

# Update on the safety and efficacy of teriparatide in the treatment of osteoporosis

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**Abstract:** Following the completion of the Fracture Prevention Trial, teriparatide was approved by the United States Food and Drug Administration and the European Medicine Agency as the first therapeutic anabolic agent for the treatment of postmenopausal women with severe osteoporosis. It subsequently received additional approval for the treatment of osteoporosis in men, and for the treatment of osteoporosis associated with glucocorticoid therapy in men and women at risk of fracture. In this review, we summarize the most important data concerning PTH 1-34 therapy before 2016 in the treatment of osteoporosis, and report some outstanding results published in the last 2 years. New data on safety will also be discussed, together with the state of art of nonclassical utilization. Finally, in view of the recent approval of biosimilars, possible future landscapes are discussed.

**Keywords:** fractures, osteoporosis, safety, teriparatide

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## Introduction

At the time of writing, clicking ‘teriparatide’ on PubMed resulted in 2566 papers, the first dating back to 1978. Therefore, only considering this index term, and without entering those of similar meaning (parathyroid hormone, PTH 1-34 and so on), it is apparent that a huge number of scientific studies have been carried out during this time span, achieving important scientific goals. Most importantly, these results have not been confined only to the bench but have had a positive impact on the treatment of patients with the most common metabolic bone disease (i.e. osteoporosis). Even more impressive is the fact that the production of original investigations has been relentless, indicating both the prolonged interest of the scientific community and that there are still areas to be explored.

Following completion of the Fracture Prevention Trial (FPT),<sup>1</sup> teriparatide (PTH 1-34, Forsteo®) was approved by the United States Food and Drug Administration (FDA) and the European Medicine Agency (EMA) as the first therapeutic

anabolic agent for the treatment of postmenopausal women with severe osteoporosis. It subsequently received additional approval for the treatment of osteoporosis in men, and for the treatment of osteoporosis associated with glucocorticoid therapy in men and women at risk of fracture. Initially planned as a 36-month study, the FPT was interrupted early owing to rat toxicology findings of osteosarcoma. The effects of the drug were therefore analyzed for 19 months, while maximum duration of teriparatide treatment was 24 months. As a consequence, the drug was initially approved for a period of 18 months; however, more recently, a further extension of 6 months has been granted.

There is impressive geographical variability regarding criteria for reimbursability. Table 1 reports these criteria by National Health Systems in a few representative countries around the world, considering one country in each main continent. Although limited, this table gives an idea of the different criteria adopted throughout the world. Nowadays, another anabolic agent is available in

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**Table 1.** National Health Systems' criteria for reimbursement.

	Reimbursement level			Disease			Length	BMD			Fractures				
	Reimbursement Level (% covered by public payer)	Reimbursed under Govt. Program	Review Timing	PMOP Women	Male	GIOP	months	n/a	≤-2.5	≤-3.0	≤-3.5	n/a	≥1	≥2	≥3
<b>ARGENTINA</b>	not reimbursed nationally	no	no specific timeline as no social security	yes	yes	yes		x				x			
<b>AUSTRALIA</b>	100%			yes	yes	no	18			x					x
<b>BRAZIL</b>	not reimbursed nationally	YES (9 STATES HAVE A PROTOCOL) & NO (FEDERAL)										x	x		
<b>CANADA</b>	not reimbursed nationally	Coverage on government program in Quebec. Otherwise coverage is on private insurance programs only							x	select. pop.			x		
<b>FRANCE</b>	65%	yes	In France each drug is reviewed by the Transparency Commission every 5 years after the first decision for reimbursement.	yes	yes	yes	18	x							x
<b>ITALY</b>	100%	yes		yes	yes	yes	24						X [GIOP or T-score ≤ -4.0]	X	x
<b>JAPAN</b>	100%			yes	no	no	24		x				x		
<b>SOUTH AFRICA</b>	not reimbursed nationally			yes	yes	yes									

BP trial	Reimbursement criteria	Additional comments
n/a	12+ months	
x	PMO Women and Male reimbursed. GIOP and 24 Month, not yet	In Argentina, the procedure is similar to Colombia, every patient is in a 'obra social' or 'medicina prepaga' system. If the reimbursement has been denied. The patients need to go to a court to ask them to force their 'obra social' to reimburse Forteo. In Argentina, when they go to court they do not get the reimbursement for the total 18 month treatment. It is valid for only 3 months. It is also approved for PMW and men
x	<p>Initial treatment, as the sole PBS-subsidized agent, by a specialist or consultant physician, for severe, established osteoporosis in a patient with a very high risk of fracture who:</p> <ol style="list-style-type: none"> <li>has a BMD T-score of <math>-3.0</math> or less, and</li> <li>has had two or more fractures due to minimal trauma, and</li> <li>has experienced at least one symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent at adequate doses or</li> <li>treatment with anti-resorptive therapy is contraindicated according to the relevant TGA-approved Product Information, or intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use. Details of the contraindication or intolerance must be provided at the time of application.</li> </ol> <p>Link to PBS site: <a href="http://www.pbs.gov.au/medicine/item/9411H">http://www.pbs.gov.au/medicine/item/9411H</a></p> <p>AT LEAST 1 FRACTURE: Vertebral or nonvertebral based on Rx or DEXA Exam BMD Less than <math>-4.0</math> based on DEXA Exam (patient usually over 70) BP failure required (patients still losing BMD while on BP)</p>	
x	<p>Physician should fill out forms detailing BMD and X ray results of previous fractures. patient has reached a low enough T-score, used BP for a period of time (e.g.: 1–2 years) and has fracture on it</p> <p>Reimbursed in Quebec:</p> <p>Forteo is reimbursed with private insurances. Criteria for coverage varies.</p> <p>Teriparatide is newly reimbursed for a very select patient population with AFF or ONJ, under the Ontario Public Drug Program through the Exceptional Access Program. Up to two years of teriparatide treatment is reimbursed for patients who:</p> <ol style="list-style-type: none"> <li>Require teriparatide for treatment of osteoporosis, according to the prescribing physician</li> <li>Are at least 65 years old and mobile</li> <li>Are at high risk of fragility fracture (prior fragility fracture and BMD T-score <math>&lt;-3.0</math>)</li> <li>Have ONJ or AFF believed to be due to use of an AR agent.</li> </ol> <p>(Note: Teriparatide is prescribed on the basis of adverse events [ONJ, AFF] sustained on previous ARs and on the basis of the failure or intolerance to previous osteoporosis therapy. Teriparatide is used as a treatment to address underlying osteoporosis, but is not to be used to treat ONJ or AFFs.)</p>	<p>In Canada, Forteo is reimbursed with private insurances. Criteria for coverage varies. For the public market, Forteo is not listed on any provincial or territorial except Quebec.</p> <p>Quebec- For treatment of severe OP in PMO:</p> <ul style="list-style-type: none"> <li>Whose OP fxs are documented by a t-score of <math>-3.0</math> or less: AND</li> <li>Who have shown an inadequate response to continued taking of a BP (or raloxifene, if a BP is contraindicated), that is, who have shown the following characteristics:</li> <li>A new fragility fracture following continued taking of the antiresorptive therapy for at least 12 months;</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>Significant decrease in BMD, less than the t-score observed during pretreatment, despite continued taking of the antiresorptive therapy for at least 24 months.</li> <li>The total duration of the authorization is 18 months</li> </ul>
x	<p>Women and men with established osteoporosis with at least 2 vertebral fractures. [The treatment by FORSTEO could consequently precede or follow a treatment by BP or by SERM].</p> <p>When Forsteo is initiating in second intent after a BP, a wash out period of unknown duration (between 6 and 12 months according the expert opinion) could be observed, due to the persistent effect of the BP. This wash out period could be less longer in case of a previous treatment by a SERM). Those criteria are more for PMW, Men, and GIOP ( since January 09)</p> <p>New criteria (Nota 79) (2015): PMO, Males and GIOP: Forsteo is reimbursed as a First line treatment in these different cases:</p> <ol style="list-style-type: none"> <li>New vertebral or femoral fracture despite being in treatment with other Nota 79 drug for 1 or more years</li> <li><math>\geq 3</math> vertebral or femoral fracture</li> <li><math>\geq 1</math> fracture + back or femoral T-score <math>\leq -4</math></li> <li>Patient treated for more than a year with <math>&gt;5</math> mg dose per day of prednisone or (or equivalent) that report one or more fracture</li> </ol>	<p>GIOP: <a href="http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-09/forsteo_ct_5572.pdf">http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-09/forsteo_ct_5572.pdf</a></p> <p>MEN: <a href="http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-06/forsteo_ct_5200.pdf">http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-06/forsteo_ct_5200.pdf</a></p> <p>PMO: <a href="http://www.has-sante.fr/portail/jcms/c_854109/fr/forsteo">http://www.has-sante.fr/portail/jcms/c_854109/fr/forsteo</a></p> <p>GPs can only prescribe for refills only; reimbursement has to be renewed every 6 months. Unrestricted access has been granted to all regions for PMOP, male, and GIOP indications. The 24-month indication was approved nationally in June 2011. As of October 2011, 20/21 regions have changed reimbursement from 18 to 24 months. <a href="http://www.agenziafarmaco.gov.it/content/nota-79">http://www.agenziafarmaco.gov.it/content/nota-79</a></p>
x	Fully reimbursed based on the label. PI states that efficacy and safety in men has not been confirmed so use in men is not recommended. No description of GIOP in label. If doctors believe it is appropriate for these patients then they can use it and each local authority can determine if it is appropriate for reimbursement. There are no reimbursement guidelines.	

AFF, atypical femoral fracture; AR, anti-resorptive; BMD, bone mineral density; BP, bisphosphonate; GIOP, glucocorticoid-induced osteoporosis; GP, general practitioner; ONJ, osteonecrosis of the jaw; OP, osteoporosis; PMOP/PMO, *postmenopausal* osteoporosis, PMW *postmenopausal* women; SERM, selective estrogen receptor modulator; TGA therapeutic goods administration.

the United States, that is, abaloparatide; another one, romosozumab, has been approved in Japan, South Korea, Canada and the United States while waiting approval by the EMA.

In this review, we will summarize the most important data concerning PTH 1-34 before 2016 in the treatment of osteoporosis, concentrating on results published in the last 2 years. New data on safety will also be reported.

### Chief seminal studies

The primary outcome for a drug treating osteoporosis is a reduction in the incidence of new fractures. In the FPT, the relative risk reduction of vertebral fractures was 84% (absolute risk reduction 9.6%) by quantitative morphometry, as confirmed by semiquantitative visual methodology.<sup>1</sup> Subsequent analyses also demonstrated that teriparatide was more effective in those with multiple and severe vertebral fractures.<sup>2</sup> Concerning non-vertebral fracture, the FPT showed that treatment with teriparatide 20 µg/day reduced the risk of nonvertebral fractures by 53% compared with placebo after a median treatment of 19 months ( $p=0.02$ ). Interestingly, inspection of Kaplan–Meier curves demonstrated divergence between the treated and placebo group after about 9 months; this divergence tended to increase as long as the treatment was continued.

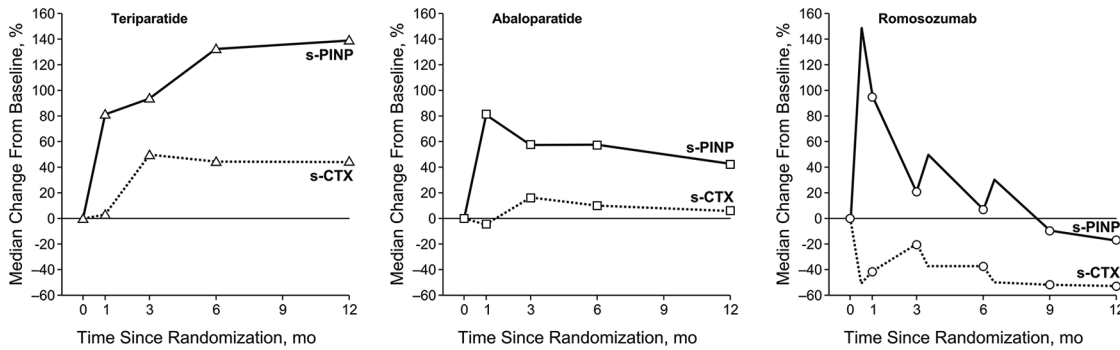
One of the criticisms concerning teriparatide therapy has been the lack of clear demonstration of an effect on the prevention of hip fractures. The FPT was not powered to detect significant differences at individual nonvertebral fracture sites; this is demonstrated by the fact that the trial reported only five hip fragility fractures occurring between the placebo and the teriparatide 20 µg treatment arms. To better characterize this issue, Diez-Perez and coworkers carried out a systematic review and meta-analysis of the efficacy of teriparatide in the reduction of hip fractures in women and men with osteoporosis.<sup>3</sup> They included 23 randomized controlled trials, 19 of them with an active-controlled arm and 11 double blind, for a total number of 8644 patients investigated. Meta-analysis results showed an odds ratio for hip fracture of 0.44 (0.22–0.87,  $p<0.019$ ) in patients treated with teriparatide compared with controls.<sup>3</sup>

Two recent papers better define the role of teriparatide in respect to antiresorptive agents and in

specific categories of patients. In the first, Kendler and coworkers compared the anti-fracture efficacy of teriparatide with risedronate in patients with severe osteoporosis (i.e. women with at least two moderate or one severe vertebral fracture, and a bone mineral density (BMD) T-score of less than or equal to  $-1.5$ ).<sup>4</sup> At the completion of the study period of 24 months, the risk ratio of new vertebral fractures was significantly reduced in those taking teriparatide (0.44, 95% confidence interval 0.29–0.68;  $p<0.0001$ ). Statistical significant reductions were also observed for clinical fractures.<sup>4</sup> This study, one of the few existing in the literature comparing two active drugs, clearly indicate that, in patients with severe postmenopausal osteoporosis, the risk of new vertebral and clinical fractures is significantly reduced in patients receiving teriparatide compared with those taking risedronate. Geusens and coworkers then published a preplanned subgroup analysis of this study.<sup>5</sup> The subgroups were predefined by the following characteristics: age, number and severity of prevalent vertebral fractures, prevalent nonvertebral fractures, glucocorticoid use, prior osteoporosis drugs, recent bisphosphonate use, clinical vertebral fractures in the year before study entry and baseline BMD. The results indicated that, for most fracture end points, the risk reduction of teriparatide with respect to risedronate did not differ significantly in any of the subgroups investigated. That is, the results in most of the subgroups taken into consideration were similar to those observed in the population as a whole. In particular, the finding that patients previously treated with bisphosphonates have a better response in terms of vertebral and clinical fractures with respect to risedronate, has important consequences for clinical practice.

### Mechanism underlying fracture risk reduction

Both the pivotal FPT and subsequent studies carried out for the full course of therapy (i.e. 24 months) consistently showed that teriparatide treatment increases BMD values at the lumbar spine, femur neck and total hip.<sup>1</sup> Without discussing specific details, for which the reader is referred to a comprehensive review on this subject,<sup>6</sup> two issues deserve specific attention. The first is represented by the fact that, in general, patients previously treated with bisphosphonates have a slower response in terms of BMD accrual when subsequently treated with PTH 1-34,<sup>7,8</sup> even though there are differences within the class of



**Figure 1.** Behavior of biochemical markers of bone formation (serum P1NP) and resorption (serum bCTX) following treatment with teriparatide, abaloparatide, and romosozumab. Redrawn with permission from Minisola *et al.*<sup>18</sup> bCTX, carboxy-terminal cross-linking telopeptide of type I collagen; P1NP, procollagen type I N-terminal propeptide.

bisphosphonates.<sup>9</sup> Secondly, regarding the radius site, a tendency to decrease that is nonsignificant in respect to basal values but statistically significant when compared with other drugs, such as denosumab, has been reported,<sup>10</sup> even though this latter study was carried out with a relatively small number of subjects. It must be stressed that these changes are offset by periosteal apposition. Furthermore, increased cortical porosity (weak bone) should be viewed as a transient phenomenon; indeed, these voids represent a tiny fraction of all cortical areas, and their overfilling will result in a final increase of cortical bone mass by new, mechanically competent bone. The effect of teriparatide has also been investigated using quantitative computed tomography, including finite element analysis and strength. Without discussing specific issues that are outside the scope of this review, a couple of studies deserve attention since they help to better understand the pharmacological effect of the hormone. Poole and coworkers employed a novel CT processing technique to analyze the effect of teriparatide therapy on hips.<sup>11</sup> They found that teriparatide increases cortical thickening, especially at sites of hip mechanical loading. These results seem to indicate that there is a synergistic effect between habitual loading and teriparatide. Lastly, Hansen and coworkers analyzed volumetric BMD of distal radius and tibia at the end of 18 months treatment with teriparatide.<sup>12</sup> They found a significant decrease in volumetric BMD, with a concomitant significant increase of both cortical porosity and cortical thickness. Interestingly, these changes were not accompanied by a decrease in bone strength as evaluated by finite element analysis. A number of factors have been hypothesized to explain the finding of decreased radial volumetric BMD.

Among them increased endocortical remodeling, increased remodeling space within the cortical harversian system, and an increase in measured area owing to periosteal apposition.<sup>13</sup>

Concerning the behavior of bone remodeling markers, in the beginning there is a quick increase of those reflecting bone formation without a concomitant rise of those reflecting bone resorption; then, once reached a peak at about 6–12 months of therapy, a gradual decrease of both can be observed. Some studies carried out for 24–36 months showed that, for the entire period of observation, the increase of procollagen type I N-terminal propeptide (PINP) exceeds the increase of the typical marker of bone resorption, that is, serum C-terminal cross-linking telopeptide of type I collagen (BCTX).<sup>14</sup> These results seem therefore to suggest that the so-called anabolic window might persist as long as the PTH 1–34 is administered. Even though this hypothesis might be true, caution must be used when considering markers with different characteristics, the most important being metabolism and the sensitivity of the assay.<sup>15–17</sup> Taking into consideration the above limits, Figure 1 reports the behavior of these two biomarkers in patients treated with teriparatide, abaloparatide, and romosozumab, respectively. Despite the fact that these are not head-to-head trials (at least for romosozumab), a different time course can be observed.<sup>18</sup> This should be considered in case one would expect that adherence to therapy or prediction of pharmacological effect could be inferred by measuring these markers.<sup>19–21</sup>

The effect of teriparatide on remodeling process determines the removal of old bone with

consequent overfilling of the resorption sites with new bone. Indeed, previous research has shown that PTH 1-34 treatment determines a collagen profile similar to young matrix, as shown by the ratio between  $\alpha$ -CTX and  $\beta$ -CTX.<sup>22,23</sup> Another important point that should be considered is the effect on modeling. This is important since the modeling process adds new bone to the bone surface, thus increasing bone mass; by means of this process, old bone is not remodeled and remains below the bone being formed.<sup>6,24</sup> The behavior of the bone formation marker PINP is, in some way, paralleled by the analysis of bone data obtained by histomorphometry. Indeed, bone formation in postmenopausal osteoporotic women treated with PTH 1-34, as reflected by mineralizing surface divided by bone surface, was significantly higher in respect to basal values considering the cancellous, endocortical, and periosteal envelopes; the only exception being represented by the intracortical envelope.<sup>6</sup>

#### Clinical practical considerations

What generally happens in clinical practice is that parathyroid hormone is administered in patients already exposed to bisphosphonates; this, with few exceptions,<sup>4,25</sup> is not the approach in clinical trials, where patients enrolled are naïve to any kind of treatment. As discussed previously, a number of papers have shown a blunting of the BMD effect when PTH 1-34 is given to patients previously treated with bisphosphonates. Concerning the hip site, all studies published to date have demonstrated a decrease in the total region lasting for the first 12 months of therapy, with gains thereafter.<sup>9,26,27</sup>

A situation that deserves particular attention is represented by the transition from denosumab to teriparatide. This is because, in some countries, for example, Italy, teriparatide is reimbursed if a fracture (vertebral or hip) occurs after at least 1 year of antiresorptive therapy. This is potentially a very dangerous situation; indeed, Leader and coworkers have shown that, in the first 6 months of switch, there is a rapid decline in spine BMD, with concomitant extensive and progressive bone loss at the hip and distal radius. Accelerated bone remodeling, as evidenced by sustained increases in biomarkers of skeletal turnover to levels greater than 200% above baseline has been also documented.<sup>28</sup> There are no studies specifically addressing pathophysiological mechanisms underlying bone loss with this particular

sequence. Most importantly, guidance for physicians on the best behavior to follow is not well established. However, also considering the detrimental effects of denosumab discontinuation *per se*,<sup>29,30</sup> it is prudent to continue treatment with denosumab or to shift to another antiresorptive agent while treating with teriparatide.

There are a number of chronic diseases like osteoporosis (obstructive pulmonary disease, hypertension, heart failure, rheumatoid arthritis and so on) where we generally prescribe two or three drugs simultaneously. Taking advantage of different mechanisms of action or targeting different receptors, the combination of two or more drugs enables the achievement of therapeutic goals. This strategy is not the usual practice in the field of osteoporosis. However, there are at least two conditions in which a combinations of an anabolic and an antiresorptive agent is mandatory, or at least desirable. The first is represented, as previously reported, by the discontinuation of denosumab treatment in case we want to transition to teriparatide. Indeed, the most encouraging combination seems to be the concomitant administration of teriparatide; the benefits of this combination were seen during the first 12 months of treatment, during which spine BMD increased by over 9% and total BMD by about 5%.<sup>10,31</sup> Once again, these latter two studies were carried out in a relatively small number of subjects. The second is represented by clinical conditions where a rapid bone loss is expected in a short period of time. An example of this is steroid therapy; indeed, a number of studies have shown that the most vulnerable period is constituted by the first 3–6 month time interval after initiation of treatment.<sup>20,32–35</sup> In this context, it is worth reporting the findings by Cosman and coworkers.<sup>36</sup> In a 12-month randomized controlled trial, postmenopausal women with osteoporosis were randomized to a single infusion of zoledronic 5 mg, teriparatide or a combination of the two drugs. Independently of the results obtained at the end of the study period, an important observation, not often emphasized, is the striking increase of BMD at 13 weeks of therapy. In the combination group, this increment was significantly higher at the total hip and lumbar spine site compared with the other 2 groups. Therefore, in just 3 months, we can offer a good protection (in terms of BMD increase) to those who are most in need.

Finally, a number of studies investigating whether alternate combination treatment strategies could

have more favorable effects with respect to administration of a single agent have been published. The last of these researches aimed at evaluating if equivalent doses of teriparatide given cyclically over 4 years could increase BMD more than teriparatide administered daily. At the end of the study, the authors found no difference between the two modalities, considering both untreated women and women previously treated with bisphosphonates.<sup>37</sup>

### Optimizing teriparatide therapy in the context of existing treatments

Osteoporosis is a chronic disease, and, as such, implies lifelong treatment. However, the Achilles' heel of osteoporosis treatment is represented by the low rate of treatment adherence.<sup>38</sup> For example, concerning oral bisphosphonates, persistence of 45% and 30% after 12 and 24 months, respectively, has been recently reported.<sup>39</sup> The issue is further compounded by concerns regarding feared side effects, which are often overemphasized by media reports.<sup>40,41</sup> As far as PTH 1-34 is concerned, the regulatory limit of 2 years duration requires a logical approach for each individual patient to optimize the effects of treatment. Such strategies should also taking into account the cost of the drug. Most authorities in the field believe that the best sequence to follow is one that considers initial treatment with an anabolic agent followed by an antiresorptive drug. This kind of approach is supported by at least two findings: the first is derived from the VERO study, showing superiority of teriparatide in respect to the bisphosphonate utilized (i.e. risedronate) in the first head-to-head trial in the field of osteoporosis. The second line of evidence derives from data from the FRAME study showing that the addition of 2 years denosumab to 1 year romosozumab treatment is similar in terms of BMD increase compared with around 6–8 years of denosumab therapy alone.<sup>42</sup>

Another important point to consider is maintenance of skeletal strength when teriparatide must be stopped after 2 years; indeed, when the drug is discontinued, BMD starts to decline. Lindsay and coworkers suggested that part of the antifracture efficacy may persist for up to 18 months after the drug has been stopped<sup>43</sup>; however, as with other drugs, it is likely a vanishing effect over time. A number of studies investigating the role of alendronate,<sup>44,45</sup> raloxifene,<sup>46</sup> or denosumab<sup>28</sup> to

maintain or even increase the accrual of bone mass obtained with teriparatide, have been published. In this context, Napoli and coworkers recently reported clinical outcomes in patients prescribed teriparatide and followed for 18 months after stopping the drug in a real-life setting.<sup>47</sup> They found that, compared with the first 6-month interval, there was a significant reduction in the adjusted odds of clinical fractures at all subsequent time points, but not for nonvertebral fractures. Following teriparatide discontinuation, the risk of fractures of any category remained very low; of note, 98% took no osteoporosis medication (24% only took vitamin D and calcium).

### Safety

The planned duration of treatment of the phase III FPT was 36 months; however, the study was terminated early because of rat toxicology findings of osteosarcoma. Most of the problems related to the safety of PTH 1-34 administration are related to data obtained in rats. Indeed, during a 2-year carcinogenicity study, a 26% incidence of osteosarcoma in 360 Fischer 344 rats was reported. Of note, the doses administered were 5, 30, or 75 µg/kg/day, beginning at 6 weeks of age for up to 2 years' duration.<sup>48</sup>

These experimental conditions are clearly different in respect to the therapeutic indications subsequently licensed by the FDA and EMA. Actually, a 2-year exposure in rats represents most of the life span of these animals; secondly, the doses used are very large (3-fold to 58-fold) compared with the doses used in human patients. Interestingly osteosarcoma did not develop in nonhuman primates (cynomolgus monkeys) with exposure to approximately eight times the human dose,<sup>49</sup> mainly because their skeletal biology is similar to that of humans. Without discussing this specific effect of huge administration of PTH in rats and mice in greater detail, it appears that similar problems are not encountered in human beings. The three cases of osteosarcoma reported until 2012 in patients treated with teriparatide do not reflect a greater than expected incidence with respect to an unselected population of adult humans who develop osteosarcoma and are not receiving teriparatide.<sup>50</sup> Therefore, these cases do not seem to have any apparent connection with PTH 1-34 treatment, and may be viewed in the context of the incidence of osteosarcoma in subjects aged ≥60 years, which is approximately 1:520,000.

In this context, more reassuring data comes from the Forteo Patient Registry, a study designated to estimate the incidence of osteosarcoma in patients in the United States treated with teriparatide. An interim analysis published recently based on approximately 242,782 person-years follow-up, showed no incident osteosarcoma cases among teriparatide users after 8 years of follow up.<sup>51</sup>

The tumorigenic effect of PTH in selected animal species seems to be specific to skeletal tissue. No increase in nonskeletal tissue has been reported, also when evaluating data coming from clinical trials. However, in clinical practice, the history of any cancer in the past 5 years represents a contraindication to the use of PTH. The rationale behind this relates to the possible presence of PTH receptors in malignant cells. However, the 5-year limitation is hard to explain in light of the finding showing that dormant cancer cells may persist lifelong in niches.<sup>52</sup>

### Side effects

In the FPT, the two most frequent complaints reported by patients treated with teriparatide, that were significantly different from those reported by patients in the placebo arm, were dizziness and leg cramps. Other frequently reported adverse events in the EuroFors and EFOS study were nausea, arthralgia, hypertension, headache, fatigue and depression.<sup>7,53</sup> From our personal experience, these side effects, when present, generally appear at the beginning of treatment and are less likely to occur after the therapy has exceeded the first 3–6 months.

Some of the biochemical abnormalities encountered during PTH 1-34 therapy simply recapitulate the action of the hormone at its target organs. Some (i.e. hypercalcemia) may be of concern in clinical practice; others (i.e. increased 24-h urinary calcium excretion and serum uric acid, reduced serum magnesium), although important to recognize, rarely cause interruption of treatment.<sup>54,55</sup> For patients developing an increase in serum and urinary calcium, a reduction in the intake of calcium is initially suggested. In this context, Minisola and coworkers reported a significant decrease of serum 25(OH)D concentrations during teriparatide treatment.<sup>56</sup> This finding is in full agreement with the well-known mechanism of action of parathyroid hormone, which stimulates 1-alpha-hydroxylase thus converting the

substrate 25(OH)D to its biologically active metabolite [1.25(OH)<sub>2</sub>D].

A recent paper by Gafni and coworkers<sup>57</sup> seems to suggest that treatment with subcutaneous PTH 1-34 in patients with hypoparathyroidism may have untoward effects of hypocitraturia, thus increasing renal morbidity. No similar study has been carried out in the setting of osteoporosis; however, this possible biochemical abnormality should be better defined in patients receiving the hormone not as a substitution therapy.

### Nonclassical utilization of teriparatide

Fracture healing is a complex process, that can be divided schematically into an initial anabolic and a late prolonged catabolic phase. Owing to the anabolic properties of teriparatide, and following case reports suggesting its utilization to accelerate fracture healing, few randomized controlled trials have been published exploring this possibility. The most recent meta-analysis demonstrated that administration of teriparatide following fracture lacked effectiveness for fracture healing, in contrast with another meta-analysis reaching different conclusions.<sup>58,59</sup> It should be noted that very few studies so far have targeted this problem; in addition, a number of parameters, such as type of fracture, age of patients, and duration of treatment, to cite the most important, are very heterogeneous in these trials.

Even though the estimated prevalence of osteonecrosis of the jaw (ONJ) ranges from 0.001% to 0.01% among oral-bisphosphonate-treated populations, this still represents a feared complication both for patients and doctors.<sup>60</sup> Owing to an initial report showing that teriparatide determines greater regaining of alveolar bone defects and accelerated osseous healing in the oral cavity of chronic periodontitis,<sup>61</sup> its use has been suggested as a possible treatment for ONJ. The rationale behind this is taking advantage of the initial anabolic effect of the hormone in the initial period of treatment. A few clinical studies and case reports have been published,<sup>62</sup> generally showing beneficial effects. A randomized clinical trial is clearly needed, particularly addressing duration of therapy in this particular setting.

### Future landscapes

PTH 1-34 was initially approved by the FDA in November 2002 and by the EMA in June 2003.



The patent of this product expired in the United States and Europe in August 2019. In this context, teriparatide biosimilars and nonoriginator biologicals have been developed. Indeed, on 11 November 2016, the EMA's Committee for Medical Products for Human use (CHMP) announced that it had recommended granting marketing authorization for the teriparatide biosimilars Movymia<sup>®</sup> and Terrosa<sup>®</sup> produced by German generics Stada Arzneimittel and Hungary-based Gedeon Richter, respectively. A paper comparing the pharmacokinetic and pharmacodynamics of Terrosa<sup>®</sup> and Forsteo<sup>®</sup> has been published recently.<sup>63</sup> So called 'similar biologics' have been approved, mainly in countries such as India, where they were developed and produced; other examples of biosimilar products are produced in other countries.<sup>64</sup> However, before being commercialized in Europe they should pass through EMA regulatory requirements.

How the introduction of biosimilars and similar biologics will change the policy of Ely Lilly is, at this point in time, uncertain. Most importantly, if these drugs prove to be effective and safe, they could change the landscape of osteoporosis treatment, provided that the price is affordable.

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### Ethical approval

Not applicable; this is a review without direct involvement of patients by the authors

### Conflict of interest statement

Prof. S. Minisola served as speaker for Abiogen, Amgen, Bruno Farmaceutici, Diasorin, Eli Lilly, Italfarmaco, Shire. He also served in advisory board of Abiogen, Kyowa Kirin, Pfizer, UCB.

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