nature reviews rheumatology

https://doi.org/10.1038/s41584-025-01287-w

Review article

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Parathyroid hormone receptor agonists in the management of osteoporosis

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Abstract

Parathyroid hormone (PTH) regulates bone homeostasis. Intermittent exposure to PTH results in bone formation being greater than bone resorption, and this effect has been harnessed through the development of agonists of the PTH and PTH-related protein type 1 receptor (PTH1R) to treat osteoporosis. Teriparatide, an analogue of the first 34 amino acids of PTH, and abaloparatide, which resembles PTH-related protein (PTHrP) in structure, are PTH1R agonists currently in clinical use. Both medications have been shown to increase bone mineral density at the lumbar spine, femoral neck and total hip. Randomized controlled trials with teriparatide or abaloparatide have also provided evidence of reduction in vertebral and non-vertebral fractures. The ACTIVE trial suggested slightly greater efficacy for major osteoporotic fractures (as an exploratory end point) for abaloparatide than for teriparatide. A similar potential superiority was suggested for hip fracture in a real-world, observational study. Side effects of these medications are usually transient, and although a risk of osteosarcoma was suggested by studies using murine models, no such risk has been observed in extensive human studies. Overall, both teriparatide and abaloparatide have demonstrated convincing clinical effectiveness and cost-effectiveness, with a reassuring safety profile. Potential differences in their effects on bone mineral density and their antifracture effects offer avenues for differentiation but require further validation in appropriately designed studies.

Sections

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Key points

- Parathyroid hormone type 1 receptor (PTH1R) agonists stimulate bone formation and effectively reduce the risk of vertebral and non-vertebral fractures.
- The PTH1R agonists teriparatide and abaloparatide act via intermittent PTH1R stimulation, as opposed to the constant PTH1R stimulation seen in hyperparathyroidism.
- The safety profiles of teriparatide and abaloparatide are favourable, with previous concerns regarding osteosarcoma in murine models not born out in humans, and with cardiovascular safety having been consistently demonstrated.
- Exploratory analysis of data from the ACTIVE trial suggests that abaloparatide might have greater efficacy in reducing the risk of major osteoporotic fractures than teriparatide.

Introduction

Osteoporosis is defined in terms of low bone mineral density (BMD) and constitutes a major risk factor for fracture. Such fractures are common, affecting half of women and a fifth of men over the age of 50 years, and are responsible for an estimated US$19 billion of costs per year in the USA alone.

Anti-osteoporosis medications are roughly divided into antiresorptive and bone-forming (or anabolic) therapies. Antiresorptives prevent bone breakdown, largely through effects on osteoclasts. This class of drugs includes bisphosphonates such as alendronate, risedronate and zoledronate — which all inhibit farnesyl pyrophosphate synthase[1] — denosumab, which inhibits receptor activator of NF-κB ligand (RANKL)[2], selective oestrogen-receptor modulators (SERMs)[3] that mimic oestrogenic effects on bone during hormone replacement therapy[4], and the sclerostin inhibitor romosozumab. Bone-forming therapies involve agonism of parathyroid hormone receptors (PTHR).

Parathyroid hormone (PTH) and PTH-related protein (PTHrP) have vital roles in bone homeostasis[5], and agonists of their receptor, PTH1R, have thus been evaluated as therapeutic interventions in osteoporosis. Teriparatide (previously referred to as PTH (1–34)) is an analogue of the first 34 amino acids of PTH, whereas abaloparatide resembles PTHrP in structure. Both PTH1R agonists have a well-established mechanism of action, and substantial clinical trial and real-world data support their use in the treatment of osteoporosis[6–8]. This has led to the incorporation of both agents into treatment algorithms for osteoporosis[9,10].

In October 2024, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) convened a working group consisting of rheumatologists, endocrinologists, orthopaedic surgeons, researchers, regulatory experts and health economic specialists. The purpose of this working group was to analyse the latest literature and leverage expert opinion in order to collate expert insights on PTH1R agonists in the management of osteoporosis. These insights fed into the current Review, which explores the functions of PTH and PTHrP in bone physiology, and discusses the efficacy, safety, health economic status and deployment of teriparatide and abaloparatide in clinical practice.

Parathyroid hormones in bone physiology

PTH is mainly released from the parathyroid glands and is a primary controller of calcium–phosphate homeostasis. As such, PTH maintains serum calcium levels within a tight, functional window and is released in response to hypocalcaemia[11] (Fig. 1). PTH has a triple effect on the kidney: increasing tubular reabsorption of calcium; increasing urinary phosphate excretion by inhibiting phosphate reabsorption in the proximal tubule; and promoting the conversion — via 1α-hydroxylase CYP27B1 — of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (also known as calcitriol), which leads to increased intestinal absorption of calcium and phosphate. PTH also increases calcium levels in the serum via effects on the bone that are discussed below; when released continuously PTH acts on the bone to increase bone resorption so that calcium stored in the bone is released in the circulation[12]. PTHrP is an important regulator of calcium balance during pregnancy and lactation[13], but is also released by many other tissues and manifests a paracrine action on the brain, smooth muscle, skin, cartilage and fetal tissues[13]. Both PTH and PTHrP act predominantly via the PTH1R receptor, which is expressed on osteoblasts. However, PTH, as well as tuberoinfundibular protein 39 (TIP39), also activates PTHR2 (ref. 14).

The *PTH* gene is found on chromosome 11 and the *PTHLH* gene (which encodes PTHrP) is located on chromosome 12 (ref. 15). Although they are encoded by different chromosomes, PTH and PTHrP share substantial homology at their N termini (62%)[16]. The C-terminal portions of the molecules share no homology.

PTH1R is a G-protein-coupled receptor and has two different conformations: R^0 and R^G. Both conformations lead to cAMP release, but the R^0 conformation causes a prolonged release of cAMP that is associated with a catabolic (resorptive) downstream effect, whereas the R^G conformation leads to a tightly regulated and short release of cAMP that is linked to anabolic actions[17].

As briefly mentioned above, intermittent (once-daily or once-weekly) and continuous stimulation of PTH receptors have distinct effects. Continuous stimulation (for example, in primary hyperparathyroidism) is associated with increased levels of RANK ligand, a decrease in osteoprotegerin, downstream activation of osteoclasts, and subsequent increased bone resorption and increased serum calcium (one of the clinical hallmarks of primary hyperparathyroidism)[18,19]. The catabolic effects are largely observed in cortical sites such as the middle third of the radius with relative preservation of the trabecular compartment[20,21]. By contrast, when PTH receptors are stimulated only once daily, their activation prolongs the survival of the osteoblast population by reducing apoptosis via inhibition of the WNT signalling inhibitors dickkopf-related protein 1 (DKK1) and sclerostin, and promotes pre-osteoblasts via CBFA1-mediated transcription, thus enhancing bone formation and bone strength[18,19] (Fig. 1). The increase in bone mass and structure downstream of PTH receptor stimulation are evident via the imaging of bone microarchitecture and of iliac crest biopsies[22,23].

Synthetic ligands of parathyroid hormone receptors

Synthetic ligands that operate via PTH1R have been used as treatments to optimize bone health in individuals with osteoporosis. Full-length PTH has 84 amino acids and the synthetic ligand teriparatide contains just 34, these 34 being identical to the first 34 N-terminal amino acids in PTH. Abaloparatide is identical to the first 21 N-terminal amino acids of PTHrP and shows 76% homology with PTHrP (PTHrP amino acids 1–34) and 41% homology with PTH (PTH amino acids 1–34)[24]. Abaloparatide

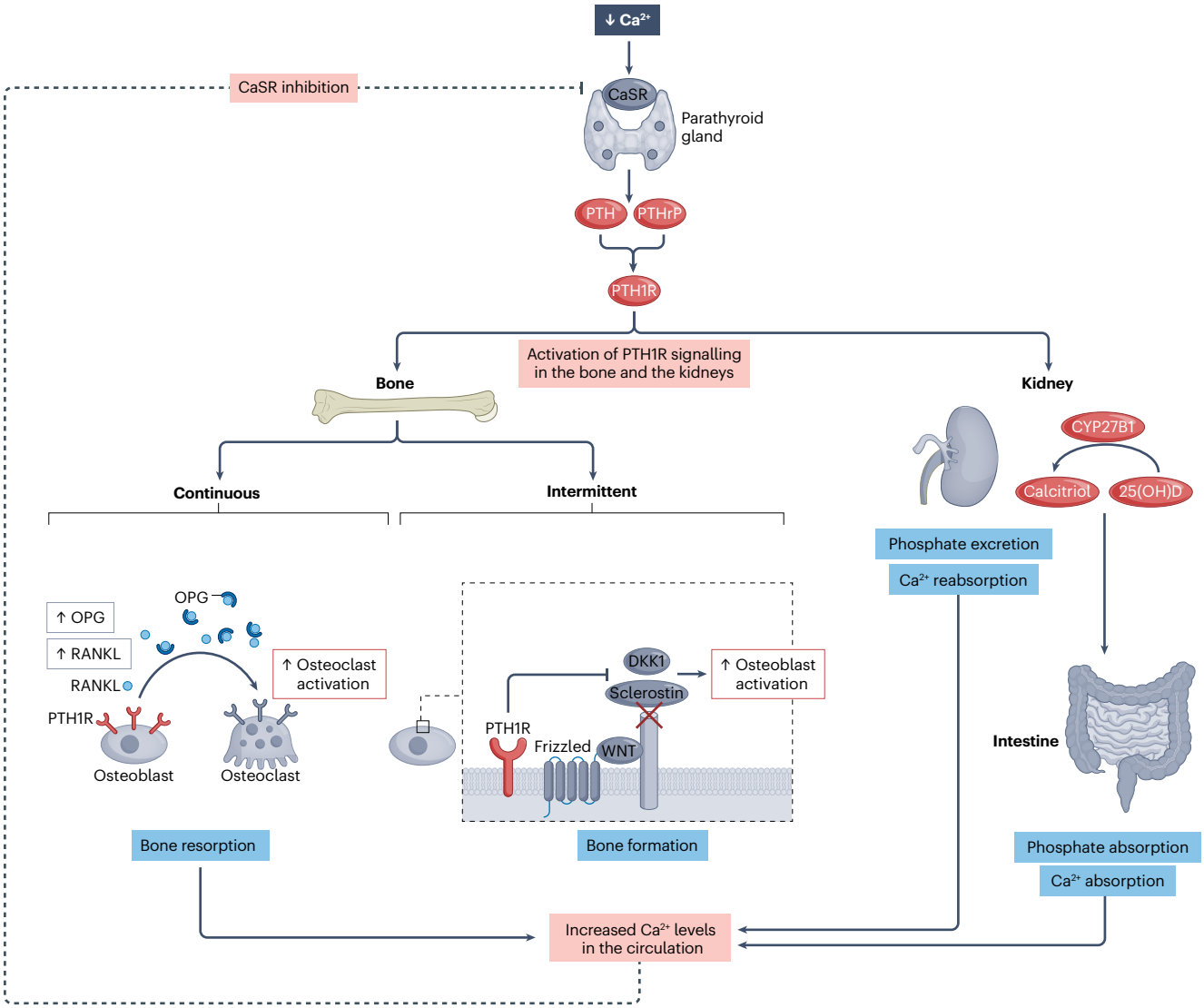

Fig. 1 | PTH and PTHrP signalling via PTH1R. Continuous activation and intermittent activation of PTH type 1 receptor (PTH1R) have distinct effects on bone biology. Continuous release of parathyroid hormone (PTH) from the parathyroid gland, as seen in hyperparathyroidism, results in increased expression of receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG) in osteoclasts, and sustained RANKL–OPG signalling supports osteoclast activation, resulting in bone resorption. Intermittent release of PTH or PTH-related protein (PTHrP), as simulated via once daily dosing of teriparatide and abaloparatide, leads to inhibition of dickkopf-related protein 1 (DKK1)-mediated and sclerostin-mediated WNT signalling via the Frizzled receptor. WNT signalling inhibition results in activation of osteoblasts, supporting bone formation. PTH1R signalling also regulates calcium (Ca^{2+}) levels in the circulation, and thereby parathyroid gland function, via its effects in the kidneys and intestine. PTH1R signalling in the kidneys promotes phosphate excretion and Ca^{2+} reabsorption, leading to increased Ca^{2+} levels in the circulation, while also promoting calcitriol conversion from 25-hydroxyvitamin D (25(OH)D) via the enzyme CYP27B1. Calcitriol in turn increases absorption of phosphate and Ca^{2+} in the intestine. CaSR, calcium-sensing receptor.

leads to more potent cAMP release downstream of PTH1R activation[25] and has a shorter duration of cAMP stimulation compared with teriparatide, with reduced stimulation of resorption being a potential benefit of the former[26]. The affinity of both teriparatide and abaloparatide is greater for R^G than for R^0, thus favouring the anabolic PTH1R conformation. Nevertheless, the affinities of the two agonists for PTH1R differ substantially, with affinity ratios (R^G/R^0) of 3:1 for teriparatide and 1,600:1 for abaloparatide[17,19].

Teriparatide has a half-life of approximately 1 h when delivered subcutaneously, and is eliminated by hepatic and extrahepatic clearance[27]. It requires refrigeration, and a cold chain must be organized for patients needing to travel. Teriparatide has an EMA indication for the treatment of osteoporosis in postmenopausal women and in men at high risk of fracture. Recommended treatment duration is up to 24 months, increased from the original maximum of 18 months[27]. As efficacy data for this class of drugs are not yet available for beyond a 24-month period,

the opinion of our expert working group is that continued use or re-use should be based on an individualized risk profile assessment.

Micro-computed tomography (Micro-CT) has been used to map the microarchitectural effects of treatment with teriparatide, with benefits including an anabolic action on cortical bone, without contemporaneous increases in cortical porosity, and improvements in cancellous bone microarchitecture[22]. The histomorphometric effects of teriparatide as observed via bone biopsy studies include: modelling-based bone formation with smooth cement lines; remodelling-based bone formation with filling of resorption pits, and with scalloped cement lines; and remodelling at quiescent sites[19,23]. This process is particularly observed in cancellous bone and at the endocortical surface with increases in endocortical wall width and reductions in the eroded perimeter[23].

Abaloparatide also has a half-life of 1 h and is delivered subcutaneously, but is eliminated via non-specific proteolytic degradation with subsequent renal clearance. Refrigeration is only required before the first dose of abaloparatide, but after that point it can be stored at ambient temperatures. Abaloparatide has an EMA indication for the treatment of osteoporosis in postmenopausal women who have an increased risk of fracture, and the maximum duration of therapy with abaloparatide is 18 months[28].

The relative anabolic and resorptive effects of teriparatide and abaloparatide have been documented using bone turnover markers, namely procollagen type I N-terminal propeptide (PINP) as a marker of bone formation and β-isomerized C-terminal telopeptide of type I collagen (β-CTX) as a marker of bone resorption. Notably, in the ACTIVE trial both medications were associated with an initial rapid rise in PINP, reaching a greater peak for teriparatide than for abaloparatide[6] (Fig. 2). Compared with teriparatide, abaloparatide increased β-CTX levels more gradually than teriparatide over the first 3 months of treatment, and was associated with a lower peak and a subsequently faster decline in β-CTX levels[6]. These differences have been interpreted as demonstrating a more positive bone balance with abaloparatide than with teriparatide; although this notion awaits direct empirical confirmation, it would be consistent with observed differences in efficacy in improving BMD and reducing fracture risk[11].

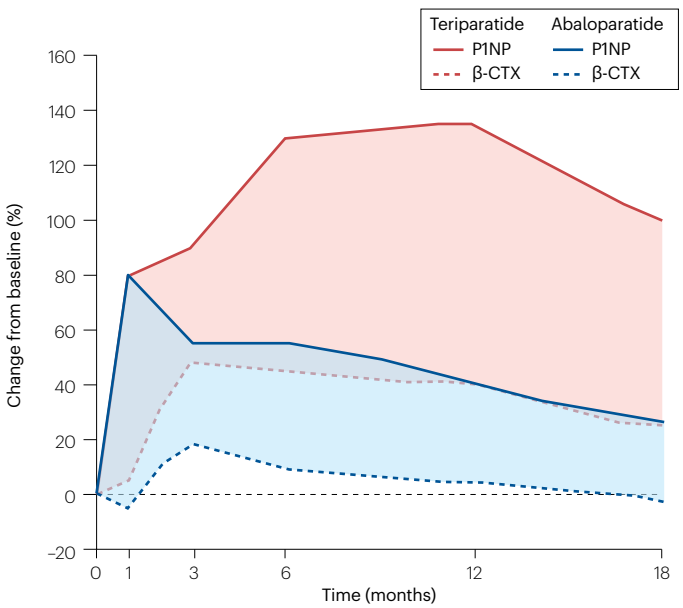

Fig. 2 | Bone turnover marker profiles and anabolic windows of teriparatide and abaloparatide. Percentage changes in bone turnover markers shown over time from baseline (in months). The relative levels of the bone formation marker procollagen type 1 N-terminal propeptide (P1NP) and the bone resorption marker β-isomerized C-terminal telopeptide of type I collagen (β-CTX) might provide information on the timing of the maximal anabolic effect, a concept which has been termed the 'anabolic window'. The graph is based on data from the ACTIVE trial[6].

Efficacy of PTH1R agonists in osteoporosis

The efficacy of PTH1R agonists in increasing BMD and reducing fracture risk is supported by clear evidence from randomized controlled trials, real-world studies and meta-analyses. PTH1R agonists are not administered in isolation, and the effect of combined and sequential therapy has been investigated.

Teriparatide

The 2021 seminal Fracture Prevention Trial (FPT) studied the efficacy of teriparatide in 1,637 postmenopausal women divided approximately equally between daily 20 μg teriparatide, daily 40 μg teriparatide and daily placebo arms for a period of approximately 18 months. The FPT demonstrated a reduction in new vertebral and non-vertebral fractures in the teriparatide arms after treatment for around 18 months. Although the study was not powered to investigate the effect of teriparatide on hip fracture, relative risks for vertebral fracture were 0.35 (95% confidence interval (CI) 0.22–0.55) for 20 μg teriparatide and 0.31 (95% CI 0.19–0.50) for 40 μg teriparatide compared with placebo[7]. A post hoc analysis of this study investigated the effect in a population of adults older than 75 years, demonstrating similar protection against vertebral fracture for this age group, although, again, the study was insufficiently powered to draw conclusions on the effect on non-vertebral or hip fractures[29]. Further analysis demonstrated that the fracture risk reductions for non-vertebral and morphometric vertebral fractures were unaffected by baseline 10-year fracture probability in those taking teriparatide[30].

The FPT participants were invited to take part in an extension, with >90% participant uptake, for a period of another 30 months after the initial trial completion[31]. During this time, about half of the participants in each arm were started on bisphosphonates (after completion of teriparatide), with about 10% receiving SERMs and approximately 5% receiving hormone replacement therapy. Of the 1,262 participants, non-vertebral fragility fractures occurred in 55 (13.3%) of those initially receiving placebo, 37 (8.5%) of those who had received 20 μg teriparatide and 30 (7.3%) of those who received 40 μg teriparatide (20 μg teriparatide hazard ratio (HR) 0.62, 95% CI 0.41–0.93 (P = 0.022); 40 μg teriparatide HR 0.52, 95% CI 0.34–0.82 (P = 0.004); combined teriparatide doses (20 μg and 40 μg) HR 0.57, 95% CI 0.40–0.82 (P = 0.002)) for the duration of the FPT and the trial extension. If the extension alone was considered, a statistically significant protection against non-vertebral fractures was not seen for the 20 μg teriparatide dose (HR 0.73, 95% CI 0.45–1.18 (P = 0.204)), but was observed for the 40 μg teriparatide dose (HR 0.54, 95% CI 0.32–0.92; teriparatide (P = 0.022)) and the amalgamation of both teriparatide doses (HR 0.64, 95% CI 0.42–0.97 (P = 0.035))[31]. During the extension period of the study, both total hip and femoral neck BMD decreased in study participants who had been treated with teriparatide and received no other anti-osteoporosis medication; by contrast, BMD plateaued or even increased in participants who received bisphosphonate therapy following teriparatide[31], providing an early indication of the benefits of sequential antiresorptive therapy.

The Vertebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) study aimed to compare the antifracture efficacy of daily 20 μg teriparatide with weekly 35 mg risedronate and, as such, represents a head-to-head comparison of teriparatide and a bisphosphonate[32]. The study population comprised postmenopausal women with at least two moderate vertebral fractures or one severe vertebral fracture, and with osteopenia or osteoporosis, as evidenced by dual-energy X-ray absorptiometry (DXA). Over the course of 2 years, the study used comprehensive placebo-treated controls, with one arm receiving subcutaneous teriparatide with oral placebo (n = 680) and the other arm receiving a subcutaneous placebo and oral risedronate (n = 680). The primary outcome was incident vertebral fracture, which occurred in 28 (5.4%) participants in the teriparatide group and 64 (12.0%) participants in the risedronate group (risk ratio (RR) 0.44; 95% CI 0.29–0.68; P < 0.0001). The results for clinical fracture were similar (HR 0.48, 95% CI 0.32–0.74; P = 0.0009) although non-significant for non-vertebral fracture (HR 0.66, 95% CI 0.39–1.10; P = 0.10)[32].

A 2019 systematic review of 23 randomized controlled trials, 19 studies with an active-controlled arm and 11 double-blind studies — all representing data from 8,644 individuals with osteoporosis, 3,893 of whom had been treated with teriparatide — demonstrated an odds ratio (OR) for hip fractures of 0.44 (95% CI 0.22–0.87; P = 0.019) in individuals treated with teriparatide compared with individuals treated with placebo (four studies) or at least one active comparator (19 studies), evaluating in total 34 incident events. There was no difference in the risk of fractures of the humerus (OR 1.02, 95% CI 0.50– 2.08), forearm (OR 0.53, 95% CI 0.26–1.08) or wrist (OR 1.21, 95% CI 0.72– 2.04)[33].

Murine studies have highlighted the fact that long-term bisphosphonate exposure blunts the bone-forming response to teriparatide, possibly owing to the exposure of osteoblasts to bisphosphonates[34]. Indeed, the Parathyroid Hormone and Alendronate (PaTH) study, a randomized, 12-month trial in a population of postmenopausal women with DXA-measured osteoporosis or with a T score of <−2.0 and an additional risk factor for osteoporosis (n = 238), investigated the potential for a synergistic relationship between full-length PTH and alendronate in three arms: PTH alone, alendronate alone, or both agents concurrently[35]. Rather than demonstrating a benefit from the combined effects of PTH and alendronate on bone formation and antiresorption, respectively, the increase in trabecular volumetric BMD (as measured by quantitative CT) in the group receiving PTH was twofold higher than that in the combination therapy group, and serum markers of bone formation only increased significantly in the group receiving PTH alone. These findings suggest that the dual use of alendronate with PTH is not synergistic but, in fact, restricts some bone forming effects of PTH.

To investigate whether this apparent deleterious effect of combination therapy was due to the relatively frequent (weekly) administration of oral alendronate, a study was undertaken in postmenopausal women with osteoporosis (n = 412) randomized to 12-months of subcutaneous teriparatide at a dose of 20 μg, a yearly intravenous administration of zoledronate, or combination therapy with both[36]. The greatest gains in lumbar spine BMD were observed in the combination therapy group and the group receiving teriparatide alone, whereas the greatest gains in total hip BMD were observed in the combination group and the group receiving zoledronate alone. These results might reflect the superior ability of teriparatide to improve BMD at trabecular sites via bone formation.

Combination therapy with teriparatide and denosumab was similarly investigated in the Denosumab and Teriparatide Administration (DATA) study over a duration of 24 months[37]. The combination therapy provided greater gains in BMD at the lumbar spine (9.1% (s.d. 3.9)) compared with teriparatide alone (6.2% (s.d. 4.6); P = 0.0139) or denosumab alone (5.5% (s.d. 3.3); P = 0.0005), with similar findings at the total hip (4.9% (s.d. 2.9) with the combination; 0.7% (s.d. 2.7) with teriparatide alone (P < 0.0001); 2.5% (s.d. 2.6) with denosumab alone (P = 0.0011))[37]. However, the bone turnover profile of the combination therapy group was more similar to that of the denosumab-alone group (antiresorptive) rather than the teriparatide group (bone-forming), demonstrating that combination therapy blunts the bone-forming effect of teriparatide.

A blunted bone-forming effect of teriparatide in combination therapy was also demonstrated in a study in postmenopausal women taking either alendronate or raloxifene (for at least 18 months) who were then either prescribed additional teriparatide or switched to teriparatide alone[38]. In this setting, gains in BMD after a period of at least 18 months of treatment were greater in the combination group than in the sequential therapy group, although dual administration of antiresorptive and bone-forming agents decreased the levels of bone turnover markers[38].

The DATA-Switch study, which included 77 postmenopausal women and was an extension of the DATA study, assessed 4-year lumbar spine BMD in three arms: denosumab followed by 24 months of teriparatide; teriparatide followed by 24 months of denosumab; and combination therapy followed by 24 months of denosumab. At 4 years, increases in spinal BMD were observed in all groups with no significant differences between them. At the femoral neck and the hip, increases in BMD and volumetric BMD were greatest in the arm of combination treatment followed by denosumab. Switching from denosumab to teriparatide led to transient reductions in lumbar spine and hip BMD, increases in bone turnover and large losses in BMD at the distal radius in both total and cortical volumetric BMD[39,40]. These results highlighted that the sequence of treatment matters, with teriparatide potentially being more beneficial in terms of BMD gain in individuals who are naive to antiresorptive therapy compared with those who have previously received antiresorptive medication[41,42].

Further real-world evidence was provided by the European Forsteo Observational Study (EFOS), which analysed the efficacy of 18 months of treatment with teriparatide followed by an 18-month period during which most participants (postmenopausal women) were treated with alendronate. There was a persistent reduction in fracture rate following discontinuation of teriparatide with reductions observed for all fractures, both vertebral and non-vertebral[43]. At 36 months, there were 258 fractures (from a total of 1,576 participants), of which 34% were clinical vertebral fractures and 66% were non-vertebral fractures. The risk of fracture was significantly lower between 30 and 36 months after treatment initiation than during the initial period of treatment with teriparatide, with a 74% decrease in the adjusted odds of fracture compared with the first 6 months of treatment (P < 0.001)[44]. This emphasizes the efficacy of teriparatide and the persisting fracture risk reduction after completing the course of treatment.

Meta-analysis of six randomized controlled trials comparing teriparatide with alendronate in postmenopausal women (n = 618 patients) demonstrated that teriparatide leads to significantly greater increases in BMD than alendronate at the lumbar spine (weighted mean difference (WMD) 3.46, 95% CI 2.15–4.77; P < 0.00001) with a smaller apparent benefit at the femoral neck (WMD 1.50, 95% CI 0.04–2.95; P = 0.04)[45]. This same meta-analysis investigated fracture risk, but was limited by the number of fracture events (23 in the teriparatide group versus 27

in the alendronate group), and showed no differences in fracture rates between the two treatments (OR −0.03, 95% CI −0.12–0.07; $P = 0.52$)[45].

In conclusion, the above evidence underscores the efficacy of teriparatide in reducing vertebral risk and, to a lesser extent, non-vertebral and hip fracture risks, particularly in postmenopausal women with osteoporosis (Table 1). The bone-accruing benefits are most pronounced when commenced in antiresorptive-naive individuals and then used in sequence with bisphosphonates or denosumab. However, combination with antiresorptive therapies in those already receiving denosumab might still help to optimize BMD outcomes, albeit with potential attenuation of bone formation markers.

Abaloparatide

Randomized controlled trials have, in some cases, included teriparatide as a comparator to abaloparatide, providing the opportunity to compare these two PTH1R agonists head-to-head.

The Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) study examined the efficacy of abaloparatide (80 μg daily) compared with placebo and open-label teriparatide (20 μg daily) over 18 months in a group of postmenopausal women ($n = 2,463$)[6]. The inclusion criteria were that participants had to have a previous radiographic vertebral fracture, or recent non-vertebral fracture with either DXA-proven osteoporosis if aged ≤65 years or a T score of ≤−2.0 if aged <65 years. Participants were also included if they had no prior fracture but very low BMD ($T \leq -3.0$) and were aged >65 years. The main outcomes of the ACTIVE trial were vertebral, non-vertebral, clinical and major osteoporotic fractures, DXA-measured BMD and bone turnover markers[6].

New vertebral fractures were significantly reduced by abaloparatide (RR 0.14, 95% CI 0.05–0.39; $P < 0.001$) and teriparatide (RR 0.20, 95% CI 0.08–0.47; $P < 0.001$). Abaloparatide significantly reduced non-vertebral fractures (HR 0.57, 95% CI 0.32–1.00; $P = 0.049$), whereas teriparatide non-significantly lowered the risk of non-vertebral fractures (HR 0.72, 95% CI 0.42–1.22; $P = 0.22$). Major osteoporotic fracture constituted an exploratory end point, for which evidence supported a greater risk reduction for abaloparatide than for teriparatide (HR 0.45, 95% CI 0.21–0.95; $P = 0.03$). In this study, the risk reductions with open-label teriparatide compared with placebo did not reach formal statistical significance for non-vertebral, clinical or major fracture outcomes. However, the absolute differences in risk reduction between the two PTH1R agonists were small, as were the number of events, and the licensed dose of teriparatide is lower than that tested for abaloparatide. In terms of BMD, both teriparatide and abaloparatide were associated with significantly greater gains than placebo at all time points (6, 12 and 18 months) and at all sites (lumbar spine, femoral neck and total hip). Compared with teriparatide, abaloparatide was associated with greater gains in BMD at all sites and at all time points, except for 18-month follow-up at the lumbar spine. Bone turnover marker profiles differed between the PTH1R agonists. Teriparatide induced an initial peak with subsequent plateaus for both PINP and β-CTX. By contrast, abaloparatide induced an initial peak for PINP and then gradual declined over 18 months, while slightly increasing the levels of β-CTX, which, however, remained consistently lower than those observed in individuals receiving teriparatide throughout the study.

A post hoc analysis of the ACTIVE study examined the relationship between baseline fracture risk and the efficacy of abaloparatide[46]. In the trial, the mean baseline major osteoporotic fracture risk was 13.2%. Abaloparatide was associated with a 69% reduction in major osteoporotic fracture risk and 43% reduction in any clinical fracture risk versus placebo. There was no significant interaction between efficacy of abaloparatide and baseline fracture risk, indicating that the efficacy of abaloparatide observed in the ACTIVE trial was independent of the baseline fracture risk of the participants[46]. Using a random subset of the ACTIVE trial ($n = 250$ per arm), bone microarchitectural changes, derived from 3D active shape modelling within DXA images, showed differential effects on the cortical and trabecular compartments between abaloparatide and teriparatide[47]. Compared with placebo, both anabolic agents increased trabecular volumetric BMD (9% gain; $P < 0.001$) and cortical thickness (1.5% gain; $P < 0.001$). However, cortical hip volumetric BMD was increased with abaloparatide (1.3% gain; $P < 0.001$) but not with teriparatide. The degree of increase in cortical volumetric BMD at the hip was inversely correlated with levels of β-CTX, indicating that a higher bone turnover might have attenuated cortical gains[47].

The ACTIVExtend study included 1,139 (92%) of the original ACTIVE participants and extended the abaloparatide and placebo arms with 24 months of oral alendronate[48]. Lumbar spine and femoral neck BMD continued to increase after abaloparatide treatment in participants taking the oral bisphosphonate, with suppression of PINP and β-CTX being similar in both groups. In terms of fractures, 0.9% of women in the abaloparatide group and 5.6% of women in the placebo group sustained a new radiographic vertebral fracture, indicating a relative risk reduction of 84% ($P < 0.001$) with abaloparatide[48]. The reduction in vertebral fracture risk observed during the 18 months treatment with abaloparatide persisted during the 24 months therapy with alendronate. A further post hoc analysis of ACTIVExtend examined the efficacy of abaloparatide followed by alendronate in the oldest participants of the study (in this case ≥80 years of age). This included 46 participants with a mean age of 83.3 years, and abaloparatide was well tolerated and effective for the gain in BMD versus placebo in this subgroup[49].

A transdermal formulation of abaloparatide was trialled in an open-label study against the subcutaneous form in 511 postmenopausal women[50]. The results for the primary outcome at 12 months demonstrated inferiority of the 'microstructured transdermal system' compared with the subcutaneous version, with significantly lower percentage gain in lumbar spine BMD (transdermal 7.14% (s.e.m. 0.46%), subcutaneous 10.86% (s.e.m. 0.48%)). No placebo group was included in this study. A 24-week dose-ranging trial of abaloparatide at doses of 20 μg, 40 μg and 80 μg was performed with two other arms including 20 μg teriparatide and placebo[51]. This randomized controlled trial on 222 postmenopausal women revealed a significantly greater BMD increase at the lumbar spine for abaloparatide doses of 40 μg and 80 μg compared with placebo, and greater gains in total hip BMD for these two doses (40 μg and 80 μg) compared with teriparatide. Trabecular bone score, a measure of bone microarchitecture, was significantly higher in the 80 μg abaloparatide arm than in the teriparatide arm, and greater than placebo at all doses[51]. Given the short duration of the study, it might not represent a true comparison of abaloparatide and teriparatide. Further clinical studies have investigated the differences between these two PTH1R agonists.

An analysis of health insurance claims data from the USA provides real-world evidence of the benefits of abaloparatide over teriparatide with regard to fracture prevention[8]. In a propensity score-matched investigation that monitored over 20,000 patients in each group for 18 months, abaloparatide was associated with a lower risk of fracture compared with teriparatide; reduced risk was determined for hip fracture (HR 0.83, 95% CI 0.70–0.98; $P = 0.027$) and non-vertebral fracture (HR 0.88, 95% CI 0.80–0.96; $P = 0.003$). Similarly, significantly lower

Table 1 | Key clinical trials of teriparatide

Study	Study participants (*n*)	Duration (months)	Study arms	Key outcomes for teriparatide
FPT[7]	Postmenopausal women with prior vertebral fracture (*n* = 1,637)	21	Teriparatide 20 µg Teriparatide 40 µg Placebo	Reduced vertebral fractures (RR 0.35, 95% CI 0.22–0.55, with 20 µg; RR 0.31, 95% CI 0.19–0.50, with 40 µg) and non-vertebral fractures (RR 0.47, 95% CI 0.25–0.88, with 20 µg; RR 0.46, 95% CI 0.25–0.861, with 40 µg)
FPT, subgroup analysis[29]	Postmenopausal women with prior vertebral fracture age <75 years (*n* = 841) and age ≥75 years (*n* = 244)	19	Participants aged ≥75 years receiving teriparatide Participants aged <75 years receiving teriparatide	No difference in efficacy and safety of teriparatide in those aged ≥75 years
FPT, post hoc analysis[30]	Postmenopausal women with prior vertebral fracture (*n* = 1,637)	21	Teriparatide combined (20+40 µg) Placebo	Non-vertebral fractures: RRR 37% (95% CI 10–56%) Low-energy non-vertebral fractures: RRR 56% (95% CI 24–75%) Morphometric vertebral fractures: RRR 66% (95% CI 50–77%) Fracture risk reduction was consistent across all baseline fracture probabilities, as assessed by FRAX with or without BMD (no significant interaction, *P* > 0.30)
FPT extension[31]	Postmenopausal women with prior vertebral fracture (*n* = 1,262)	50	Teriparatide combined doses (20+40 µg) Placebo	Hazard ratio for non-vertebral fragility fractures (combined teriparatide group vs placebo): 0.57 (*P* = 0.002) for over 50 months Significant fracture risk reduction persisted up to 30 months after discontinuation of teriparatide BMD declined in teriparatide-treated patients with no follow-up treatment BMD stabilized or increased in those who received bisphosphonates after teriparatide
VERO study[32]	Postmenopausal women with two or more moderate or one or more severe vertebral fracture+BMD T score ≤–1.5 (*n* = 1,360)	24	Teriparatide 20 µg Risedronate	Incident vertebral fracture (RR 0.44, 95% CI 0.29–0.68) Clinical fractures (HR 0.48, 95% CI 0.32–0.74) Non-vertebral fragility fractures (HR 0.66, 95% CI 0.39–1.10)
PaTH trial[35]	Postmenopausal women with T score ≤–2.5 at hip or spine, or ≤–2.0 with additional risk factors (*n* = 238)	12	PTH (1–84) 100 µg Alendronate Combination therapy	Lumbar spine BMD increased in lumbar spine by 6.3% with PTH, 4.6% with alendronate, and 6.1% with combination therapy Trabecular spine volumetric BMD increased by 25.5% with PTH, 10.5% with alendronate, and 12.9% with combination therapy
Zoledronate combination study[36]	Postmenopausal women with T score ≤–2.5 at hip or spine, or ≤–2.0 with fracture history (*n* = 412)	12	Teriparatide 20 µg Zoledronate Combination therapy	Lumbar spine BMD increase at 52 weeks: 7.0% with teriparatide, 4.4% with zoledronic acid, 7.5% with combination therapy; early greater gains with combination therapy at 13 and 26 weeks (*P* < 0.001) Total hip BMD at 52 weeks: 1.1% with teriparatide, 2.2% with zoledronic acid, 2.3% with combination therapy; significantly higher with combination therapy vs teriparatide at all time points (*P* ≤ 0.02) Clinical fracture incidence: 8 (5.8%) with teriparatide, 13 (9.5%) with zoledronic acid, 4 (2.9%) with combination therapy; significantly lower with combination therapy vs zoledronic acid (*P* = 0.04)
DATA study[37]	Postmenopausal women with T scores ≤–2.5 or ≤–2.0 with risk factors (*n* = 100)	24	Teriparatide 20 µg Denosumab Combination therapy	Lumbar spine BMD increased by 9.5% with teriparatide (*P* = 0.01 vs combination therapy), 8.3% with denosumab (*P* = 0.008 vs combination therapy), and 12.9% with combination therapy (24 months) Femoral neck BMD increased by 2.8% with teriparatide (*P* = 0.003 vs combination therapy), 4.1% with denosumab (*P* = 0.008 vs combination therapy), and 6.8% with combination therapy Total hip BMD increased by 2% with teriparatide, 3.2% with denosumab, and 6.3% with combination therapy (*P* < 0.001 for the combination vs both)
DATA-Switch[39]	Postmenopausal women (*n* = 83)	28	Teriparatide 20 µg to denosumab Denosumab to teriparatide Combination therapy to denosumab	Lumbar spine BMD increased by 18.3% with teriparatide to denosumab, 14% with denosumab to teriparatide, and 16% with combination therapy to denosumab Femoral neck BMD increased by 8.3% with teriparatide to denosumab, 4.9% with denosumab to teriparatide, and 9.1% with combination therapy to denosumab Total hip BMD increased by 6.6% with teriparatide to denosumab, 2.8% with denosumab to teriparatide, and 8.6% with combination therapy to denosumab
EFOS[44]	Postmenopausal women with severe osteoporosis in routine clinical practice (*n* = 1,649)	36	Teriparatide (observational study)	208 patients (13.2%) sustained 258 fractures over 36 months 74% decrease in adjusted odds of fracture for the months 30–36 vs the months 0–6 (OR 0.265; *P* < 0.001)

BMD, bone mineral density; DATA study, Denosumab and Teriparatide Administration study; EFOS, European Forsteo Observational Study; FPT, Fracture Prevention Trial; PaTH trial, Parathyroid Hormone and Alendronate trial; PTH, parathyroid hormone; RR, relative risk; RRR, relative risk reduction; VERO study, Vertebral Fracture Treatment Comparisons in Osteoporotic Women study.

risks of both hip and non-vertebral fractures were observed as early as 6 months after commencing treatment[8]. Although this analysis used state-of-the-art epidemiological methods, it still should be viewed as hypothesis-generating rather than definitive evidence equivalent to that from a randomized controlled trial.

Meta-analyses have further compared available data, including data from the trials discussed above, in terms of abaloparatide and teriparatide efficacy[51]. One of these studies showed significant benefits of abaloparatide over teriparatide in terms of gain in BMD at the femoral neck (mean difference 1.58, 95% CI 0.52–2.63) and total hip (mean difference 1.46, 95% CI 0.59–2.32)[52]. However, this meta-analysis only included group comparisons from dose-ranging studies and might therefore show limited generalizability. In a Bayesian network meta-analysis including 17 studies — 11 randomized controlled trials and six studies incorporating real-world evidence[53] — both abaloparatide and teriparatide were effective for the prevention of vertebral and non-vertebral fractures compared with placebo. This analysis also demonstrated that abaloparatide was more protective than teriparatide for non-vertebral fracture (OR 0.87, 95% CI 0.80–0.95) and hip fracture (OR 0.81, 95% CI 0.71–0.93). Moreover, teriparatide and abaloparatide were found to be superior to placebo, raloxifene and calcitonin for the prevention of vertebral fracture, teriparatide was superior to denosumab and risedronate for the prevention of vertebral fracture, and abaloparatide was superior to all other interventions for the prevention of non-vertebral fracture. No differences between interventions was observed for hip fracture. These data from meta-analyses demonstrate the substantial antifracture efficacy of the PTH1R agonists.

In summary, abaloparatide has demonstrated robust efficacy in reducing fracture risk and improving BMD across multiple studies (Table 2), including head-to-head comparisons with teriparatide. The consistency of effect across age groups, baseline fracture risk levels, and in real-world data supports abaloparatide as a valuable therapeutic option in the management of women with postmenopausal osteoporosis.

Osteoporosis in men

Given the higher incidence of osteoporosis in women, most studies evaluating PTH1R agonists have focused on women and, particularly, on postmenopausal women. However, osteoporosis is also a substantial burden in men[10].

Teriparatide has been shown to be effective in men in increasing lumbar spine BMD and femoral neck BMD compared with placebo[54–56], similar to the observations in postmenopausal women[7]. Sequential antiresorptive therapy has demonstrated similar benefits in men and women[57]. In a study in men with low BMD, 83 men were treated with alendronate, or alendronate and PTH in combination or sequentially over 30 months[58]. Among 73 men analysed (mean age 58 years), the combination and sequential treatments led to greater gains in BMD than alendronate alone in the lumbar spine (18.1% sequential, 14.8% combination, 7.9% alendronate alone), in the femoral neck (9.7% sequential, 6.2% combination, 3.2% alendronate alone) and in spinal trabecular bone (measured by quantitative CT; 48% sequential, 17% combination, 3% alendronate alone).

The Abaloparatide-SC for the Treatment of Men with Osteoporosis (ATOM) study randomized osteoporotic or hypogonadal men to 80 µg abaloparatide subcutaneously ($n = 149$) or placebo ($n = 79$) and demonstrated increases in BMD at all sites with abaloparatide compared with placebo[59], similar to the findings of the ACTIVE study[6]. Significant and more rapid improvements were observed at 3, 6 and 12 months with >3% increases in BMD at all measured sites (lumbar spine, total hip and femoral neck). Although a greater body of evidence supports the use of PTH1R agonists in postmenopausal women than in men, these studies do support the use of PTH1R agonists as anti-osteoporosis medications in men.

Safety

The efficacy of PTH1R agonists should be balanced against the safety profile of these medications. In gaining a holistic view of the safety profile, particularly for the oldest patients (>75 years) who are more

Table 2 | Key clinical trials of abaloparatide

Study	Study participants (*n*)	Duration (months)	Study arms	Key outcomes for abaloparatide
ACTIVE[6]	Postmenopausal women with osteoporosis, with or without previous vertebral or low-trauma nonvertebral fractures ($n = 2,463$)	18	Abaloparatide 80 µg (blinded) Placebo (blinded) Teriparatide 20 µg (open-label)	Vertebral fracture: RR 0.14, 95% CI 0.05–0.39 ($P < 0.001$, abaloparatide vs placebo) Non-vertebral fracture: HR 0.57, 95% CI 0.32–1.00 ($P = 0.049$, abaloparatide vs placebo)
ACTIVE trial, subgroup analysis[46]	Postmenopausal women with osteoporosis, with or without previous vertebral or low-trauma non-vertebral fractures ($n = 1,645$)	18	Abaloparatide 80 µg (blinded) Placebo daily subcutaneously (blinded)	Major osteoporotic fracture: RRR 69%, 95% CI 38–85% Clinical fracture: RRR 43%, 95% CI 9–64%
ACTIVExtend[48]	Postmenopausal women with osteoporosis, with or without previous vertebral or low-trauma nonvertebral fractures (92% of eligible women from the ACTIVE trial) ($n = 1,139$)	43	Placebo switched to alendronate Abaloparatide switched to alendronate	Vertebral fracture: RRR 84% ($P < 0.001$) Major osteoporotic fracture, clinical fracture and non-vertebral fracture significantly lower in abaloparatide switched to alendronate vs placebo switched to alendronate group
ACTIVExtend, subgroup analysis[49]	Postmenopausal women aged ≥80 years with osteoporosis and high fracture risk ($n = 56$)	43	Placebo switched to aldosterone Abaloparatide switched to aldosterone	Significant gains in BMD vs placebo at all sites, particularly at the spine (abaloparatide +17.2% vs placebo +8.6%, $P < 0.0001$)

ACTIVE, Abaloparatide Comparator Trial in Vertebral Endpoints; BMD, bone mineral density; RR, relative risk; RRR, relative risk reduction.

susceptible to adverse effects via comorbidity and polypharmacy, adverse events in the intervention and control arms of randomized controlled trials of PTH1R agonists can be compared. As previously mentioned, PTH1R receptors are expressed on smooth muscle cells including those of the vessels, bladder, gallbladder, uterus and myocardium. Receptor activation in cardiomyocytes might lead to potential reductions in blood pressure through relaxation of smooth muscle and to increases in heart rate via chronotropic effects on the myocardium[60].

Data from the VERO trial provide a perspective on the comparison of adverse effects for teriparatide and risedronate[32]. Adverse effects that were significantly more common in participants taking teriparatide included dizziness (4.4% with teriparatide vs 1.8% with risedronate; $P = 0.007$) and arthralgia (5.4% with teriparatide vs 2.6% with risedronate; $P = 0.013$). Despite the potential of teriparatide to target the cardiovascular system, it was not associated with excessive risk of cardiovascular events. The cardiovascular risks of bisphosphonates and teriparatide were further compared using data from VigiBase[61], the World Health Organization (WHO) global database for adverse event reporting for medicines and vaccines. Meta-analysis of the adverse events from over 130 countries indicated that teriparatide and bisphosphonates are comparable in terms of clinical manifestations of cardiac disease including angina, myocardial infarction and stroke[62].

Data from the FPT were used to further assess the risks of adverse events in the oldest participants receiving teriparatide: data from a population of individuals aged ≥75 years were compared with data from a population of patients aged <75 years[29]. The adverse events that significantly differed between teriparatide and placebo included constipation ($P = 0.04$), cataracts ($P = 0.003$), deafness ($P = 0.006$), weight loss ($P = 0.03$) and pruritus ($P = 0.02$), but all occurred significantly more commonly in the placebo arm[29]. Even in this high-risk population of women (>75 years), no increased cardiovascular risks were observed. Thus, evidence from extensive pre-market and post-market studies demonstrate no increase in the cardiovascular risk of teriparatide, including in high-risk groups such as participants >75 years.

An increased risk of osteosarcoma has been reported in rats treated with teriparatide from weaning and over the course of 24 months[63]. Rat skeletons continue to grow throughout their life course, and 2 years of treatment covers a high percentage of a rat's lifespan, which might explain the reported increased risk in osteosarcoma in this particular study. Moreover, in these studies, teriparatide was administered at doses that were three times higher than the dose given to humans[64]. Data from clinical trials and extensive post-marketing surveillance studies using cancer registers in the USA have convincingly demonstrated no increased risk of osteosarcoma over the course of 15 years, from 2003 to 2016 (ref. 65). A further systematic review found only 3 patients with osteosarcoma among 253,704 patients taking teriparatide in North America, Europe and Asia[66]. These findings justified the removal of the box warning and the extension of the duration of treatment from 18 to 24 months in 2020 in the USA. Similar concerns for abaloparatide were derived from murine models[63] but have not been borne out in real-world analyses of large cohorts ($n = 44{,}728$) investigating the rate of primary bone malignancy in high-risk patients. This rate was 5.96% for the anabolic-exposed patients versus 8.13% for non-exposed patients[67].

Regarding other adverse effects of abaloparatide, the ACTIVE trial found dizziness in 10.0% of participants taking abaloparatide, but this proportion was not significantly different from the 6.1% of participants taking placebo and 7.3% of participants taking teriparatide. Moreover, the proportions of individuals developing nausea were 8.3% for abaloparatide, 3.0% for placebo and 5.1% for teriparatide (differences not statistically significant). The proportions of individuals developing palpitations was 5.1% for abaloparatide, compared with 0.4% for placebo and 1.6% for teriparatide (differences not statistically significant)[6]. No excessive risk of myocardial infarction, falls or syncope were observed in this study among participants in the abaloparatide arm. Abaloparatide is associated with a transient increase in heart rate and a small reduction in blood pressure, which might account for the dizziness experienced by some individuals, but did not translate to an increase in major adverse cardiovascular events (MACE) or heart failure in a cohort of postmenopausal women[68].

The low cardiovascular risk profile of both PTH1R agonists is supported by real-world evidence from a US database of administrative claims that showed no difference in the risk of myocardial infarction, stroke and heart failure between abaloparatide and teriparatide. The data also indicate equivalent rates of MACE (3.0% for abaloparatide and 3.1% for teriparatide[69]) and comparable risks of new events (HR 1.00, 95% CI 0.84–1.20; $P = 0.97$)[8,69]. A Bayesian network meta-analysis of data from 75 studies testing anti-osteoporosis medications in postmenopausal women, of which one investigated abaloparatide, found that abaloparatide was protective against MACE-4, which includes myocardial infarction, stroke, cardiovascular death and heart failure (OR 0.28, 95% CI 0.06–0.88). No significant association was found between teriparatide and MACE-4 (OR 0.68, 95% CI 0.34–1.31)[70]. A meta-analysis of the data from four studies indicated a non-significant increase in the odds of hypercalcaemia with teriparatide versus abaloparatide (OR 0.49, 95% CI 0.18–1.35; $P = 0.117$). The same meta-analysis showed a non-significant odds of hypercalcaemia with abaloparatide versus placebo (OR 1.30, 95% CI 0.58–2.91)[52]. Incidentally, the same study found increased odds of nausea (OR 2.61, 95% CI 1.73–3.95; $P < 0.00001$) and palpitations (OR 12.54, 95% CI 4.50–34.93; $P < 0.00001$) for those taking abaloparatide compared with placebo[52].

To summarize the safety data, although dizziness and nausea are likely to be more common with PTH1R agonists than with placebo, there is no evidence of meaningful cardiovascular risk. Osteosarcoma is not an issue in humans, and there is little evidence that any potentially increased propensity to hypercalcaemia or hypercalciuria result in any clinically apparent manifestations.

Health economics

PTH1R agonists are effective and safe options for fracture prevention but are more expensive than oral bisphosphonates. Health economic analyses are therefore crucial to understand the positioning of these drugs in the treatment algorithm for osteoporosis and are certainly of understandable interest for reimbursement decisions. Cost-effectiveness is assessed via the incremental cost-effectiveness ratio (ICER), in which the difference in total societal and health-care costs between the intervention of interest and a control intervention are divided by the difference in the quality-adjusted life years (QALYs) between the two interventions. The lower the ICER, the more cost-effective the intervention of interest.

Initial health economic analyses focused on cost-effectiveness of teriparatide as a sole intervention, without sequential therapy (with an antiresorptive agent). In this context, in studies in Iran[71] and Sweden[72], teriparatide was found to be cost-effective for the treatment of postmenopausal women when compared with no treatment. However, when compared with antiresorptives, the cost-effectiveness of teriparatide was heterogeneous. In a study in Sweden, teriparatide was more cost-effective than oral

bisphosphonates for the treatment of postmenopausal osteoporosis and glucocorticoid-induced osteoporosis[73]; by contrast, in a study in Iran, oral risedronate was more cost-effective than teriparatide for the treatment of severe postmenopausal osteoporosis[74]. In a study in the USA, denosumab was also found to be more cost-effective than teriparatide in the treatment of osteoporosis in men[75]. However, these findings might not be clinically relevant, as it is unusual for teriparatide to be used in isolation in current clinical practice.

In studies of sequential therapy versus antiresorptive monotherapy, teriparatide (for 2 years) succeeded by alendronate (for 8 years) was not as cost-effective as 10 years of alendronate alone in a population of community-dwelling women in Japan with a history of vertebral fracture (except at the age of 80 years)[76]. Similar findings (except without the cost-effectiveness for the oldest participants) were found for the cheaper biosimilar formulations of teriparatide in a Japanese population[77]. Abaloparatide was cost-effective when used for 18 months followed by 3 years of alendronate, compared with 5 years of alendronate alone, in a US population of women ≥60 years of age[78]. Indeed, dominance of abaloparatide sequential therapy was demonstrated in those with T scores ≤−3.5 and those with T scores from −2.5 to −3.5 and a history of one or more osteoporotic fractures[78].

In a systematic review of ten studies published up to 2022 investigating the cost-effectiveness of sequential therapies for the treatment of osteoporosis, 75% of studies showed that sequential therapy was at least cost-effective, if not dominant (that is, less cost for more QALYs), compared with other sole antiresorptive therapy[79]. Thus, cost-effectiveness differs between abaloparatide and teriparatide, with more favourable cost-effectiveness observed for abaloparatide. In direct head-to-head comparisons of cost-effectiveness in a population based in the USA, sequential therapy with abaloparatide followed by alendronate was more effective than teriparatide followed by alendronate in women with postmenopausal osteoporosis aged <65 years, in those aged ≥65 years with a prior vertebral fracture over a 10-year time horizon, and in those aged ≥65 years with a prior vertebral fracture over a lifetime horizon[80]. Similarly, in another study, abaloparatide–alendronate was more effective than teriparatide–alendronate sequential therapy in those with T scores ≤−3.5 and in those with T scores from −2.5 to −3.5 and a history of one or more osteoporotic fractures from a US payer perspective[81]. Not only was abaloparatide shown to be more effective than teriparatide when each was combined with alendronate for sequential therapy, but also abaloparatide–alendronate sequential therapy was more cost-effective than alendronate monotherapy in men aged ≥50 years with any type of fracture, in women aged ≥65 years with any fracture, and women aged ≥55 years with a history of hip or vertebral fracture[82].

The limitations of the current health economic literature include the scarcity of evidence available for European countries (except Sweden[83] and the UK for teriparatide only) and other countries, and the limited transferability of cost-effectiveness findings and comparisons of medications between health systems, given the regional differences in drug costs and fracture costs.

Clinical deployment

Although in the ideal world the most effective drugs would be available to use freely in all patients, in many health-care systems, anabolic therapies for osteoporosis are reserved for those with the highest fracture risk of or as second-line agents[84,85]. Recommendations from the ESCEO have set out how baseline risk assessment may be used to target therapy according to fracture risk, with anabolic medications used first in those with the highest fracture risk[85,86]. These include using the fracture risk assessment tool FRAX to assess fracture risk and as a gateway to the assessment of BMD in borderline cases. In this way, 10-year fracture risk is used to classify individuals into low-risk, high-risk or very high-risk categories using a nomogram, with those at very high risk being most appropriate to target with bone-forming therapies.

Although definitive data are awaited, exploratory outcomes from the ACTIVE trial, findings from real-world evidence, and potential implications from patterns of bone turnover markers, all suggest that abaloparatide might have broader antifracture efficacy than teriparatide, with a consistent health economic picture in some settings[53,79,87]. A practical advantage of abaloparatide is the lack of requirement for ongoing refrigeration after first use, and this might be helpful, for example, in patients required to travel. Beyond these considerations, the choice of PTH1R agonist may be dictated by availability and local policy as much as by any clinical imperatives.

For many patients, a tangible benefit of PTH1R agonists compared with bisphosphonates is the lack of concern regarding the rare, but important adverse effects of osteonecrosis of the jaw or atypical femoral shaft fractures. Although transient dizziness and potentially transient hypotension are potential adverse effects of PTH1R agonists, they rarely limit treatment, and cardiovascular safety has been conclusively demonstrated. Human studies have provided no evidence of osteosarcoma[88,86], but the contraindication to use in individuals with previous bone malignancy, skeletal radiation or Paget disease of course remains.

Research priorities

There is substantial and excellent research in the area of PTH1R agonists for the treatment of osteoporosis. However, particular areas of research need to be expanded as the field moves forwards. These include further health economic analyses and the development of bodies of real-world evidence.

Owing to the availability of large databases of health-care claims in the USA, health economics analyses have so far focused on the US population and health-care system. Further research is required to take account of the individual nuances of costs and reimbursement in the European, African, Australasian, Asian and South American contexts. Similarly, most real-world evidence on the use of PTH1R agonists has been accrued in the North American geographic region. Work focused on other regions is required to ensure that the use of PTH1R agonists is based on robust, real-world research and alleviates rather than reinforces health inequalities.

Conclusions

In conclusion, there is excellent evidence for the use of PTH1R agonists in the treatment of osteoporosis. In the absence of definitive head-to-head findings, taken as a whole, data from clinical trials, real-world evidence and meta-analysis suggest possible superiority of abaloparatide compared with teriparatide for BMD, health economic and non-vertebral fracture outcomes. These medications seem to show better efficacy than antiresorptives (with slightly differing clinical profiles), and there is clinical and economic evidence to support the use of sequential antiresorptive treatment following the anabolic agents. Future research should expand the reach of the current real-world data and health economic analyses.

Published online: 11 August 2025

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Acknowledgements
This ESCEO Working Group was funded by the ESCEO. The ESCEO receives unrestricted educational grants to support its educational and scientific activities from non-governmental organisations, not-for-profit organisations, non-commercial or corporate partners. The choice of topics, participants, content and agenda of the Working Groups as well as the writing, editing, submission and reviewing of the manuscript are the sole responsibility of the ESCEO, without any influence from third parties. This work was supported by the Distinguished Scientist Fellowship Program (DSFP) of the King Saud University, Riyadh, Kingdom of Saudi Arabia.

Author contributions
N.F., N.C.H., J.Y.-R. and R.R. wrote the initial draft of the article. All authors contributed substantially to discussion of the content, and reviewed and edited the manuscript before submission.

Competing interests
N.F. has received honoraria and speaker fees from UCB and Viatris, and travel bursaries from Eli Lilly and Pfizer. B.C. has received occasional fees as an expert or speaker from Alexion, Amgen, Aptissen, Expanscience, Lilly, Kyowa Kirin, Novartis, Theramex, UCB and Viatris. E.M.C. has received speaker fees from Eli Lilly, Thornton and Ross, and UCB, and travel bursaries or conference support from Amgen and Eli Lilly. M.H. has received research grants (paid to his institution) from Angelini Pharma and Radius Health, and lecture fees from IBSA (paid to his institution) and Mylan Pharmaceuticals, and was grant adviser for Pfizer (paid to his institution). N.V. declares personal fees from Bayer, Fidia, Nestlè and Viatris. B.H.A. reports research grants from Amgen and UCB, and honoraria from Amgen, Theramex and UCB. M.L.B. declares honoraria from Amgen, Ascendis, Bruno Farmaceutici, Calcilytix and Kyowa Kirin, grants or speaker fees from Alexion, Amgen, Amolyt, Bruno Farmaceutici, CoGeDi, Echolight, Gedeon Richter, Kyowa Kirin, Monte Rosa Therapeutics and UCB, and consultancy for Aboca, Alexion, Amolyt, Bruno Farmaceutici, Calcilytix, Echolight, Enterabio, Kyowa Kirin, Personal Genomics and Septern. O.B. has received consulting or lecture fees from Amgen, Aptissen, Biophytis, IBSA, Mylan, Novartis, Nutricia, Orifarm, Sanofi, UCB and Viatris outside the submitted work. E. Casado has received honoraria and speaker fees from FAES, Gedeon-Richter, STADA, Theramex and UCB, and travel bursaries from Amgen, Rubió, STADA and Theramex. M.C. has received honoraria and travel grants from Amgen and Promedius AI solutions. P.D'A. declares research grants and honoraria from ErreKappa, Nestlé, OM Pharma and Schwabe Pharma. P.R.E. declares research grants from Amgen, Alexion and Sanofi, and honoraria from Amgen, Alexion and Kyowa Kirin. J.A.K. is a director of Osteoporosis Research, which maintains FRAX. A.K. declares honoraria for scientific advisory board, research grants and speakers fees from AgNovos bioscience, Alexion, Amgen, Celltrion Deutschland, Echolight, Eli Lilly, Ipsen, Imaging Biopsy Lab (IBL), Kyowa Kirin, Merit Medical, new4med, Novartis, NovoNordisk, Roche, Sandoz, Servier, Stadapharm, Theramex and UCB. E.McC. is a director of Osteoporosis Research, which maintains FRAX, and has also received honoraria and research funding from Amgen, Fresenius Kabi, Lilly, ObsEva, Radius Pharma, Theramex and UCB. M.McC. declares consulting fees or honoraria from Amgen, Alexion, Pfizer and UCB. O.M. declares lecture fees or honoraria from Bottu Johnson and Johnson, Pfizer and Sanofi. J.-Y.R. declares speaker's Bureau for Radius Health and Theramex, and consultancy agreement for Theramex. N.C.H. has received personal fees, consultancy, lecture fees or honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Internis Pharma, Kyowa Kirin, Servier, Shire, Consilient Healthcare, Theramex and UCB outside the submitted work. R.R., C.B., J.-M.K, N.A.-D., M.A., N.B., C. Campusano, E. Cavalier, C. Cooper, B.D.-H., R.M., N.N., R.P. R., F.R., S.S. S.T., and L.Z. have no competing interests to declare.

Informed consent
This narrative article contains no original data and thus issues of ethics, informed consent and patient confidentiality do not apply.

Additional information
Peer review information *Nature Reviews Rheumatology* thanks Torben Harsløf and Bart Clarke for their contribution to the peer review of this work.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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