

# Long-Term Cancer Surveillance: Five-Year Update for the Forteo Patient Registry Surveillance Study

David Harris,<sup>1</sup> Alicia Gilsenan,<sup>1</sup> Abenah Harding,<sup>1</sup> Elizabeth Andrews,<sup>1</sup> Nicole Kellier,<sup>2</sup> Daniel Masica<sup>2</sup>  
<sup>1</sup>RTI Health Solutions, Research Triangle Park, NC, United States; <sup>2</sup>Eli Lilly and Company, Indianapolis, IN, United States

## ABSTRACT

**Background:** Postmarketing safety surveillance studies can be challenging to implement, especially when the outcome of interest is a rare cancer. Interim results from an ongoing study to examine adult osteosarcoma (occurring at a rate of 2.7 cases per million population in adults in the US) using data linkage with population-based state cancer registries are presented.

**Objective:** To provide a study update of the voluntary Forteo Patient Registry, designed to estimate the incidence of osteosarcoma in patients who have received treatment with teriparatide (Forteo).

**Methods:** This surveillance study is a multiyear, prospective registry in the US designed to link information from adult patients with a history of teriparatide use who enroll during the 10-year recruitment period (initiated in July 2009) with participating state cancer registries annually for 15 years (through 2024) to identify osteosarcoma cases diagnosed after patients started treatment. Patients are invited to participate through multiple pathways of communication and enrollment is tracked by pathway type when possible. The linkage algorithm uses enrollment information (name, birth date, sex, address, telephone number, race, ethnicity, and last 4 digits of social security number) provided with patient consent to match with participating cancer registries.

**Results:** In October 2014, the 5th annual linkage was completed with 42,544 patients enrolled in the Forteo Patient Registry (equivalent to 100,400 person-years of follow-up adjusted for mortality) linked to 3,171 adult cases of osteosarcoma from 41 state cancer registries, (covering 92% of the US population aged 18 years and older) and no matches were found. The most common pathway leading to enrollment was the medication packaging (60%) followed by the starter kit (21%).

**Conclusions:** Although no incident cases of osteosarcoma among patients in the Forteo Patient Registry have been identified through the linkage process, our ability to draw conclusions after 5 years about the incidence of osteosarcoma among teriparatide users is limited due to follow-up time currently available.

## BACKGROUND

- Teriparatide is a recombinant human parathyroid hormone analog; it was approved in 2002 in the United States (US) for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture and for increase in bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture.
- In initial studies in rats, teriparatide caused a dose-dependent increase in the incidence of osteosarcoma,<sup>1</sup> although a subsequent study demonstrated a “no effect” dose.<sup>2</sup>
- Osteosarcoma is a rare bone cancer in humans, with an estimated background incidence in adults aged 18 years and older of 2.7 cases per million population per year.<sup>3</sup>
- A retrospective case-series postapproval safety surveillance study was implemented in 2003 to monitor for a signal of a potential association between teriparatide and osteosarcoma in humans.<sup>4</sup>
- 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. The Forteo Patient Registry was established in 2009, also to monitor for a signal of a possible association between teriparatide and adult osteosarcoma.

## OBJECTIVE

- To provide a study update on the Forteo Patient Registry study after more than 5 years of data collection, including patient enrollment and five annual data linkages with participating cancer registries.

## METHODS

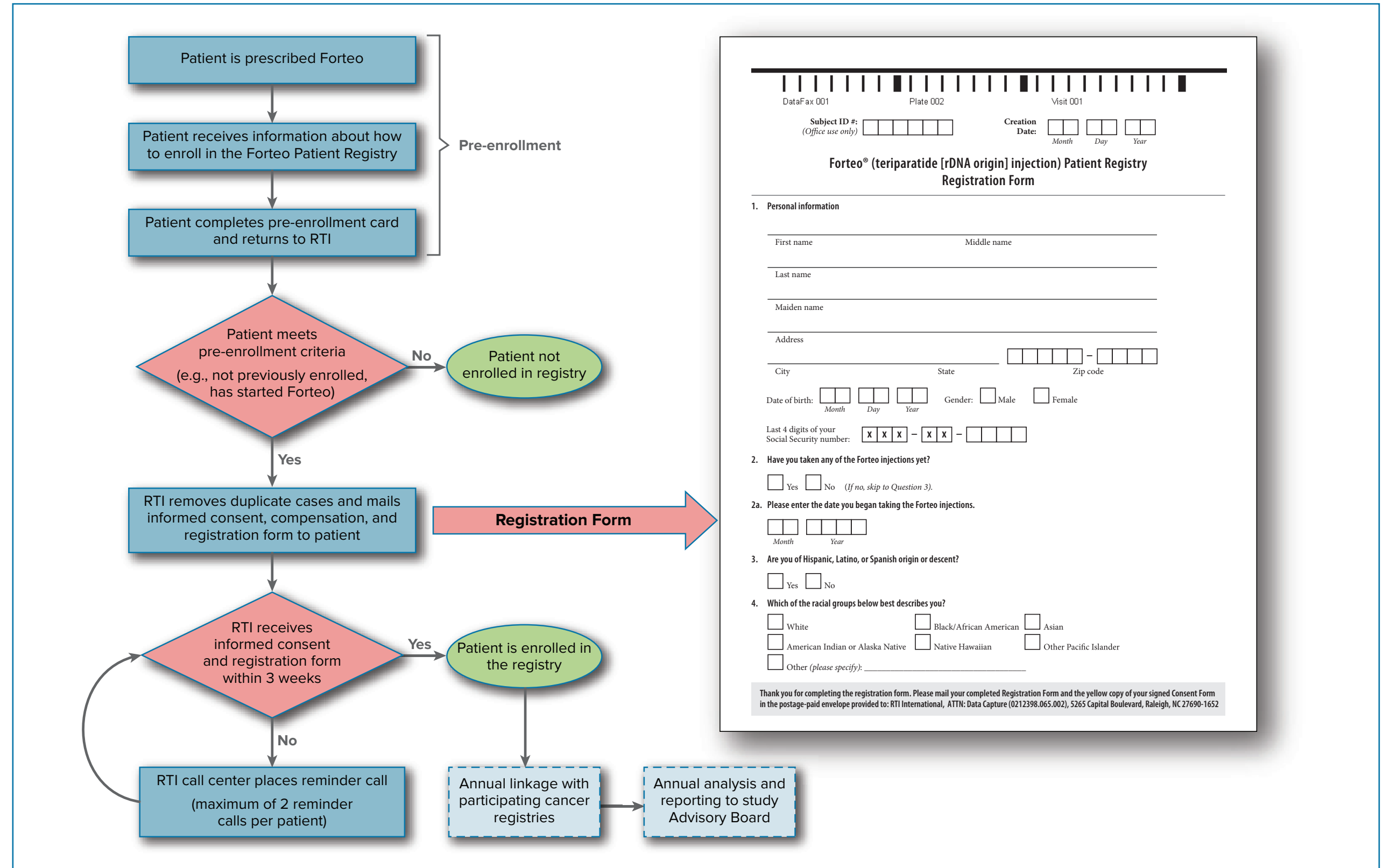
### Study Design

- The study is a voluntary, prospective cohort study of adults residing in the US who receive treatment with a Forteo delivery device during the enrollment period (2009-2019) and who provide voluntary consent to have their personal data linked to cancer registry data.
- On an annual basis from 2010 to 2024, data from registered patients are linked with participating state cancer registries to ascertain any new confirmed cases of osteosarcoma diagnosed after the initiation of Forteo.
  - State cancer registries include all osteosarcoma cases diagnosed 2009 or later among patients aged 18 years and older at the time of diagnosis in an annual cumulative linkage file.
  - Twelve International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology codes are used to define osteosarcoma: 9180-9187 and 9192-9195; all primary tumor sites are allowed (not just bone).
- All participating cancer registries use Link Plus and a standard data linkage algorithm provided by RTI Health Solutions (RTI-HS) to perform the annual data linkage. Link Plus is a free probabilistic data linkage software program created by the Centers for Disease Control and Prevention.

### Patient Enrollment

- Patients enroll in the registry by providing informed consent and contributing a limited amount of personal data necessary to conduct linkage with the cancer registries (name, address, date of birth, last 4 digits of social security number, telephone number, race, and ethnicity) and start date of treatment on a one-time only basis.
  - No additional information is routinely collected from the patients or their physicians.
- Patients are recruited through multiple pathways including:
  - Medication packaging (pre-enrollment form included)
  - Medication starter kit, which includes the dosing pen, instructions for use of this self-injected daily medication, and other relevant material
  - Forteo Patient Registry website (www.forteoregistry.rti.org)
  - Forteo Patient Registry toll-free telephone number (1-866-382-6813)
  - Materials available through their physicians or nurses (tear pad)
- Figure 1 describes the enrollment process for the Forteo Patient Registry.
  - Only those patients who complete and return the consent and registration forms are included.

Figure 1. Forteo Patient Registry Patient Enrollment Process



## RESULTS

- Figure 2 shows the total number of patients registered by year and cumulatively from the beginning of patient enrollment (September 2009) through June 30, 2015.
  - Annual enrollment has declined slightly since 2012 but has held relatively steady through 2015. Based on market estimates provided by Eli Lilly and Company, we estimate that approximately 25% of patients starting teriparatide enroll in the Forteo Patient Registry.
- Figure 3 displays the cumulative number of registered patients by mode of pre-enrollment.
  - Medication packaging is the most common pathway to registration, accounting for 60% of all registration forms received, followed by the medication starter kit at 20%.
  - Other promotional materials account for 13% and include discussion aids given by providers to patients, letters mailed to patients from pharmacies, and the Forteo patient support program.

Figure 2. Annual Patient Enrollment by Year and Cumulatively, as of June 30, 2015

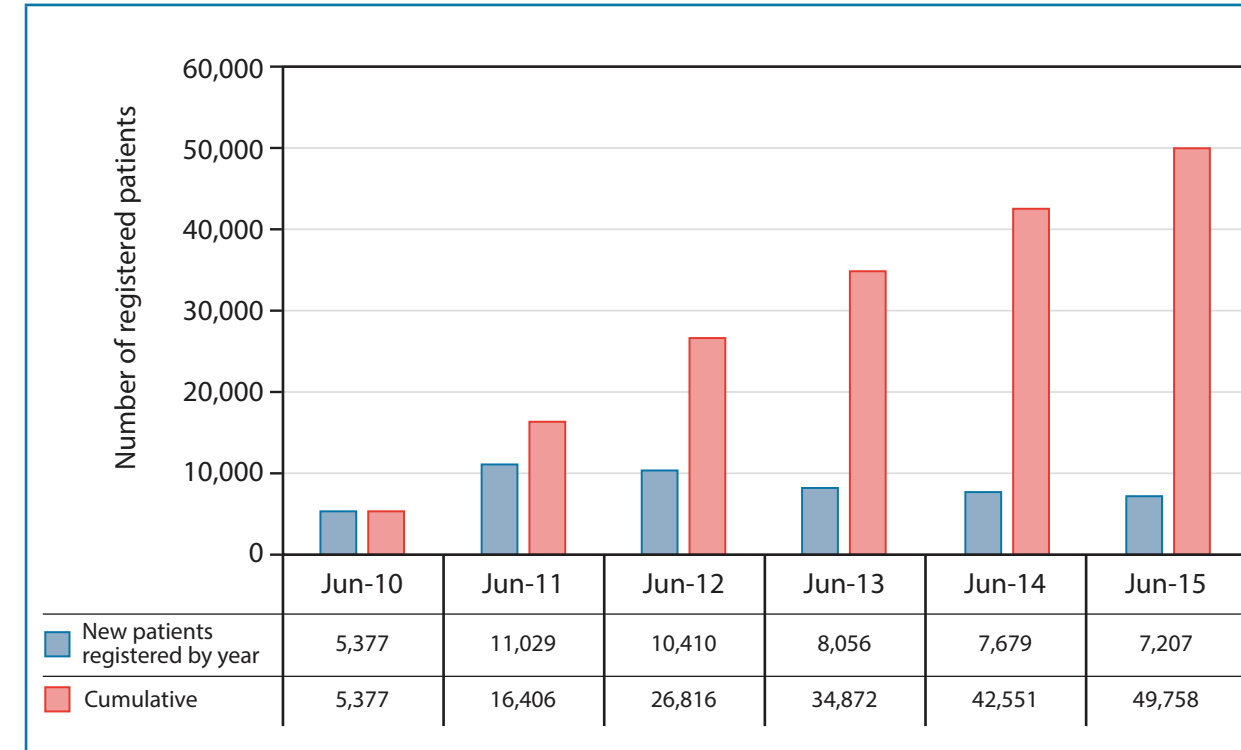
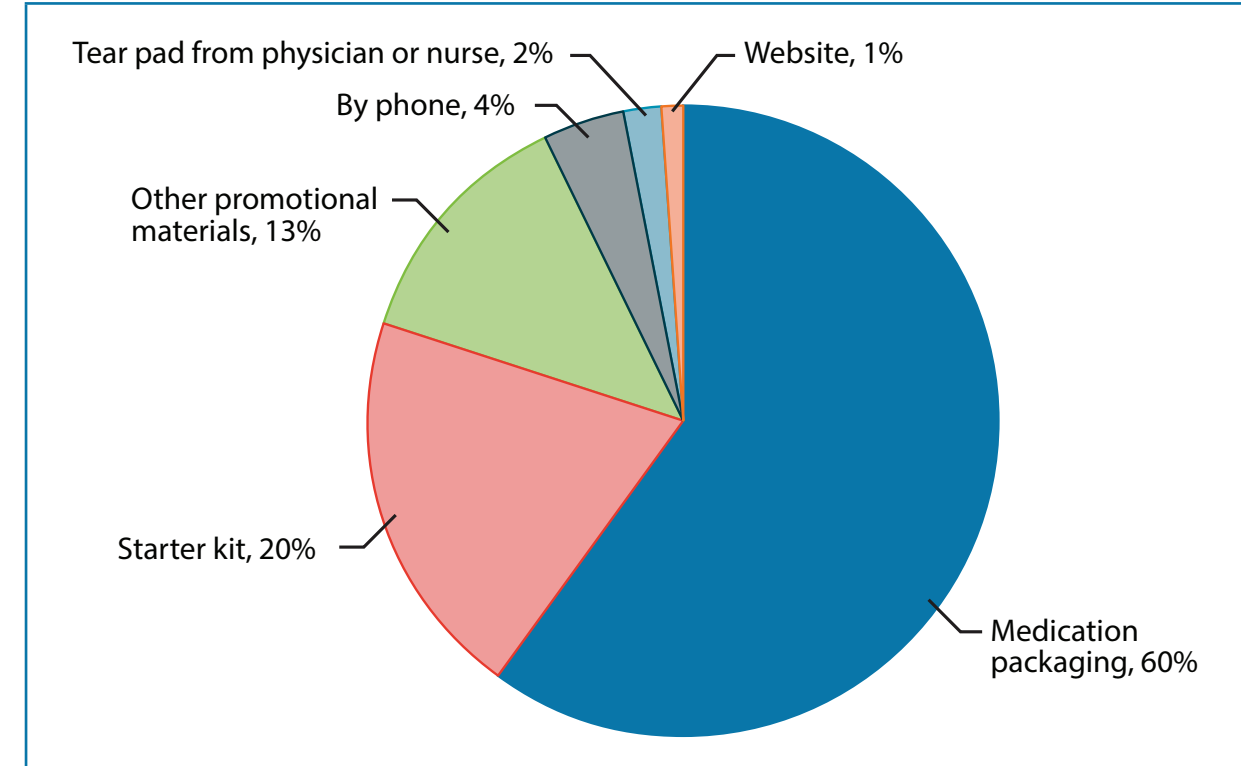


Figure 3. Mode of Pre-Enrollment Among Registered Patients, Cumulatively as of June 30, 2015



### Cancer Registry Enrollment

- All 50 state cancer registries in the US, plus the registry in Washington, DC, were invited to participate in the study in May 2009.
- Overall, 27 registries, covering 70% of the US population, participated in the first linkage in 2010.
- Figure 4 describes the results of the fifth annual data linkage with participating state cancer registries.
  - The linkage was completed on October 14, 2014, with 41 US state cancer registries, covering 92% of the US population aged 18 years and older.<sup>5</sup>
  - No matches between patients treated with Forteo and osteosarcoma cases in the cancer registry databases were found in any of the first five linkages. The sixth annual linkage is scheduled to be completed in September 2015.
- Table 1 shows the details of the first five linkages with cancer registries.
  - Each annual linkage includes all patients ever enrolled in the Forteo Patient Registry, irrespective of geographic location, and all osteosarcoma cases over the full period of the Registry.
  - We estimate that the study had accumulated approximately 100,000 person-years of follow-up, adjusted for estimated mortality, at the last linkage.

Figure 4. Results From the Fifth Annual Data Linkage With State Cancer Registries

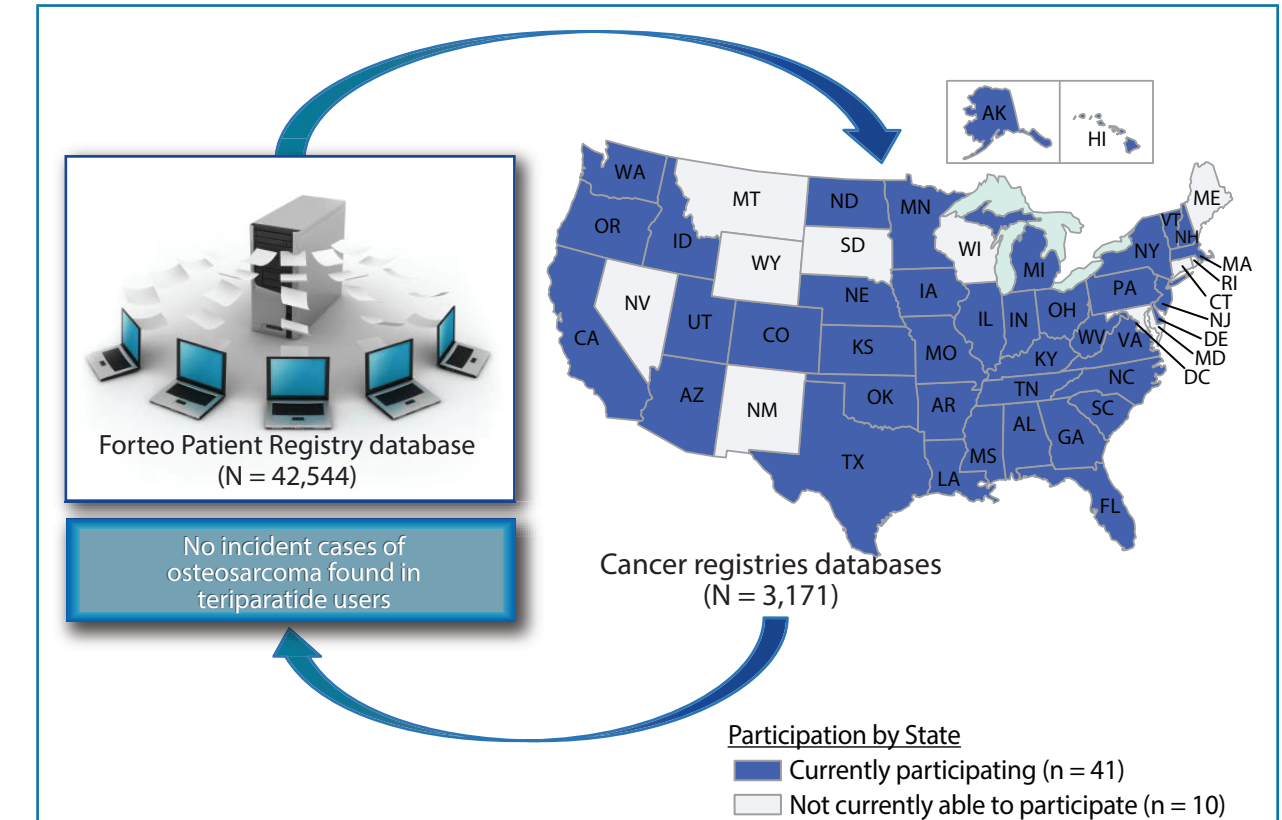


Table 1. Characteristics of the First Five Annual Linkages

Year of Linkage	Number of Participating Registries	US Population Aged ≥ 18 Years Covered by Participating Registries	Osteosarcoma Cases From Participating Registries	Forteo Patient Registry Enrollees
2010	27	70%	431	6,338
2011	37	85%	961	16,365
2012	38	86%	1,641	26,810
2013	41	92%	2,408	34,869
2014	41	92%	3,171	42,544

## CONCLUSIONS

- No cases of osteosarcoma were identified by linking the full Forteo Patient Registry population to cancer registries in the first five linkages.
- Based on the estimated person-years of follow-up, adjusted for estimated mortality, no cases would have been expected if patients receiving teriparatide had the same incidence of osteosarcoma as the general population.
- The study is currently planned to enroll patients through 2019 and link with cancer registries through 2024.

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## CONFLICT OF INTEREST

This study was funded by Eli Lilly and Company. Nicole Kellier and Daniel Masica are employees of Eli Lilly and Company. David Harris, Alicia Gilsenan, Abenah Harding, and Elizabeth Andrews are employees of RTI Health Solutions, a nonprofit research organization that conducts research with multiple pharmaceutical companies and has an independent right to publish the results of this study.

## CONTACT INFORMATION

David Harris, MPH  
Research Epidemiologist  
RTI Health Solutions  
200 Park Offices Drive  
Research Triangle Park, NC 27709  
Phone: +1.919.541.7493  
Fax: +1.919.541.7222  
E-mail: dharris@rti.org

