

The Direct Assessment of Nonvertebral Fractures in Community Experience (DANCE) study: 2-year nonvertebral fragility fracture results

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Received: 18 June 2012 / Accepted: 3 January 2013 / Published online: 12 February 2013
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Abstract

Summary This observational study evaluated the occurrence of nonvertebral fragility fractures (NVFX) in over 4,000 men and women with osteoporosis treated with teriparatide (TPTD). The incidence of new NVFX decreased for patients receiving TPTD treatment for greater than 6 months. No new significant safety findings were observed in this large trial.

Introduction The Direct Assessment of Nonvertebral Fractures in Community Experience (DANCE) study evaluated the occurrence of NVFX in patients receiving TPTD for osteoporosis in a real-world setting.

Methods DANCE is a multicenter, prospective, observational trial that examined the long-term effectiveness of TPTD in men and women with osteoporosis whom study physicians judged to be suitable for TPTD therapy. Patients received 20 µg TPTD per day by subcutaneous injection for

up to 24 months and were followed for 24 months after treatment cessation. The incidence of patients experiencing a new NVFX, defined as a fracture associated with low trauma, was evaluated during four 6-month periods in both the treatment and cessation phases with >0 to ≤6 months serving as the reference. We also observed the spectrum and occurrence of serious adverse events.

Results Of the 4,167 patients enrolled, 4,085 took one or more doses of TPTD (safety population); 3,720 were included in the efficacy analysis. The incidence of patients experiencing a NVFX was 1.42, 0.91, 0.70, and 0.81 % for the four treatment periods, respectively, and 0.80, 0.68, 0.33, and 0.33 % for the four periods after treatment cessation. Differences for each period were statistically significant compared with the reference period (first 6-month interval, each $p < 0.05$). No new significant safety findings were observed.

Conclusions In this study, the incidence of NVFX decreased for patients receiving TPTD for all three treatment periods >6 months compared to 0 to ≤6 months, and this trend persisted throughout the cessation phase. TPTD was generally well tolerated.

Keywords DANCE · Nonvertebral fracture · Osteoporosis · Parathyroid hormone · PTH · Teriparatide

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Introduction

Teriparatide [rhPTH(1–34), TPTD], a once-daily subcutaneous injection, is the only bone-forming agent approved by the US Food and Drug Administration for treatment of men and postmenopausal women with osteoporosis at high risk

for fracture. Teriparatide is also approved for treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture. The effects of TPTD on the reduction of vertebral and nonvertebral fractures have been demonstrated in clinical trials and observational studies [1–3].

This report focuses on the incidence of nonvertebral fragility fractures (NVFX) following treatment with TPTD, which has been evaluated in several studies. For example, the Fracture Prevention Trial (FPT) was a randomized, placebo-controlled clinical trial designed to evaluate the impact of TPTD treatment on vertebral and nonvertebral fractures, including NVFX. In the FPT, nonvertebral fractures were classified as fragility fractures if, in the opinion of the local investigator, the fracture was caused by minor trauma insufficient to cause a fracture in normal, healthy adult women. Results demonstrated that women treated with 20 µg TPTD per day had a significant reduction (53 %, $p=0.02$) in the risk of new NVFX compared to women receiving placebo [1]. The cumulative incidence of one or more new nonvertebral fractures or NVFX was initially similar in the study groups; the protective effects of TPTD treatment became evident after 9 to 12 months and became significantly different at the end of the trial ($p<0.05$) [1].

A post hoc analysis of data from the FPT evaluated the impact of duration of TPTD treatment on the occurrence of vertebral and nonvertebral fractures [2]. The results indicated that the relative hazard for NVFX decreased by 7.3 % for each additional month of treatment with 20 µg TPTD per day compared with placebo. Clinical vertebral fractures appeared to increase over time in the placebo group and occurred primarily in the first time interval (0 to 6 months) in the TPTD treatment group. These findings indicate that increased duration of TPTD versus placebo treatment was associated with a progressive decrease in the rates of new NVFX [2].

The pivotal phase 3 TPTD clinical studies were initiated when few therapeutic options for osteoporosis were available. Only about 15 % of study participants had received prior antiresorptive therapies [1]. Since that time, the therapeutic landscape has changed with availability of a selective estrogen receptor modulator and several bisphosphonates, as well as a RANK ligand inhibitor (denosumab) that is approved for the prevention and/or treatment of osteoporosis. Furthermore, the experience in randomized, placebo-controlled clinical trials may differ from that in community practice [4]. Therefore, there is a need to observe fracture occurrence in patients taking TPTD in the context of a real-world clinical practice, which includes those who are treatment naïve and those who have received prior antiresorptive therapy. Observation of fracture and safety endpoints in a setting that more closely resembles a real-world practice was expected to provide practical information for the prescribing

physician. The Direct Assessment of Nonvertebral Fractures in Community Experience (DANCE) study was designed using an observational methodology to assess the clinical effectiveness, safety, and tolerability of TPTD in a larger, more diverse patient population than when it was studied in controlled clinical trials. An observational study is defined as, “a type of nonrandomized study in which the investigators do not intervene, instead simply observing the course of events” [5].

The primary goals of the DANCE study were to evaluate the occurrence of new NVFX in patients treated with TPTD for osteoporosis for up to 24 months in a community-based setting, and then followed for 24 months post-TPTD treatment, and to observe the spectrum and occurrence of serious adverse events (SAEs) in this large study population.

Methods

Study design and participants

The DANCE study is a multicenter, prospective, observational trial designed to examine the long-term effectiveness, safety, and tolerability of TPTD in a community-based population of men and women judged by study physicians to be suitable for TPTD therapy [6]. Patients received 20 µg TPTD per day by subcutaneous injection for up to 24 months and then were followed for another 24 months after treatment cessation. This paper reports the incidence of new NVFX during the treatment phase of the study, which was defined as the completion of 18 to 24 months of treatment (i.e., a full course of therapy) and the incidence of NVFX that occurred during the 24 months after cessation of treatment with TPTD (cessation phase).

All patients who received a TPTD prescription from their study physician, who consented to release the information, and for whom treatment initiation was documented, were included in the overall analysis. Patients who had been administered TPTD for more than 2 weeks directly before study entry were not eligible for enrollment. The protocol instructed that, in accordance with product labeling, certain patients were to be excluded if they had an increased baseline risk for osteosarcoma, including those that had Paget’s disease of the bone, unexplained elevation of serum alkaline phosphatase, open epiphyses, or a history of prior radiation therapy involving the skeleton. As per product labeling, it was recommended that patients with bone metastases, skeletal malignancy, or any active metabolic bone disease other than osteoporosis should not receive TPTD, as well as patients who had a pre-existing history of hypercalcemia or hypersensitivity to TPTD [7] or any of its excipients. Product labeling was provided to investigators for reference. Treatment with TPTD is limited to 24-month duration by the

product label. Adherence to these instructions by individual investigators was not monitored.

All aspects of patient care, including diagnostic and therapeutic interventions, were chosen and conducted at the discretion of the participating study physicians according to their clinical judgment and the local standard of medical care. Patients participating in this study were prescribed TPTD as part of routine clinical practice. Thus, Eli Lilly and Company (the manufacturer) did not provide TPTD as part of this study.

In keeping with the observational design of this study, specific patient visits were not mandated. It was anticipated that patients who were prescribed TPTD were likely to undergo medical evaluation at approximately 6-month intervals because (1) they were at high risk for fracture and (2) they had initiated a new treatment for osteoporosis. In addition, study physicians could choose to evaluate patients 1 to 2 months after starting TPTD therapy to assess compliance with treatment and to address questions about the injection device (pen).

Main outcome measures

The primary hypothesis of the DANCE study was that longer duration of therapy with TPTD would be associated with a progressive reduction in risk of NVFX. The primary efficacy variable was the occurrence of new NVFX in patients treated with TPTD for up to 24 months. The efficacy analysis was based on the duration of treatment with TPTD. Therefore, the efficacy population included those patients for whom we had available dates for starting and stopping TPTD therapy.

Nonvertebral fracture sites recorded included the ankle, clavicle, distal forearm, fingers, foot, hand, hip, humerus, knee, leg, pelvis, rib, shoulder, skull, sternum, and toes. Fragility fracture was defined as a fracture associated with low trauma, such as a fall from standing height, and was based on either patient self-report, investigator opinion, or x-ray report. Patients were also followed for 24 months after the treatment phase, and NVFXs were recorded by the investigators during the 24-month cessation phase.

Serious adverse events were collected in all patients who received at least one dose of TPTD during the entire treatment phase plus 30 days after cessation of treatment and if the SAE was deemed to be related to TPTD during the 24-month cessation phase.

Statistical methods

In this analysis, treatment exposure was defined as follows: if a patient discontinued treatment for more than 3 months, he or she was considered discontinued from the treatment due to noncompliance (even if TPTD therapy was resumed

later); if a patient resumed TPTD treatment after stopping it for 3 months or less, he or she was considered to have received continuous treatment regardless of the intermittent gap(s).

The percentage of patients experiencing a new NVFX while receiving treatment with TPTD was assessed during four treatment periods: >0 to ≤ 6 , >6 to ≤ 12 , >12 to ≤ 18 , and >18 to ≤ 24 months. The incidence of patients reporting new NVFX during the three later TPTD treatment periods was compared to the proportion receiving treatment for >0 to ≤ 6 months (the reference period) using a binomial proportion test. The >0 to ≤ 6 months of treatment period was chosen as the reference since Kaplan–Meier analysis of NVFX in the FPT showed that the TPTD and placebo groups appeared to begin to separate after approximately 9 months of study drug [1]. Incidence was defined as the number of patients with a new NVFX divided by the total number of patients at risk $\times 100$. The 24-month cessation phase also was divided into 6-month periods, and the incidence of NVFX was calculated in the same way as during the treatment phase. The baseline for the cessation phase was defined as the >0 to ≤ 6 months interval of the treatment phase.

The number of patients at risk for a given treatment period was defined as the total number of patients whose treatment duration overlapped with the given treatment duration. For example, the number of patients at risk for the >0 to ≤ 6 months interval were those who received at least one dose of study drug; the number of patients at risk for the >6 to ≤ 12 months interval were those whose treatment duration was longer than 6 months and did not experience a NVFX before 6 months. Patients who experienced a NVFX in a specific period were excluded from the risk set of the next consecutive intervals. The number of patients with a new NVFX was defined as the number of patients whose first NVFX happened during the given period. The number of patients at risk for the cessation phase was defined as the number of patients who completed treatment and had not had a NVFX. The cessation phase intervals were divided into 6-month periods, and patients who experienced a NVFX in a specific period were excluded from the risk set of the next consecutive intervals.

Ninety-five percent confidence intervals for the single proportion were calculated using the Clopper–Pearson analysis [8]. Differential treatment effect over time was tested from a one-sample binominal proportion test on fracture incidence for each time interval after 6 months of therapy versus the first 6-month treatment period (reference). Analysis by gender subgroup was also performed. Unless otherwise noted, all tests of statistical inference were conducted at a two-sided significance level of 0.05.

A sample size of 4,000 patients was calculated to have approximately 80 % power to detect a reduction in the

absolute fracture rate by 0.8 % from 0–6 to 18–24 months, including a 50 % dropout rate with a maximum duration of treatment of 24 months. As a secondary objective, the spectrum and occurrence of SAEs while on therapy was analyzed after the first dose of TPTD.

Ethics

The study protocol was approved by the study center Ethical Review Boards, and all patients provided written consent to release information before enrollment. The study was conducted in accordance with regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996).

Results

Participant characteristics

Of the 4,167 patients enrolled between August 2004 and February 2007 at 198 US investigator sites, 4,085 started open-label treatment phase with TPTD (safety population), 3,720 were included in the 24-month treatment phase (and comprised the efficacy population), and 1,066 completed the 24-month cessation phase (Fig. 1). Baseline characteristics for those patients included in the efficacy analysis are presented in Table 1. The mean age of the female patients was 68.3 years (standard deviation [SD]=11.5 years) and that of male patients was 65.1 years (SD=13.1 years); the men were significantly younger than the women ($p<0.001$). The majority of women (87.8 %) and men (92.1 %) were Caucasian. Significantly more women than men had a family history of osteoporosis (39.8 versus 28.5 %, $p<0.001$) and had previously been treated for osteoporosis (88.4 versus 61.5 %, $p<0.001$). Women also had a lower mean lumbar spine bone mineral density (BMD) T-score (-2.51 versus -2.21 , $p=0.003$), and lower mean total hip BMD T-score (-2.20 versus -1.97 , $p=0.002$) than men at baseline. Significantly fewer women than men reported using alcohol (24.8 versus 33.6 %, $p=0.001$) and smoking (12.8 versus 16.8 %, $p=0.033$).

A total of 1,421 of 3,720 (38.2 %) patients were discontinued prior to month 18 and 2,426 of 3,720 (65.2 %) were discontinued prior to month 24; 1,294 of 3,720 patients (34.8 %) completed 24 months of therapy. The primary reasons for discontinuations prior to completing a full course of therapy (i.e., ≥ 18 months) were the patient's and physician's decisions. The mean TPTD exposure (for men and women combined) was 18 months, and the median TPTD exposure was 23 months.

Some patients may have received TPTD for more than 24 months, even though the labeling for TPTD limits therapy to 24 months. However, in many cases, duration of

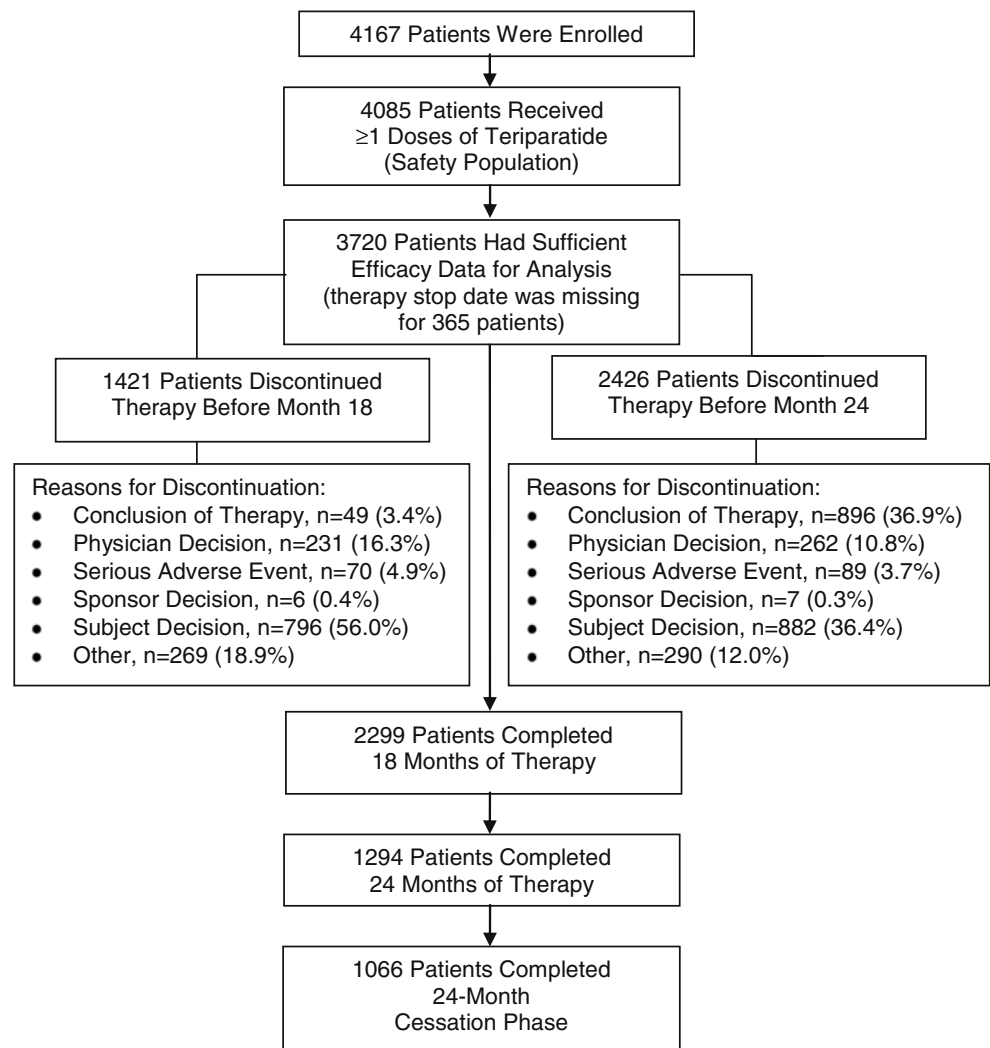
greater than 24 months of TPTD therapy was recorded due to the method of reporting data in this observational study. For example, there may not have been a scheduled visit to collect the date that TPTD was stopped or the next scheduled visit at which this date was recorded could have occurred after the 24-month calendar time point. The sponsor asked physicians to use TPTD according to product labeling but did not intervene with clinical decision making.

Incidence of nonvertebral fragility fractures

The incidence of patients experiencing new NVFX during the four TPTD treatment periods was 1.42, 0.91, 0.70, and 0.81 %, respectively (Table 2). The incidence of new NVFX occurring during each of the three TPTD treatment periods was significantly lower than the incidence during the reference treatment period of >0 to ≤ 6 months ($p<0.05$ for all comparisons). Compared to the reference period, the incidence of new NVFX was 36, 51, and 43 % lower when patients were treated for periods of 6 to 12, 12 to 18, and 18 to 24 months, respectively. During the 24-month cessation phase, the incidence of patients experiencing new NVFX was 0.80, 0.68, 0.33, and 0.33 % during the four periods, respectively. As shown in Table 2 and Fig. 2, the incidence of new NVFX occurring during each of the four cessation periods was significantly lower than the incidence during the reference treatment period of >0 to ≤ 6 months ($p<0.05$ for all comparisons).

Fracture sites included, in decreasing order of frequency, the distal forearm ($n=21$), foot/toes ($n=20$), hip ($n=16$), rib ($n=14$), "other" sites ($n=14$), leg ($n=9$), hand/fingers ($n=7$), pelvis ($n=7$), knee ($n=7$), ankle ($n=6$), humerus ($n=3$), shoulder ($n=2$), skull ($n=1$), breastbone ($n=0$), and clavicle ($n=0$). "Other" sites were not specifically identified by patients but were considered sites other than the following: ankle, arm (humerus), breast bone (sternum), collarbone (clavicle), distal forearm (wrist), foot/toes, hand/fingers, hip, knee, leg, pelvis, ribs, shoulder, skull, spine L1-L4, and spine T4-T12. Most fractures were either self-reported or confirmed by x-ray report. The incidence of fractures was not compared by type of fracture or whether fractures were self-reported versus radiologically confirmed due to the small sample sizes in the subgroups. Many osteoporosis studies exclude fractures of fingers and toes in the NVFX analysis. We performed an additional analysis that excluded foot/toes, hand/fingers, and "other sites" (which was a separate category). The findings were very similar to those reported, which included all NVFXs (data for additional analysis not shown).

When the efficacy population was analyzed by gender (Table 3), the incidence of new NVFX in women was significantly lower for each of the three later treatment periods compared with the >0 to ≤ 6 months reference period

Fig. 1 Study flow diagram

(each $p < 0.05$), while significant differences did not emerge in any group for the men. However, there were only a small number of fracture events ($n=6$) in the male cohort, which may have limited the ability to detect differences.

As shown in Table 4, a significantly greater percentage of patients who reported a new NVFX had a prior fragility fracture compared to patients with no new fracture. Also, patients with a new NVFX had a significantly greater mean number of comorbid conditions.

Safety

Based on preclinical rodent studies of TPTD, osteosarcoma surveillance has represented a special focus. In clinical trial studies starting in the mid-1990s, there have been no reports of osteosarcoma in patients who have received TPTD either during the clinical trial or following completion of the clinical trials. The DANCE study represents the largest observational study involving

TPTD. Of the 4,085 patients who comprised the safety population, there were no reports of osteosarcoma during the 24-month treatment phase. Furthermore, there were no reports of osteosarcoma in an additional 24 months of follow-up after cessation of treatment.

In reviewing safety information from DANCE, it is important to note that this was not a controlled clinical trial. It was a prospective, observational study. There was no placebo control group. The study did not contain randomized treatment group assignments because it was non-interventional and observational in design. The study occurred in a naturalistic setting with all care provided by the participating study physicians according to their clinical judgment.

The study population in DANCE was elderly with severe osteoporosis and at high risk for fractures. Typically, the study participants had several comorbid conditions and were taking multiple concomitant medications. Collection of safety information was appropriate for an observational study with this patient population. Only

Table 1 Baseline characteristics of the DANCE study cohort

Baseline characteristic	Women (<i>n</i> =3,350)	Men (<i>n</i> =369)	Overall (<i>n</i> =3,720 ^a)
Age, years (mean, SD)	68.3 (11.5)***	65.1 (13.1)	68.0 (11.7)
Ethnicity (<i>n</i> , %)			
African	52 (1.6)	5 (1.4)	57 (1.5)
Asian	10 (0.3)	1 (0.3)	11 (0.3)
Caucasian	2,942 (87.8)	340 (92.1)	3,282 (88.2)
East Asian	25 (0.7)	4 (1.1)	29 (0.8)
Hispanic	302 (9.0)	19 (5.1)	321 (8.6)
Other	18 (0.5)	0 (0.0)	18 (0.5)
Lumbar spine T-score (mean, SD)	−2.51 (1.36)**	−2.21 (1.57)	−2.48 (1.38)
Femoral neck T-score (mean, SD)	−2.45 (0.92)	−2.35 (0.91)	−2.44 (0.92)
Total hip T-score (mean, SD)	−2.20 (1.00)**	−1.97 (0.96)	−2.18 (0.99)
Prior fragility fracture (% yes)	56.7	59.1	57.0
Prior osteoporosis therapy (% yes) ^b	88.4***	61.5	85.7
Patients with comorbid conditions (% yes) ^c	83.1	83.5	83.1
Number of comorbid conditions (mean, SD)	1.79 (1.41)	1.91 (1.51)	1.80 (1.42)
Family history of osteoporosis (% yes)	39.8***	28.5	38.6
Smoking (% yes)	12.8	16.8*	13.2
Alcohol use (% yes)	24.8	33.6***	25.7
Caffeine (% yes)	71.2	71.3	71.2

DANCE Direct Assessment of Nonvertebral Fractures in Community Experience, SD standard deviation

* $p < 0.05$; ** $p < 0.01$; *** $p \leq 0.001$ for difference between women and men

^a Gender information was missing for one patient

^b Includes prescription osteoporosis medications only

^c Comorbid conditions that contribute to increased fracture risk

SAEs were collected. Given the above framing considerations, there were no new significant safety findings

identified during the study. In controlled clinical trials, possible hypercalcemia events were carefully studied.

Table 2 Incidence of new nonvertebral fragility fractures

Duration (months)	Number of patients with a new NVFX ^a	Number of patients at risk	Incidence (95 % CI) ^b	<i>p</i> value ^c
Treatment phase				
>0 to ≤6	53	3,720	1.42 (1.07, 1.86)	NA
>6 to ≤12	27	2,970	0.91 (0.60, 1.32)	0.0177
>12 to ≤18	18	2,570	0.70 (0.42, 1.10)	0.0019
>18 to ≤24	18	2,225	0.81 (0.48, 1.28)	0.0143
Cessation phase				
Baseline ^d	53	3,720	1.42 (1.07, 1.86)	NA
>0 to ≤6	16	2,008	0.80 (0.46, 1.29)	0.0176
>6 to ≤12	12	1,757	0.68 (0.35, 1.19)	0.0087
>12 to ≤18	5	1,536	0.33 (0.11, 0.76)	0.0003
>18 to ≤24	4	1,227	0.33 (0.09, 0.83)	0.0012

NVFX nonvertebral fragility fractures, NA not applicable

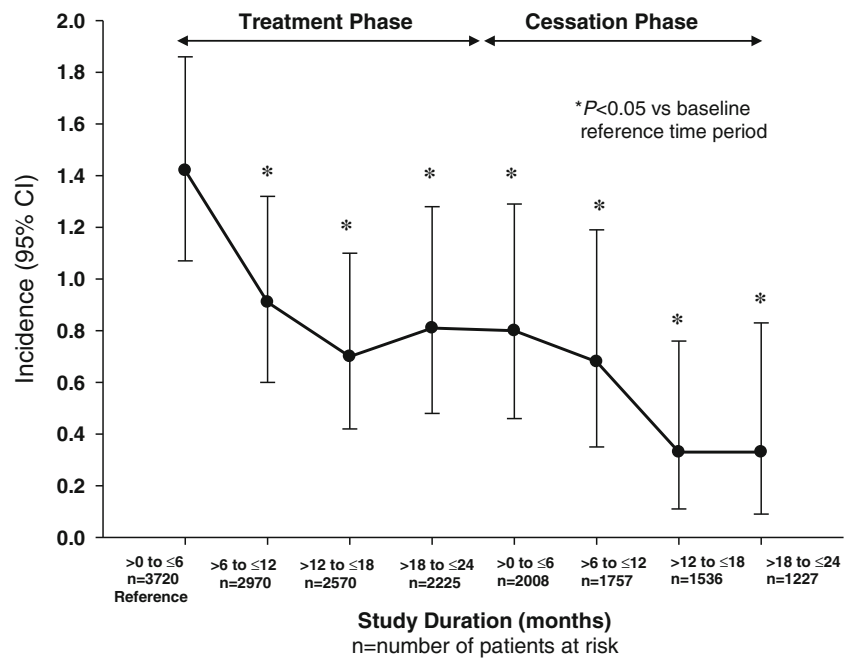
^a Number represents total of men and women combined

^b Incidence=number of patients with new NVFX/number of patients at risk×100

^c *p* value from a one-sample binominal proportion test versus the first period incidence rate (reference period)

^d Baseline for the cessation phase is defined as >0 to ≤6 months (reference period)

Fig. 2 Incidence of NVFX during treatment with TPTD and after treatment cessation. Incidence=number of patients with new NVFX/number of patients at risk×100



During the DANCE study, only two patients were discontinued from the study due to hypercalcemia.

Approximately 432 of 4,085 patients (10.6 %) in the safety population experienced at least one SAE. No individual SAE exceeded 1 %, with the highest event terms being pneumonia (0.9 %) and fall (0.9 %). At the System Organ Class level of aggregation, the highest frequency was “infections and infestations” (2.4 %). Overall, TPTD was adequately tolerated and no new significant safety patterns were identified.

Discussion

In this study, the incidence rate of NVFX decreased with duration of TPTD treatment beyond 6 months compared with 0 to 6 months of treatment. These results are largely consistent with previous TPTD studies. For example, the European Forsteo Observational Study (EFOS) [3] was

designed to examine the effectiveness of TPTD in postmenopausal women with osteoporosis treated for up to 18 months in normal clinical practice in eight European countries. Among other variables, the incidence of clinical vertebral fractures and NVFX was assessed. Of the 168 reported fractures, 61.3 % were nonvertebral; 50.6 % of all fractures occurred at the main nonvertebral sites (forearm/wrist [n=26], hip [n=21], leg [n=15], sternum/ribs [n=12], and humerus [n=11]). A 47 % decrease in the odds of fracture in the last 6-month period compared to the first 6-month period was observed (p<0.005). The clinical vertebral and main nonvertebral fracture rates were significantly decreased between the first 6-month period and the last 6-month period of treatment. The authors concluded that postmenopausal women with severe osteoporosis who were prescribed TPTD in standard clinical practice had a significant reduction in the incidence of fragility fractures over an 18-month treatment period.

Table 3 Incidence of nonvertebral fragility fractures by gender during the treatment phase

Duration (months)	Gender	Number of patients with new NVFX	Number of patients at risk	Incidence (95 % CI) ^a
>0 to ≤6	Female	50	3,350	1.49 (1.11, 1.96)
	Male	3	369	0.81 (0.17, 2.36)
>6 to ≤12	Female	25	2,665	0.94* (0.61, 1.38)
	Male	2	305	0.66 (0.08, 2.35)
>12 to ≤18	Female	17	2,306	0.74** (0.43, 1.18)
	Male	1	264	0.38 (0.01, 2.09)
>18 to ≤24	Female	18	2,003	0.90* (0.53, 1.42)
	Male	0	222	0.00 (0.00, 1.65)

NVFX nonvertebral fragility fractures

*p<0.05; **p<0.01 compared to the incidence rate from >0 to ≤6 months (reference period)
^aIncidence=number of patients with NVFX/total patients at risk×100

Table 4 Baseline characteristics of patients who reported new nonvertebral fragility fractures during the study versus those who did not report a new NVFX

Baseline characteristic	No new NVFX (<i>n</i> =3,604)	New NVFX (<i>n</i> =116)
Age, years (mean, SD)	67.9 (11.8)	69.3 (10.8)
Ethnicity (%)		
African	1.6	0.0
Asian	0.3	0.9
Caucasian	88.1	92.2
East Asian	0.8	0.0
Hispanic	8.7	6.0
Other	0.5	0.9
Lumbar spine T-score (mean, SD)	-2.48 (1.38)	-2.50 (1.33)
Femoral neck T-score (mean, SD)	-2.44 (0.92)	-2.53 (0.98)
Total hip T-score (mean, SD)	-2.17 (0.99)	-2.36 (1.12)
Prior fragility fracture (% yes)	56.1	81.0***
Prior osteoporosis therapy (% yes) ^a	85.6	90.5
Patients with comorbid conditions (% yes) ^b	82.9	90.5*
Number of comorbid conditions (mean, SD)	1.8 (1.42)	2.1 (1.43)*
Family history of osteoporosis (% yes)	38.6	38.8
Smoking (% yes)	13.3	11.2
Alcohol (% yes)	25.7	25.0
Caffeine (% yes)	71.3	65.5

* $p < 0.05$; *** $p < 0.0001$ patients with no new fracture versus new fracture

^aIncludes prescription osteoporosis medications only

^bComorbid conditions that contribute to increased fracture risk

The results of the DANCE study appear to be similar to those of the EFOS study, since the incidence rate of NVFX decreased with >6 months of treatment with TPTD compared with the reference period [3]. The baseline characteristics of the DANCE cohort appear to be similar to those of patients in the EFOS study; for example, the mean age of the DANCE patients was 68 years and of the EFOS patients was 72 years [9]. It is important to note that in the community-based DANCE study, a schedule of follow-up visits was at the discretion of the physician investigator, whereas the follow-up schedule was more structured in the EFOS study (i.e., patients attended visits at baseline and approximately 3, 6, 12, and 18 months after treatment initiation) [3].

The results of DANCE are also consistent with findings from the FPT, in which the protective effects of TPTD treatment for NVFX became evident after 9 to 12 months of treatment [1]. In a post hoc analysis of the FPT data, the relative hazard for NVFX decreased significantly compared to placebo for each additional month of 20 µg TPTD daily use [2]. There was no placebo arm in the DANCE study, so direct comparisons to FPT data are not possible.

There were several study limitations, including the lack of an untreated control group and the small number of patients in certain subgroups; for example, because only six men reported fractures, comparisons by gender were limited. Furthermore, compliance to study drug was not quantified; rather, adherence was assessed via patient self-report. Also, patients who were reportedly noncompliant for at least 3 months were considered discontinued. However,

many patients who were considered to be compliant may have had smaller gaps in their therapy, which may have impacted their fracture risk. Therefore, it was not possible to assess this factor in this study. The median duration of 23 months of TPTD treatment in this observational study may be higher than the typical community experience. This may be attributed to the types of practices that participated in the DANCE study. Most of the investigators were bone specialists with primarily a referral practice. Patient motivation and physician attitudes about treating osteoporosis with TPTD may be different from a primary care practice and could influence patient persistence. It is possible that the higher incidence of fracture during the first 6 months of the study was due to a history of a recent fracture. However, many patients had a history of fracture that predated initiation of TPTD by a considerable length of time.

The reduction in fracture incidence during the 24-month cessation phase remained significant compared to the reference (>0 to ≤6 months of treatment). During the cessation phase, physicians were asked to treat their patients per their standard of care after a course of TPTD. Most patients were placed on an antiresorptive drug (55.5 % had an antiresorptive drug documented during cessation phase); therefore, these reductions cannot be solely attributed to the previous treatment with TPTD. However, it is reassuring that with standard care, which usually includes use of an antiresorptive drug after treatment with TPTD, the incidence of NVFX remained significantly lower than the baseline reference period.

Nonvertebral fracture sites recorded included the ankle, clavicle, distal forearm, fingers, foot, hand, hip, humerus, knee, leg, pelvis, rib, shoulder, skull, sternum, and toes. While most clinical trials do not include sites such as finger, toes, and skull, the authors feel comfortable including all NVFX in the analysis. All NVFX sites were included in both the reference time period and all subsequent time periods. The biologic effect of TPTD is not likely to alter the incidence of fractures of fingers, toes, and skull significantly. Therefore, the likelihood of these fracture sites significantly altering the overall incidence is low. Unfortunately, because of the way the data were collected, it was not possible to separate out the toe or finger fractures. A post hoc analysis of the fracture data with exclusion of hand/finger, foot/toe, and other fractures gave very similar results to “all NVFX” reported in this analysis.

The observational nature of this study allowed for the examination of the effect of TPTD treatment in a real-world clinical setting; thus, the results are more applicable to the general population. Also, the study population in an observational study may be larger and more diverse compared with the study population in a randomized clinical trial. The data reported from this study, which examined the use of TPTD in a real-world clinical setting, complement and add to previously published data regarding the effectiveness of TPTD treatment on the reduction of NVFX. However, caution should be used in interpretation of the results due to lack of an untreated control group.

Conclusions

Overall, the results of this observational study indicate that the incidence of new NVFX decreased for patients receiving TPTD treatment for durations of longer than 6 months compared with the baseline reference time period (>0 to ≤6 months of treatment) and that this improvement persisted throughout the 24-month cessation phase. There were no new safety findings observed among patients who received one or more dose of TPTD over the 24-month treatment period or for 24 months after treatment cessation. This study is consistent with other clinical and observational trials that have shown that a treatment period of greater than 6 months with TPTD is associated with an increased benefit in reducing the incidence of NVFX.

Acknowledgments This work was sponsored by Eli Lilly and/or one of its subsidiaries. The authors extend their sincere thanks to all of the DANCE investigators and study coordinators for their dedicated work on this study. Writing assistance was provided by Eileen R. Gallagher, a full-time employee of PharmaNet/i3, a part of the inVentiv Health Company.

Conflicts of interest S.S. is on the Speaker’s Bureau and is a consultant for and has received research support from Eli Lilly; P.M. has received research grants and consulting fees from Eli Lilly; S.S. has no conflicts to disclose; M.W. is on the Speaker’s Bureau and involved in clinical trials with Eli Lilly; X.W., D.M., K.A.T., V.A.R., and K.K. are employees of Eli Lilly and Company and or/one of its subsidiaries and own stock in the company. J.A. is an employee of Lilly USA, LLC.

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