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Paggiosi, M.A. orcid.org/0000-0002-1030-0723, Yang, L., Blackwell, D. et al. (4 more authors) (2018) Teriparatide treatment exerts differential effects on the central and peripheral skeleton: results from the MOAT study. Osteoporosis International, 29 (6). pp. 1367-1378. ISSN 0937-941X

https://doi.org/10.1007/s00198-018-4445-5

Teriparatide Treatment Exerts Differential Effects on the Central and Peripheral Skeleton: Results from the MOAT Study

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Conflicts of interest and grant supporters (disclosures):

MAP, LY and DB state NO DISCLOSURE. *JSW* has received speaker's honoraria from Lilly, grant funding from Alexion and Immunodiagnostic Systems, donation of drug from Prostrakan for a clinical trial, consulting fees from Shire and Mereo Biopharma. *NP* has received speaker's honoraria and participated in advisory board activities for Eli Lilly and Prostraken. *EVM* has received consultancy payments from Merck, UCB, Consilient, speaker fees from Bayer, Consilient, GSK, Amgen, UCB, Roche, Servier, Lilly and payment for development from Lilly. *RE* has received consultancy payments, speaker fees and grant funding from Eli Lilly and Company. Teriparatide was provided by Eli Lilly and Company, Basingstoke, UK to The University of Sheffield through an Investigator-Initiated Trial (IIT) award. This work was funded by The National Institute for Health Research (NIHR) via its Biomedical Research Units Funding Scheme and the Sheffield Clinical Research Facility. The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service (NHS), the NIHR or the Department of Health (DoH).

Abstract

Introduction

Teriparatide stimulates bone formation and resorption and therefore can cause bone gain and loss. We simultaneously characterised the central and peripheral skeleton using imaging techniques to better understand the mechanism of action of teriparatide.

Methods

Postmenopausal, osteoporotic women (n=20, 65.4±5.5 years) were recruited into a 104-week study of teriparatide. Imaging techniques included DXA, quantitative computed tomography (QCT) and high-resolution peripheral quantitative computed tomography (HR-pQCT).

Results

Total lumbar spine areal bone mineral content (aBMC) (+11.2%), total lumbar spine areal bone mineral density (aBMD) (+8.1%), sub-regional thoracic spine aBMD (+7.5%), lumbar spine aBMC (+23.5%), lumbar spine aBMD (+11.9%), pelvis aBMC (+9.3%) and pelvis aBMD (+4.3%) increased. However, skull aBMC (-5.0%), arms aBMC (-5.1%), legs aBMC (-2.9%) and legs aBMD (-2.5%) decreased. Overall, we did not observe a change in total body bone mineral.

Increases in L1-L3 volumetric BMD (vBMD) (+28.5%) occurred but there was no change in total proximal femur vBMD.

Radius and tibia cortical vBMD (-3.3% and -3.4%) and tissue mineral density (-3.2% and -3.8%) decreased and there was an increase in porosity (+21.2% and +10.3%). Tibia, but not radius, trabecular inhomogeneity (+3.2%) and failure load (+0.2%) increased, but cortical thickness (-3.1%), area (-2.9%) and pore volume (-1.6%) decreased.

Conclusions

Teriparatide exerts differential effects on the central and the peripheral skeleton. Central trabecular vBMD (L1-L3) is improved, but there is a concomitant decrease in peripheral cortical vBMD and an increase in porosity. Overall, we did not observe a change in total body bone mineral. We acknowledge that our conclusions may be speculative and are constrained by the technical limitations of the imaging techniques used, the lack of a control group and the small sample size studied.

Keywords

Osteoporosis; teriparatide; mechanism of action; densitometry; treatment response

Mini Abstract

The central and peripheral skeleton were characterised using imaging techniques during 104-weeks of teriparatide treatment. Teriparatide exerts differential effects on the central and the peripheral skeleton. Overall, we did not observe a change in total body bone mineral. Our conclusions are constrained by the study limitations.

Introduction

Teriparatide is the active fragment (1-34) of human parathyroid hormone. It is one of only two anabolic agents licensed for the management of osteoporosis; the other being abaloparatide which received FDA approval in April 2017. Teriparatide stimulates both bone formation and bone resorption and therefore has the potential to cause bone gain and bone loss [1-3].

The effects of teriparatide to increase lumbar spine areal bone mineral density (aBMD), as measured using dual-energy x-ray absorptiometry (DXA), are well established [4-8]. However, calcium balance, assessed in the early development of teriparatide, did not show a positive balance [9]. Furthermore, a study that measured total body areal bone mineral content (aBMC) by DXA over a period of one year in patients on teriparatide following prior osteoporosis therapy also showed no significant change [10]. These studies suggest that there must be bone loss in some skeletal sites to balance the bone gain in the central skeleton.

The mechanisms underlying teriparatide-induced changes in densitometric and geometric bone properties can be elucidated using techniques that allow interrogation of the separate bone compartments, i.e. quantitative computed tomography (QCT). Mean changes in proximal femur total volumetric BMD (vBMD) of +1.2% and +0.5% and in lumbar spine total vBMD of +12.9% and +18.2% have been reported following 12 months of teriparatide treatment [4,11]. During the European Forsteo Observational Study (EUROFORS), 24 months of teriparatide resulted in increases in total vBMD of 4.0% at the proximal femur [12]. There is evidence that teriparatide exerts differential effects on the trabecular and cortical bone compartments. Following 12 months of teriparatide treatment, Genant et al. [4] demonstrated an increase in proximal femur trabecular vBMD (4.0%) but a decrease in proximal femur cortical vBMD (-0.9%). Similar effects (proximal femur trabecular vBMD = +2.6% and proximal femur cortical vBMD = -2.6%) were observed during EUROFORS [12]. Borggrefe et al. [12] reported an increase in proximal femur trabecular vBMD (+5.2%) with 24 months

of teriparatide treatment, proximal femur cortical vBMD remained reduced (-2.0%), but cortical thickness increased in treatment-naïve patients. An early decrease in proximal femur cortical BMD appears to be transient, caused by an increase in bone turnover and would not likely impact bone strength [12,13]. Finite element analysis of the spine revealed significant increases in both cortical (+16.2%) and trabecular (+21.4%) bone strength after 12 months of teriparatide treatment [13].

High-resolution quantitative computed tomography (HR-QCT) can be used to provide some information about teriparatide-induced effects on the trabecular microstructure of vertebra T12. Graeff et al [11] reported increases in apparent trabecular number (app.Tb.N: +12.9%), apparent trabecular thickness (app.Tb.Th: +8.4%) and apparent bone volume:total volume (app.BV/TV: +23.3%) and a decrease in apparent trabecular separation (app.Tb.Sp: -10.5%) after treatment-naïve patients received 12 months of teriparatide. However, Graeff et al. [11] concluded that it was not possible to accurately measure trabecular thickness or trabecular number due to the limited spatial resolution of the HR-QCT technique (approximately 200 μm) and report only changes in app.BV/TV (+54.7%) following 24 months of teriparatide treatment [14]. Finite element models revealed that vertebral bone strength in compression and in bending increased by +28.1% and +28.3% respectively at 24 months.

The microstructural effects of teriparatide treatment on the peripheral skeleton (arms and legs) are not so well understood and are less frequently reported. McDonald et al [15], Tsai et al [16] and Hansen et al [17] reported significant decreases in radius and tibia cortical vBMD (between -1.6% and -4.5%) and increases in cortical porosity (between +5.6 and +32.0%) following 12 and 18 months of teriparatide treatment, but these effects did not appear to impact on bone strength [15-17]. A consensus on the effects of teriparatide on the trabecular bone

compartment has yet to be reached, and the reporting of study findings is inconsistent [15-17].

Our study objective was to perform quantitative assessments of bone using imaging techniques to simultaneously characterise the central and peripheral skeleton over 104 weeks of treatment to better understand the mechanism of action of teriparatide. To our knowledge this is the first study to simultaneously quantify the densitometric, microarchitectural and strength changes, induced during the licenced treatment duration for teriparatide, using DXA, QCT and HR-pQCT.

Materials and Methods

Study Design

We conducted a 104 week, single centre, single-arm, exploratory, open-label study of subcutaneous teriparatide at the licensed dose (Forsteo 20 mcg daily) to fully characterise its actions on the central and peripheral skeleton; the Mechanism Of Action of Teriparatide (MOAT) study. The study was registered with clinicalTrials.gov (http://clinicaltrials.gov/, number - NCT01293292) and with the European Union Drug Regulating Authorities Clinical Trials (EudraCT, number - 2010-021009-19).

Study Population

Postmenopausal women (n = 20, ages 65.4 ± 5.5 years) with osteoporosis, defined as an aBMD T score $\leq$ -2.5 at the lumbar spine or proximal femur, were enrolled into the study. All individuals were recruited in accordance with the Summary of Product Characteristics (SmPc). The recommended indications of the National Institute for Health and Care Excellence (NICE HTA 161, http://www.nice.org.uk/Guidance/TA161) were not applied during the recruitment process as these state that only patients who have failed on or are intolerant to bisphosphonates

should be prescribed teriparatide. Prior use of bisphosphonate would have affected the key study efficacy measures; hence, we only studied women who were bisphosphonate-naïve. Inclusion criteria specified that the women should be >5 years postmenopausal but aged <85 years, ambulatory, with serum 25-hydroxyvitamin D >50 nmol/L (after oral cholecalciferol loading), and willing and able to give informed consent. Women with ongoing conditions or diseases known to cause abnormalities of calcium metabolism or skeletal health were not eligible to participate in the study. Individuals who were morbidly obese (body mass index (BMI)>35 kg/m^2) or underweight (BMI<18 kg/m^2) and those that had sustained a fracture in the past year were not enrolled. We identified women with postmenopausal osteoporosis from Sheffield metabolic bone clinics, general practitioner (GP) referrals for bone densitometry and via GP mail-outs. Former research participants who had consented to participate in future research projects were also approached.

This study was approved by the North West 2 Research Ethics Committee – Liverpool Central and the Medicines and Healthcare Products Regulatory Agency (MHRA), UK, and all participants gave fully informed written consent before their participation. All investigations were carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.

Study Intervention

The study drug was teriparatide (Forsteo 20 mcg daily: Eli Lilly and Company, Basingstoke, UK). Participants received 104 weeks of teriparatide treatment delivered by a daily self-administered subcutaneous injection in the thigh or abdomen. The drug was supplied in pre-filled pens which administered 20 mcg doses. All participants were trained in correct injection technique.

To ensure that all study volunteers were vitamin D replete before administration of the teriparatide, a 100,000 IU cholecalciferol (vitamin D3) load was given orally to each volunteer at the end of their screening visit (-9 weeks from baseline: week -9). A blood sample to assess the serum 25-hydroxyvitamin D level was then taken at week -8. Sixteen of the twenty enrolled participants were vitamin D replete by week -8 (serum 25-hydroxyvitamin D = 84.0 ± 19.6 nmol/L (mean ± SD)). If the results of the blood test at week -8 revealed that the volunteer's serum 25-hydroxyvitamin D level <50 nmol/L, then a second loading dose was given at week -6. Four of the twenty enrolled participants received a further 100,000 IU cholecalciferol load at week -6 as their serum 25-hydroxyvitamin D levels at week -8 was 29.3 ± 6.7 nmol/L. A further blood sample to assess the serum 25-hydroxyvitamin D level was then taken at week -5 in those four volunteers who had received a 100,000 IU cholecalciferol load at week -6 (week -5 serum 25-hydroxyvitamin D = 65.3 ± 6.1 nmol/L). Only volunteers with a serum 25-hydroxyvitamin D level >50 nmol/L by week -5 were enrolled as study participants and received the study drug. Further 100,000 IU cholecalciferol loads were administered to all study participants at six-monthly intervals throughout the study (weeks 26, 52 and 78) to ensure that they remained vitamin D replete.

In keeping with usual clinical practice, all participants also received daily calcium (600mg) and vitamin D3 (400IU) supplements as Adcal D3 (Prostrakan: Galashiels, UK) throughout the study.

Study drug compliance

Study drug compliance was assessed at each study visit by measuring medication usage in the pre-filled pen syringe devices and comparing it to expected usage. If teriparatide usage was less than 75% of that expected for the number of days between visits, study participants were questioned further on their compliance and then a decision was made as to whether the

participant should continue on the study. Self-reported compliance was assessed at weeks 24, 36 and 72 by telephone calls.

Information regarding all adverse events (AEs) and serious adverse events (SAEs) collected from the participants, whether volunteered or discovered through questioning, was recorded and followed up in accordance with the study protocol guidelines. Concomitant medications were recorded for all participants during the study period.

Anthropometric assessments

Anthropometric measurements, height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg), were measured using a wall-mounted stadiometer (Seca 242, Seca, Birmingham, UK) and an electronic column scale (Seca), respectively. Body mass index was calculated to the nearest 0.1 kg/m^2.

Dual-energy x-ray absorptiometry of the central and peripheral skeleton

Areal BMD (in g/cm^2) of the lumbar spine, right proximal femur and total body was measured at baseline, 26, 52 and 104 weeks by DXA using a Discovery A densitometer (Hologic Inc, Bedford MA). Vertebral fracture assessments (VFA) by DXA were also performed at baseline and week 104 to identify prevalent and incident vertebral fractures. All VFA images were visually assessed by a single operator (without measurement of vertebral dimensions) using the algorithm-based qualitative (ABQ) approach [18]. If a vertebral fracture was suspected, plain radiographs of the thoracic and lumbar spine in the anteroposterior and lateral projections were acquired.

Quantitative computed tomography of the central skeleton

Quantitative computed tomography (QCT) of vertebrae L1-L3 and the proximal femur was

performed at baseline, 26, 52, and 104 weeks using a 64-row LightSpeed volumetric computed tomography system (Lightspeed 64 VCT XT: GE Medical Systems).

Images of L1-L3 were acquired in the axial plane with a helical full 1.0 s rotation time and a table height of 155 cm. All scans were performed using the following scan settings: pitch = 0.969, tube current = 140 mA, tube voltage = 80 kVp and slice thickness = 0.625 mm. Scanning began 5mm above the superior endplate of L1 (inclusive of the T12-L1 joint space) and ended 5mm below the inferior endplate of L3 (inclusive of the L3-L4 joint space). Images were reconstructed at 0.625mm x 0.625mm using the standard algorithm and a field of view of 480 mm. Images were analysed using QCT Pro software (V5.0.3, Mindways Software Inc., Austin, TX, USA). Trabecular vBMD of vertebrae L1, L2, L3 and L1-L3 was determined by positioning an elliptical volume of interest (VOI) within the frontal trabecular region of each vertebral body to exclude the cortical and sub-cortical bone.

Images of the proximal femur were acquired in the axial plane with a helical full 1.0 s rotation time and a table height of 155 cm. All scans were performed using the following scan settings: pitch = 0.969, tube current = 200 mA, tube voltage = 120 kVp and slice thickness = 0.625 mm. Scanning began 3 cm above the head of the femur and ended 3 cm below the lesser trochanters. Images were reconstructed at 0.625mm x 0.625mm using the standard algorithm and a field of view of 480 mm. Images were analysed using QCT Pro CTXA-Hip software (Mindways Software Inc., Austin, TX, USA) to yield values for total and integral vBMD and volumetric BMC (vBMC).

A Model 3 CT density calibration phantom (Mindways, Mindways Software Inc.: Austin, TX, USA) was positioned under the participants during each L1-L3 and proximal femur scan. Information extracted from the calibration phantom allowed the conversion of measured Hounsfield units to units of bone mineral.

High-resolution peripheral quantitative computed tomography of the peripheral skeleton

High-resolution peripheral quantitative computed tomography (HR-pQCT) examinations of the distal radius and distal tibia were performed at baseline, 12, 26, 52, 104 weeks using the XtremeCT (Scanco Medical AG, Zurich, Switzerland). All examinations were performed on the non-dominant limb [20] except when a participant had sustained a prior fracture of the non-dominant radius and/or tibia, in which case the contralateral limb was measured. A maximum of one repeat scan at either or both anatomical sites was performed in the event of patient movement [21]. The quality of the HR-pQCT scan images was assessed by a single operator, using the visual grading system reported by Engelke et al. [22].

HR-pQCT image segmentation and analysis of densitometric, geometric and micro-structural bone properties were performed using the standard in-built software (version 6.0, Scanco Medical AG, Zurich, Switzerland). Extended cortical bone analysis techniques were applied to the segmented scans following the approach described by Burghardt et al. [23]. Measures of bone strength, for the distal radius and tibia, were determined by finite element analysis using software developed by Scanco Medical AG (version 1.13; FE-solver included in the Image Processing Language) [24].

Statistical analyses

Our sample size calculations were based on teriparatide-induced changes in lumbar spine aBMD in osteoporosis treatment-naïve patients. A one standard deviation decrease in BMD has been associated with a 2-fold increase in the risk of spine fracture [25]. Thus, our clinically significant difference was a change from baseline of 1.0 standard deviation and we calculated that 16 patients would provide > 90% power, at the 5% significance level, to detect changes in lumbar spine aBMD due to teriparatide treatment. Allowing for a 10% drop-out per year, a total of 20 women were recruited into the study.

We performed per-protocol analyses which only used data acquired from those participants who attended for all study visits, adhered to all study procedures and demonstrated ≥ 75% compliance with study medication; referred to as completers. A medication compliance threshold of 75% was chosen as it equated approximately to 5 injections of teriparatide per week. Baseline demographics were reported as the mean ± standard deviation (SD). Absolute and percentage change from baseline to all time-points for the physical measurement variables (mean ± SD or mean ± standard error of the mean (SEM)) were calculated. Repeated measures ANOVA were used to assess changes in measurement variables after 52 and 104 weeks of teriparatide treatment. Statistical analyses were performed using GraphPad Prism 6 for Windows (version 6.03. GraphPad Software, Inc. La Jolla, CA 92037 USA). A level of $p<0.05$ was considered to show statistical significance.

Results

Study population

We recruited twenty postmenopausal women with osteoporosis into the MOAT study. Summary information on the number of individuals screened, enrolled, withdrawn and progressing to each further study phase is shown as a CONSORT diagram in Figure 1. Examination of the baseline self-reported fracture history revealed that 11 participants had sustained a total of 16 prior non-vertebral fractures, comprising fractures of the foot (n = 5), wrist (n = 4), ankle (n = 2), pelvis (n = 4), hand (n = 1), ribs (n = 1) and clavicle (n = 1). There was no evidence of prior vertebral fractures as assessed by VFA.

Sixteen of the twenty women completed the 2-year study as per protocol. Nineteen participants completed ≥ 52 weeks but < 104 weeks of teriparatide treatment (range = 52 to 87 weeks), and one participant completed 35 weeks of teriparatide treatment. Baseline demographic details were similar for those participants enrolled on and those completing the MOAT study (Table

1). *Changes in aBMD and aBMC within the lumbar spine and proximal femur (central skeleton)* Following 52 weeks of teriparatide treatment, lumbar spine aBMC (+11.2 ± 4.5%; p<0.0001) and aBMD (+8.1 ± 3.2%; p<0.0001) increased. Further increases in lumbar spine aBMC (+5.2 ± 6.0%; p=0.004 week 52 versus week 104) and aBMD (+3.7 ± 4.2%; p=0.004 week 52 versus week 104) were observed between weeks 52 and 104. Increases in lumbar spine aBMC of +16.4 ± 7.6% (p<0.0001 versus baseline) and aBMD of +11.8 ± 5.8% (p<0.0001 versus baseline) occurred by 104 weeks.

Following 104 weeks of teriparatide treatment, no significant changes in total proximal femur aBMC, total proximal femur aBMD, femoral neck aBMC or femoral neck aBMD were evident.

Changes in aBMD and aBMC within the whole body (central and peripheral skeleton)

Changes in total body and sub-regional aBMC and aBMD following 104 weeks of teriparatide treatment are presented in Table 2. Overall, there was no significant change in total body or sub-total body aBMD and aBMC. When examining the total body sub-regions at week 104 however, increases in aBMC and aBMD occurred in the lumbar spine and pelvis. Areal BMD increased within the thoracic spine. In contrast, aBMC and aBMD decreased in the legs. Areal BMC decreased in the skull and arms.

Changes in QCT measures of L1-L3 and the proximal femur (central skeleton)

Changes in QCT measures of L1-L3 and the proximal femur are presented in Table 3. By week 52, L1-L3 vBMD increased. No further increases in L1-L3 vBMD occurred by week 104. Proximal femur total vBMD remained unchanged. By week 52, increases in trabecular vBMD of the proximal femur and concomitant decreases in proximal femur cortical vBMD were evident. These initial changes did not appear to affect proximal femur strength, as there was

no significant change in buckling ratio. By week 104, no significant changes in proximal femur total, trabecular and cortical vBMD or vBMC and cross-sectional area were apparent.

Changes in HR-pQCT measures of the radius and tibia (peripheral skeleton)

Effects of teriparatide treatment were also observed in the peripheral skeleton. Changes in HR-pQCT measures at the radius and tibia are presented in Table 4. By week 52, radius cortical TMD, tibia cortical TMD and tibia endosteal perimeter decreased. An increase in radius cortical porosity was also observed. By week 104, differential effects due to teriparatide treatment were observed between (i) the radius and the tibia and (ii) the trabecular and cortical bone compartments. Radius and tibia cortical vBMD, cortical TMD and total vBMD decreased by week 104. There was a concomitant increase in cortical porosity at both anatomical sites. At the tibia, teriparatide-induced effects included decreases in cortical thickness, cortical area and cortical pore diameter and increases in the endocortical perimeter, periosteal perimeter, trabecular area, trabecular inhomogeneity and failure load. All other radius and tibia parameters remained unchanged.

Evidence for Redistribution of Bone Mineral

We observed a loss of 35.01 ± 8.86 g (mean ± SEM) (95% CI = -53.89 to -16.14 g, p=0.001) of bone mineral from the peripheral skeleton and a gain of 28.23 ± 5.32 g (mean ± SEM) (95% CI = +16.89 to +39.57 g, p<0.0001) of bone mineral within the central skeleton (Table 2). This is equivalent to a -4.09 ± 1.08 % (mean ± SEM) (95% CI = -6.39 to -1.79 %, p=0.002) loss of bone mineral from the peripheral skeleton and an 8.52 ± 1.57 % (mean ± SEM) (95% CI = +5.16 to +11.87 %, p<0.0001) gain in bone mineral within the central skeleton. From these results we can infer that there is a redistribution of bone mineral from the peripheral to the central skeleton. Thus, as a minimum, there would be a gain in 17g of mineral in the central

skeleton and a loss of 16g from the peripheral skeleton as these are the 95% confidence limits. These are sizeable fluxes in bone mineral and therefore of clinical significance.

Adverse Events

Adverse events consisted of (i) gastrointestinal disorder; nausea, vomiting and reflux (n = 7), (ii) nervous system disorder; headache and dizziness (n = 3), (iii) injection site reaction; inflammation (n = 2), (iv) cardiac disorder; palpitations (n = 2), and (v) musculoskeletal disorder; (n = 2). There was one incident fracture of the ankle. No incident vertebral fractures occurred during the 2 year study.

Discussion

The MOAT Study is the first study to simultaneously quantify densitometric, microarchitectural and strength changes due to 104 weeks of teriparatide treatment using DXA, QCT and HR-pQCT. It demonstrates that teriparatide treatment exerts differential effects on the central and peripheral skeleton. Our in-depth characterisation of these skeletal changes contributes to a better understanding of the mechanism of action of teriparatide within the trabecular and cortical bone compartments.

In the MOAT Study, no significant changes in total body aBMC or aBMD occurred as a result of 104 weeks of teriparatide therapy for postmenopausal osteoporosis in bisphosphonate-naïve patients. The observed increase in bone mineral in the spine and pelvis appears to be countered by a decrease in bone mineral in the arms, legs and skull. It could be inferred that there is a redistribution of bone mineral from the peripheral to the central skeleton. Loss of bone mineral from the skull during teriparatide treatment has been revealed by isotope bone scanning [26]; similar effects are observed in patients with primary and secondary hyperparathyroidism

('pepperpot skull'). When teriparatide was administered to treatment-naïve patients at its licenced dose (20 μg daily), no significant changes in sub-total body BMD were evident [27-30]. Neer et al however, demonstrated a +3.1 ± 4.3% increase in total body aBMD when using only GE/Lunar DXA devices [28]. One study examined changes in total body aBMC with the head, but again, no significant changes were observed [31].

Our study demonstrates that teriparatide treatment exerts differential effects on the trabecular and cortical bone compartments within the central skeleton.

Within the central skeleton, significant increases in spine aBMD, aBMC and trabecular vBMD were evident following 52 and 104 weeks of teriparatide treatment. This is in keeping with the findings of Genant et al. [4], Kleerkoper et al. [5], Miyauchi et al. [6], and the EUROFORS study [7,11]. We observed increases in spine BMD and aBMC as early as 26 weeks after treatment commencement.

Reported findings from histomorphometric and bone turnover marker studies enable us to better understand the mechanisms behind these large and early changes in trabecular bone. Histomorphometric studies have shown that the effects of teriparatide on bone at the tissue level begin with an increase in activation frequency [2]. Within the first few weeks of treatment, there is a preferential stimulation of trabecular bone formation over bone resorption. At the cellular level, teriparatide exerts its effects through two main mechanisms, inhibition of osteoblast apoptosis and stimulation of osteoblast proliferation [32,33]. Overall, there is an increase in modelling at previously quiescent bone surfaces and an overfilling of remodelling sites leading to an eventual increase in bone mass [2,8,32] and an improvement in trabecular microarchitecture.

By week 52, increases in trabecular vBMD of the proximal femur and concomitant decreases in proximal femur cortical vBMD were evident. However, there was no overall change in

proximal femur total vBMD. These early changes in aBMC, vBMC and vBMD have been reported previously and do not appear to impact femoral bone strength [4,6,7,13,34]. During the MOAT Study, no significant changes in total proximal femur aBMC and aBMD or proximal femur vBMC and vBMD were apparent following 104 weeks of teriparatide treatment. Our 52-week findings are in keeping with those reported by Genant et al. [4], Obermayer-Pietsch et al. [7] and Borgreffe et al. [12]. However, our 104-week findings differ from those of the EUROFORS study [7,12]. Obermayer-Pietsch et al. [7] and Borgreffe et al. [12] reported increased total proximal femur aBMD and vBMD in the EUROFORS Study following 24 months of teriparatide treatment [12]. Although there was an increase in proximal femur trabecular vBMD, cortical vBMD and buckling ratio was still reduced [12].

The proximal femur is a skeletal site comprising both cortical and trabecular bone, in contrast to the vertebrae, which consist predominantly of trabecular bone. The mechanism of action of teriparatide within the femur can be explained through its effects on both bone compartments. There is evidence that teriparatide simultaneously induces both periosteal apposition of new bone and endosteal resorption of old bone within the cortical bone compartment [4,6-8]. Initially, older, highly mineralised bone is removed through 'intracortical tunnelling'. The pores that result are then filled with new bone therefore, any initial decrease in BMD is transient [35]. By week 78, there appears to be a resolution of these effects through the process of trabecular bone formation and mineralisation of the osteoid. No deleterious effects on femoral bone strength have been reported despite this initial catabolic action of teriparatide on cortical bone [36,37]. Our study findings emphasise the importance of completing a full 104-week course of treatment; only then can the full anabolic effect of teriparatide be observed at the femur [38].

Our study also demonstrates that teriparatide treatment exerts differential effects (i) within the central (spine, trunk and proximal femur) and peripheral (arms and legs) skeleton, (ii) within

the trabecular and cortical bone compartments of the peripheral skeleton and (iii) on the radius and tibia.

Within the arms and the legs we observed a decrease in aBMC and aBMD. There was also a significant decrease in aBMC and aBMD of the skull.

At both the radius and the tibia, we observed a decrease in total vBMD, cortical vBMD and cortical TMD with a concomitant increase in cortical porosity following 104 weeks of treatment. Also at the tibia, there was a decrease in cortical area, thickness and pore diameter with a concomitant increase in the endosteal and periosteal perimeters. At the radius there was no apparent change in the trabecular bone compartment however, at the tibia there was an increase in trabecular area and inhomogeneity. These changes in both the cortical and trabecular bone compartments appear to have minimal impact on bone strength, although a slight decrease in tibia failure load was observed. Our findings are in keeping with those reported by McDonald et al. [15], Tsai et al. [16] and Hansen et al. [17].

We propose that the predominant mechanism of action of teriparatide within the peripheral skeleton is through its effect on cortical bone. As described above, the catabolic effects of teriparatide are mediated through the removal of old, highly mineralised bone and the apposition of new osteoid. Any anabolic effects on the trabecular bone in the peripheral skeleton appear to be minimal. Despite the observed increase in cortical porosity at the radius and the tibia, peripheral bone strength measures remained almost unchanged. This is in keeping with previously reported findings following 12 and 18 months of teriparatide treatment [15,16]. The differential effects observed at the tibia and radius may result from the different loading conditions under which the two long bones are placed during daily activities, i.e. weight-bearing and non-weight bearing.

Our study does have limitations. This was an open-label study of 20 postmenopausal women with osteoporosis. We did not include a control group. We assumed that the open-label design

would not influence the study outcomes and the inclusion of a control group of postmenopausal women with osteoporosis was deemed to be unethical. As all the enrolled participants received loading doses of 100,000 IU cholecalciferol to ensure that they were vitamin D replete before receiving and during teriparatide treatment, they were not representative of a typical patient group. All participants also received daily calcium and vitamin D3 supplements throughout the study. Although this is in keeping with usual clinical practice, the dose of the supplements prescribed to participants does differ between studies. For example, women participating in the MOAT Study received lower daily doses of calcium (600mg versus 1000mg), and vitamin D3 (400 IU versus 400 to 1200 IU) compared to the women studied by Neer et al. [28]. With these caveats in mind, we acknowledge that the changes observed within the central and peripheral skeleton during the MOAT Study cannot be unequivocally attributed to teriparatide treatment alone.

The technical limitations of the imaging techniques used must also be acknowledged. Firstly, DXA cannot provide information about separate bone compartments or bone microstructure. Moreover during the MOAT study, we observed that when added together the total body sub-regional changes in aBMC did not equate to the overall change in total body aBMC, thus further demonstrating the limitations of DXA. Secondly, QCT cannot be used to directly measure the effects of teriparatide treatment on vertebral trabecular microarchitecture as the spatial resolution of the technique is characterised by voxel sizes larger than the typical diameter of the individual trabeculae. We have therefore assumed that the increase in vertebral vBMD reflects an improvement in vertebral trabecular microarchitecture. The use of HRQCT was considered, however Graeff et al. [11] concluded that it was not possible to accurately measure trabecular thickness or trabecular number due to the limited spatial resolution of the HR-QCT technique (approximately 200 μm). Finally, current imaging technologies also limit our ability to investigate whether bone mineral is redistributed within the same bone. HR-pQCT can be

used to study the cortical and trabecular bone compartments independently but it cannot be used to determine whether bone mineral is redistributed from ultradistal to more proximal sites within the radius and the tibia.

In summary, the mechanism of action of teriparatide to increase BMD within the central skeleton appears to be predominantly due to an improvement in trabecular microarchitecture. In contrast, within the peripheral skeleton, cortical BMD decreases primarily through a reduction in cortical TMD and an increase in cortical porosity.

To conclude, teriparatide exerts differential effects on the central and the peripheral skeleton. Trabecular microarchitecture is improved, but there is a concomitant decrease in peripheral cortical vBMD and an increase in porosity. Overall, we did not observe a change in total body bone mineral. We acknowledge that our conclusions are constrained by the technical limitations of DXA, QCT and HR-pQCT, the lack of a control group and the small sample size studied. Our hypothesis that teriparatide results in the redistribution of bone mineral from the peripheral to the central skeleton is speculative.

The MOAT Study contributes to a better understanding of the mechanism of action of teriparatide, however, our study findings should be interpreted with caution when treating patients within the clinical setting.

Acknowledgements

This work was funded by The National Institute for Health Research (NIHR) via its Biomedical Research Units Funding Scheme and the Sheffield Clinical Research Facility. The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service (NHS), the NIHR or the Department of Health (DoH). Teriparatide was provided by Eli Lilly and Company, Basingstoke, UK to Professor R Eastell (PI) through an Investigator-Initiated Trial (IIT). We acknowledge the Clinical Trials Research Unit, School

of Health and Related Research (ScHARR), The University of Sheffield for study data management and statistical advice.

Authors' roles: Study design and execution: RE, JSW, NP, EVM, MAP and LY. Data collection: MAP, LY and DB. Statistical analyses: MAP, RE, LY and DB. RE takes responsibility for the integrity of the data analysis. Writing and revision of the manuscript: MAP, RE, NP, JSW, EVM, LY, and DB. Data interpretation and approving the final version of manuscript: MAP, RE, NP, JSW, EVM, LY, and DB.

References

1. Chen P, Satterwhite JH, Licata AA et al. 2006 Early changes in biochemical markers of bone formation predict BMD response to teriparatide in postmenopausal women with osteoporosis. J Bone Miner Res 20:962-70.
2. Ma YL, Zeng Q, Donley DW et al. 2006 Teriparatide increase bone formation in modeling and remodeling osteons and enhances IGF-II immunoreactivity in postmenopausal women with osteoporosis. J Bone Miner Res 21:855-864.
3. Eastell R, Krege JH, Chen P, Glass EV, Reginster JY 2006 Development of an algorithm for using PINP to monitor treatment of patients with teriparatide. Curr Med Res Opin 22: 61-66.
4. Genant HK, Engelke K, Bolognese MA et al 2017 Effects of romosozumab compared with teriparatide on bone mineral density and mass at the spine and hip in postmenopausal women with low bone mass. J Bone Miner Res 32:181-187.
5. Kleerekoper M, Greenspan SL, Lewiecki M et al 2014 Assessing the Effects of Teriparatide Treatment on Bone Mineral Density, Bone Microarchitecture, and Bone Strength. J Bone Joint Surg Am 96 (11):e90.
6. Miyauchi A, Matsumoto T, Sugimoto T, Tsujimoto M, Warner MR, Nakamura T 2010

Effects of teriparatide on bone mineral density and bone turnover markers in Japanese subjects with osteoporosis at high risk of fracture in a 24-month clinical study: 12-month, randomized, placebo-controlled, double-blind and 12-month open-label phases. Bone 47:493-502.

7. Obermayer-Pietsch BM, Marin F, McCloskey EV et al 2008 Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. J Bone Miner Res 23:1591-600.
8. McClung MR, San MJ, Miller PD et al 2005 Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Arch Intern Med 165: 1762-68.
9. Slovik DM, Neer RM, Potts JT Jr 1981 Short-term effects of synthetic human parathyroid hormone-(1-34) administration on bone mineral metabolism in osteoporotic patients. J Clin Invest 68(5):1261-71.
10. Gonnelli S1, Martini G, Caffarelli C et al 2006 Teriparatide's effects on quantitative ultrasound parameters and bone density in women with established osteoporosis. Osteoporos Int 17(10):1524-31.
11. Graeff C, Timm W, Nickelsen TN et al 2007 Monitoring teriparatide-associated changes in vertebral microstructure by high-resolution CT in vivo: results from the EUROFORS study. J Bone Miner Res 22: 1426-33.
12. Borgreffe J, Graeff C, Nickelson TN, Marin F, Glüer CC 2010 Quantitative Computed Tomographic Assessment of the Effects of 24 Months of Teriparatide Treatment on 3D Femoral Neck Bone Distribution, Geometry, and Bone Strength: Results From the EUROFORS Study. J Bone Miner Res 25:472-481.
13. Keaveny TM, Crittenden DB, Bolognese MA, Genant HK, Engelke K, Oliveri B, Brown JP, Langdahl BL, Yan C, Grayer A, Libanati C 2017 Greater gains in spine and hip strength for romosozumab compared with teriparatide in postmenopausal women with low bone

mass. J Bone Mineral Res 32:1956-1962.

14. Graeff C, Chevalier Y, Charlebois M et al 2009 Improvements in vertebral body strength under teriparatide treatment assess in vivo by finite element analysis: results from the Eurofors Study. J Bone Miner Res 24(10):1672-1680.
15. McDonald HM, Nishiyama KK, Hanley DA, Boyd SK 2010 Changes in trabecular and cortical bone microarchitecture at peripheral sites associated with 18 months of teriparatide therapy in postmenopausal women with osteoporosis. Osteoporos Int 22:357-362
16. Tsai JN, Uihlein AV, Burnett-Bowie S-AM et al 2015 Comparative effects of teriparatide, Denosumab, and combination therapy on peripheral compartmental bone density, microarchitecture and estimated strength: the DATA-HRpQCT study. J Bone Miner Res 30(1):39-45.
17. Hansen S, Hauge EM, Jensen JEB, Brixen K 2013 Differing effects of PTH 1–34, PTH 1–84, and zoledronic acid on bone microarchitecture and estimated strength in postmenopausal women with osteoporosis: an 18-month open-labeled observational study using HR-pQCT. J Bone Miner Res 28(4):736–745
18. Jiang G, Eastell R, Barrington NA, Ferrar L 2004 Comparison of methods for the visual identification of prevalent vertebral fracture in osteoporosis. Osteoporos Int 15(11):887-896.
19. Parfitt AM, Mathews CH, Villanueva AR, Kleerekoper M, Frame B, Rao DS 1983 Relationships between surface, volume, and thickness of iliac trabecular bone in aging and in osteoporosis. Implications for the microanatomic and cellular mechanisms of bone loss. J Clin Invest 72:1396–1409.
20. Hildebrandt EM, Manske SL, Hanley DA, Boyd SK 2016. Bilateral Asymmetry of Radius and Tibia Bone Macroarchitecture and Microarchitecture: A High-Resolution Peripheral Quantitative Computed Tomography Study. J Clin Densitom 19(2):250-254.

21. Sode M, Burghardt AJ, Pialat J-B, Link TM and Majumdar S 2011 Quantitative characterisation of subject motion in HR-pQCT images of the distal radius and tibia. Bone 48(6):1291-1297.
22. Engelke K, Stampa B, Timm W 2012 Short-term in vivo precision of BMD and parameters of trabecular architecture at the distal forearm and tibia. Osteoporos Int 23(8):2151-2158.
23. Burghardt AJ, Buie HR, Laib A, Majumdar S and Boyd SK 2010 Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT. Bone 47(3):519-528.
24. Boutroy S, Van Rietbergen B, Sornay-Rendu E, Munoz F, Bouxsein ML, Delmas PD 2008 Finite element analysis based on in vivo HR-pQCT images of the radius is associated with wrist fracture in postmenopausal women. J Bone Miner Res 23(3):392-399.
25. Marshall D, Johnell O, Wedel H 1996 Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 18;312(7041):1254-9.
26. Moore AE, Blake GM, Taylor KA et al 2010 Assessment of regional changes in skeletal metabolism following 3 and 18 months of teriparatide treatment. J Bone Miner Res 25(5):960-7.
27. Finkelstein JS, Wyland JJ, Lee H, Neer RM 2010 Effects of teriparatide, alendronate, or both in women with postmenopausal osteoporosis J Clin Endocrinol Metab 95(4):1838-45.
28. Neer RM, Arnaud CD, Zanchetta JR et al 2001. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 10;344(19):1434-41.
29. Orwell ES, Scheele WH, Paul S et al 2003. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density on men with osteoporosis. J Bone Miner Res 18:9-17.

30. Yu EW, Neer RM, Lee H et al 2011. Time-dependent changes in skeletal response to teriparatide: Escalating versus constant dose teriparatide (PTH 1–34) in osteoporotic women. Bone 48(4): 713-719.
31. Gonnelli S, Martini G, Caffarelli C, Salvadori S, Cadirni A, Montagnami A, Nuti R 2006, Teriparatide's effects on quantitative ultrasound parameters and bone density in women with established osteoporosis. Osteoporos Int 17:1524-1531.
32. Arlot M, Meunier PJ, Boivin G et al 2005 Differential effects of teriparatide and alendronate on bone remodeling in postmenopausal women assessed by histomorphometric parameters. J Bone Miner Res 20:1244-53
33. Jilka RL, Weinstein RS, Bellido T, Roberson P, Parfitt AM, Manolagas SC 1999 Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone J Clin Invest 104:439-446.
34. Boonen S, Marin F, Obermayer-Pietsch et al for the EUROFORS investigators 2008 Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 93(3):852-860.
35. Ettinger B, San Martin J, Crans G, Pavo I 2004 Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. J Bone Miner Res 19:745-751.
36. Whitmarsh T, Treece GM, Gee AH, Poole KES 2015 Mapping bone changes at the proximal femoral cortex of postmenopausal women in response to alendronate and teriparatide alone, combined or sequentially. J Bone Miner Res 30(7):1309-1318.
37. Uusi-Rasi K, Semanick LM, Zanchetta JR et al 2005 Effects of teriparatide [rhPTH (1-34)] treatment on structural geometry of the proximal femur in elderly osteoporotic women. Bone 36:948-958.
38. Lindsay R, Krege JH, Marin F Jin L, Stepan JJ 2016 Teriparatide for osteoporosis:

importance of the full course. Osteoporos Int 27(8):2395-410

39. Tjong W, Kazakia GJ, Burghardt A, Majumdard S 2012 The effects of voxel size on high-resolution peripheral computed tomography measurements of trabecular and cortical bone microstructure. Med Phys 39(4): 1893-1903.

Table 1. Baseline demographics for all participants (i) enrolled on the MOAT study and (ii) completing the MOAT study as per protocol (completers). All data are mean ± SD except number of participants and vertebral fracture at baseline which are shown as n.

Demographic	All enrolled participants	All completers
N	20	16
Age (years)	65.4 ± 5.5	64.6 ± 4.5
Height (cm)	160.9 ± 4.4	162.3 ± 3.1
Weight (kg)	64.3 ± 8.1	64.1 ± 8.8
Body Mass Index (kg/m^2)	24.9 ± 3.8	24.4 ± 3.8
Lumbar spine aBMD T-score	-2.8 ± 0.3	-2.8 ± 0.2
Total proximal femur aBMD T-score	-2.2 ± 0.5	-1.5 ± 0.7
Femoral neck aBMD T-score	-1.5 ± 0.6	-2.1 ± 0.5
Vertebral fracture at baseline	0	0

Abbreviations: aBMD = areal bone mineral density

Table 2. Absolute and percent changes in total body and sub-regional aBMC and aBMD in response to 104 weeks of teriparatide treatment. Data are shown as mean ± SEM and 95% CI. p values are given to 1 significant figure.

Region	Baseline absolute aBMC (g)	Absolute change in aBMC (g)	95% CI for absolute change in aBMC (g)	p	% change in aBMC (%)	95% CI for % change in aBMC (%)	p
Total body	1669.00 ± 33.68	-20.07 ± 15.88	-53.92 to +13.79	0.2	-1.17 ± 0.94	-3.17 to +0.84	0.2
Sub-total body	1258.00 ± 27.69	+0.32 ± 11.62	-24.45 to +25.10	0.9	-0.04 ± 0.90	-1.96 to +1.88	0.9
Skull	411.40 ± 21.10	**-20.39 ± 6.69**	-34.64 to -6.134	**0.008**	**-4.96 ± 1.87**	-8.94 to -0.98	**0.02**
Arms	118.80 ± 3.41	**-5.88 ± 1.22**	-8.49 to -3.27	**0.0002**	**-5.12 ± 1.08**	-7.43 to -2.81	**0.0003**
Thoracic spine	84.63 ± 2.91	+5.03 ± 2.86	-1.07 to +11.13	0.1	+7.20 ± 3.97	-1.26 to +15.67	0.09
Lumbar spine	34.98 ± 1.58	**+7.66 ± 1.40**	+4.69 to +10.64	**<0.0001**	**+23.49 ± 4.34**	+14.24 to +32.74	**<0.0001**
Ribs	57.50 ± 2.36	+1.34 ± 1.89	-2.69 to +5.36	0.5	+3.07 ± 3.42	-4.24 to +10.37	0.4
Pelvis	157.80 ± 5.17	**+14.19 ± 3.23**	+7.32 to +21.07	**0.0005**	**+9.29 ± 2.09**	+4.83 to +13.75	**0.0005**
Legs	313.80 ± 40.04	**-8.75 ± 3.30**	-15.78 to -1.71	**0.02**	**-2.94 ± 1.07**	-5.21 to -0.67	**0.01**
Central skeleton	334.90 ± 6.33	**+28.23 ± 5.33**	+16.89 to +39.57	**<0.0001**	**+8.52 ± 1.57**	+5.16 to +11.87	**<0.0001**
Peripheral skeleton	844.00 ± 23.28	**-35.01 ± 8.86**	-53.89 to -16.14	**0.001**	**-4.09 ± 1.08**	-6.39 to -1.79	**0.002**
Region	Baseline absolute aBMD (g/cm2)	Absolute change in aBMD (g/cm2)	95% CI for absolute change in aBMD (g/cm2)	p	% change in aBMD (%)	95% CI for % change in aBMD (%)	p
Total body	0.921 ± 0.013	-0.005 ± 0.006	-0.017 to +0.007	0.4	-0.52 ± 0.63	-1.85 to +0.82	0.4
Sub-total body	0.786 ± 0.009	+0.003 ± 0.004	-0.006 to +0.013	0.4	+0.41 ± 0.55	-0.76 to +1.58	0.5
Skull	1.932 ± 0.077	-0.053 ± 0.026	-0.110 to +0.003	0.06	-2.78 ± 1.48	-5.95 to +0.38	0.08
Arms	0.606 ± 0.009	+0.006 ± 0.004	-0.014 to +0.001	0.09	-1.12 ± 0.60	-2.40 to +0.16	0.08
Thoracic spine	0.677 ± 0.017	**+0.049 ± 0.013**	+0.022 to +0.076	**0.002**	**+7.46 ± 1.95**	+3.31 to +11.61	**0.002**
Lumbar spine	0.775 ± 0.015	**+0.090 ± 0.015**	+0.058 to +0.122	**<0.0001**	**+11.94 ± 2.11**	+7.45 to +16.42	**<0.0001**
Ribs	0.513 ± 0.038	+0.008 ± 0.007	-0.007 to +0.024	0.3	+1.84 ± 1.41	-1.17 to +4.84	0.2
Pelvis	0.986 ± 0.022	**+0.042 ± 0.009**	+0.023 to +0.061	**0.0003**	**+4.27 ± 0.87**	+2.41 to +6.12	**0.0002**
Legs	0.960 ± 0.016	**-0.011 ± 0.004**	-0.020 to -0.002	**0.02**	**-2.47 ± 0.71**	-3.98 to -0.95	**0.004**
Central skeleton	2.952 ± 0.025	**+0.189 ± 0.027**	+0.132 to +0.247	**<0.0001**	**+6.43 ± 0.91**	+4.49 to +8.38	**<0.0001**
Peripheral skeleton	3.497 ± 0.076	**-0.071 ± 0.027**	-0.129 to -0.013	**0.02**	**-2.19 ± 0.83**	-3.95 to -0.42	**0.02**

Abbreviations: aBMD = areal bone mineral density, aBMC = areal bone mineral content, SEM = standard error of the mean, 95% CI = 95% confidence intervals
Definitions: Central skeleton = spine, ribs and pelvis. Peripheral skeleton = skull, arms and legs

Table 3. Absolute baseline values and percent changes in bone parameters as assessed using QCT of L1-L3 and the proximal femur in response to 52 and 104 weeks of teriparatide treatment. All data are shown as mean ± SD and p values are given to 1 significant figure.

Site	Bone parameter	Absolute baseline	Week 52		Week 104	
			Change (%)	p	Change (%)	p
Spine L1-L3	Trabecular vBMD (mg/cm^3)	87.5 ± 18.6	**+25.5 ± 12.3**	**<0.0001**	**+28.5 ± 19.4**	**<0.0001**
Proximal femur	Total vBMD (mg/cm^3)	253.8 ± 39.6	+1.5 ± 14.2	0.7	+2.5 ± 22.0	0.7
	Trabecular vBMD (mg/cm^3)	118.0 ± 15.1	**+5.7 ± 5.8**	**0.008**	+3.4 ± 21.7	0.6
	Cortical vBMD (mg/cm^3)	1,013.4 ± 92.1	**-4.9 ± 5.6**	**0.01**	+0.6 ± 13.5	0.9
	Total vBMC (mg)	24,540 ± 4658	+2.4 ± 27.4	0.8	+1.3 ± 34.8	0.9
	Trabecular vBMC (mg)	9,618 ± 1307	+3.9 ± 7.3	0.08	-2.0 ± 20.7	0.7
	Cortical vBMC (mg)	14,922 ± 3751	+3.6 ± 43.1	0.8	+6.1 ± 49.6	0.7
	Total CSA (cm^2)	8.7 ± 1.6	-2.6 ± 10.7	0.4	-2.3 ± 11.4	0.5
	Trabecular CSA (cm^2)	6.9 ± 1.4	-3.6 ± 10.7	0.3	-3.6 ± 15.0	0.4
	Cortical CSA (cm^2)	1.8 ± 0.3	+2.2 ± 16.6	0.7	+3.1 ± 12.8	0.4
	Buckling ratio (1)	9.2 ± 1.4	-3.4 ± 10.2	0.3	-4.0 ± 19.8	0.5

Abbreviations: vBMD = Volumetric bone mineral density, vBMC = volumetric bone mineral content, CSA = cross-sectional area.

Table 4. Absolute baseline values and percent changes in bone parameters as assessed using HR-pQCT at the distal radius and distal tibia in response to 52 and 104 weeks of teriparatide treatment. All data are shown as mean ± SD and p values are given to 1 significant figure.

Bone parameter	Absolute baseline	Week 52		Week 104	
		Change (%)	p	Change (%)	p
RADIUS					
Total vBMD (mgHA/cm^3)	222.9 ± 48.5	-0.1 ± 4.9	0.9	**-2.8 ± 6.7**	**0.03**
Stiffness (kN/mm)	53.3 ± 7.4	+0.1 ± 9.1	0.9	+0.7 ± 8.1	0.5
Failure load (kN)	2.76 ± 0.40	+0.3 ± 8.4	0.9	+0.6 ± 7.0	0.5
Trabecular area (mm^2)	255.72 ± 45.34	-0.2 ± 0.9	0.5	-0.4 ± 1.6	0.9
Trabecular vBMD (mgHA/cm^3)	120.3 ± 36.0	+0.7 ± 3.1	0.5	-1.4 ± 6.3	0.4
Trabecular number (mm^{-1})	1.78 ± 0.40	-2.0 ± 7.8	0.4	-3.5 ± 7.6	0.2
Trabecular thickness (mm)	0.056 ± 0.008	+3.2 ± 8.2	0.2	+2.7 ± 8.0	0.4
Trabecular separation (mm)	0.536 ± 0.142	+2.4 ± 8.5	0.3	+4.2 ± 8.3	0.1
Trabecular inhomogeneity (mm^{-1})	0.29 ± 0.17	+2.2 ± 5.4	0.2	+4.6 ± 7.1	0.2
Trabecular BV/TV (%)	10.01 ± 3.00	+0.8 ± 3.3	0.4	-1.2 ± 6.4	0.5
Cortical area (mm^2)	35.40 ± 7.32	-0.4 ± 10.7	0.9	-4.5 ± 12.9	0.05
Cortical vBMD (mgHA/cm^3)	772.0 ± 61.2	-1.5 ± 4.5	0.3	**-3.3 ± 5.8**	**0.004**
Cortical thickness (mm)	0.48 ± 0.12	-0.4 ± 10.9	0.9	-4.7 ± 12.3	0.08
Periosteal perimeter (mm)	79.59 ± 8.20	+2.0 ± 5.5	0.2	-0.3 ± 4.2	0.7
Endocortical perimeter (mm)	74.11 ± 8.17	+0.4 ± 6.4	0.8	-0.4 ± 4.3	0.9
Cortical porosity (%)	2.89 ± 0.97	**+11.9 ± 17.9**	**0.04**	**+21.2 ± 20.7**	**<0.0001**
Cortical TMD (mgHA/cm^3)	976.6 ± 40.0	**-2.5 ± 3.1**	**0.02**	**-3.2 ± 4.2**	**0.005**
Cortical pore diameter (mm)	0.172 ± 0.028	-2.2 ± 6.9	0.3	-1.3 ± 6.5	0.7
TIBIA					
Total vBMD (mgHA/cm^3)	232.2 ± 50.9	+0.2 ± 3.9	0.9	**-2.5 ± 5.5**	**0.008**
Stiffness (kN/mm)	160.1 ± 22.6	+1.7 ± 3.6	0.08	-5.6 ± 23.1	0.2
Failure load (kN)	8.11 ± 1.09	+1.6 ± 3.0	0.05	**+0.2 ± 4.4**	**0.04**
Trabecular area (mm^2)	602.39 ± 90.72	-0.1 ± 0.5	0.4	**+0.2 ± 0.6**	**0.04**
Trabecular vBMD (mgHA/cm^3)	143.6 ± 40.1	+0.2 ± 4.2	0.8	-1.4 ± 6.4	0.6
Trabecular number (mm^{-1})	1.61 ± 0.36	-1.1 ± 6.9	0.5	-1.0 ± 9.3	0.06
Trabecular thickness (mm)	0.073 ± 0.011	+1.6 ± 7.1	0.4	-0.2 ± 9.2	0.05
Trabecular separation (mm)	0.592 ± 0.244	+1.5 ± 7.1	0.4	+1.9 ± 9.8	0.06
Trabecular inhomogeneity (mm^{-1})	0.33 ± 0.30	+1.4 ± 8.3	0.5	**+3.2 ± 11.6**	**0.04**
Trabecular BV/TV (%)	11.96 ± 3.3	+0.3 ± 4.2	0.8	-1.4 ± 6.1	0.6
Cortical area (mm^2)	82.78 ± 15.56	+1.0 ± 6.5	0.6	**-2.9 ± 8.6**	**0.006**
Cortical vBMD (mgHA/cm^3)	787.4 ± 45.4	-0.8 ± 2.3	0.2	**-3.4 ± 3.7**	**<0.0001**
Cortical thickness (mm)	0.80 ± 0.19	+0.8 ± 6.3	0.6	**-3.1 ± 8.9**	**0.002**
Periosteal perimeter (mm)	110.65 ± 12.84	-0.5 ± 3.4	0.5	**+0.5 ± 4.8**	**0.02**
Endocortical perimeter (mm)	99.86 ± 8.92	**-1.6 ± 2.1**	**0.01**	**+0.6 ± 3.2**	**0.02**
Cortical porosity (%)	9.3 ± 1.9	+3.5 ± 10.4	0.2	**+10.3 ± 17.5**	**0.0002**
Cortical TMD (mgHA/cm^3)	947.4 ± 41.3	**-1.4 ± 2.1**	**0.01**	**-3.8 ± 3.6**	**<0.0001**
Cortical pore diameter (mm)	0.193 ± 0.015	-0.6 ± 5.1	0.6	**-1.6 ± 7.7**	**0.009**

Abbreviations: vBMD = volumetric bone mineral density, BV/TV = Bone volume/tissue volume, TMD = tissue mineral density

Figure legends

Figure 1. A CONSORT diagram for the MOAT study.