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ORIGINAL ARTICLE

The Forteo Patient Registry linkage to multiple state cancer registries: study design and results from the first 8 years

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Abstract

Summary The Forteo Patient Registry (FPR) aims to estimate the incidence of osteosarcoma in US patients treated with teriparatide. Enrollment began in 2009 and will continue through 2019, with linkage planned through 2024. To date, no incident cases of osteosarcoma have been identified among patients registered in the FPR.

Introduction The Forteo Patient Registry (FPR) was established in 2009 to estimate the incidence of osteosarcoma in US patients treated with teriparatide. The objective of this paper is to describe study methods, challenges encountered, and progress to date.

Methods The FPR is a prospective US registry designed to link data from participants annually with state cancer registries. Patient enrollment is planned for 10 years (2009–2019) and annual linkage with US state cancer registries for 15 years (2010–2024). All US state cancer registries and DC were invited to participate. Patients are recruited using pre-enrollment materials included in teriparatide device packaging, kits, and brochures distributed by health-care providers; a toll-free number; and a study website. A linkage algorithm is used to match data from enrolled participants with cancer registry data.

Results For the eighth annual linkage in 2017, information necessary for linkage with 63,270 patients in the FPR was submitted to each of the 42 participating registries. These patients contributed approximately 242,782 person-years of follow-up. A total of 5268 adult osteosarcoma cases diagnosed since January 1, 2009, were available for linkage from participating state cancer registries. To date, no incident cases of osteosarcoma have been identified among patients registered in the FPR.

Conclusions Based on the estimated 242,782 person-years of observation as of the eighth annual linkage and projecting current enrollment rate to study end in 2024, it is anticipated that the completed study will be able to detect a fourfold increase in the risk of osteosarcoma if one exists.

Keywords Linkage · Osteosarcoma · Registry · Teriparatide · United States

Introduction

Osteoporosis is estimated to affect 10.2 million US individuals aged 50 years or older [1]. Teriparatide (Forteo; Eli Lilly and Company) is a recombinant human parathyroid hormone analog that stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. Recent research has shown teriparatide to significantly increase modeling-based, remodeling-based, and overflow modeling-based bone formation [2]. Teriparatide was first approved in November 2002 in the United States (US) and is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, and to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture. In July 2009, teriparatide was approved for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy (glucocorticoid-induced osteoporosis [GIO]) in both men and women. Teriparatide is administered daily by subcutaneous injection with a recommended duration of up to 2 years.

Results from safety analyses conducted in clinical trials suggest that teriparatide has an acceptable safety profile, with

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side effects including (but not limited to) pain, headache, nausea, dizziness, and depression [3]. However, in rat toxicology studies, teriparatide caused increases in bone mass and a dose-dependent increase in the incidence of osteosarcoma [4]. In subsequent animal studies, a no-effect dose of 5 μg/kg/day was identified in rats [5], and a long-term study found no bone tumors after treatment with this dose in cynomolgus monkeys, in which skeletal biology is similar to that in humans [6]. Differences in bone physiology between rodents and primates may partly explain the greater sensitivity of the rat skeleton to parathyroid hormone relative to the primate skeleton [4]. Moreover, administration of teriparatide for up to 2 years in rat studies spanned more than 80% of the normal life span and 25 to 30 cycles of bone turnover (in contrast with 1 to 3 cycles of bone turnover during the anticipated duration of treatment with teriparatide for osteoporosis in humans) [4].

Owing to the uncertainties in applying results from animal studies to humans, two large-scale safety studies were initiated in 2003 [7] and 2004 [8] to assess the risk of osteosarcoma in humans exposed to teriparatide [9]. As a condition for approval of teriparatide for a new GIO indication, the Food and Drug Administration (FDA) required the implementation of an additional study, a voluntary, prospective registry to estimate the incidence of osteosarcoma in patients receiving treatment with teriparatide [10]. The Forteo Patient Registry was established in 2009 as a prospective voluntary registry of patients treated with teriparatide to better understand its long-term safety.

The objective of the Forteo Patient Registry study is to estimate the incidence of osteosarcoma in patients who have received treatment with teriparatide. Because adult osteosarcoma is rare (2.6 cases per million persons per year [11]), the study requires a large number of teriparatide users from across the US and participation by a large percentage of US cancer registries. A prospective study design of teriparatide users linked with cancer registries was chosen because cancer registries offer comprehensive and accurate capture of tumor cases, including osteosarcomas. Cancer reporting is mandatory in all states of the US, and individual states determine how, if, and when data can be released to external researchers. Registries receive reports from physicians, treatment and radiation facilities, hospitals, and pathology laboratories and collect detailed clinical data, including tumor site and tumor stage at diagnosis. The aim of this paper is to describe overall study methods, challenges faced, and progress of the Forteo Patient Registry.

Methods

Registry overview

The Forteo Patient Registry was established in 2009 to estimate the incidence of osteosarcoma in patients who have received treatment with teriparatide. Patients aged 18 years and older who have used teriparatide at least once and reside in the US are eligible to enroll. Patients become aware of the registry from a variety of sources and can voluntarily elect to enroll, following simple pre-enrollment, consent, and enrollment processes. To protect patient privacy and minimize patient burden, only teriparatide treatment information that is necessary to confirm exposure to teriparatide and demographic information to enable subsequent linkage with cancer registries are collected. Annually, the information from all enrolled participants is linked with all participating cancer registries to ascertain any incident cases of osteosarcoma. Patient enrollment is planned for a total of 10 years (2009–2019), and linkage is planned for a total of 15 years (2010–2024).

A patient is considered exposed to teriparatide if they have self-reported use of the drug at least once. Patients are classified as new users if they initiated teriparatide less than 3 months from the date of registration, recent users if the teriparatide start date is 3 to 6 months prior to registration, and past users if they initiated more than 6 months prior to registration. An osteosarcoma case is defined as histologically confirmed osteosarcoma that produces osseous matrix and falls within one of the categories identified using International Classification of Diseases for Oncology, Third Edition (ICD-O-3). This study includes only incident osteosarcoma cases, which are defined as diagnosis of osteosarcoma after date of first starting teriparatide and after enrollment in the Forteo Patient Registry.

The study was approved by the RTI International (RTI) institutional review board (IRB) on June 11, 2009. Local IRBs affiliated with participating state cancer registries also approved the study when required.

Study size and power

The initial registry target was to observe 1.7 million patient-years of follow-up within the study population by the end of the study. This target was based on projected sales, anticipated number of patients that would enroll in the registry, and number of registries expected to participate and a goal to have sufficient power to observe a threefold increase in risk of osteosarcoma compared with the background rate at the time of study planning of 2.7 cases per million population per year (95% confidence interval, 2.4–3.0; age-adjusted to the 2000 US standard population) [12]. A threefold increase in risk would equate to an absolute risk increase of approximately one extra case per 185,000 patient-years observed.

Patient recruitment

The primary means of recruitment is pre-enrollment forms included in the teriparatide device packaging, starter kits, and brochures distributed by physicians or nurses. To educate physicians and key office staff about the registry and support

conversations with patients encouraging them to enroll, educational materials (i.e., a Highlighted Information for Prescribers document summarizing safety information and describing the registry, a Dear Health Care Professional letter, and a summary in the teriparatide US prescribing information) and communication materials (i.e., a conversation tool, introductory materials about the registry, and pre-enrollment forms) have been distributed to physicians known to have prescribed teriparatide. The method for recruitment is tracked based on codes embedded on each of the individual pre-enrollment forms. Patients also may enroll through a toll-free number or study-specific website (www.forteoregistry.org).

Patient enrollment

Patients express interest in the registry via a completed pre-enrollment form. Pre-enrollment information includes patient contact information and confirmation that they have received teriparatide (i.e., the month and year they started using Forteo). Eligible pre-enrolled patients are mailed a registration letter, registration form, informed consent form, and small monetary token of appreciation for their time in completing the forms. The registration letter and study forms were tested through an iterative cognitive interviewing process with representative patients and treating physicians to maximize patient acceptance and understanding. Patient registration is complete once completed forms are returned. Up to 10 reminder call attempts are made for patients who do not return their consent and registration forms within 3 weeks.

After registration, no further data are actively collected on teriparatide use or other clinical events. Patient information is subsequently included in the annual linkage with state cancer registries (see Fig. S-1 in the electronic supplementary material).

Cancer registry linkage

Cancer registry recruitment

In May 2009, registries in all 50 states and the District of Columbia were invited to participate in the Forteo Patient Registry. Of these, 42 expressed initial interest in participating. All necessary applications and agreements for study approval, including ethics and data use agreements, were submitted to individual state cancer registries that expressed interest. States were considered "linkage-ready" once all required approvals were obtained and a work agreement was established.

Linkage

RTI Health Solutions created and tested a standard linkage algorithm before implementation in the field [13]. Link Plus (v2.0), a probabilistic matching software program available from the Centers for Disease Control and Prevention (CDC), was used to develop the algorithm. The software was selected because it was designed specifically for linking with state cancer registry data, is easy to use, and is readily accessible. Link Plus utilizes probabilistic methods to assign a "weight" to possible matched pairs based on the number of variables that agree (match) between the two records. Specifically, a set of blocking variables was established (see Fig. S-2 in the electronic supplementary material), at least one of which had to exactly match between the two data sources. If there was an exact match on a blocking variable, additional matching variables were used to calculate maximum likelihood weights for the potential matching pair; clarifying variables assisted in helping to determine if a possible pair was a match. The weights were calculated based on the number of matching variables (i.e., the more matching variables, the higher the weight) and their uniqueness (i.e., less common values were given higher weights). We used a cutoff value of 1 to determine if a weight for a given pair indicated a potential match. Potential matches were subsequently reviewed manually according to pre-specified guidelines to determine the final match status. A match was counted as a reportable study outcome only if the date of osteosarcoma diagnosis occurred after the date of starting teriparatide and after enrollment in the study. This is considered an incident case.

Before field implementation, a test linkage was performed with three participating state cancer registries using the proposed standard algorithm, instructions, and guidelines [13]. Briefly, true cases of osteosarcoma with missing or intentionally miscoded data ($n = 161$) and true negative cases consisting of mock data ($n = 156$) were sent to the cancer registries. These cases were linked to the existing registry database to assess the accuracy of the linkage algorithm. A pair was considered a match if it exceeded the set cutoff value of 1 in Link Plus. The individual state cancer registries resolved any possible linkages using written guidelines that included manual review of similarities in key linkage variables. The overall test sensitivity was 97%, and the overall test specificity was 95%; approximately 96% of all cases matched, including both positive and negative matches. Cancer registries then were trained to use the algorithm via in-person and web-enabled training sessions. Registry staff were instructed on which variables to use as blocking, matching, and clarifying variables.

Annually, to complete the linkage, cumulative registration data, including name, date of birth, last four digits of social security number (to increase probability of response to this item on the registration form), and race and ethnicity from all eligible patients enrolled to date in the study, are sent to all participating state cancer registries via a secure file transfer protocol. State cancer registries then conduct the linkage locally with all incident osteosarcoma cases in adults aged

18 years and older diagnosed since January 1, 2009, in their state cancer registry database.

Cancer registry variables

If a match occurs during linkage, the following variables are requested from the cancer registry: date of diagnosis; age at diagnosis; histology (ICD-O code); state of residence at diagnosis; site and laterality, where applicable; stage; and grade.

Adverse event reporting

Although adverse events (AEs) and product complaints (PCs) are not solicited in the Forteo Patient Registry, any spontaneous reports of Forteo AEs and/or PCs from patients by mail or telephone during the conduct of the study are reported to the teriparatide manufacturer as spontaneous events. Any matches that occur during the course of linkage with the cancer registries are considered serious AEs and are also reported to the teriparatide manufacturer.

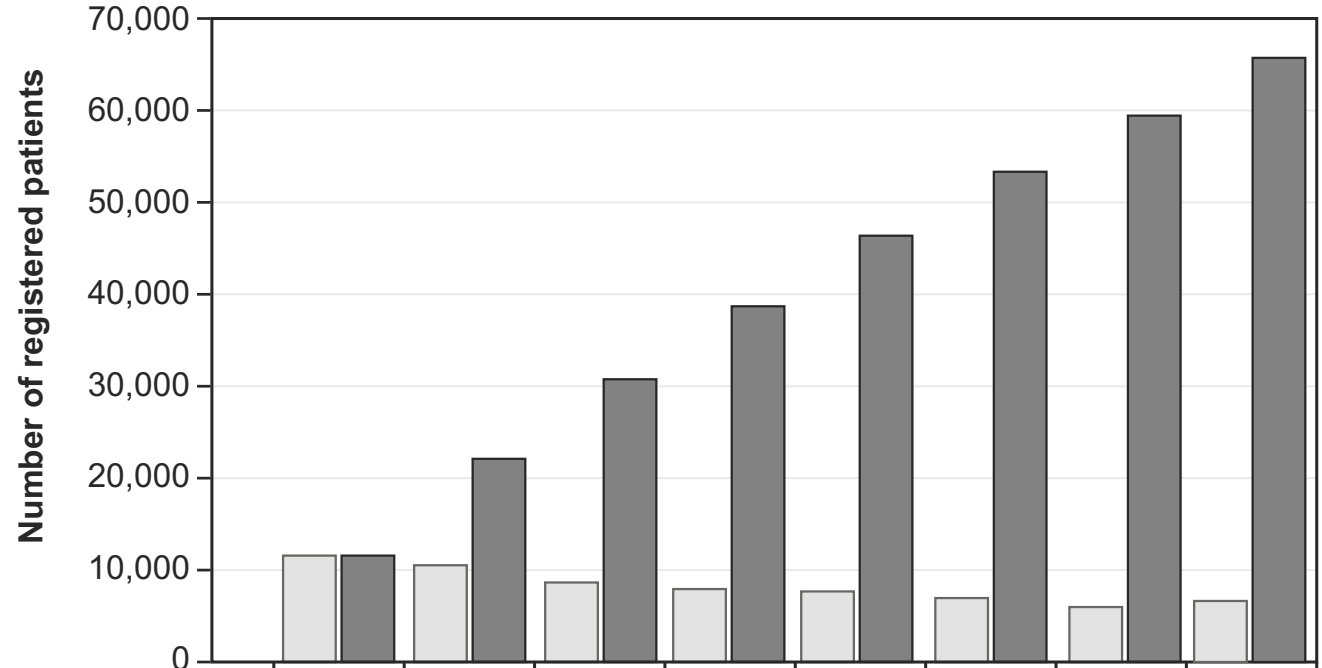
Results

To date, eight linkages have been conducted. As of September 30, 2017, 64,975 patients have been registered (Fig. 1).

Patient characteristics: demographics and teriparatide experience

Patients who completed registration in the Forteo Patient Registry were predominantly non-Hispanic white females aged 65 years or older (Table 1). The overall sex distribution of patients in the registry (89% female, 11% male) is similar to the sex distribution of the general Forteo user population in the US (91% female, 9% male) [14]. Figure 2 displays the distribution of age category stratified by sex of patients enrolled in the registry. The distribution of age by sex for those enrolled in the Forteo Patient Registry is generally similar to that of Forteo users in the general population [14]. At least one patient from each state is included in the Forteo Patient Registry, and the distribution of patients is consistent with the size of the population in each state (Fig. 3).

"New use" of teriparatide was defined as a teriparatide start date less than 3 months from the date of registration. Overall,



	Dec 2010	Dec 2011	Dec 2012	Dec 2013	Dec 2014	Dec 2015	Dec 2016	Dec 2017[a]
New patients registered by year	11,577	10,528	8,653	7,937	7,678	6,958	6,437	6,943
Cumulative	11,577	22,105	30,758	38,695	46,373	53,331	59,768	66,711

Fig. 1 Yearly and cumulative number of new patients registered from 2010 through the fourth quarter of 2017. [a]Projected number of patients for calendar year 2017 based on actuals through September 30, 2017

Table 1 Characteristics of patients included in the Forteo Patient Registry linkage file ($n = 63,270$) as of 2017

Characteristic	Category	Number (%)
Age	Mean, 69 years (range, 18–104 years)	
Sex	Male	7083 (11.2)
	Female	56,176 (88.8)
	Unknown	11 (< 0.1)
Race	White	59,464 (94.0)
	Black	834 (1.3)
	Asian	1328 (2.1)
	American Indian or Alaska Native	195 (0.3)
	Native Hawaiian	14 (< 0.1)
	Other Pacific Islander	30 (< 0.1)
	Other	1059 (1.7)
	Unknown	346 (0.5)
Ethnicity	Non-Hispanic	59,599 (94.2)
	Hispanic	2646 (4.2)
	Unknown	1025 (1.6)

70% of registrants were "new users" at the time of enrollment, 18% of registered patients started teriparatide 3–6 months prior to enrollment, and 12% of registered patients started Forteo more than 6 months before enrollment.

Distribution of registered patients by method of pre-enrollment

Table 2 shows the cumulative number of patients registered through September 30, 2017, by mode of pre-enrollment based on the type of forms received to date. Forteo packaging was the main source of pre-enrollment forms among registered patients, with other promotional materials the second most frequent source.

Cancer registry recruitment

Of the 42 registries (out of 51 invited) that initially expressed interest in participating, 27 completed all necessary approvals in time to participate in the first annual linkage in 2010. Table S-1 in the electronic supplementary material presents the participation among registries in the annual linkages from 2010 to 2017. The 42nd registry, which was initially unable to participate, joined during the seventh linkage in 2016 (Table S-1). The 42 registries currently participating cover 92% of the US population aged 18 and older, with 93% coverage of osteosarcoma cases in patients aged 18 years and older.

Cancer registry linkage

For the eighth annual linkage, a total of 63,270 patients in the Forteo Patient Registry were linked with a total of 5268 adult osteosarcoma cases. These cases were diagnosed since January 1, 2009, through the latest available date in the research database of each of the 42 individual state cancer registries at the time they performed the 2017 linkage. To date, no incident cases of osteosarcoma have been identified among the patients registered in the Forteo Patient Registry.

Due to the average lag time of 9 to 18 months between date of diagnosis and the date that complete data are available for cases in the cancer registry database, not all cases for more recent diagnosis years are available. On average, registries reported being mostly complete for diagnosis years 2009–2014, almost complete for diagnosis year 2015, partially complete for diagnosis year 2016, and only 5% complete for diagnosis year 2017, as reflected in the actual number of cases reported by year, shown in Table 3.

Progress toward target study size and power

An estimated 242,782 person-years of observation were available as of the 2017 annual linkage ($n = 63,270$). Projecting the current enrollment rate to the planned end of the study in 2024, it is anticipated that the completed study will be able to detect a fourfold increase in the risk of osteosarcoma if one exists. This would translate into approximately one additional case per 123,000 person-years of observation.

Discussion

After 8 years of follow-up, we found no incident osteosarcoma cases among teriparatide users registered in the study. Although one patient who enrolled in the Forteo Patient Registry matched to an osteosarcoma case from a participating state cancer registry during the seventh linkage, details on this case revealed this was not an incident osteosarcoma case. Prior to enrolling in the Forteo Patient Registry, the patient had been diagnosed with osteosarcoma after being treated with Forteo. Because this case did not qualify as incident or newly diagnosed after study enrollment, it did not qualify as a reportable study outcome. This case was reported to the FDA by the teriparatide manufacturer, as required.

Our ability to draw conclusions about the incidence of osteosarcoma in teriparatide patients in this interim report is limited, as the study has not completed. The initial registry target was to observe 1.7 million patient-years of observation within the study population. Based on the estimated 242,782 person-years of observation as of the 2017 annual linkage and projecting the current enrollment rate to the end of the study in 2024, it is anticipated that the completed study will be able to detect a fourfold increase in the risk of osteosarcoma if one exists. Among adults older than 24 years, an estimated 15 to 35% of tumors were classified as having distant metastases upon diagnosis [15].

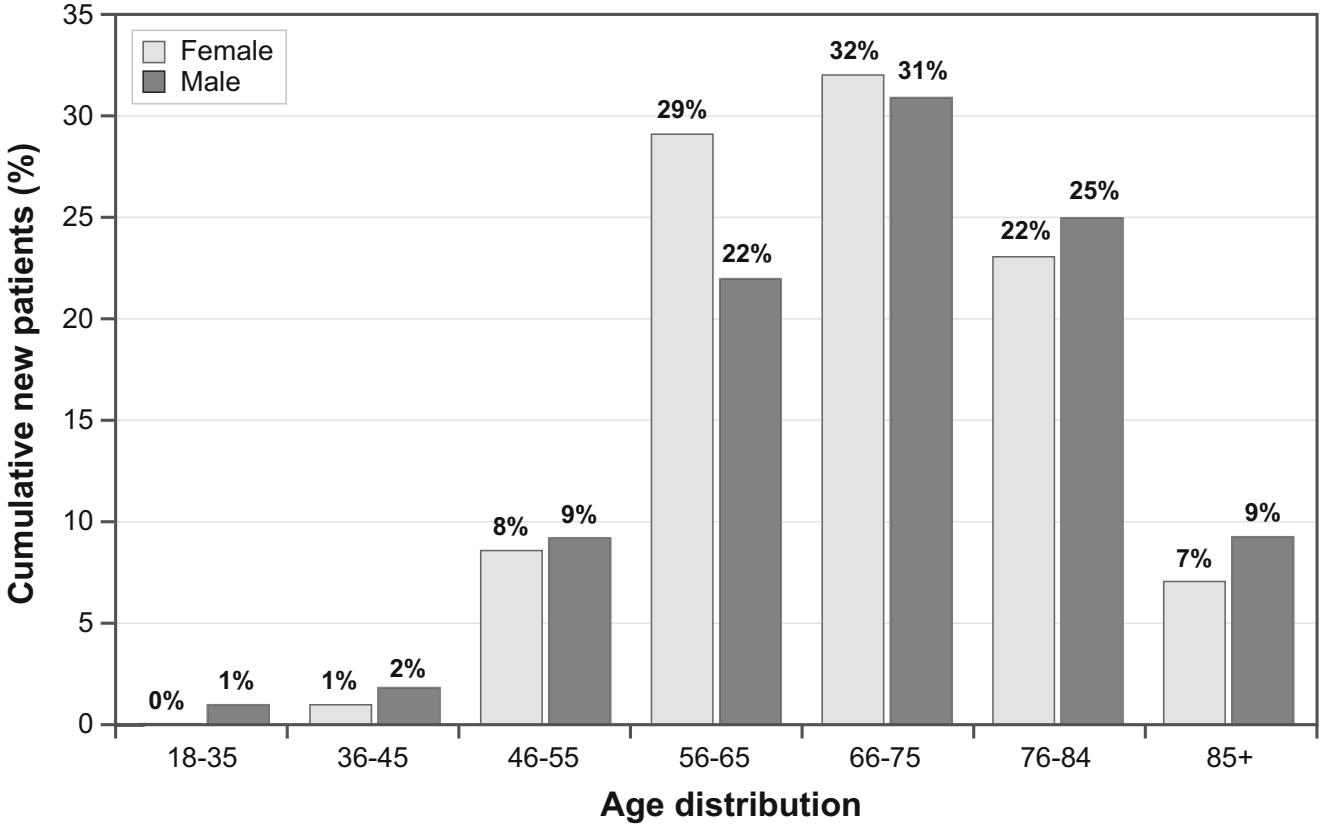


Fig. 2 **Age distribution of registered patients stratified by sex**, Note: $N = 64{,}729$. A total of 246 patients were missing data for age or sex and were excluded from counts in this figure

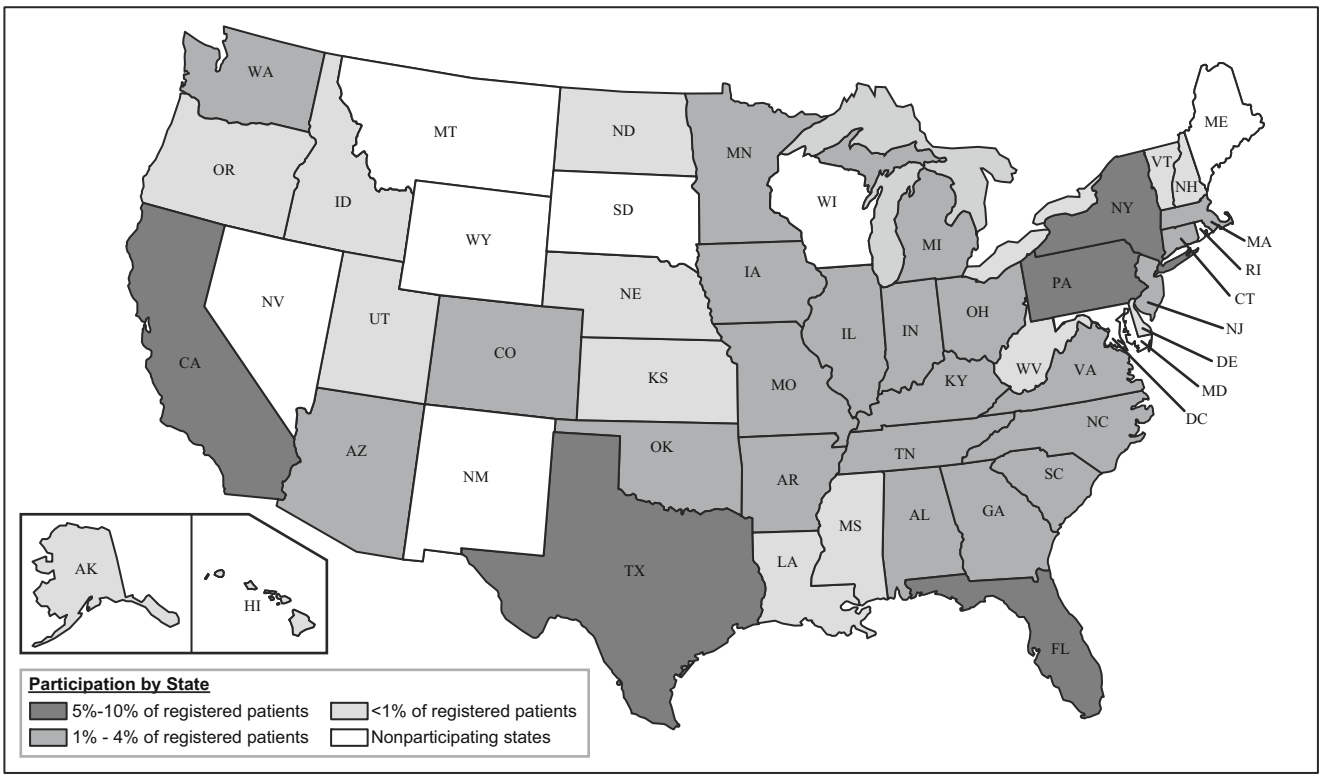


Fig. 3 Geographic distribution of registered patients

Table 2 Cumulative number of registered patients by mode of pre-enrollment for the quarter ending September 30, 2017

Mode of pre-enrollment among registered patients ($N = 64,975$)	Number (%)
Packaging	39,404 (61)
Other promotional materials[a]	11,563 (18)
Starter kit	9865 (15)
By phone	2646 (4)
Tear pad for physicians and nurse educators	893 (1)
Website	604 (1)

[a] Includes conversation tool, letters mailed from pharmacies, and Forteo connect brochure

It must be noted that the Forteo Patient Registry does not collect information on duration of teriparatide use or other clinical events after registration. In general, the depth of clinical information available from the study is somewhat limited. Given low exposure to teriparatide and the rare outcome of osteosarcoma, a simple registration process was used to optimize patient enrollment by minimizing patient burden. The recruitment process used in the Forteo Patient Registry was novel in that patients were informed about the study directly through teriparatide packaging, rather than by study sites selected to recruit patients. This approach was intended to encourage broad participation and maximize registry recruitment rate, a known challenge in registry studies.

A previous study using prescription records and the Danish National Patient Register (using ICD-10 discharge codes for inpatient and outpatient contacts) examined the incidence of malignancies including osteosarcoma and mortality in patients with osteoporosis treated with teriparatide. This study showed no evidence of an association (i.e., no cases occurred in any of the approximately 3500 patients treated with teriparatide, although the study had fewer than 9000 person-years of follow-up) [16]. In addition to the Forteo Patient Registry, a long-term study, the Osteosarcoma Surveillance Study, is being conducted concurrently in the US using a different study design [17]. This 15-year retrospective study identifies all osteosarcoma cases and then attempts to assess teriparatide exposure through patient interviews. A study using a similar design was implemented in Europe in 2004 under a postmarketing commitment to the European Medicines Agency and has been completed with no evidence of an increased risk (although the study was powered to only detect a large risk if one existed) [9]. In addition, two studies using US claims data to identify exposure and linkage with state cancer registries to identify osteosarcoma are ongoing to also examine whether use of teriparatide causes an increased risk of osteosarcoma compared with a general population matched to age, sex, geographic location, and overall health status [18]. Findings from all of these studies will help provide a better understanding of the long-term safety of teriparatide.

Table 3 Osteosarcoma cases in adults (aged 18 years or older), by diagnosis year

Year	Number of osteosarcoma cases in adults	Average percentage complete reported by cancer registries
2009	718	99.3
2010	744	98.7
2011	686	98.9
2012	704	98.7
2013	638	98.7
2014	689	98.9
2015	650	89.6
2016	417	60.0
2017	20	4.5
Total	5268	

The results of the linkage between the Forteo Patient Registry and cancer registry data indicate that it is feasible for many US state cancer registries to perform a data linkage using a standard algorithm to evaluate medication exposure. Previous studies conducting linkage with multiple cancer registries have been limited, most likely because of the time and coordination commitment that are needed, and use of SEER-Medicare files which are already linked are of limited value when studying rare cancers. One other study has been identified that is attempting linkage to multiple cancer registries. The Adventist Health Study-2, a nationwide cohort investigating the effects of diet on cancer, is attempting to link to cancer registries of all 50 US states and the Canadian provinces [19, 20]. Although there may be significant administrative requirements, using multiple registries provides clear advantages in estimating the population-level incidence of cancer-related outcomes for rare cancers. This is particularly important for outcomes, like osteosarcoma, that cannot be identified using ICD-9/10 codes. Registry data include detailed clinical information that is unavailable in traditional administrative claims databases and cancer diagnostic coding that is more specific than coding used for claims that are commonly used for studying rare disease outcomes. Data that cancer registries provide can include tumor stage and site, information on metastases. Additionally, cancer registries can provide partial social security numbers during the linkage process, which increases sensitivity and specificity of the match substantially above linkages without social security numbers [21]. Finally, most of the state registries have a mandate to use their data for research purposes and thus were interested in participating in the research project, indicating that there is willingness to engage in studies with outside partners.

There are challenges in conducting a linkage study with multiple cancer registries. Most notably, extensive coordination with individual state cancer registries and navigating the various application and approval processes are necessary to gain participation from each registry [22]. Many states require multiple approvals, including review by their affiliated local IRBs, and considerable time (i.e., 5 to 18 months for approval, plus additional time to identify registries) was invested in effective communication and collaboration with cancer registries. The Virtual Pooled Registry (VPR), a future potential solution, is a project coordinated by the North American Association of Central Cancer Registries (NAACCR) with funding by the National Cancer Institute (NCI) [23]. The VPR seeks to make the process for minimal risk data linkage with multiple state cancer registries more efficient. Once fully operational, researchers will submit a single application to NAACCR for approval. The researcher's cohort file will then be securely sent to all interested registries simultaneously. Each registry then conducts the linkage behind their local firewall and reports only the number of matched cases, by state, back to the researcher. The researcher can then prioritize which registries to approach for release of cancer information, which may include applying to that state's IRB. NAACCR is also developing ways to streamline the registry and IRB application process, including using a central IRB or a standard set of application materials acceptable to local IRBs. NAACCR is currently performing pilot linkages and finalizing processes and anticipates making the VPR available to researchers in 2019. An additional challenge of this study was registry participation: some registries declined to participate in the study because of lack of interest or available staffing resources. Nevertheless, this study ultimately enrolled all registries (42) that expressed an interest out of 51 registries in the US, covering 93% of osteosarcoma cases diagnosed in the US population aged 18 years and older, which far exceeded the original goal of 25 registries, covering 60% of osteosarcoma cases.

No incident osteosarcoma cases among teriparatide users registered in the Forteo Patient Registry have been identified after 8 years of follow-up. This article represents an interim report on the study. Patients will continue to be enrolled through 2019, and annual linkages are planned to be conducted through 2024. Population-based studies that use data from state cancer registries can play an important role in drug safety surveillance activities, particularly for outcomes not identified using ICD-9/10 codes. There is significant opportunity for further collaboration serving the public and regulatory interest in clarifying the long-term risk of cancer associated with many therapies. In the absence of a national cancer registry with patient-level identifying data in the US, studies in the future will require participation of multiple statewide cancer registries.

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Compliance with ethical standards

The study was approved by the RTI International (RTI) institutional review board (IRB) on June 11, 2009. Local IRBs affiliated with participating state cancer registries also approved the study when required.

Conflicts of interest This study was performed under a research contract between RTI Health Solutions and Eli Lilly and Company and was funded by Eli Lilly and Company. Elizabeth Andrews, Alicia Gilsenan, Abenah Harding, David Harris, and Kirk Midkiff are salaried employees of RTI Health Solutions. Nicole Kellier-Steele is a salaried employee of Eli Lilly and Company.

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