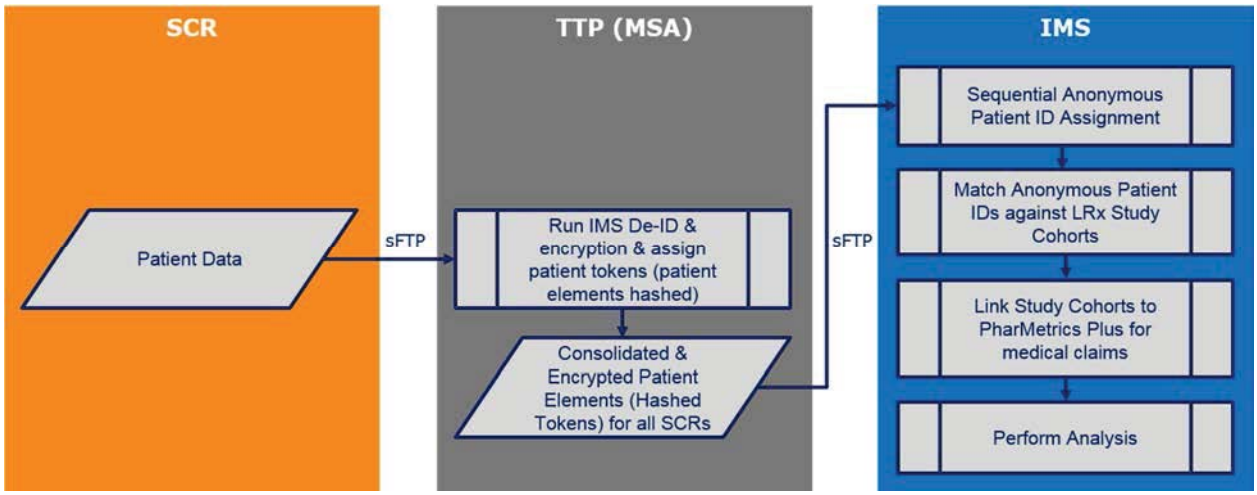
Option 1a: Prepare data files containing prespecified patient information for osteosarcoma patients and send resulting files to a trusted third party for de-identification of variables necessary for linkage.

Option 1b: Run the encryption engine locally at the cancer registry and transfer resulting encrypted patient token to the trusted third party.

Step 3

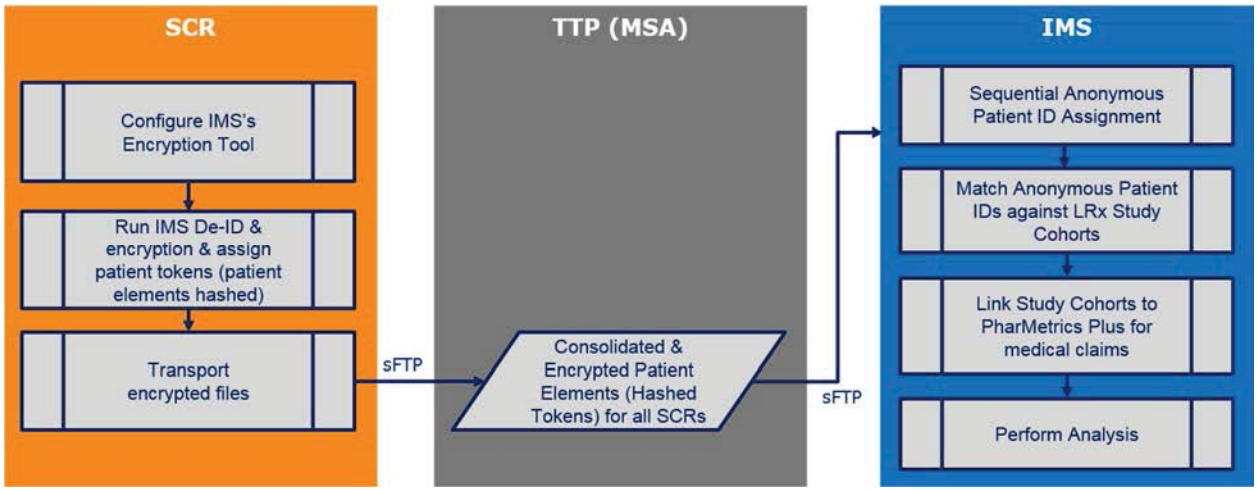
The trusted third party will send the encrypted tokens to the research team at IMS where they will be linked to encrypted study cohorts (Forteo-treated cohort and the 2 matched comparator cohorts) created using the LRx database.

Figure 2 and Figure 3 describe the steps for linkage for each option.



Abbreviations: ID = identification; LRx = IMS longitudinal prescription database; MSA = Metropolitan Statistical Area; SCR = state cancer registry; sFTP = secure file transfer protocol; TTP = trusted third party.

Figure 2. Option 1a. State cancer registry data transmission/linkage: encryption at the trusted third party.



Abbreviations: LRx = IMS longitudinal prescription database; MSA = Metropolitan Statistical Area; SCR = state cancer registry; sFTP = secure file transfer protocol; TTP = trusted third party.

Figure 3. Option 1b. State cancer registry data transmission/linkage: encryption at the state cancer registry.

3.5.3. Data Management

The IMS investigators are responsible for the integrity of the data reported to Lilly. Datasets and analytic programs will be stored according to IMS procedures with access restricted to study personnel. Data provided by the state cancer registries will be destroyed following data destruction procedures specified by the cancer registries and agreed to by IMS.

The IMS confidentiality agreements are signed by all employees and include data protection and strict prohibitions on re-identification attempts. All aspects of the study will be conducted within the framework of the IMS Quality Management System. A Quality Control plan for the study will be developed and executed. The IMS will document and retain a quality review of all final deliverables.

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.

4. References

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Attachment 1. Adult Patients Treated with Forteo by Age Group, National Drug Codes, and ICD-O-3

ICD-O-3 CODES

Table 1: Osteosarcoma ICD-O-3 diagnosis codes			
9180/3	Osteosarcoma NOS	9186/3	Central osteosarcoma
9181/3	Chondroblastic osteosarcoma	9187/3	Intraosseous well differentiated Osteosarcoma
9182/3	Fibroblastic osteosarcoma	9192/3	Parosteal osteosarcoma
9183/3	Telangiectatic osteosarcoma	9193/3	Periosteal osteosarcoma
9184/3	Osteosarcoma in Paget's disease of Bone	9194/3	High-grade surface osteosarcoma
9185/3	Small cell osteosarcoma	9195/3	Intracortical osteosarcoma

National Drug Codes

Table 2: Forteo 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

Attachment 2. Observational Research Protocol B3D-MC-GHBX Addendum 2.3(b) Summary: 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 (Observational Study Assessing Incidence of Osteosarcoma Among Forteo [teriparatide] Users by Linking State Cancer Registry Data to Large National Pharmacy Database Data) has been amended. The new protocol is indicated by amendment (b) 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:

- In Section 3.3.1, information was added and modified to better describe the cohorts used in Study GHBX Addendum 2.3b and the optional secondary analysis.
- In Sections 3.3.2 and 3.2.2.1, information was added regarding the source of medical claims information from IMS PharMetrics Plus and the optional secondary objective.
- In Section 3.3.4.2, additional details on the linkages using the IMS PharMetrics Plus database were added.
- Figures 1 and 2 were updated to include the IMS PharMetrics Plus database.
- Administrative updates due to the addendum letter change were completed throughout the document.
- Minor editorial corrections and updates throughout that do not affect the content or procedures of the addendum.