Taylor & Francis
Taylor & Francis Group

Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

Abaloparatide in patients with mild or moderate renal impairment: results from the ACTIVE phase 3 trial

John P. Bilezikian, Gary Hattersley, Bruce H. Mitlak, Ming-Yi Hu, Lorraine A. Fitzpatrick, Christine Dabrowski, Paul D. Miller & Socrates E. Papapoulos

To cite this article: John P. Bilezikian, Gary Hattersley, Bruce H. Mitlak, Ming-Yi Hu, Lorraine A. Fitzpatrick, Christine Dabrowski, Paul D. Miller & Socrates E. Papapoulos (2019) Abaloparatide in patients with mild or moderate renal impairment: results from the ACTIVE phase 3 trial, Current Medical Research and Opinion, 35:12, 2097-2102, DOI: 10.1080/03007995.2019.1656955

To link to this article: https://doi.org/10.1080/03007995.2019.1656955

CURRENT MEDICAL RESEARCH AND OPINION
2019, VOL. 35, NO. 12, 2097–2102
https://doi.org/10.1080/03007995.2019.1656955
Article ST-0269/1656955

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Abaloparatide in patients with mild or moderate renal impairment: results from the ACTIVE phase 3 trial

John P. Bilezikian[a], Gary Hattersley[b], Bruce H. Mitlak[b], Ming-Yi Hu[b], Lorraine A. Fitzpatrick[b], Christine Dabrowski[b], Paul D. Miller[c] and Socrates E. Papapoulos[d]

[a]College of Physicians and Surgeons, Columbia University, New York, NY, USA; [b]Research & Development, Radius Health, Inc, Waltham, MA, USA; [c]Colorado Center for Bone Research at Panorama Orthopedics and Spine Center, Golden, CO, USA; [d]Center for Bone Quality, Leiden University Medical Center, Leiden, The Netherlands

ABSTRACT

Objective: To evaluate, post hoc, the efficacy and safety of abaloparatide by degree of renal impairment.

Methods: ACTIVE was a phase 3, 18-month, randomized, double-blind, active-comparator, placebo-controlled study of postmenopausal women with osteoporosis who received subcutaneous abaloparatide 80 μg, placebo, or open-label teriparatide 20 μg daily. Patients with serum creatinine >2.0 mg/dL or 1.5–2.0 mg/dL with an estimated glomerular filtration rate (eGFR) <37 mL/min, calculated by Cockcroft-Gault formula, were excluded.

Results: At baseline, 660 patients had eGFR ≥90 mL/min, 1276 had 60 to <90 mL/min, and 527 had <60 mL/min. Older age and lower T-scores were associated with greater renal impairment. Among renal-function subgroups, there were no meaningful changes in bone mineral density, fracture risk reduction, or overall incidence of treatment-emergent adverse events in the active-treatment arms. Anemia, nausea, hypercalcemia, and upper-respiratory-tract infection tended to be more frequent with increasing renal impairment. Hypercalcemia measured by albumin-adjusted serum calcium occurred significantly less frequently with abaloparatide than teriparatide in patients with eGFR <60 mL/min (3.6% versus 10.9%; $p = .008$) and in the overall ACTIVE safety population (3.4% versus 6.4%; $p = .006$). Computed tomography scans in 376 patients revealed no evidence of increased renal calcification.

Conclusion: Increased exposure to abaloparatide and teriparatide in patients with renal impairment led to no meaningful differences in efficacy or safety. These results support the use of abaloparatide without dosage adjustment in patients with renal impairment, provided those with severe renal impairments are monitored for adverse events.

ARTICLE HISTORY
Received 29 January 2019
Revised 16 July 2019
Accepted 14 August 2019

KEYWORDS
Osteoporosis; postmenopausal; renal insufficiency; abaloparatide; bone density conservation agents; bone regeneration

Introduction

While the incidence of osteoporotic fractures increases as people age[1], renal function declines[2]. Consequently, osteoporosis is often accompanied by some form of renal compromise, with an estimated 85% of women with osteoporosis having estimated glomerular filtration rate (eGFR) ≤60 mL/min[3]. Bisphosphonates are not recommended, or are contraindicated, in patients with eGFR <30[4,5] or <35 mL/min[4–7], limiting the choice of therapies in this patient population.

Abaloparatide is a selective activator of the parathyroid hormone 1 receptor (PTH1R) signaling pathway and was developed for the treatment of women with postmenopausal osteoporosis at high risk for fracture. Abaloparatide is associated with transient PTH1R signaling through its selectivity for the G protein-dependent receptor (RG) conformation over the R^0 receptor conformation, consistent with a net anabolic effect on bone[8,9]. Women with postmenopausal osteoporosis treated with abaloparatide in the Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE; NCT01343004) demonstrated significantly increased bone mineral density (BMD) and risk reduction of vertebral, nonvertebral, clinical, and major osteoporotic fractures compared with women who received placebo[10]. Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and SAEs leading to death were balanced between treatment arms, although adverse events (AEs) leading to study discontinuation were more frequent in the abaloparatide arm (9.9%) than in either the open-label teriparatide (6.8%) or blinded placebo (6.1%) arms. Additionally, the frequency of hypercalcemia, defined as albumin-corrected serum calcium of at least 10.7 mg/dL, was significantly lower in the abaloparatide arm than in the teriparatide arm ($p = .006$), with the lowest incidence in the placebo arm[10].

CONTACT John P. Bilezikian jpb2@cumc.columbia.edu Department of Medicine, College of Physicians and Surgeons, 630 West 168th Street, New York, NY 10032, USA

Supplemental data for this article is available online at https://doi.org/10.1080/03007995.2019.1656955.

Abaloparatide metabolism has been studied in rats and in human liver and kidney preparations. The in vitro data were consistent with nonspecific proteolytic cleavage and evidence from a rat model also indicated that the majority of peptide fragments are excreted in urine[11].

Given the potential role of the kidney in abaloparatide metabolism, it is important to understand whether the efficacy and safety of abaloparatide are affected by reduced clearance rates in patients with renal impairment. Accordingly, a post hoc analysis of ACTIVE findings by renal function was conducted. Prespecified computed tomography (CT) renal imaging of a subset of ACTIVE patients was also assessed for evidence of renal calcification at therapeutic doses.

Materials and methods

ACTIVE was a phase 3, randomized, double-blind, active-comparator, placebo-controlled study. Inclusion and exclusion criteria, study design, and methodology of ACTIVE have been described in detail previously[10]. Briefly, women with postmenopausal osteoporosis were randomized to receive subcutaneous double-blind abaloparatide (80 μg) or placebo or to receive open-label teriparatide (20 μg) daily over 18 months. Patients were excluded from the trial if their serum creatinine was >2.0 mg/dL (177 μmol/L), or was 1.5–2.0 mg/dL with an eGFR <37 mL/min.

eGFR was calculated as estimated creatinine clearance using the Cockcroft–Gault formula at baseline and Day 1 and at Months 1, 3, 6, 9, 12, and 18[12]:

$$\text{eGFR (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times f}{\text{serum creatinine (μmol/L)}}$$

$f = 1.04$ for women.

24-h urine creatinine clearance and calcium:creatinine ratio were assessed at Day 1, and Months 1, 3, 6, 9, 12, and 18.

Samples for measurement of serum abaloparatide concentrations were collected on Day 1 and Months 1, 3, 6, and 12 during the treatment period. One sample was drawn per patient per visit at the following, varying post-injection time periods: 10–30 min; 30 min–1 h; 1–2 h; 2–3 h; 3–4 h. These draw times were randomized to visits across Day 1 to Month 12. At Month 18, only a trough level was measured. Abaloparatide concentrations were measured using a validated radioimmune assay method with a lower limit of quantitation of 20 pg/mL.

In a subset of patients, serum levels of the bone turnover biomarkers, procollagen type I N-terminal propeptide (s-PINP) and carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) were measured at months 1, 3, 6, 12, and 18.

In selected centers, a subset of ACTIVE patients underwent at least 1 renal CT scan to assess kidney calcification, obtained through standard abdominal/pelvic CT scanning procedures. Patients asked to undergo 2 renal CT scans underwent the first scan prior to treatment and the second between the end-of-treatment visit (18 months) and the end-of-study (EOS) visit (19 months). A subset of ACTIVE patients who enrolled early in the study was asked only to undergo a single EOS renal CT scan. CT scans were centrally assessed on a binary basis for nephrolithiasis, urolithiasis, and nephrocalcinosis.

Analyses

The ACTIVE intent-to-treat (ITT) population included all patients who were randomized into the study and received a study medication kit on Day 1. The safety population included all ITT patients who started treatment. The renal CT scan population included all patients who underwent at least 1 renal CT scan. A post hoc analysis evaluated the effect of renal function as assessed by baseline eGFR on safety and efficacy endpoints. The ITT population was divided into three renal function subgroups based on the eGFR ranges of chronic kidney disease (CKD) stages[12,13]: those patients with baseline eGFR of ≥90 mL/min (stage I CKD), those with eGFR 60 to < 90mL/min (stage II CKD), and those with eGFR <60 mL/min (stage III CKD). Patients were not assessed for other CKD staging criteria for the purposes of subgroup assignment. Fracture incidence between treatment arms was compared using Fisher's exact test, and incidence of hypercalcemia was compared using the chi-square test.

Results

Patients

The population was female with a mean age of 69 years[10]. Baseline characteristics were similar between treatment arms[10] but differed between renal function subgroups. Subgroups with a greater degree of renal impairment included patients who were older and had lower BMD T-scores compared with the normal renal function subgroup (Table 1). The median eGFR for the study population was 76.3 mL/min. Across treatment arms at baseline, there were 27% ($n = 660$) with eGFR ≥90 mL/min, 52% ($n = 1276$) with eGFR 60 to <90 mL/min, and 21% ($n = 527$) with eGFR 25 to <60 mL/min.

As no patients had serum creatinine >1.5 mg/dL at baseline, 11 (1.34%), 8 (0.98%), and 6 (0.73%) patients with eGFR <37 mL/min were admitted to the abaloparatide, teriparatide, and placebo arms, respectively. The lowest baseline eGFR in each treatment arm was 30 mL/min for abaloparatide, 25 mL/min for teriparatide, and 29 mL/min for placebo.

Efficacy in ACTIVE renal function subgroups

Overall fracture rates in this analysis were low. In patients with eGFR ≥90 mL/min, there were significantly fewer new vertebral fractures in the abaloparatide group (1 fracture; $n = 188$; $p = .009$) and in the teriparatide group (1 fracture; $n = 184$; $p = .010$) compared with placebo (9 fractures; $n = 178$). In patients with eGFR 60 to <90 mL/min, there were also statistically significant reductions versus placebo (17 fractures; $n = 392$) for those treated with abaloparatide (2 fractures;

Table 1. Demographic and baseline characteristics by renal function (ITT population).

	eGFR* <60 mL/min ($n = 527$)	eGFR* 60 to <90 mL/min ($n = 1276$)	eGFR* ≥90 mL/min ($n = 660$)
Age, mean year (SD)	74.0 (5.54)	69.0 (5.52)	64.3 (5.77)
Age groups, years, %			
<65	2.5	13.5	42.3
65 to <75	49.9	71.2	54.7
≥75	47.6	15.4	3.0
Total hip BMD mean T-score	−2.19	−1.88	−1.62
Femoral neck BMD mean T-score	−2.42	−2.16	−1.89
Lumbar spine BMD mean T-score	−2.98	−2.87	−2.83
Baseline prevalent vertebral fracture, %	24.5	23.4	23.9
At least one prior NVF within 5 years, %	21.8	29.0	40.8
1,25 – dihydroxy vitamin D, pg/ mL, mean (SD)	51.0 (18.8)	55.6 (19.1)	55.5 (17.5)
25 hydroxy vitamin D, nmol/ L, mean (SD)	67.1 (26.2)	67.2 (25.0)	65.2 (24.5)
Parathyroid hormone (PTH), pg/mL, mean (SD)	45.4 (11.3)	44.3 (10.6)	43.0 (10.8)
Prior statin use, %	23.7	23.5	22.6

*Estimated creatinine clearance by Cockcroft-Gault formula.
Abbreviations. BMD: bone mineral density; eGFR: estimated glomerular filtration rate; ITT: intent-to-treat; NVF: nonvertebral fracture; SD: standard deviation.

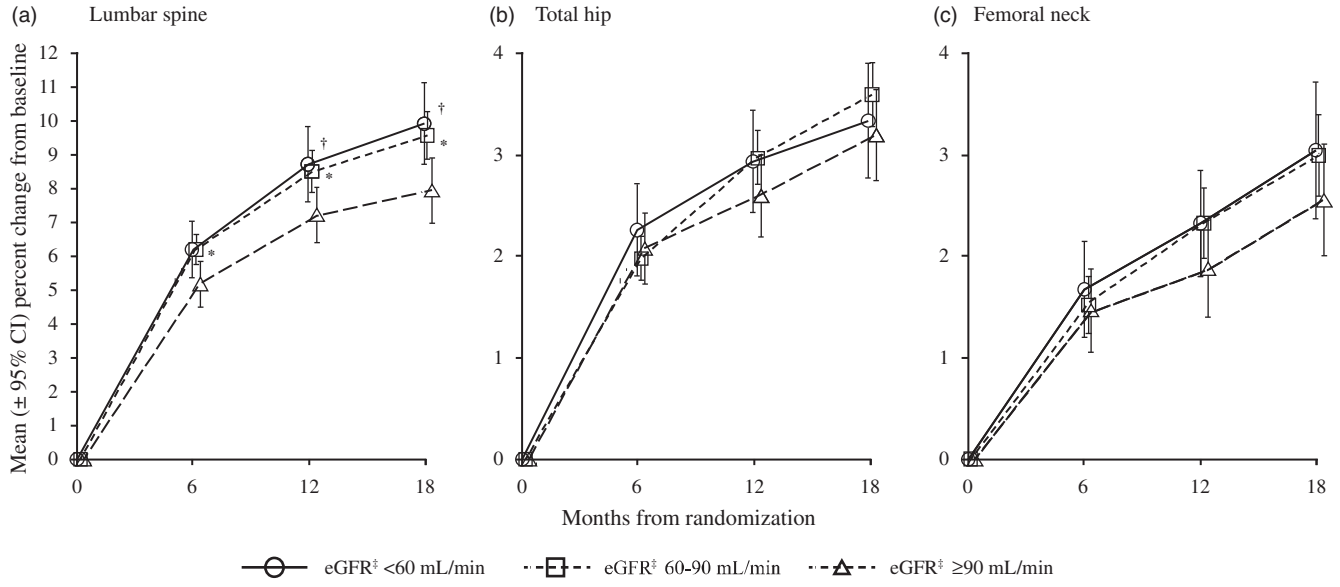

Figure 1. BMD changes in patients treated with abaloparatide by renal function at (a) lumbar spine, (b) total hip, and (c) femoral neck (ITT population in abaloparatide treatment arm using LOCF). *$p < .05$ eGFR‡ ≥90 mL/min versus eGFR‡ 60 to <90 mL/min. †$p < .05$ eGFR‡ <60 mL/min versus eGFR‡ 60 to <90 mL/min. ‡Estimated creatinine clearance by Cockcroft-Gault formula. Abbrevation. BMD: bone mineral density; CI: confidence interval; eGFR: estimated glomerular filtration rate; ITT: intent to treat; LOCF: last observation carried forward.

$n = 365$; $p < .001$) and teriparatide (3 fractures; $n = 369$; $p = .003$). In patients with eGFR 25 to <60 mL/min, new vertebral fractures were less frequent in the abaloparatide and teriparatide arms compared with placebo, but the differences were not statistically significant (abaloparatide, 1 fracture, $n = 137$; teriparatide, 2 fractures, $n = 164$; placebo, 4 fractures, $n = 141$).

In patients treated with abaloparatide or teriparatide, differing baseline renal function was associated with small variations in BMD change from baseline. In patients treated with abaloparatide, at the lumbar spine, there was a significantly greater ($p < .05$) mean BMD percentage increase from baseline at 18 months in patients with eGFR < 60 mL/min (9.91%) compared with those with eGFR ≥90 mL/min (7.95%, Figure 1). At the femoral neck, the mean BMD percentage increase from baseline at 18 months was also greater in abaloparatide patients who had eGFR <60 mL/min (3.06%) than in those with eGFR ≥90 mL/min (2.56%). The differences in mean BMD increase between patients with eGFR <60 mL/min and those with eGFR ≥60 to <90 mL/min were small in the abaloparatide arm. For the total hip, there were no consistent differences in BMD among patients in the different renal function subgroups who were treated with abaloparatide.

In the teriparatide arm, the mean BMD percentage increase at 18 months in patients with eGFR <60 mL/min was 0.84% greater at the lumbar spine and 0.23% greater at the total hip than in patients with eGFR ≥90 mL/min (Figure 2). Although percentage change from baseline in femoral neck BMD was significantly higher in patients with eGFR <60 mL/min compared with patients with eGFR 60 to <90 mL/min at 12 months ($p < .05$), there were no consistent differences between renal function subgroups over the study duration.

There was a modest trend toward higher levels of the bone turnover biomarkers s-PINP and s-CTX in patients with eGFR <60 mL/min compared with those with eGFR >90 mL/min in the abaloparatide and teriparatide arms (Supplementary Figure 1).

Adverse events in ACTIVE renal function subgroups

In general, the renal function subgroups had similar incidences of TEAEs, serious TEAEs, drug-related TEAEs, severe TEAEs, and AEs leading to death or to study drug

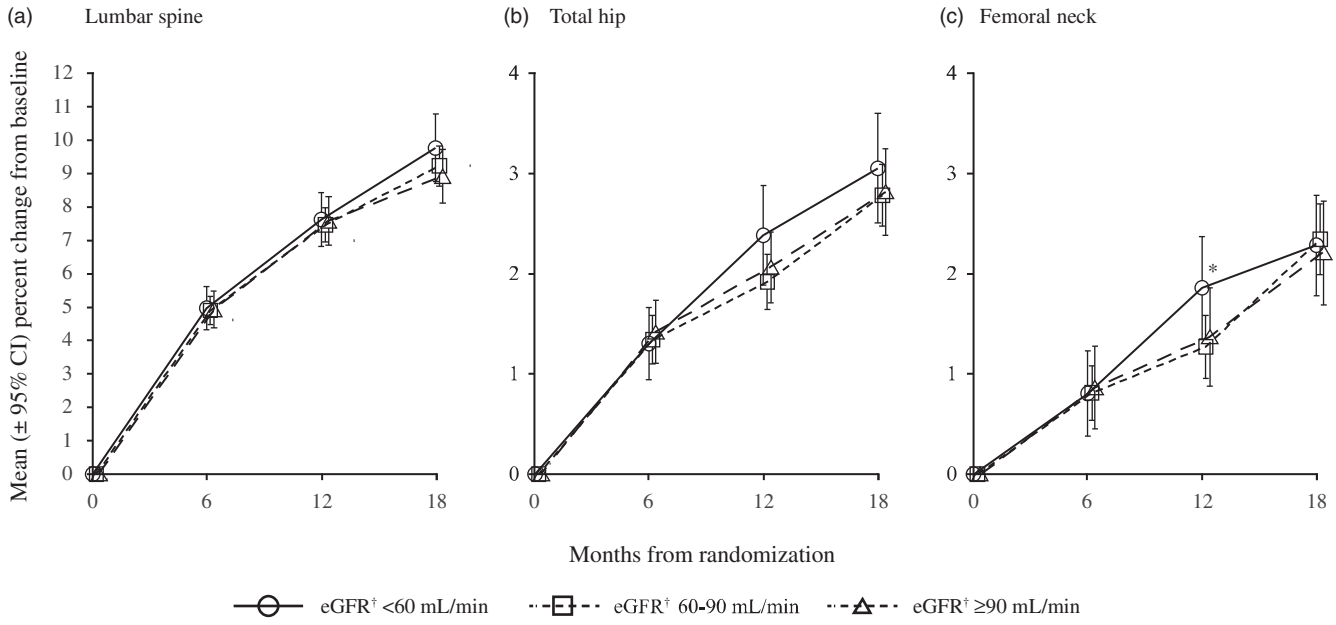

Figure 2. BMD changes in patients treated with teriparatide by renal function at (a) lumbar spine, (b) total hip, and (c) femoral neck (ITT population in teriparatide treatment arm using LOCF). *$p < .05$ eGFR† <60 mL/min versus eGFR† 60 to <90 mL/min. †Estimated creatinine clearance by Cockcroft-Gault formula. Abbreviations. BMD: bone mineral density; CI: confidence interval; eGFR: estimated glomerular filtration rate; ITT: intent to treat; LOCF: last observation carried forward.

discontinuation within each treatment group. The proportion of patients experiencing TEAEs did not increase with worsening renal impairment (Table 2), and in general there was no discernible pattern of increased incidence of TEAEs with increasing renal impairment. However, the frequency of anemia, hypercalcemia, nausea, and upper-respiratory-tract infection TEAEs trended higher with decreasing renal function in the abaloparatide group. In patients treated with abaloparatide, the incidence of palpitations did not trend higher with decreasing renal function.

Table 3 shows the incidence of hypercalcemia defined as albumin-adjusted serum calcium ≥10.7 mg/dL. The incidences of this measure of hypercalcemia increased in patients with renal impairment compared to those with normal renal function in the abaloparatide and teriparatide treatment arms. However, incidence was lower for abaloparatide than for teriparatide within each renal function subgroup and significantly lower for abaloparatide than for teriparatide in the overall ACTIVE safety population (3.4% versus 6.4%; $p = .006$)[10]. By the same measure, the incidence of hypercalcemia based on laboratory values in the teriparatide arm was significantly higher compared with abaloparatide in patients with eGFR <60 mL/min (10.94% versus 3.76%, respectively; $p = .008$).

At 18 months, the mean change (SD) from baseline for 24-h urine creatinine clearance was −7.9 (36.8) mL/min in the abaloparatide arm ($n = 670$), −5.5 (37.1) mL/min in the teriparatide arm ($n = 676$), and −2.8 (32.5) mL/min in the placebo arm ($n = 686$). There was no apparent trend in 24-h urine calcium or in mean change from baseline eGFR levels estimated by Cockcroft–Gault in any treatment group.

Renal CT substudy

A subset of patients ($n = 131$ placebo; $n = 123$ abaloparatide; $n = 122$ teriparatide) underwent at least 1 renal CT scan to assess kidney calcification. Baseline demographics and patient characteristics of patients in this renal CT substudy were similar to those of the overall ACTIVE population. Calculi were present at baseline in the kidney calyces in all treatment groups, but there was no pattern of increased incidence of calculi at any location across treatment groups from baseline to EOS renal CT scans.

Among women in the renal CT substudy, 45 placebo, 42 abaloparatide, and 46 teriparatide patients had renal CT scans at both baseline and EOS. At baseline, 13.3% of placebo, 4.8% of abaloparatide, and 0 teriparatide patients had calculi at the left kidney calyx; at EOS, these proportions were 8.9% placebo, 4.8% abaloparatide, and 6.5% teriparatide. At baseline, 13.3% of placebo, 9.5% of abaloparatide, and 2.2% of teriparatide patients had calculi at the right kidney calyx; at EOS, these proportions were 8.9% placebo, 11.9% abaloparatide, and 2.2% teriparatide.

Discussion

We observed no meaningful differences in the efficacy or safety of abaloparatide among patients with different degrees of baseline renal function. Generally, similar results were observed in patients treated with open-label teriparatide.

Although abaloparatide C_{max} and AUC have been shown to increase in patients with moderate renal impairment compared with healthy subjects,[11], this did not translate into clinically meaningful differences in BMD in the equivalent subgroup of ACTIVE patients with estimated eGFR 25 to <60 mL/min. Exposure to teriparatide also increased in patients with renal impairment compared with patients with normal renal function[14]. However, as with patients assigned to abaloparatide, patients in the teriparatide arm with estimated eGFR 25 to <60 mL/min did not experience clinically meaningful

Table 2. TEAEs of interest by baseline renal function (safety population).

Preferred term	Placebo *n/N* (%)	Abaloparatide *n/N* (%)	Teriparatide *n/N* (%)
At least one TEAE			
eGFR* <60 mL/min	145/167 (86.8)	148/168 (88.1)	172/192 (89.6)
eGFR* 60 to <90 mL/min	381/435 (87.6)	383/428 (89.5)	368/413 (89.1)
eGFR* ≥90 mL/min	192/218 (88.1)	204/226 (90.3)	187/213 (87.8)
TEAEs that increased in frequency with decreasing renal function			
Anemia			
eGFR* <60 mL/min	5/167 (3.0)	13/168 (7.7)	7/192 (3.6)
eGFR* 60 to <90 mL/min	7/435 (1.6)	8/428 (1.9)	16/413 (3.9)
eGFR* ≥90 mL/min	3/218 (1.4)	2/226 (0.9)	0/213 (0.0)
Hypercalcemia			
eGFR* <60 mL/min	1/167 (0.6)	3/168 (1.8)	14/192 (7.3)
eGFR* 60 to <90 mL/min	1/435 (0.2)	7/428 (1.6)	13/413 (3.1)
eGFR* ≥90 mL/min	1/218 (0.5)	1/226 (0.4)	2/213 (0.9)
Nausea			
eGFR* <60 mL/min	5/167 (3.0)	16/168 (9.5)	11/192 (5.7)
eGFR* 60 to <90 mL/min	13/435 (3.0)	36/428 (8.4)	20/413 (4.8)
eGFR* ≥90 mL/min	7/218 (3.2)	16/226 (7.1)	11/213 (5.2)
Upper-respiratory-tract infection			
eGFR* <60 mL/min	17/167 (10.2)	24/168 (14.3)	22/192 (11.5)
eGFR* 60 to <90 mL/min	37/435 (8.5)	36/428 (8.4)	32/413 (7.7)
eGFR* ≥90 mL/min	9/218 (4.1)	8/226 (3.5)	19/213 (8.9)
Other TEAEs of interest			
Palpitations			
eGFR* <60 mL/min	0/167 (0.0)	6/168 (3.6)	6/192 (3.1)
eGFR* 60 to <90 mL/min	3/435 (0.7)	22/428 (5.1)	5/413 (1.2)
eGFR* ≥90 mL/min	0/218 (0.0)	14/226 (6.2)	2/213 (0.9)
Orthostatic hypotension			
eGFR* <60 mL/min	1/167 (0.6)	2/168 (1.2)	1/192 (0.5)
eGFR* 60 to <90 mL/min	3/435 (0.7)	4/428 (0.9)	2/413 (0.5)
eGFR* ≥90 mL/min	0/218 (0.0)	1/226 (0.4)	0/213 (0.0)
Hyperuricemia			
eGFR* <60 mL/min	1/167 (0.6)	2/168 (1.2)	2/192 (1.0)
eGFR* 60 to <90 mL/min	1/435 (0.2)	3/428 (0.7)	3/413 (0.7)
eGFR* ≥90 mL/min	0/218 (0.0)	1/226 (0.4)	0/213 (0.0)

*Estimated creatinine clearance by Cockcroft-Gault formula.
Abbreviations. eGFR: estimated glomerular filtration rate; *n*: number of patients with event; *N*: total number of patients in subgroup; TEAE: treatment emergent adverse event.

Table 3. Incidence of hypercalcemia (albumin-adjusted serum calcium ≥10.7 mg/dL) by baseline renal function (safety population).

	Incidence of hypercalcemia*		
	Placebo n/*N* (%)	Abaloparatide n/*N* (%)	Teriparatide n/*N* (%)
Overall	3/817 (0.37)	28/820 (3.41)	52/816 (6.37)
eGFR† <60 mL/min	0/166 (0.00)	6/168 (3.57)	21/192 (10.94)
eGFR† 60 to <90 mL/min	1/433 (0.23)	19/428 (4.44)	23/411 (5.60)
eGFR† ≥90 mL/min	2/218 (0.92)	3/224 (1.34)	8/213 (3.76)

*Hypercalcemia assessed as albumin-corrected serum calcium level ≥10.7 mg/dL.
†Estimated creatinine clearance by Cockcroft-Gault formula.
Abbreviations. eGFR: estimated glomerular filtration rate; *n*: number of patients with event; *N*: total number of patients in subgroup with at least one post-baseline assessment.

differences in BMD compared with patients with estimated eGFR ≥90 mL/min. Similarly, the rate of fracture reduction compared with placebo did not increase in the lower renal function subgroups who were subjected to greater abaloparatide or teriparatide exposure. The observed small effect on the efficacy of abaloparatide is consistent with the dose-response relationship observed by Leder *et al.*: in this phase 2 dosing study, doubling the abaloparatide dose in the range 20–80 μg resulted in an approximately linear increase in BMD[15].

Increased abaloparatide exposure did not correspond to an increase in the overall incidence of AEs or abnormal laboratory values. However, the frequency of anemia, hypercalcemia, nausea, and upper-respiratory-tract infection trended higher at greater degrees of renal impairment.

All ACTIVE patients received supplemental calcium (mean dosage per group: placebo 986 mg, abaloparatide 955 mg, teriparatide 894 mg), so there was an expectation that calcium levels in serum or urine would be elevated in all treatment arms. Incidence of hypercalcemia trended to be higher in both the treatment arms when compared with placebo but trended toward being lower in the abaloparatide arm compared with the teriparatide arm. These results are consistent with the overall ACTIVE study population in which bone resorption was lower with abaloparatide than with teriparatide[10,15]. The frequency of hypercalcemia events trended toward being higher in patients with renal impairment compared with those with normal renal function in the abaloparatide and teriparatide arms. This result was consistent with observations in a similar study evaluating the effects of teriparatide in patients with renal impairment, although in that teriparatide study, most of the differences were not statistically significant[16]. Notably, authors of a subsequent

systematic review found the teriparatide study to be at high risk of bias due to unclear sequence generation, allocation concealment, blinding, and outcome reporting methods[17].

Soft tissue mineralization was observed in rats after they were given supratherapeutic doses of abaloparatide or teriparatide for up to 2 years[18], with some of the highest mineralization observed in renal tissues. In ACTIVE, patients treated with therapeutic doses of abaloparatide or teriparatide for 18 months showed no pattern of increased incidence of calculi in any of the assessed renal locations.

Study limitations

Although the safety evaluation by renal status was preplanned, ACTIVE was not primarily designed to examine renal function. Furthermore, teriparatide was administered open-label so any differences in subjective measures should be interpreted with caution. The small number of fractures in patients with eGFR 25 to <60 mL/min limited statistical analysis of fracture rates in that group. Assessments of new vertebral fracture and BMD by renal status were *post hoc* exploratory analyses. Patients with severely impaired renal function, history of nephrolithiasis or urolithiasis within 5 years, or history of chronic or recurrent renal disturbances were excluded from entry into ACTIVE.

Conclusions

The present study found no meaningful differences in efficacy or safety of abaloparatide among patients with different degrees of baseline renal function. Our findings support the use of abaloparatide in patients with mild or moderate renal impairment without dose adjustments., Patients with severe renal impairment should be monitored for adverse reactions. Abaloparatide is particularly suitable as an osteoanabolic agent to treat patients at high risk for fracture with impaired renal function.

Transparency

Declaration of funding

This study was sponsored by Radius Health, Inc., Waltham, MA, USA.

Declaration of financial/other relationships

Dr. Bilezikian is a consultant for Radius Health, Inc., Amgen, Regeneron, Shire, and Ultragenyx. Dr. Hattersley, Dr. Mitlak, Dr. Hu, Dr. Fitzpatrick, and Dr. Dabrowski are employees of, and own stock in Radius Health, Inc. Dr. Papapoulos is a consultant and adviser for Radius Health, Inc., Amgen, Axsome, Gador, and UCB and a speaker for Amgen and UCB. Dr. Miller is a consultant to Radius Health, Inc.; has participated on scientific advisory boards for AgNovos, Alexion, Amgen, Eli Lilly, Merck, Radius Health, Inc., and Roche; and has received research grants from Alexion, Amgen, Boehringer Ingelheim, Immunodiagnostics, Eli Lilly, Merck, Merck Serono, National Bone Health Alliance, Novartis, Novo Nordisk, Roche Diagnostics, and Takeda. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements

J.F. Marier provided input into earlier versions of this manuscript. Editorial assistance was provided by Ed Childs, PhD, Adelphi Communications, Bollington, UK, and was funded by Radius Health, Inc., Waltham, MA, USA.

References

[1] Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet. 2002;359:1761–1767.
[2] Weinstein JR, Anderson S. S. The ageing kidney: physiological changes. Adv Chronic Kidney Dis. 2010;17:302–307.
[3] Klawansky S, Komaroff E, Cavanaugh PF Jr, et al. Relationship between age, renal function and bone mineral density in the US population. Osteoporos Int. 2003;14:570–576.
[4] Fosamax (alendronate sodium) [prescribing information]. Kenilworth (NJ): Merck & Co. Inc.; 1995.
[5] Reclast (zoledronic acid) [prescribing information]. Basel (Switzerland): Novartis Pharmaceuticals Corporation; 2001.
[6] Boniva (ibandronate sodium) [prescribing information]. San Francisco (CA): Genentech USA, Inc.; 2003.
[7] Atelvia (risedronate sodium) [prescribing information]. Rockaway (NJ): Warner Chilcott (US), LLC; 1998.
[8] Hattersley G, Dean T, Corbin BA, et al. Binding selectivity of abaloparatide for PTH-type-1-receptor conformations and effects on downstream signaling. Endocrinology. 2016;157:141–149.
[9] Jilka RL. Molecular and cellular mechanisms of the anabolic effect of intermittent PTH. Bone. 2007;40:1434–1446.
[10] Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA. 2016;316:722–733.
[11] Tymlos (abaloparatide) [prescribing information]. Waltham (MA): Radius Health, Inc.; 2018.
[12] Center for Drug Evaluation and Research (CDER) Food and Drug Administration. Guidance for industry: pharmacokinetics in patients with impaired renal function — study design, data analysis, and impact on dosing and labeling. 2010 [last accessed 2018 June 7]. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm204959.pdf
[13] National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1–S266.
[14] Forteo (teriparatide) [prescribing information]. Indianapolis (IN): Eli Lilly and Co.; 2012.
[15] Leder BZ, O'Dea LS, Zanchetta JR, et al. Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2015;100:697–706.
[16] Miller PD, Schwartz EN, Chen P, et al. Teriparatide in postmenopausal women with osteoporosis and mild or moderate renal impairment. Osteoporos Int. 2007;18:59–68.
[17] Wilson LM, Rebholz CM, Jirru E, et al. Benefits and harms of osteoporosis medications in patients with chronic kidney disease: A systematic review and meta-analysis. Ann Intern Med. 2017;166:649–658.
[18] Jolette J, Attalla B, Varela A, et al. Comparing the incidence of bone tumors in rats chronically exposed to the selective PTH type 1 receptor agonist abaloparatide or PTH(1-34). Regul Toxicol Pharmacol. 2017;86:356–365.