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# Real-world effectiveness of teriparatide on fracture reduction in patients with osteoporosis and comorbidities or risk factors for fractures: Integrated analysis of 4 prospective observational studies

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ABSTRACT

*Introduction:* Teriparatide significantly reduces fracture rates in clinical trials; however, those study populations were relatively restricted and included too few patients to analyze fracture outcomes within clinically important patient subgroups. We assessed fracture outcomes in subgroups of osteoporosis patients from 4 real-world teriparatide observational studies.

*Methods:* Patients received teriparatide 20 μg/day for up to 24 months. Fracture rates were compared between 0 to 6 months versus > 6 months using a piecewise exponential model for first fracture. Analyses included incident clinical vertebral fractures (CVF) and nonvertebral fractures (NVF), and clinical fractures (CVF and NVF) by subgroups of gender, age < 75 or ≥75 years, diabetes, prior bisphosphonates use, rheumatoid arthritis (RA), glucocorticoid use, prior hip, and prior vertebral fracture.

*Results:* The population included 8828 patients (8117 women, 92%) with mean (SD) age 71 (10.6) years and teriparatide treatment duration 17.4 (8.6) months. Overall, CVF, NVF, clinical fracture, and hip fracture rates decreased by 62%, 43%, 50%, and 56%, respectively (all $p < .005$) for > 6 months versus 0 to 6 months. Subgroup analyses all showed significantly decreased rates after > 6 months except for NVF reduction in males (n = 710, fracture rate low during months 0 to 6) and in patients using glucocorticoids, and CVF in patients with prior hip fracture. The effects of teriparatide on CVF, NVF, and clinical fractures over time were statistically consistent in all subgroups except age for CVF ($p = .074$, patients < 75 years of age responded better), and diabetes for clinical fractures ($p = .046$, patients with diabetes responded better), although all of these subgroups experienced significant reductions over time. Glucocorticoids, prior bisphosphonate, and prior vertebral fracture were associated with increased CVF, NVF, and clinical fracture rates; RA, prior hip fracture and female gender were associated with higher NVF and clinical fracture rates; increased age was associated with higher CVF and clinical fracture rates.

*Conclusions:* Data from 4 real-world observational studies showed statistically significant reductions during

*Abbreviations:* BMD, bone mineral density; CVF, clinical vertebral fracture; DANCE, The Direct Assessment of Nonvertebral Fractures in Community Experience; EFOS, European Forsteo Observational Study; ExFOS, Extended Forsteo Observational Study; JFOS, Japan Fracture Observational Study; MedDRA, Medical Dictionary for Regulatory Activities; NVF, nonvertebral fracture; p-y, patient-years; RA, rheumatoid arthritis

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teriparatide treatment in rates of CVF, NVF, and clinical fractures in clinically relevant patient subgroups. These results should be interpreted in the context of the non-controlled design of the source studies.

## 1. Introduction

Teriparatide [recombinant human parathyroid hormone (1–34)] stimulates bone formation and is approved worldwide for the treatment of men and postmenopausal women with osteoporosis at high risk for fracture and in some geographies for the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture.

Teriparatide reduced osteoporotic fracture risk in clinical trials compared with placebo [1] or oral bisphosphonates [2–4], and in observational studies [5–8]. While randomized, controlled trials remain the gold standard in establishing the efficacy of therapies in defined populations, they also exclude many patients, including prior or concomitant therapies, and include visit structures, interactions, information collection, and other factors that may differ substantially from common clinical practice [9]. Thus, observational studies may be useful to assess the effectiveness of drugs in the setting of community care of patients having particular comorbid conditions, risk factors, or prior therapies.

The Direct Assessment of Nonvertebral Fractures in Community Experience (DANCE) [7], European Forsteo Observational Study (EFOS) [5], Extended Forsteo Observational Study (ExFOS) [6], and Japan Fracture Observational Study (JFOS) [8] were prospective, observational studies conducted at a large numbers of sites in the United States, Europe, and Japan, respectively. Each assessed fracture rates during up to either 18 to 24 months of teriparatide therapy in patients selected according to normal clinical practice and the local approved label. In a separate report, we have presented detailed analysis of fracture rates for clinical vertebral fracture (CVF), nonvertebral fracture (NVF), clinical fracture, hip fracture, and wrist fracture in the combined study population (submitted). In the present report, we used the combined database to examine rates of CVF, NVF, and clinical fractures during teriparatide treatment in clinically relevant subgroups.

## 2. Materials and methods

### 2.1. Study designs and populations

DANCE, EFOS, ExFOS, and JFOS were multicenter, prospective, observational studies to examine the long-term effectiveness, safety, and tolerability of teriparatide in a community-based population of men and women (or women only, in EFOS). These studies were conducted in the USA, Japan and 12 European countries (Supplemental Table 1), and the results have been reported previously for each study [5–8]. Patients were enrolled based on the local product labeling and investigators' clinical judgment on the appropriateness of teriparatide treatment. Contraindications or warnings to the use of teriparatide included increased baseline risk for osteosarcoma, including Paget's disease of the bone, unexplained elevation of serum alkaline phosphatase, open epiphyses, or a history of prior radiation therapy involving the skeleton. Bone metastases, skeletal malignancy, or any active metabolic bone disease other than osteoporosis, and a pre-existing history of hypercalcemia or hypersensitivity to the drug were additional contraindications or warnings to teriparatide use. In all studies, patients received 20 μg teriparatide per day by subcutaneous injection; teriparatide was not provided by the sponsor. The lengths of treatment were up to 18 months in EFOS and up to 24 months in DANCE, ExFOS, and JFOS, although in ExFOS reimbursement was limited to 18 months in France and Sweden. Additional details for the individual studies are shown in Supplemental Table 1.

Patients were included in these analyses if they received a teriparatide prescription from the study physician, consented to release information, and had treatment start and stop dates. Study physicians conducted patient care, including diagnostic and therapeutic interventions, according to their clinical judgment and the local standard of medical care. Patients typically underwent a visit soon after beginning therapy to assess compliance and address any questions and then subsequently had visits at approximately 3- to 6-month intervals, depending on local standards; specific visits were not explicitly required for participation.

All patients gave written informed consent; the study physician was responsible for ensuring that patients gave consent to release information. Patients could withdraw from participation in the study without consequence at any time. Each study was approved by local ethics committees or review boards, depending on the local requirements for each participating country, and was performed in accordance with the Declaration of Helsinki Good Clinical Practice guidelines.

### 2.2. Fracture definitions

A CVF was defined as signs and/or symptoms suggestive of vertebral fracture confirmed by a new or worsened vertebral fracture by radiography. That definition would exclude pure morphometric (clinically asymptomatic) vertebral fractures. NVF were collected based on patient self-report, investigator opinion, or radiographic or surgical report, in DANCE, ExFOS, and JFOS, but were confirmed by the clinician in the EFOS study; a list of sites recorded for NVF is provided in Supplemental Table 1. Clinical fractures were a composite of CVF and NVF.

### 2.3. Subgroup definitions

Data were recorded on prior and comorbid conditions in each study. For the DANCE, EFOS, and ExFOS studies, specific conditions were queried in the case report forms. For JFOS, conditions were collected using medical history coded into MedDRA. The diabetes mellitus subgroup was defined by any reported presence of diabetes, as diabetes type was not recorded in all studies. Definitions for rheumatoid arthritis (RA) included, depending on the study, patients with current or past RA; or rheumatoid arthritis per MedDRA. Glucocorticoid use was defined as recorded systemic glucocorticoid use at baseline or postbaseline, or either glucocorticoid-induced osteoporosis or glucocorticoids recorded as the reason for teriparatide use. Bisphosphonate use was defined as any prior or ongoing bisphosphonate use. Prior hip fracture was defined as any previous hip fracture. Prevalent vertebral fracture was based on radiographic assessment and/or physician report. Detailed information about these conditions was not collected.

### 2.4. Statistical analysis

Analyses were performed on the modified intent-to-treat population. The analysis approach and subgroups for investigation were prespecified prior to the integration of the studies. Statistical tests were 2-sided at the 0.05 level except for interactions, where a 0.10 level of significance was used.

These observational studies did not include control arms. Accordingly, the first 6 months of treatment were considered a reference period for fracture rate, based on the rates of NVF in the teriparatide and placebo groups separating after approximately 7 to 9 months in the Fracture Prevention Trial [1,10]. The fracture rate during this reference period was compared with the fracture rates in the