PASS Information

Title	Forteo/Forsteo Post-Approval Osteosarcoma Surveillance Study [Study B3D-MC-GHBX]
Version identifier of the final study report	1.0
Date of last version of the final study report	Not applicable
EU PAS register number	
Active substance	Teriparatide (Calcium homeostasis, parathyroid hormones and analogues; ATC code, H05AA02)
Medicinal product(s):	FORSTEO 20 micrograms/80 microlitres solution for injection in pre-filled pen
Product reference:	EU/1/03/247/001-002
Procedure number:	
Marketing authorisation holder(s)	Eli Lilly Nederland B.V.
Joint PASS	No
Research question and objectives	Teriparatide caused dose-dependent increases in the incidence of osteosarcoma in rats during preclinical testing. Studies have shown that the rat skeleton is more sensitive to the pharmacological effects of parathyroid hormone in formation of new bone and osteosarcoma than monkey or human skeletons. Study GHBX has three components: case-finding surveillance in Europe and the United States and a Forteo Patient Registry in the United States. The case-finding surveillance components were designed to identify documented cases of osteosarcoma among men and women aged 40 years and older and determine which cases, if any, had a history of teriparatide treatment. This report contains results of the European case-finding surveillance component.
Country(-ies) of study	European component: Denmark, Finland, Iceland, Norway, Sweden
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Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly Nederland B.V, Grootslag 1-5, NL-3991 RA Houten, The Netherlands

Table of Contents

Section **Page**

List of Tables

List of Figures

1. Abstract

Title: Forteo/Forsteo Post-Approval Osteosarcoma Surveillance Study [Study B3D-MC-GHBX]

Keywords: osteosarcoma; epidemiology; teriparatide, surveillance; parathyroid hormone (PTH)

Rationale and background: Teriparatide is identical to the 34 N-terminal amino acid sequence of endogenous human parathyroid hormone that stimulates new bone formation. Teriparatide is indicated in adults for the treatment of osteoporosis in postmenopausal women and in men at increased risk for fracture, and for men and women who are at increased risk for fracture due to osteoporosis associated with sustained systemic glucocorticoid therapy. In clinical studies in postmenopausal women, teriparatide significantly reduced the incidence of vertebral and non-vertebral fractures, except hip fractures. In preclinical studies, teriparatide showed dose-dependent increases in the incidence of osteosarcoma in rats.

Research question and objectives: Study GHBX was initiated post approval/launch in the United States of America (US) and in Europe. The study commenced in 2003 in the US and 2004 in Europe as a postmarketing regulatory commitment to evaluate a potential association between teriparatide and adult osteosarcoma in humans. The primary objective was to identify newly diagnosed cases of osteosarcoma among men and women aged 40 years or older in selected countries and identify incident osteosarcoma cases with a history of teriparatide treatment. The secondary objective was to collect additional patient information and data related to other risk factors for osteosarcoma. This report follows the conclusion of the 10-year surveillance period in European countries taking part in the study: the US components of the study are continuing.

Study design: Case-series. Data on patients with osteosarcoma were collected; medical history, including drug exposure, was ascertained through abstraction of medical records.

Setting: The study takes place in the US and the Nordic countries of Europe **(**Denmark, Finland, Iceland, Norway, and Sweden); data from only the European component of the study are presented in this report.

Subjects and study size, including dropouts: Potential subjects were identified through the Scandinavian Sarcoma Group (SSG) registry and the Finnish and Swedish National Cancer Registries. Patients were eligible if they were aged 40 years or older at the time of diagnosis and had histological confirmation of osteosarcoma or one of five other tumour types with a primary bone site.

Variables and data sources: Demographic information; personal cancer information; osteoporosis history and treatments, including teriparatide; brief personal and family medical history; and lifestyle and occupational exposures were ascertained from the patient's general practitioner/primary care physician medical record.

Results: As of 31 December 2013, using 12 ICD-O-3 morphology codes representing osteosarcoma, 129 cases of osteosarcoma diagnosed since January 2004 were reported by the participating Nordic countries. There were 14 patients who did not provide consent, and medical records could not be obtained for 3 patients. A total of 112 patient medical records were abstracted. None of these 112 patients had a record of teriparatide use. All 112 patients were white, most were men (56%), 54% were alive when the case was reported to the study, and 60 years was the mean age at the time of diagnosis. Of 46 patients diagnosed with one of five other ICD-O-3 morphology codes where records designated a primary bone site, none had a record of teriparatide use.

Discussion:

After 10 years of population-based surveillance, no patient diagnosed with osteosarcoma had prior teriparatide exposure, which is consistent with other published study findings.[1] Due to the inherent lag time between diagnosis and reporting to the SSG registry the main study result is focused on the 8-year period from 2004-2011, during which there was nearly complete coverage of osteosarcoma cases by the surveillance study. Given the infrequent occurrence of osteosarcoma and teriparatide use relative to the population size of these countries in the age group of interest, we expected to identify patients with osteosarcoma previously treated with teriparatide only if teriparatide were associated with a large increased risk. In other words, if a single case of osteosarcoma with prior teriparatide treatment had been observed in the Nordic data, it would indicate a 12-fold (90% confidence interval, 0.6-fold to 55-fold) increase in the risk of osteosarcoma associated with treatment compared with the background rate. This hypothetical 12-fold increase would translate to an absolute risk difference of 1 additional case of osteosarcoma per 47,000 teriparatide-treated patients per year. In conclusion, the study results do not change the current overall benefit-risk profile of teriparatide.

Marketing Authorisation Holder(s): Eli Lilly & Co.

Names and affiliations of principal investigators: Elizabeth B. Andrews and Alicia Gilsenan of RTI Health Solutions

2. List of abbreviations

Term	Definition
ATC	Anatomical Therapeutic Chemical
CCI	coordinating country investigator
CI5	*Cancer Incidence in Five Continents*
ICD-O-3	*International Classification of Diseases for Oncology, Third Edition*
NOS	not otherwise specified
PTH	parathyroid hormone
rhPTH	recombinant human parathyroid hormone
RTI-HS	RTI Health Solutions, a business unit of RTI International
SD	standard deviation
SSG	Scandinavian Sarcoma Group
US	United States of America

3. Investigators

Principal Investigator	**Country**	**Institutional Affiliation**
Dr. Elizabeth Andrews	United States	RTI Health Solutions Research Triangle Park, NC USA
Dr. Alicia Gilsenan	United States	RTI Health Solutions Research Triangle Park, NC USA

Coordinating Country Investigators	**Country (Year Participated)**	**Institutional Affiliation**
Dr. Thor Alvegård	Sweden (2004-2013)	Regional Tumor Registry Lund University Hospital Lund, Sweden
Dr. Sigbjørn Smeland	Norway (2004-2008)	Norska Radium Hospitalet Oslo, Norway
Dr. Kirsten Sundby Hall	Norway (2009-2013)	Norska Radium Hospitalet Oslo, Norway
Dr. Odd Monge	Norway – Bergen (2009-2013)	Haukeland Universitetssykehus Hospital Bergen, Norway
Dr. Clement Trovik	Norway – Bergen (2009-2013)	Haukeland Universitetssykehus Hospital Bergen, Norway
Dr. Ole Steen Nielsen	Denmark (2004-2011)	Onkologisk afdeling, Århus Sygehus, Århus Universitetshospital, Århus, Denmark
Dr. Philip Rossen	Denmark (2012-2013)	Onkologisk afdeling, Århus Sygehus, Århus Universitetshospital, Århus, Denmark
Dr. Carl Blomqvist	Finland (2004-2013)	Helsinki University Central Hospital Department of Oncology Helsinki, Finland
Dr. Halldór Jónsson Jr.	Iceland (2012-2013)	Landspítali University Hospital Institute for Surgical Sciences Reykjavik, Iceland
Dr. Oskar Johansson	Iceland (2004-2011)	Oncologiska Kliniken AMS Landspítali Reykjavik, Iceland

4. Other responsible parties

Not applicable.

5. Milestones

Table 1. Study milestones

The study milestones below are provided for only the European component of Study GHBX.

Milestone	Planned date	Actual date	Comments
Start of data collection	01 Jan 2004	01 Jan 2004	None
End of data collection	31 Dec 2013	31 Dec 2013	None
Final report of study results	30 Jun 2014	30 Jun 2014	None

6. Rationale and background

Teriparatide, rhPTH(1-34), produced in *E. coli* using recombinant DNA technology, is identical to the 34N-terminal amino acid sequence of endogenous human parathyroid hormone. Teriparatide is indicated in adults for the treatment of osteoporosis in postmenopausal women and in men at increased risk for fracture, and for men and women who are at increased risk for fracture due to osteoporosis associated with sustained systemic glucocorticoid therapy.[2] Teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. Teriparatide is administered as a subcutaneous injection into the thigh or abdominal wall with a recommended dosage of 20 μg once a day. In clinical studies, patients with osteoporosis treated for up to 2 years with teriparatide demonstrated increases in bone mineral density and a significant decrease in the incidence of fractures compared with the placebo group. Compared with the placebo group, the teriparatide 20-μg/day group experienced a 65% reduction in the proportion of patients with new vertebral fractures.[3] Across clinical studies, treatment with teriparatide was well tolerated. No cases of osteosarcoma were reported during clinical trials or in a 5-year post-treatment follow-up study (GHBJ) that included seven long-term teriparatide clinical trials.

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 humans given a 20-μg dose, teriparatide caused increases in bone mass and a dose-dependent increase in the incidence of osteosarcoma, a malignant tumour.[4] 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.[5] In a long-term study of cynomolgus monkeys (spanning 18 months of treatment plus 3 years of follow-up observation), no bone tumours were detected by radiographic or histological evaluation in any monkey in the study.[6] Studies have shown that the rat skeleton is more sensitive to the pharmacological effects of parathyroid hormone (PTH) in the formation of new bone and osteosarcomas than monkey or human skeletons.[7]

Little is known about the aetiology of osteosarcoma in adult humans.[8,9] It has been observed in association with Paget’s disease of the bone and after radiation treatment to the bones.[9,10] In addition, rare inherited disorders, including Li-Fraumeni syndrome (p53 mutation) and retinoblastoma (pRb loss) are associated with increased rates of osteosarcoma.[11] Other potential risk factors, including injury or infection at the tumour site and metallic implant at the tumour site, have been suggested.[9]

At the time of drug approval in Europe (June 2003), because of the preclinical findings, the European Agency for the Evaluation of Medicinal Products requested a 10-year safety surveillance study to evaluate a potential association between teriparatide and adult osteosarcoma in humans; this study would include European countries with national registries in addition to the United States of America (US). Interim results of the first 4 years of data collection, presenting descriptive data on the first 37 patients with osteosarcoma whose records were abstracted, have been published.[12] None of these patients had prior history of teriparatide treatment. The European component of this study has now been completed but the US components are still ongoing. The Forteo Patient Registry in the US adds a prospective voluntary registry of patients treated with teriparatide as a second method to complement the ongoing retrospective US component of study GHBX. The voluntary Forteo Patient Registry was launched on 23 July 2009, following US Food and Drug Administration approval of teriparatide for use in the treatment of men and women with glucocorticoid-induced osteoporosis.[1] Information on the progress of each of these components has been reported in periodic safety update reports following drug approval. Across all three components, there have been no patients with osteosarcoma with previous exposure to teriparatide. An overview of all three component study designs is provided in Annex 2. Copies of prior publications are provided in Annex 3. This report details only the findings from the completed European component.

7. Research question and objectives

At the time of drug approval, a dose-dependent association between teriparatide treatment and osteosarcoma had been found in preclinical studies in a rat model. No such safety signal had been seen during the preapproval or postapproval clinical trial experience. This Nordic component of surveillance study GHBX was designed to monitor for a potential association between teriparatide exposure and osteosarcoma by examining whether patients diagnosed with osteosarcoma had a history of teriparatide treatment. The study was implemented in five Nordic countries (Denmark, Finland, Iceland, Norway, Sweden).

The primary objectives of this component of the study were to (1) identify newly diagnosed cases of osteosarcoma in selected countries among men and women aged 40 years or older, starting 1 January 2004, for a duration of 10 years and (2) determine incident osteosarcoma cases, if any, who had a history of teriparatide treatment. The secondary objective of the study was to systematically collect, for descriptive epidemiology purposes, additional patient information, including demographics and data related to other risk factors for osteosarcoma.

8. Amendments and updates

None.

9. Research methods

9.1. Study design

The study used a case-series design to identify incident cases of osteosarcoma from participating cancer registries in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). A case-series design targets collection of information regarding patients with a single outcome whose antecedent exposures are examined. In this study, information on patients' medical history and antecedent exposures, including drug exposures, was collected through abstraction of medical records.

The assessment of potential increased risk was planned as a comparison of the observed number of patients with osteosarcoma who had a possible or confirmed exposure to teriparatide to the number of patients with osteosarcoma expected to be identified by this study based on the background incidence of disease in the general population. No formal hypothesis testing for statistical inference was planned due to the overall study size and expected level of teriparatide use in the Nordic countries.

9.2. Setting

The five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) were selected for the study for two reasons: (1) their high incidence of osteoporosis, and therefore a higher potential for treatment of osteoporosis compared with other European countries, and (2) the presence of high-quality, comprehensive, population-based, national cancer registries. The Scandinavian Sarcoma Group (SSG) registry acted as the coordinating centre in Europe to identify and collect data from treating physicians in Denmark, Finland, Iceland, Norway, and Sweden.

Within each country, a physician specialising in diagnosis and/or treatment of osteosarcoma was invited to participate as a coordinating country investigator for the study (see Section 3). Once a treating physician identified an incident case of osteosarcoma in one of the five Nordic countries, he or she was to report it directly to the regional or national cancer registry and also to the SSG. Upon notification of an eligible case, the SSG contacted the coordinating country investigator (when the coordinating country investigator was not the treating physician), who was to obtain permission from the treating physician to contact the patient in order to obtain patient consent (when applicable). Once the patient consent requirements were fulfilled, the coordinating country investigator abstracted data from the patient's general practice medical record and returned a completed data collection form to the SSG.

To comply with the European Union Privacy Directive, no data with direct patient identifiers were sent outside of Europe. A de-identified, limited data form was sent by the SSG to the global coordinating centre, RTI Health Solutions (RTI-HS)[*] in the US for data entry and compilation into an analytical data file. Data collection was initiated on a country-by-country basis once an

[*] RTI Health Solutions is a business unit of RTI International.

eligible case was identified. Beginning in June 2004, data were abstracted for eligible cases diagnosed from 1 January 2004 up to 31 December 2013.

The study was approved by the RTI International institutional review board under a Federal-wide Assurance in the US and the ethics committees in each Nordic country (see Table 2). Based on the study design and a change in Swedish law early during the study period, the study was exempted from Swedish ethics committee review/approval.

Table 2. Ethics committees in European countries in the study

Country	Ethics committee
Denmark	Den videnskabsetiske Komite for Århus Amt; Århus, Denmark
Finland	Helsingin Ja Uudenmann sairaanholtopirri, Kirurgian alan eettinen toimikunta; Helsinki, Finland
Iceland	Visindasidanefnd; Reykjavik, Iceland
Norway	Universitetet I Oslo, Regional komité for medisinsk forskningsetikk; Oslo, Norway
Sweden	Region Skane Research Centre Lund University Hospital; Lund, Sweden

9.3. Subjects

Patients who met the case definition were identified through the SSG registry and the Finnish and Swedish National Cancer Registries. Additional patients were identified through cross-reference with national cancer registries by approaching the registry and comparing those cases already reported to SSG with the cases captured by the national or regional cancer registry, where possible. A summary of specific methods for identifying cases by country is shown in Table 3.

Table 3. Summary of case identification and reporting by country

Country	Case-reporting process
Denmark	The coordinating country investigator at a medical facility in Århus reported cases to the SSG and national cancer registry; the national cancer registry did not report cases directly to the SSG.
Finland	The national cancer registry reported all cases directly to the coordinating country investigator, who then reported them to the SSG.
Iceland	The coordinating country investigator at a large medical facility in Reykjavik reported cases to the SSG. The coordinating country investigator reconciled cases reported to the SSG with the cases captured by the national cancer registry.
Norway	The coordinating country investigator at a medical facility in Oslo and another investigator in Bergen reported cases to the SSG; the national cancer registry did not report cases directly to the SSG.
Sweden	Regional cancer registries, which comprise the national cancer registry, reported all cases directly to the SSG. In addition, medical facilities reported cases directly to the SSG. The SSG reconciled cases reported from the medical facilities with the cases reported from the national cancer registry.

SSG = Scandinavian Sarcoma Group.

Patients with osteosarcoma were eligible for inclusion in this study if diagnosis occurred on or after 1 January 2004. The start date was selected after the last launch of Forsteo in the five Nordic countries. Patients with a previous history of osteosarcoma were excluded, as were patients who did not have their primary residence in one of the Nordic countries.

The case definition for study inclusion was based on the following criteria:

- Male or female, 40 years of age or older;
- Diagnosis of osteosarcoma after the age of 40; and
- Histological confirmation that the cancer was osteosarcoma according to the *International Classification of Diseases for Oncology, Third Edition* (ICD-O-3) morphology codes. The following ICD-O-3 codes met the case definition of osteosarcoma:
  - 9180/3 Osteosarcoma NOS,
  - 9181/3 Chondroblastic osteosarcoma,
  - 9182/3 Fibroblastic osteosarcoma,
  - 9183/3 Telangiectatic osteosarcoma,
  - 9184/3 Osteosarcoma in Paget's disease of bone,
  - 9185/3 Small cell osteosarcoma,
  - 9186/3 Central osteosarcoma,
  - 9187/3 Intraosseous well-differentiated osteosarcoma,
  - 9192/3 Parosteal osteosarcoma,
  - 9193/3 Periosteal osteosarcoma,
  - 9194/3 High-grade surface osteosarcoma, and
  - 9195/3 Intracortical osteosarcoma.

To find all possible patients with osteosarcoma and limit misclassification bias, cases using the following five ICD-O-3 morphology codes were collected if records designated a possible primary bone site:

- 8800/3 Sarcoma, NOS;
- 8801/3 Spindle cell sarcoma;
- 8810/3 Fibrosarcoma, NOS;
- 8830/3 Malignant fibrous histiocytoma; and
- 9243/3 Dedifferentiated chondrosarcoma.

These additional 5 codes are hereafter referred to collectively as “five additional ICD-O-3 codes.”

9.4. Variables

The coordinating country investigator or designee abstracted the following information from each subject’s medical record:

- Personal cancer information
- Demographics including race, age, sex, country of residence, and vital status
- Osteoporosis history and medications, including teriparatide
- A brief medical history including cancer, Paget’s disease, bone fracture, infection at the tumour site, and radiation and chemotherapy treatment
- Family medical history of osteosarcoma, selected cancers, and Paget’s disease
- Lifestyle habits such as smoking and alcohol use
- Occupational and environmental exposures

9.5. Data sources

National or regional cancer registries were used in Finland, Sweden, and Iceland for identifying or reconciling reported cases of osteosarcoma for this research. These registries capture, code, and store data on cancer patients from hospitals, laboratories, general practitioners, and national statistics offices (for cancer deaths), with the intent to cover the entire population and use these data to estimate the incidence, trends, and burden of cancer. These registries reported eligible cases directly to the SSG or to a coordinating country investigator first, who then reported the eligible case to the SSG for consideration of study eligibility.

In the other countries, Denmark and Norway, the national cancer registries were not able to provide cases directly to the SSG for this study or be used to reconcile case reports to the SSG because of privacy restriction. In these countries, coordinating country investigators from medical centres specialising in treatment of adult osteosarcoma were responsible for identifying and reporting cases to the SSG.

The initial case reports from the SSG included the patient’s age, date of diagnosis, and tumour site so that patient eligibility could be confirmed by the coordinating centre. Once confirmed, the coordinating country investigator was notified and shipped a study packet for patient contact and data collection. Once consent was obtained (or waived due to local requirements or a patient being deceased), the medical record from the physician who was responsible for treating the patient was obtained from the treatment facility and, if necessary, the medical record was obtained from the patient’s general practitioner’s office. Once obtained, study variables were abstracted from the medical record by research nurses or coordinating country investigators that had completed training for this study onto a standardised data collection form, which was returned to the SSG. The data collection form was reviewed by the SSG for quality and

completeness, patient identifiers were removed, and the anonymised form was transferred to RTI-HS. RTI-HS also reviewed the forms for quality and completeness, and data queries were sent to the investigators if additional information or clarification was required. Once data queries were resolved, the data collection forms were entered into the study database, verified, and included in the final analytical file for analysis.

9.6. Bias

Case series studies may be confounded by selection bias, for example, the selection of cases from settings more (or less) likely to have the exposure of interest than the universe of cases. To minimise the potential for selection bias, the study was designed to capture as many cases as possible of incident osteosarcoma occurring in each country during the study period.

Misclassification of cases can also create bias. To limit the potential impact of diagnostic misclassification, cases of five additional ICD-O-3 codes were included as a separate case group in the design.

9.7. Study size

This was a case-series study to identify incident cases of osteosarcoma in each of the five countries, and the size was limited to the number of cases occurring in the participating countries. Due to the rarity of the disease, no formal hypothesis testing was planned; therefore, the study size was not based on statistical considerations.

9.8. Data transformation

Data were entered into the study database as recorded on the abstraction form and as provided by the coordinating country investigator. Discrepancies between the diagnostic data received during the initial case report to the coordinating centre and the abstracted data from the medical record were resolved in favour of the medical record. Because medical records document presence, rather than absence, of medical information, presence of treatment of disease in the medical record would be recorded by the chart abstractor as a “yes.” If there was no documentation of a medication, including teriparatide, or a condition of interest in the medical record, but other medication and disease histories had been documented in the chart, the abstractor selected “No.” If there was no indication in the chart that a medication history or disease history had been documented, the abstractor selected “Unknown.” Responses of “No” and “Unknown” were treated the same analytically for the primary outcome and main study result. No additional coding, grouping, or other transformations were made.

9.9. Statistical methods

9.9.1. Main summary measures

Data abstracted from the medical records were summarised separately for patients with an ICD-O-3 code indicating osteosarcoma and for patients diagnosed with one of the five additional ICD-O-3 codes. For each of the following data domains, continuous variables were summarised with the mean, standard deviation and range of values; categorical elements were summarised as the number and percentage of patients with each characteristic.

- Osteoporosis history and treatments, including teriparatide
- Demographic characteristics
- Medical history
- Family history
- Lifestyle and environmental exposures

9.9.2. Main statistical methods

The statistical analysis was planned to compare the observed number of patients with osteosarcoma who had a possible or confirmed exposure to teriparatide to the number of exposed osteosarcoma cases expected to be identified by cancer registries. The number of patients treated with teriparatide expected to be diagnosed with osteosarcoma was calculated using the estimated size of the exposed population and background rate for osteosarcoma in the Nordic countries (i.e., assuming no association between drug exposure and disease).

The incidence rate for osteosarcoma was generated from population estimates for each country, as well as published population-based osteosarcoma incidence rates, instead of from the SSG registry as proposed in the study protocol as they were not available from the SSG registry for each country. Population estimates for adults aged 40 years or older during the time period of interest were based on available national statistics data for each country.[13-17] Because the population aged 40 years or older grew from approximately 12 million in 2004 to 13.24 million in 2013, the population at the approximate midpoint of the study (2008), 12.6 million people aged 40 years or older, was used for relevant estimates. Population-based osteosarcoma incidence rates for the five Nordic countries were referenced using an international resource for cancer incidence rates, *Cancer Incidence in Five Continents* (CI5), produced by the International Agency for Research on Cancer.[18] Age-adjusted (to the World Standard Population) overall incidence rates from CI5 were obtained for the five Nordic countries included in the study. An estimated annual incidence of 2 cases of osteosarcoma per 1 million people aged 40 years or older was applied to the exposed population at risk for the disease in each country to estimate the number of cases projected to occur. In addition, due to the variability of incidence regarding such a rare event in the population studied, we applied a higher incidence estimate for sensitivity analyses (Section 9.9.4) to evaluate whether the study conclusions would differ based on altering this underlying assumption.

Teriparatide exposure estimates were supplied by the study sponsor, based on the amount of medication sold to wholesalers and distributors in each country. Assumptions regarding the average daily dose and length of therapy were made, resulting in an estimated number of patients likely to have been exposed during the period of interest. These estimates assumed that all teriparatide distributed in the supply chain was subsequently taken by patients. These estimates lack information on the distribution of when new patients started on medication; therefore, we assumed an even distribution of patients receiving the medication per year over the period of interest.

Cumulative person-years at risk were extrapolated after *T* years by multiplying the estimated number of new patients who took teriparatide each year by the number of years since they first took drug.

$$\text{Person-years at risk} = P_T = \sum_{k=1}^{T} \left\{ F_k \cdot \left[T - \left(k - 1 \right) \right] \right\}$$

where

F_k = estimated number of patients treated with teriparatide in the Nordic countries in the *k*th year after launch.

T = total years since drug launch.

The total person-years at risk of event among patients treated with teriparatide was then adjusted for the mortality rate of adults aged 40 years or older using the age-specific crude mortality rates from Sweden for this age group.[19] Information on the age-sex distribution of teriparatide users in the Nordic countries could not be obtained. In the absence of such data from the Nordic countries, we adjusted the mortality rate to the age and sex distribution of teriparatide users in the United States (source: IMS LRx, 2003-2008 data, provided by Lilly Marketing, 10 April 2009).

The number of person-years at risk for the event was then multiplied by the estimated background incidence rate of osteosarcoma to derive the expected number of osteosarcoma cases among teriparatide users. The calculations assumed that treated patients remained at risk from the first date of drug exposure until end of the study period and that all patients with osteosarcoma diagnosed during the study period who had taken teriparatide in these countries were identified.

The study analysis plan specified that an incidence rate ratio would be estimated using formulas for the standardised mortality ratio.[20] For statistical evaluation of the main study result presented in Section 10.4 and the sensitivity analysis result presented in Section 10.5, we restricted the analysis to diagnosis years with more complete case coverage, which included diagnosis years 2004-2011. Data from 2012 and 2013 were excluded from these analyses given incomplete population coverage for these 2 years. Incomplete population coverage was due to the inherent lag time between the date of diagnosis and when data were reported to SSG registry for this component of the study. The descriptive analyses included data captured for all diagnosis years

in the 10-year study, which includes cases diagnosed on or after 1 January 2004 through the end of data collection on 31 December 2013.

9.9.3. Missing values

No imputations were performed.

9.9.4. Sensitivity analyses

Due to the variability in the background incidence in the Nordic population for such a rare event as osteosarcoma, the uncertainty regarding population coverage where national cancer registries did not participate, and the data extrapolation used from the wholesale supply chain to derive patient-level exposure estimates to the medication of interest, sensitivity analyses were carried out to address uncertainty around these assumptions to assess whether conclusions from the study would differ based on varying the assumptions.

9.9.5. Amendments to the statistical analysis plan

None.

9.10. Quality control

Data collection forms were reviewed at several steps during the data collection process according to RTI-HS's standard operating procedures and work practice documents for quality control. When completed data collection forms were received by the SSG from coordinating country investigators, personnel at the SSG reviewed the forms for completeness before sending the forms to RTI-HS. SSG personnel queried the coordinating country investigators to get additional information or clarification when needed.

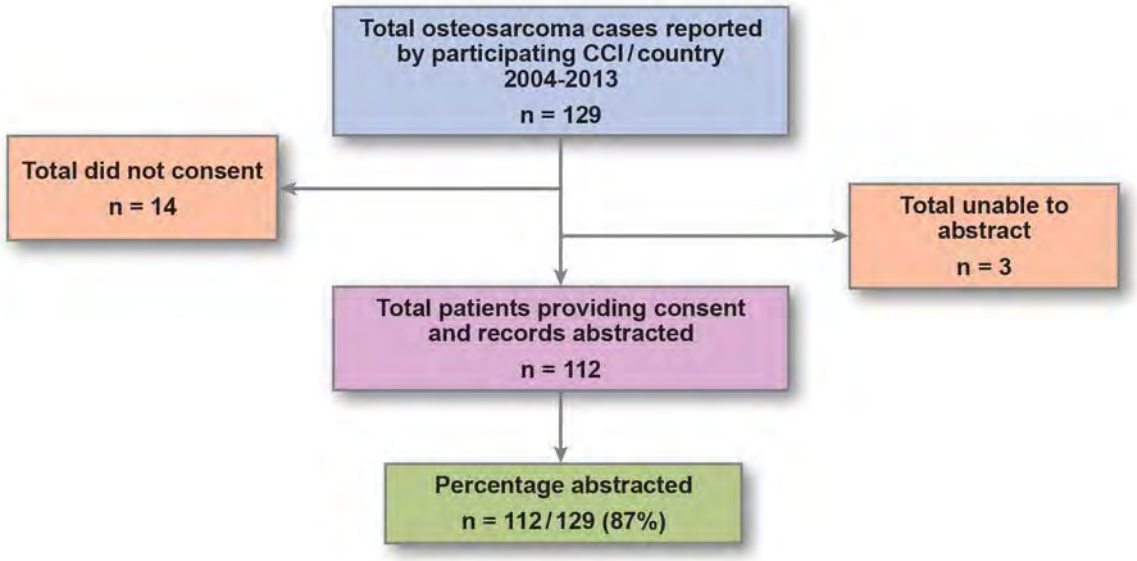
At RTI-HS, the data collection forms were reviewed for data discrepancies. The data were keyed into RTI-HS's software system using double-data entry (keying by two individuals), and a comparison was run to ensure that all values in the final data set were correct. After data entry was completed, RTI-HS staff performed another quality-control check by comparing 100% of the data entered into the study database against the hard copy data collection forms.

10. Results

10.1. Participants

At the conclusion of the study (31 December 2013), a total of 129 cases of osteosarcoma diagnosed since 1 January 2004, were reported by the five participating Nordic countries. Of these, consent for 115 patients was obtained, and records for 112 patients were abstracted (Figure 1). Additionally, 56 cases of one of the five additional ICD-O-3 codes were reported, consent was obtained for 48 of these patients, and 46 records were abstracted. Consent could not be obtained for 14 patients with osteosarcoma and for 8 patients with one of the five additional ICD-O-3 codes. There were 3 cases of osteosarcoma and 2 cases with one of the five additional ICD-O-3 codes for which the records could not be obtained for abstraction.

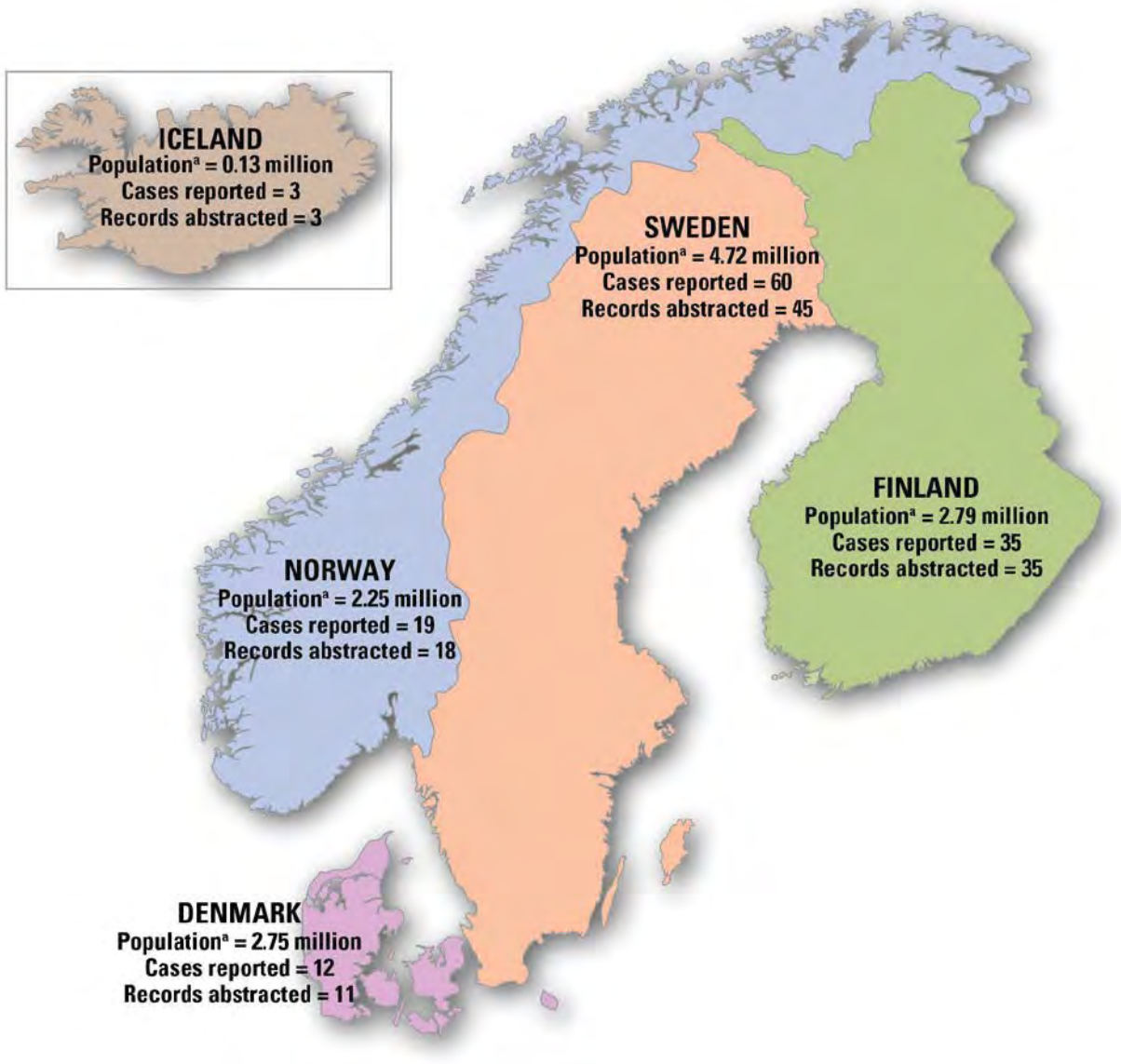
Figure 1. European Osteosarcoma Surveillance Study participants as of 31 December 2013



CCI = coordinating country investigator.

The estimated population of adults aged 40 years or older, obtained from national census estimates in the five countries as of 1 January 2008, was 12.6 million people. Figure 2 displays the population aged 40 years or older in each country and the total number of osteosarcoma cases reported to the study that were targeted for obtaining patient consent (or consent was waived) and the number abstracted. Sweden provided the largest share of the abstracted records, reflecting the population size (40%, 45 of 112), followed by Finland (31%, 35 of 112), Norway (16%, 18 of 112), Denmark (10%, 11 of 112), and Iceland (3%, 3 of 112).

Figure 2. Geographic distribution of osteosarcoma cases reported and medical records abstracted as of 31 December 2013



[a] Estimated population of adults aged 40 years or older by country as of the approximate midpoint of the study coverage period (1 January 2008) from national census estimates: Statistics Denmark,[13] Statistics Finland,[14] Statistics Iceland,[15] Statistics Norway,[16] and Statistics Sweden.[17]

10.2. Descriptive data

Descriptive results and the primary study outcome are presented for all cases diagnosed and reported since 1 January 2004 during the 10-year study duration. Data on patients with one of the five additional ICD-O-3 codes were captured to limit concern over potential diagnostic misclassification of patients who had true osteosarcoma. Because no teriparatide exposure was identified in either case group, we do not present descriptive results for the five additional ICD-O-3 codes in this section, but these results are provided in Annex 4.

10.2.1. Demographic profile

Of the 112 patients with osteosarcoma whose records were abstracted during the 10-year duration of the study, all were white, and more than half were men (56%). The mean age at the time of diagnosis of osteosarcoma was 60 years (range, 41-92 years) (Table 4). Nearly half of the patients were deceased (52 of 112) at the time they were reported to the SSG registry.

Table 4. Summary of demographic characteristics for patients with osteosarcoma with records abstracted (n = 112), overall and by country

Statistic or category	Denmark n (%)	Finland n (%)	Iceland n (%)	Norway n (%)	Sweden n (%)	Total n (%)
Number of cases	11	35	3	18	45	112
Age category (years)						
40-49	4 (36%)	4 (11%)	3 (100%)	8 (44%)	10 (22%)	29 (26%)
50-59	4 (36%)	9 (26%)		6 (33%)	11 (24%)	30 (27%)
60-69	1 (9%)	14 (40%)		3 (17%)	11 (24%)	29 (26%)
70-79		6 (17%)		1 (6%)	7 (16%)	14 (13%)
80-89	2 (18%)	2 (6%)			5 (11%)	9 (8%)
90-99					1 (2%)	1 (1%)
Age at diagnosis (years)						
Mean (SD)	57.5 (15.4)	62.5 (10.0)	45.8 (4.3)	53.8 (9.0)	61.1 (13.7)	59.6 (12.4)
Range	41 - 88	46 - 85	41 - 49	43 - 76	41 - 92	41 - 92
Sex						
Male	6 (55%)	22 (63%)		8 (44%)	27 (60%)	63 (56%)
Female	5 (45%)	13 (37%)	3 (100%)	10 (56%)	18 (40%)	49 (44%)

SD = standard deviation.

Among countries contributing data to the study, the average age at diagnosis was approximately 60 years of age except in Iceland (46 years of age) and Norway (54 years of age). The majority of patients were male, except for Norway, 56% (10 of 18) female, and Iceland, 100% (3 of 3) female.

10.2.2. Tumour morphology and topography

Of the 112 patients, 94 (84%) were diagnosed with osteosarcoma NOS (not otherwise specified), 14 with chondroblastic osteosarcoma, 2 with parosteal osteosarcoma, and 1 each with fibroblastic and telangiectatic osteosarcoma (Table 5). The tumour site varied, but there was predominance in the lower extremities, with more than half of the cases occurring in the legs and pelvic region.

Table 5. Summary of tumour characteristics, patients with osteosarcoma with records abstracted (n = 112)

Tumour designator	Category or location	Number (%)
ICD-O-3 code	9180 Osteosarcoma NOS	94 (84%)
	9181 Chondroblastic osteosarcoma	14 (13%)
	9182 Fibroblastic osteosarcoma	1 (1%)
	9183 Telangiectatic osteosarcoma	1 (1%)
	9192 Parosteal osteosarcoma	2 (2%)
Site of tumour	Leg bones	51 (46%)
	Skull/face/mandible	22 (20%)
	Pelvis/sacrum/coccyx	12 (11%)
	Scapula/hand/arm bones	8 (7%)
	Other	8 (7%)
	Ribs/sternum/clavicle	7 (6%)
	Breast	3 (3%)
	Vertebrae	1 (1%)

ICD-O-3 = International Classification of Diseases for Oncology, Third Edition; NOS = not otherwise specified.

10.2.3. Personal and family medical history

Nearly one-third of patients (30 of 112) had a recorded history of another type of cancer before the osteosarcoma diagnosis, and 25 patients had a recorded history of radiation treatment before the osteosarcoma diagnosis. Twelve patients had a recorded history of some kind of injury or infection at the site of the osteosarcoma (Table 6). Of the patients with osteosarcoma, 8 had a family history of breast cancer and 1 had a family history of leukaemia (Table 7).

Table 6. Medical history, patients with osteosarcoma with records abstracted (n = 112)

Question	Yes	No	Unknown or no response
B6. History of Paget's disease	1 (1%)	99 (88%)	12 (11%)
B10. History of bone fracture in medical record	15 (13%)	97 (87%)	
B11. History of injury or trauma/fracture to the bone; or infection of the bone at site of osteosarcoma tumour before osteosarcoma diagnosis	12 (11%)	99 (88%)	1 (1%)
B12. History of knee replacement, hip replacement, or orthopaedic implant	9 (8%)	102 (91%)	1 (1%)
B13. History of cancer before osteosarcoma diagnosis	30 (27%)	82 (73%)	
B7. History of Ewing's sarcoma		112 (100%)	
B8. History of Li-Fraumeni syndrome		112 (100%)	
B16. History of radioactive iodine treatment	1 (1%)	108 (96%)	3 (3%)
B17. History of radiation treatment before osteosarcoma diagnosis	25 (22%)	87 (78%)	
B18. Chemotherapy treatment before osteosarcoma diagnosis	11 (10%)	101 (90%)	
B9. History of primary or secondary hyperparathyroidism		112 (100%)	

Table 7. Family history, patients with osteosarcomas with records abstracted (n = 112)

Question	Yes	No	Unknown or no response
B19. Family history of osteosarcoma		68 (61%)	44 (39%)
B20. Family history of retinoblastoma		67 (60%)	45 (40%)
B21. Family history of breast cancer	8 (7%)	60 (54%)	44 (39%)
B22. Family history of leukaemia	1 (1%)	66 (59%)	45 (40%)
B23. Family history of brain cancer		67 (60%)	45 (40%)
B24. Family history of Paget's disease		66 (59%)	46 (41%)

10.2.4. Lifestyle and environmental exposures

Approximately half of the patients had a recorded history indicating they were current or former smokers, and nearly one-half consumed alcohol. A total of 21 patients were current smokers at the time of diagnosis, and 25 additional cases had stopped smoking. Three patients had been exposed to petrochemicals, and 1 had occupational exposure to pesticides (Table 8).

Table 8. Lifestyle and environmental exposures, patients with osteosarcoma with records abstracted (n = 112)

Question	Yes	No	Unknown or no response
B25. Current cigarette smoker	21 (19%)	68 (61%)	23 (21%)
B26. Former cigarette smoker	25 (22%)	34 (30%)	53 (47%)
B30. Alcohol consumption during 1 year before osteosarcoma diagnosis	53 (47%)	14 (13%)	45 (40%)
B32. History of environmental exposures	4 (4%)	53 (47%)	55 (49%)
Pesticides	1 (1%)	3 (3%)	108 (96%)
Petrochemicals	3 (3%)	2 (2%)	107 (96%)
Nuclear power	—	4 (4%)	108 (96%)
Nuclear waste	—	4 (4%)	108 (96%)

10.3. Outcome data

None of the 112 patients diagnosed with osteosarcoma whose records were abstracted had a history of teriparatide recorded in the medical record (Table 9). For one patient, the specific medication history of teriparatide treatment could not be determined (see Table 9). This patient did not have a history of osteoporosis or other medications for osteoporosis listed in the medical record. Four patients had a history of osteoporosis recorded in the medical record. No patients had a documented history of bisphosphonate use. Six patients had a history of supplement use (i.e., calcium or vitamin D or both).

In addition, of the 46 patients diagnosed with one of the five additional ICD-O-3 codes, none had a history of teriparatide use in the abstracted medical record (see Annex 4). Two patients had a history of osteoporosis, and 2 had history of bisphosphonate use.

Table 9. Osteoporosis history and treatments, patients with osteosarcoma with records abstracted (n = 112)

Question	Yes	No	Unknown or no response
B5. History of osteoporosis	4 (4%)	108 (96%)	
B14. History of teriparatide use	—	111 (99%)	1 (1%)[a]
B15. History of medication use			
Calcium	4 (4%)	67 (60%)	41 (37%)
Vitamin D	2 (2%)	69 (62%)	41 (37%)
Alendronate	—	107 (96%)	5 (4%)
Etidronate	—	107 (96%)	5 (4%)
Risedronate	—	107 (96%)	5 (4%)
Pamidronate	—	107 (96%)	5 (4%)
Tiludronate	—	107 (96%)	5 (4%)
Raloxifene	—	106 (95%)	6 (5%)
Estrogen, any delivery method (females only, n = 49)	7 (14%)	25 (51%)	17 (35%)
Testosterone, any delivery method (males only, n = 63)	—	37 (59%)	26 (41%)
Anabolic steroids	—	76 (68%)	36 (32%)
Growth hormones	—	72 (64%)	40 (36%)
Calcitonin	—	104 (93%)	8 (7%)
Glucocorticoids (continual use for at least 1 month)	6 (5%)	61 (54%)	45 (40%)

[a] The single male case in which the abstractor selected "Unknown" did not have a recorded diagnosis of osteoporosis in the medical record, making use of an osteoporosis drug in this patient unlikely.

10.4. Main results

Information was reported and captured during the entire period from 2004-2013. The time frame used for the main results analysis was diagnosis years 2004-2011, which included 109 abstracted records. Teriparatide was not available in Europe before 2004, and due to an average lag time between patient diagnosis and reporting to SSG of 1.4 years, full capture of cases was not possible for patients diagnosed after 2011. Two cases from diagnosis year 2012 and one case from 2013 (all from Norway) were abstracted. As noted in Section 10.3, Outcome data, no patients with osteosarcoma had a record of prior teriparatide exposure.

Table 10 displays the estimated background incidence rates and projected number of osteosarcoma cases, number of cases reported, and number of records abstracted for cases diagnosed from 2004-2011.The incidence rate was applied to the population in 2008 to estimate the number of osteosarcoma cases projected to occur during the 8-year period assuming complete coverage; however, the number of reported cases was lower than projected. The study abstracted data on 88% (109 of 124) of the reported osteosarcoma cases (Table 10). It is important to note that records for more than 90% of identified cases were abstracted in 4 of the 5 countries. In Sweden, records for only 75% of the cases were abstracted, and this lower proportion of abstracted data was due to lack of patient consent.

Table 10. Estimated, reported, and abstracted number of cases of osteosarcoma diagnosed 2004-2011, by country

Country	Population aged 40 years or older[a]	8 Years, estimated incidence[b]	8 Years, actual cases reported	8 Years, actual records abstracted
Denmark	2,753,529	44.1	12	11
Finland	2,790,114	44.6	35	35
Iceland	133,818	2.1	3	3
Norway	2,249,357	36.0	16	15
Sweden	4,717,365	75.5	58	45
Total	**12,644,183**	**202.3**	**124**	**109**

[a] Population estimates based on national statistics authorities in each country at the midpoint of the 8-year coverage period (1 Jan 2008). Sources: Statistics Denmark,[13] Statistics Finland,[14] Statistics Iceland,[15] Statistics Norway,[16] and Statistics Sweden.[17]

[b] Incidence rate used in the calculations is an annual rate of 2 cases per million population per year, based on country-specific incidence rates from CI5, volume X.[18]

The estimated cumulative number of patients treated with teriparatide from 1 January 2004 to 31 December 2011 is listed in Table 11.

Table 11. Estimated number of patients initiating teriparatide, 2004-2011

Country	Cumulative 8-year number of patients exposed[a]
Denmark	6,560
Finland	2,080
Iceland	80
Norway	880
Sweden	2,160
Total	**11,760**

[a] Source: Lilly internal data.

Based on information on drug use in the 5 Nordic countries, we estimate that 11,760 patients were exposed to teriparatide from 2004-2011. Assuming an even distribution of new patients initiating treatment each year, this would result in 43,272 cumulative person-years at risk (after adjusting for an observed mortality rate of 32 deaths per 1,000 patient-years). Using the background incidence rate of 2 osteosarcoma cases per million per year and assuming full coverage, the expected number of patients who took teriparatide that would be diagnosed with osteosarcoma is considerably less than one (0.087).

The incidence rate ratio based on 100% coverage of patients diagnosed with osteosarcoma (2004-2011), a background incidence rate of 2 cases per million per year, and assuming zero induction time and latency is 0 (90% confidence interval, 0-27).

10.5. Other analyses

As described in Section 9.9.4, a sensitivity analysis was performed to determine the effect of varying the observed person-time at risk for the event and the background incidence rate of all patients aged 40 years or older diagnosed with osteosarcoma.

Doubling the estimate of observed person-time calculated in Section 10.4 (43,272 × 2 = 86,544 person-years at risk for event), using a higher background incidence rate of osteosarcoma (i.e., 4 cases of osteosarcoma per million per year), and assuming full population coverage of patients diagnosed with osteosarcoma, the expected number of patients diagnosed with osteosarcoma with prior teriparatide treatment remains less than one (0.346).

10.6. Adverse events/adverse reactions

No adverse events associated with treatment were collected in this study.

11. Discussion

11.1. Key results

No instances of teriparatide exposure before diagnosis of osteosarcoma were observed in any of the five Nordic countries. These countries were selected for their high incidence of osteoporosis and therefore higher potential for treatment of osteoporosis compared with other European countries. In addition, the active participation by the SSG registry was considered a major strength in selecting the Nordic countries. As described in Section 9.1, due to the rarity of drug treatment in the Nordic countries and the low estimated background incidence rate of osteosarcoma in this population, no cases would have been expected assuming that risk of osteosarcoma was no greater among patients treated with teriparatide than the risk among those not treated.

This long-term case-series study of adult patients aged 40 years or older with osteosarcoma provides additional information relating to the demographics, tumour characteristics, and potential risk factors for a large number of patients where little information is readily available in the published literature. The mean age at diagnosis was 60 years; 56% were male and 100% were white. The most common morphology was osteosarcoma NOS, and the most common tumour site was the lower extremities, consistent with clinical expectations. In addition, approximately 20% of patients received radiation therapy before developing osteosarcoma; of these, 84% developed osteosarcoma in the same site or region as the radiation therapy.

11.2. Limitations

Although not considered a limitation, it is important to note that this European component of study GHBX was conducted to provide a population-based assessment to complement the ongoing US case-series study and the Forteo Patient Registry that form the complete study GHBX. The current status of these two additional long-term components of the Lilly surveillance programme, conducted in the US, is contained in Annex 5. No case of osteosarcoma with prior exposure to teriparatide was observed, but less than 1 case was expected, assuming that the treated population had the same incidence as the general population.

The preplanned calculation for the expected number of osteosarcoma cases with prior teriparatide exposure assumed that all patients with osteosarcoma diagnosed during the study period who had taken teriparatide would be identified in these countries. Treating physicians routinely report osteosarcoma cases to their regional or national cancer registry, and many (except those in Finland) also routinely report directly to the SSG registry. Because each of the countries has a national cancer registry intended to cover the entire population, it was theoretically possible to include all cases of osteosarcoma from these countries into the study (i.e., 100% coverage). However, there were only two countries, Finland and Sweden, where the national cancer registry reported all cases identified to the coordinating country investigator and subsequently to the SSG. In other countries, the national cancer registry did not report cases directly to the SSG, thus the overall coverage was reduced. In Iceland, cases reported to the study were cross-referenced against those captured by the Icelandic national cancer registry. In

Denmark and Norway, case reporting was much lower than anticipated considering the background rate of 2 cases of osteosarcoma per million per year. This underreporting was primarily attributable to non-participation by some medical centres who treated adult patients with osteosarcoma.

In 2012, the national cancer registries in Denmark and Norway were contacted to attempt to reconcile discrepancies between the number of osteosarcoma cases reported to the SSG from the coordinating country investigator in those countries and the total number of cases in the national registry database. Cases reported to the SSG and those captured by the cancer registry were compared using limited data available to share between the two databases (year of birth, sex, cancer site, ICD-O-3 code, date of diagnosis, and vital status at the time of case reporting). This comparison revealed that there were likely cases that had been reported to the SSG but not yet reported to the national registry. Additionally, there were cases reported to the registry but not included in the SSG study database. Owing to privacy restrictions that prohibited the national cancer registries from sharing identifiable information with the SSG, the case counts could not be reconciled. Additional efforts were made to encourage non-participating medical centres in these countries to report cases directly to the SSG. Although additional cases were identified, not all medical centres were willing to participate. Nonetheless, it is presumed that most cases were reported to the SSG. Furthermore, there is little basis to suspect that unreported cases differed from reported cases with respect to teriparatide exposure.

Given the background incidence rate of 2 cases per million per year, the number of cases identified in each country was lower than projected. It is possible that the background incidence rates reported in CI5[18] are overestimates. One mechanism that could lead to overestimation would involve cases initially reported to the national cancer registry by the treating physician as osteosarcoma but later reclassified as not osteosarcoma, with the correction being unreported to the national cancer registry.

Although it was not possible to determine the exact number of new patient starts on teriparatide during the study period, estimates based on units distributed in each country were provided by the study sponsor. The number of patients treated with teriparatide and therefore the number of person-years at risk following initial exposure to teriparatide in the five Nordic countries was low (< 45,000 person-years) and sufficient to detect only a large increased risk of osteosarcoma, if it existed.

Although it is well known that there is an induction and latency period from exposure to a carcinogen to the time cancer develops and is subsequently diagnosed, the expected number of osteosarcoma cases among exposed patients was determined assuming no induction period.

It is possible that exposure to teriparatide may not have been recorded in the medical records. However, information recorded in the abstracted records was, in general, comprehensive: the average duration captured in the medical records was nearly 8 years. Moreover, because other medications used to treat osteoporosis were recorded in the medical records for patients who had a history of osteoporosis, we are confident that teriparatide treatment would also have been recorded.

Finally, records for more than 90% of identified cases were abstracted in 4 of the 5 countries. In Sweden, records for only 75% of the cases were abstracted, and this lower participation was attributed to lack of patient consent.

11.3. Interpretation

This study collected information during a 10-year period of surveillance on patients with osteosarcoma in five Nordic countries and did not identify any patients with osteosarcoma with prior exposure to teriparatide. The same was true in the patients with one of the five other ICD-O-3 morphology codes that might have represented cases of misdiagnosed osteosarcoma. These findings are consistent with the US interim study results previously published by Andrews et al. in 2012,[1] which found that there were no reports of teriparatide use before diagnosis of osteosarcoma identified among 549 patients or proxies interviewed. As of 8 April 2014, 802 patients or proxies had been interviewed, and there were no reports of teriparatide use before diagnosis of osteosarcoma (see US interim report in Annex 6). Information on the progress of each of the studies has been reported in periodic safety update reports following drug approval. Across all three components of study GHBX, there were no patients with osteosarcoma with previous exposure to teriparatide.

11.4. Generalisability

The main limitation for generalisability is the limited amount of information stemming from the small number of exposed cases expected and observed.

12. Other information

None.

13. Conclusion

The European component of the Forsteo Osteosarcoma Post-Approval Surveillance Study was a 10-year surveillance study initiated in 2004 as part of a postmarketing regulatory commitment to evaluate a potential association between teriparatide and adult osteosarcoma in humans. The primary objective was to identify newly diagnosed cases of osteosarcoma among men and women aged 40 years or older in selected countries and identify incident osteosarcoma cases with a history of teriparatide treatment. Given the paucity of epidemiologic data on adult patients with osteosarcoma in the literature, a secondary objective was to collect additional patient information and data related to other risk factors for osteosarcoma. Descriptive data addressing the secondary objective were published in 2009.[12]

In this 10-year study, no patient diagnosed with osteosarcoma had prior teriparatide exposure, which is consistent with other published study findings.[1] Given the infrequent occurrence of osteosarcoma (2 cases per million population per year) and teriparatide use (11,760 patients treated in the 5 Nordic countries over 8 years) relative to the population size of these countries in the age group of interest (total population, 12.6 million people at the approximate midpoint of the study in 2008), we expected to identify patients with osteosarcoma previously treated with teriparatide in this study only if teriparatide were associated with a large increased risk. In other words, if a single case of osteosarcoma with prior teriparatide treatment had been observed in this Nordic study, it would indicate a 12-fold (90% confidence interval, 0.6-fold to 55-fold) increase in the risk of osteosarcoma associated with treatment compared with the background rate. This hypothetical 12-fold increase would translate to an absolute risk difference of 1 additional case of osteosarcoma per 47,000 teriparatide-treated patients per year.

In conclusion, the study results do not change the current overall benefit-risk profile of teriparatide.

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