

## Supplementary Online Content

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*. doi: 10.1001/jama.2016.11136

**eAppendix 1.** ACTIVE Study Investigators

**eAppendix 2.** Data and Safety Monitoring Board

**eAppendix 3.** Inclusion Criteria

**eAppendix 4.** Exclusion Criteria

**eTable.** Incidence of and Number of Clinical Fracture-Related End Points by Location and Treatment

**eFigure 1.** Change From Baseline in BMD Using LOCF at (A) Total Hip, (B) Femoral Neck, and (C) Lumbar Spine

**eFigure 2.** Geometric Mean of Ratio in Serum Bone Metabolism Markers Over Time by Treatment Group

**eAppendix 5.** References

This supplementary material has been provided by the authors to give readers additional information about their work.

## **eAppendix 1. ACTIVE Study Investigators**

(listed alphabetically by country)

### **Argentina**

- José R. Zanchetta, MD; Instituto de Investigaciones Metabolicas; Buenos Aires

### **Brazil**

- Ben Hur Albergaria, MD; Universidade Federal do Espirito Santo; Vitoria
- João Lindolfo Borges, MD; Universidade Catolica de Brasilia and Centro de Pesquisa Clinica do Brasil; Brasilia
- Carolina A. Moreira, MD, MSc, PhD; Federal University of Parana; Curitiba
- Luis Russo, MD, PhD; Center for Clinical and Basic Research (CCBR); Rio de Janeiro
- Cristiano A.F. Zerbini, MD; Centro Paulista de Investigaçao Clinica; São Paulo

### **China**

- Edith Lau, MD; CCBP; Hong Kong

### **Czech Republic**

- Tomas Hala, MD; CCBP; Pardubice and Brno
- Martina Machková, MD; CCBP; Prague

### **Denmark**

- Annesofie Krogsaa, MD; CCBP; Ballerup
- Bettina Storgaard Nedergaard, MD, PhD; CCBP; Aalborg
- Peter Alexandersen, MD; CCBP; Vejle

### **Estonia**

- Ivo Valter, MD; CCBP; Tallinn
- Katre Maasalu, MD; CCBP; Tartu

### **Lithuania**

- Zydrune Visockiene, MD; CCBP; Vilnius

### **Poland**

- Eugenia Czajkowska-Kaczmarek, MD; Polimedica; Zgierz
- Joanna Glogowska-Szelag, MD, PhD; Medicapf; Katowice
- Beata Jendrych, MD; CCBP; Lodz and Warsaw
- Jerzy Supronik, MD, PhD; NZNZ Centrum Medyczne Artur Racewicz; Bialystok
- Mirella Wojtecka-Grabka, MD; NZNZ Primamed; Kielce

### **Romania**

- Sorica Mustatea, MD; CCBP; Bucharest

### **United States**

- Michael Bolognese, MD; Bone Health Center of Bethesda; Bethesda, MD
- Mark Kutner, MD; Suncoast Research; Miami, FL
- Farid Marquez, MD; Palm Springs Research Center; North Miami, FL
- Paul D. Miller, MD; Colorado Center for Bone Research; Lakewood, CO
- Grattan Woodson, MD; Osteoporosis Center of Atlanta; Atlanta, GA

## **eAppendix 2. Data and Safety Monitoring Board**

John Bilezikian, MD (**Chairman**); Division of Endocrinology; Columbia University; New York, NY

Sharon Spence (**Facilitator**); Frame and Spence Consulting, LLP; Westwood, MA

B. Boyd Thompson, MD (**Independent safety expert**); Pulmonary and CCU; Massachusetts General Hospital;  
Boston, MA

Amanda Truesdale (**Statistician, unblinded**); Veristat Inc.; Holliston, MA

Barry Turnbull, PhD (**Statistician**); Biobridges, LLP; Wellesley, MA

### **eAppendix 3. Inclusion Criteria**

Patients must have met all of the following criteria to be eligible to participate in this study:

1. The patient is a healthy ambulatory postmenopausal woman from 50 to 85 years of age (inclusive) with osteoporosis.
2. The patient has been postmenopausal for at least 5 years. Postmenopausal status will be established by a history of amenorrhea for at least 5 years and by an elevated serum follicle-stimulating hormone value of  $\geq 30$  IU/L.
3. The patient has a bone mineral density T-score  $\leq -2.5$  and  $> -5.0$  at the lumbar spine (L1-L4) or hip (femoral neck) by dual energy x-ray absorptiometry (DXA) and radiologic evidence of two or more mild or one or more moderate lumbar or thoracic vertebral fractures, or history of low-trauma forearm, humerus, sacral, pelvic, hip, femoral, or tibial fracture within the past 5 years. Postmenopausal women older than 65 years who meet the above fracture criteria but have a T-score  $\leq -2.0$  and  $> -5.0$  may be enrolled. Women older than 65 years who do not meet the fracture criteria may be enrolled if their T-score is  $\leq -3.0$  and  $> -5.0$ .
4. The patient is in good general health as determined by medical history and physical examination (including vital signs), has a body mass index of 18.5 to 33, inclusive, and is without evidence of clinically significant abnormality in the opinion of the Investigator.
5. Any required concomitant medications which are not excluded (eg, statins or antihypertensives) may be continued through the study. Every effort should be made to maintain the medication at a stable dose throughout the study, subject to the Investigator's medical judgment.
6. The patient has serum calcium (albumin-corrected), intact PTH (1-84), and serum phosphorus and alkaline phosphatase values all within the normal range during the Screening Period. Patients with minor elevations or reductions in serum calcium may be enrolled if serum ionized calcium is normal. Any patient with an elevated alkaline phosphatase value, and who meets all other entry criteria, would be required to have a normal bone-specific alkaline phosphatase result to be enrolled.
7. The patient has serum 25-hydroxy Vitamin D values above 15 ng/mL and within 3 times the upper normal range.
8. The patient's resting 12-lead electrocardiogram obtained during screening shows no clinically significant abnormality and a QTc  $\leq 470$  msec (Bazett's correction).
9. The patient's systolic blood pressure is  $\geq 100$  and  $\leq 155$  mmHg, diastolic blood pressure is  $\geq 40$  and  $\leq 95$  mmHg, and heart rate is  $\geq 45$  and  $\leq 100$  bpm (sitting or supine).
10. The patient has no clinically significant abnormality of serum hemoglobin, hematocrit, white blood count and platelets, or usual serum biochemistry: electrolytes, renal function, liver function, and serum proteins.
11. The patient has read, understood, and signed the written informed consent form.

## eAppendix 4. Exclusion Criteria

Patients with any of the following characteristics were not eligible to participate in the study:

### *General exclusion criteria:*

1. History of more than four spine fractures, mild or moderate, or any severe fractures.
2. Presence of abnormalities of the lumbar spine that would prohibit assessment of spinal bone mineral density, defined as having at least two radiologically evaluable vertebrae within L1-L4.
3. Unevaluable hip bone mineral density or patients who have undergone bilateral hip replacement (unilateral hip replacement is acceptable).
4. History of bone disorders (eg, Paget's disease) other than postmenopausal osteoporosis.
5. Unexplained elevation of serum alkaline phosphatase.
6. History of radiotherapy (radiation therapy), other than radioiodine.
7. History of chronic or recurrent renal, hepatic, pulmonary, allergic, cardiovascular, gastrointestinal, endocrine, central nervous system, hematologic, or metabolic diseases or immunologic, emotional, and/or psychiatric disturbances to a degree that would interfere with the interpretation of study data or compromise the safety of the patient.
8. History of Cushing's disease, hyperthyroidism, hypo- or hyperparathyroidism, or malabsorptive syndromes within the past year.
9. History of significantly impaired renal function (serum creatinine  $>177$   $\mu\text{mol/L}$  or  $>2.0$   $\text{mg/dL}$ ). If the serum creatinine is  $>1.5$  and  $\leq 2.0$   $\text{mg/dL}$ , the calculated creatinine clearance (Cockcroft-Gault) must be  $\geq 37$   $\text{mL/min}$ .
10. History of any cancer within the past 5 years (other than basal cell or squamous cancer of the skin).
11. History of osteosarcoma at any time.
12. History of nephrolithiasis or urolithiasis within the past 5 years.
13. Decrease of 20  $\text{mmHg}$  or more in systolic blood pressure or 10  $\text{mmHg}$  or more in diastolic blood pressure from supine to standing (5 minutes lying and 3 minutes standing) and/or any symptomatic hypotension at screening.<sup>1,2</sup>
14. Patients known to be positive for Hepatitis B, Hepatitis C, HIV-1, or HIV-2. Testing is not required in the absence of clinical signs and symptoms suggestive of HIV infection or acute or chronic hepatitis.

### *Medication-related exclusion criteria:*

15. Known history of hypersensitivity to any of the test materials or related compounds.
16. Prior treatment with PTH or PTHrP drugs, including abaloparatide.
17. Prior treatment with bisphosphonates,\* fluoride or strontium in the past 5 years, prior treatment with gallium nitrate, or with as yet unapproved bone-acting investigational agents at any time.<sup>3</sup>
18. Prior treatment with denosumab, calcitonin, selective estrogen receptor modulators (such as raloxifene or tamoxifen), tibolone, or anabolic steroids in the past 12 months. Estrogens administered as hormone replacement therapy, with or without progestins, are not exclusionary.
19. Treatment with anticonvulsants that affect Vitamin D metabolism (phenobarbital, phenytoin, carbamazepine, or primidone) or with chronic heparin within the 6 months prior to the Screening Period.

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\* Patients who had a short course of bisphosphonate treatment (3 months or less) and were intolerant of the treatment are not excluded from study participation.

*continued* **eAppendix 4.**

20. Daily treatment with oral, intranasal, or inhaled corticosteroids within the 12 months prior to the Screening Period. Occasional use of corticosteroids (for seasonal allergies or asthma) is not exclusionary.
21. Exposure to general anesthesia within the 12 weeks prior to the Screening Period.
22. Exposure to an investigational drug within the 12 months prior to the Screening Period.

*Lifestyle-related exclusion criteria:*

23. Abnormal nutritional status (abnormal diets, excessive or unusual vitamin or herbal intakes, malabsorption, significant recent weight change), Vitamin D intake of  $\geq 4000$  IU/day or Vitamin A intake of  $\geq 10,000$  IU/day.\*
24. Patient is known to abuse alcohol or use illegal drugs within 12 months of the Screening Period.

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\* Vitamin D given during the pretreatment period to treat vitamin D deficiency is permissible.

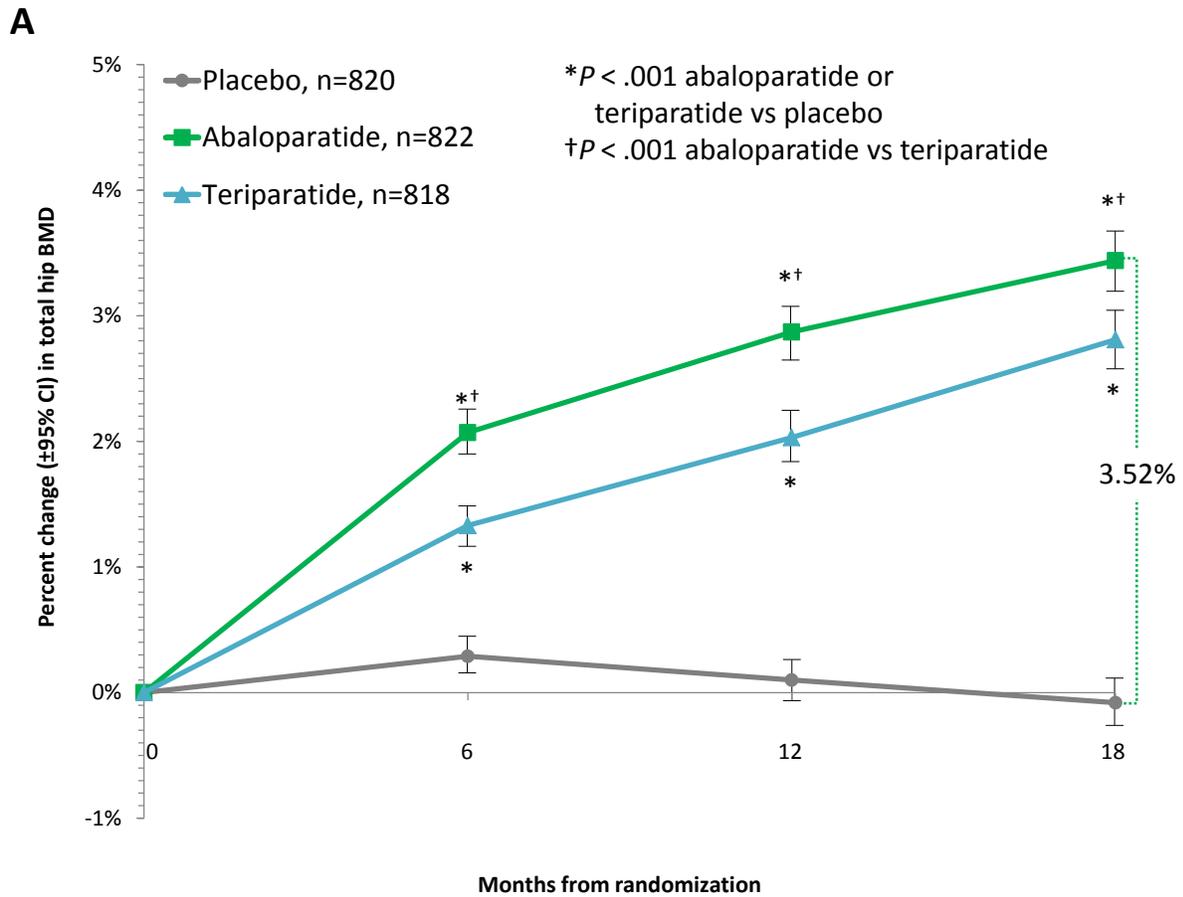
**eTable.** Incidence of and Number of Clinical Fracture-Related End Points by Location and Treatment

	Clinical fractures <sup>b</sup>		Nonvertebral fractures <sup>c</sup>		Clinical major osteoporotic fractures <sup>d</sup>		Nonvertebral fractures, including all trauma levels	
	Patients, n (%)	Fractures, n	Patients, n (%)	Fractures, n	Patients, n (%)	Fractures, n	Patients, n (%)	Fractures, n
<b>Placebo, n=821</b>								
Any clinical fracture location <sup>a</sup>	49 (6.0)	57	33 (4.0)	36	34 (4.1)	36	37 (4.5)	43
Ankle	4 (0.5)	4	4 (0.5)	4	—	—	4 (0.5)	4
Collarbone	1 (0.1)	1	—	—	—	—	1 (0.1)	1
Fingers	2 (0.2)	2	—	—	—	—	—	—
Foot	2 (0.2)	2	2 (0.2)	2	—	—	2 (0.2)	2
Forearm	4 (0.5)	4	4 (0.5)	4	4 (0.5)	4	4 (0.5)	4
Hip	2 (0.2)	2	2 (0.2)	2	2 (0.2)	2	2 (0.2)	2
Knee cap	2 (0.2)	2	—	—	—	—	—	—
Pelvis (not hip)	1 (0.1)	1	—	—	—	—	1 (0.1)	1
Ribs	5 (0.6)	7	4 (0.5)	4	—	—	5 (0.6)	7
Shoulder	1 (0.1)	1	1 (0.1)	1	1 (0.1)	1	1 (0.1)	1
Spine	9 (1.1)	9	—	—	9 (1.1)	9	—	—
Toes	1 (0.1)	1	—	—	—	—	—	—
Upper arm	3 (0.4)	3	3 (0.4)	3	3 (0.4)	3	3 (0.4)	3
Upper leg (not hip)	1 (0.1)	1	1 (0.1)	1	—	—	1 (0.1)	1
Wrist	15 (1.8)	17	13 (1.6)	15	15 (1.8)	17	15 (1.8)	17
<b>Abaloparatide, n=824</b>								
Any clinical fracture location <sup>a</sup>	27 (3.3)	33	18 (2.2)	18	10 (1.2)	10	20 (2.4)	25
Ankle	1 (0.1)	1	1 (0.1)	1	—	—	1 (0.1)	1
Breast bone	1 (0.1)	1	—	—	—	—	1 (0.1)	1
Collarbone	1 (0.1)	1	1 (0.1)	1	—	—	1 (0.1)	1
Facial bones	1 (0.1)	1	—	—	—	—	—	—
Fingers	1 (0.1)	1	—	—	—	—	—	—
Foot	3 (0.4)	3	3 (0.4)	3	—	—	3 (0.4)	3
Forearm	1 (0.1)	1	1 (0.1)	1	1 (0.1)	1	1 (0.1)	1
Knee	1 (0.1)	1	1 (0.1)	1	—	—	1 (0.1)	1
Knee cap	2 (0.2)	2	—	—	—	—	—	—
Lower leg (not knee or ankle)	1 (0.1)	1	1 (0.1)	1	—	—	1 (0.1)	1
Pelvis (not hip)	1 (0.1)	1	1 (0.1)	1	—	—	1 (0.1)	1

continued eTable.

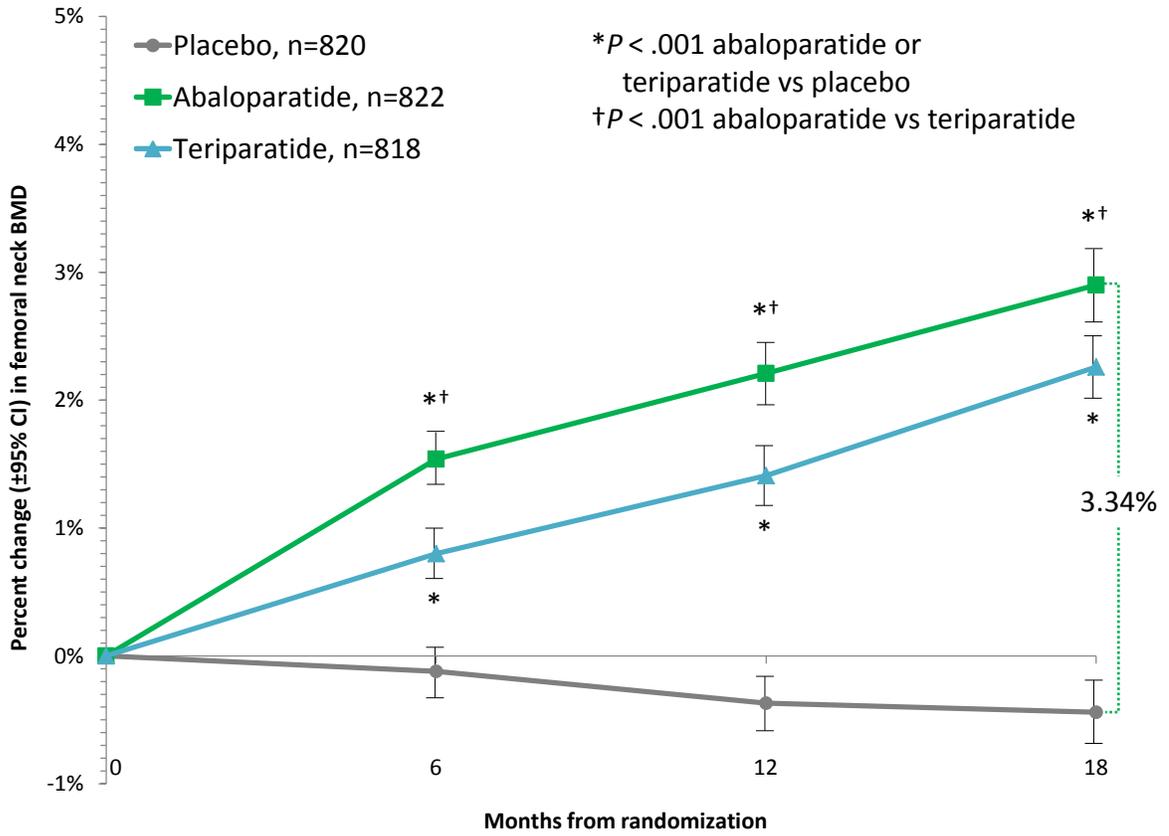
	Clinical fractures <sup>b</sup>		Nonvertebral fractures <sup>c</sup>		Clinical major osteoporotic fractures <sup>d</sup>		Nonvertebral fractures, including all trauma levels	
	Patients, n (%)	Fractures, n	Patients, n (%)	Fractures, n	Patients, n (%)	Fractures, n	Patients, n (%)	Fractures, n
Ribs	3 (0.4)	7	1 (0.1)	1	—	—	3 (0.4)	7
Spine	1 (0.1)	1	—	—	1 (0.1)	1	—	—
Toes	3 (0.4)	3	—	—	—	—	—	—
Upper arm	1 (0.1)	1	1 (0.1)	1	1 (0.1)	1	1 (0.1)	1
Wrist	7 (0.8)	7	7 (0.8)	7	7 (0.8)	7	7 (0.8)	7
<b>Teriparatide, n=818</b>								
Any clinical fracture location <sup>a</sup>	35 (4.3)	39	24 (2.9)	26	23 (2.8)	23	26 (3.2)	29
Ankle	1 (0.1)	2	1 (0.1)	2	—	—	1 (0.1)	2
Collarbone	1 (0.1)	1	1 (0.1)	1	—	—	1 (0.1)	1
Fingers	2 (0.2)	2	—	—	—	—	—	—
Hand	1 (0.1)	1	1 (0.1)	1	—	—	1 (0.1)	1
Knee cap	1 (0.1)	1	—	—	—	—	—	—
Lower leg (not knee or ankle)	2 (0.2)	3	1 (0.1)	1	—	—	2 (0.2)	3
Pelvis (not hip)	1 (0.1)	1	1 (0.1)	1	—	—	1 (0.1)	1
Ribs	1 (0.1)	1	1 (0.1)	1	—	—	1 (0.1)	1
Shoulder	1 (0.1)	1	—	—	1 (0.1)	1	1 (0.1)	1
Spine	3 (0.4)	3	—	—	3 (0.4)	3	—	—
Toes	4 (0.5)	4	—	—	—	—	—	—
Upper arm	2 (0.2)	2	2 (0.2)	2	2 (0.2)	2	2 (0.2)	2
Wrist	17 (2.1)	17	17 (2.1)	17	17 (2.1)	17	17 (2.1)	17
<sup>a</sup> Based on source document verified clinical fractures.								
<sup>b</sup> Clinical fractures were predefined as all fractures that would cause a patient to seek medical care, regardless of the level of trauma, including clinical spine.								
<sup>c</sup> Excludes those fractures associated with high trauma.								
<sup>d</sup> Major osteoporotic fractures were defined as clinical fractures of the wrist, forearm, humerus, shoulder, hip, and spine.								

**eFigure 1.** Change From Baseline in BMD, Using LOCF, at (A) Total Hip, (B) Femoral Neck, and (C) Lumbar Spine

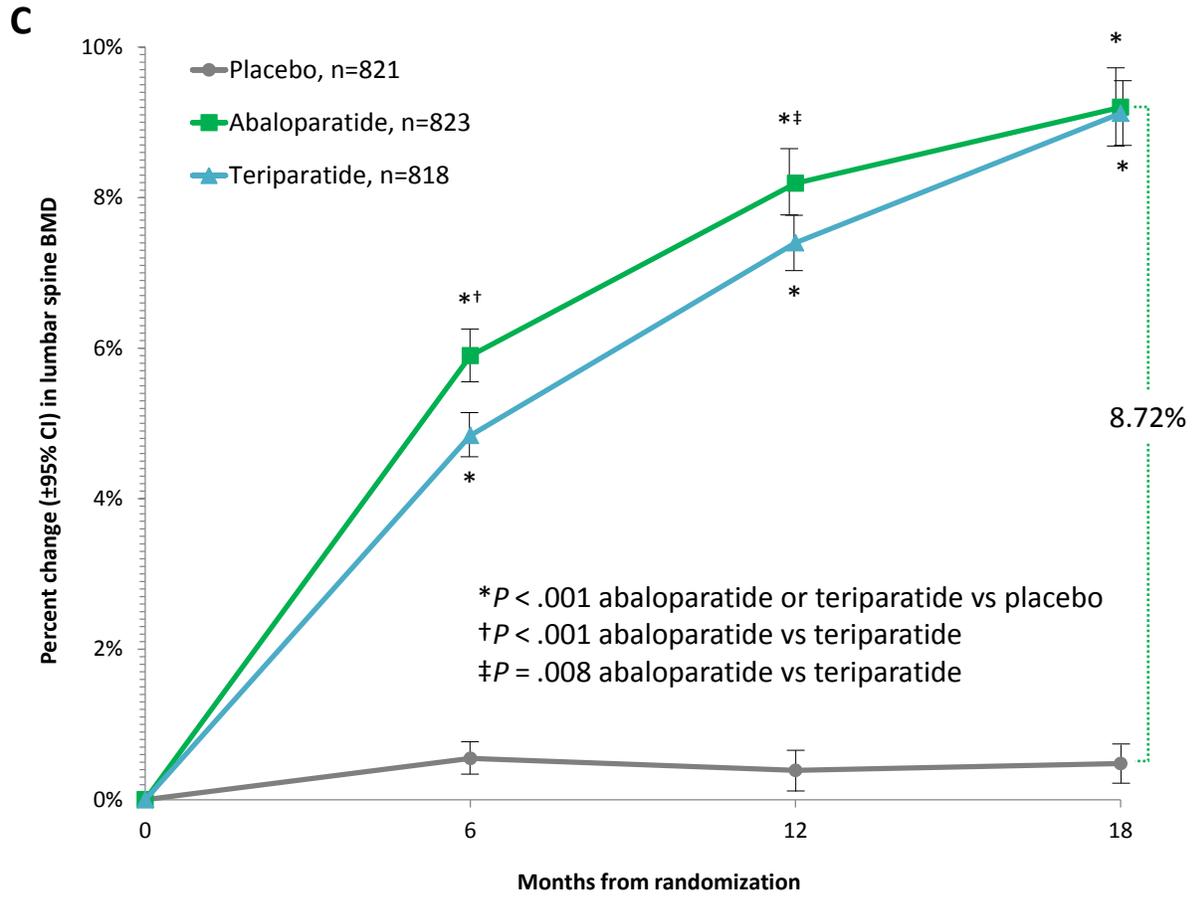


continued eFigure 1.

**B**

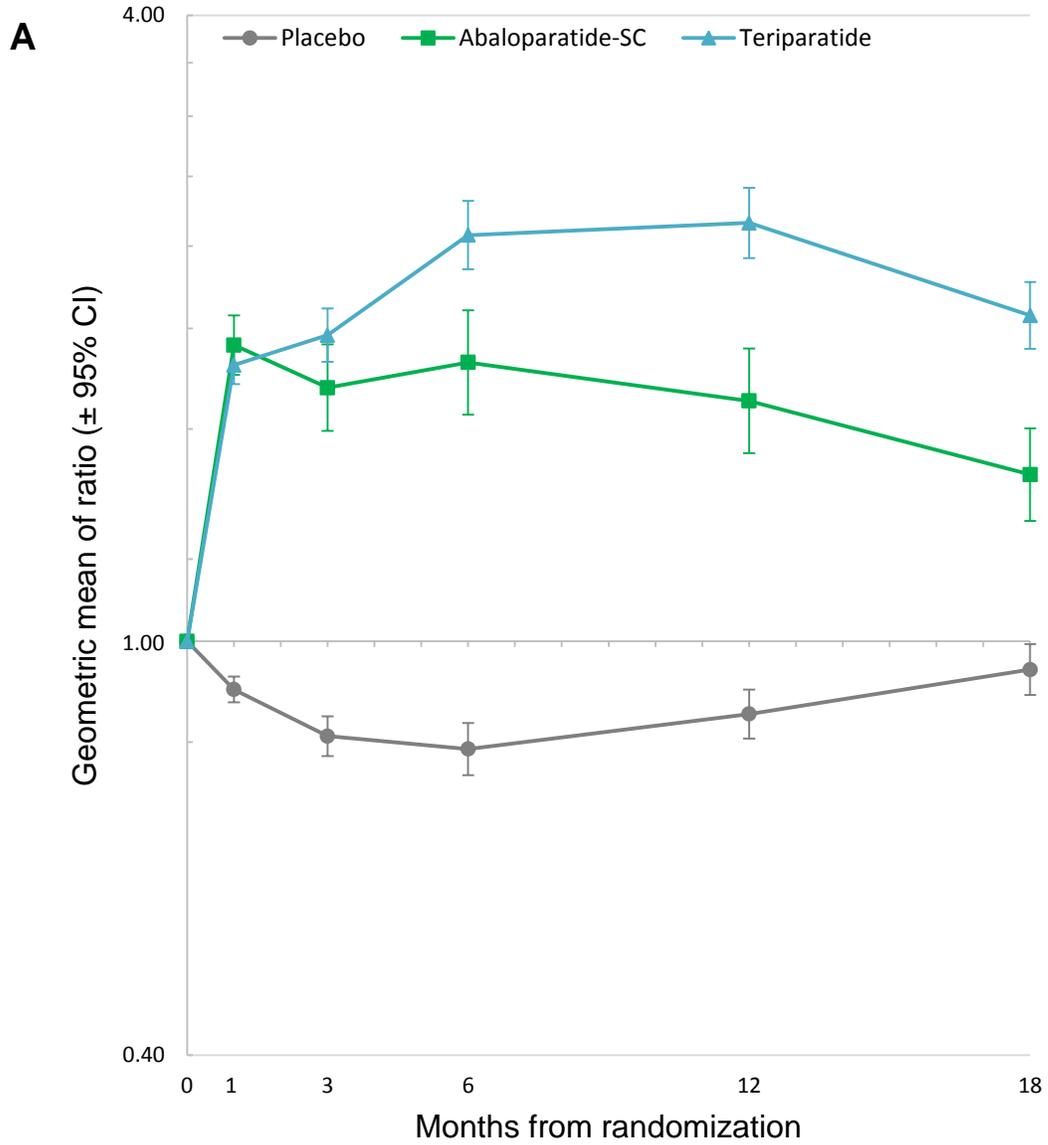


continued **eFigure 1.**



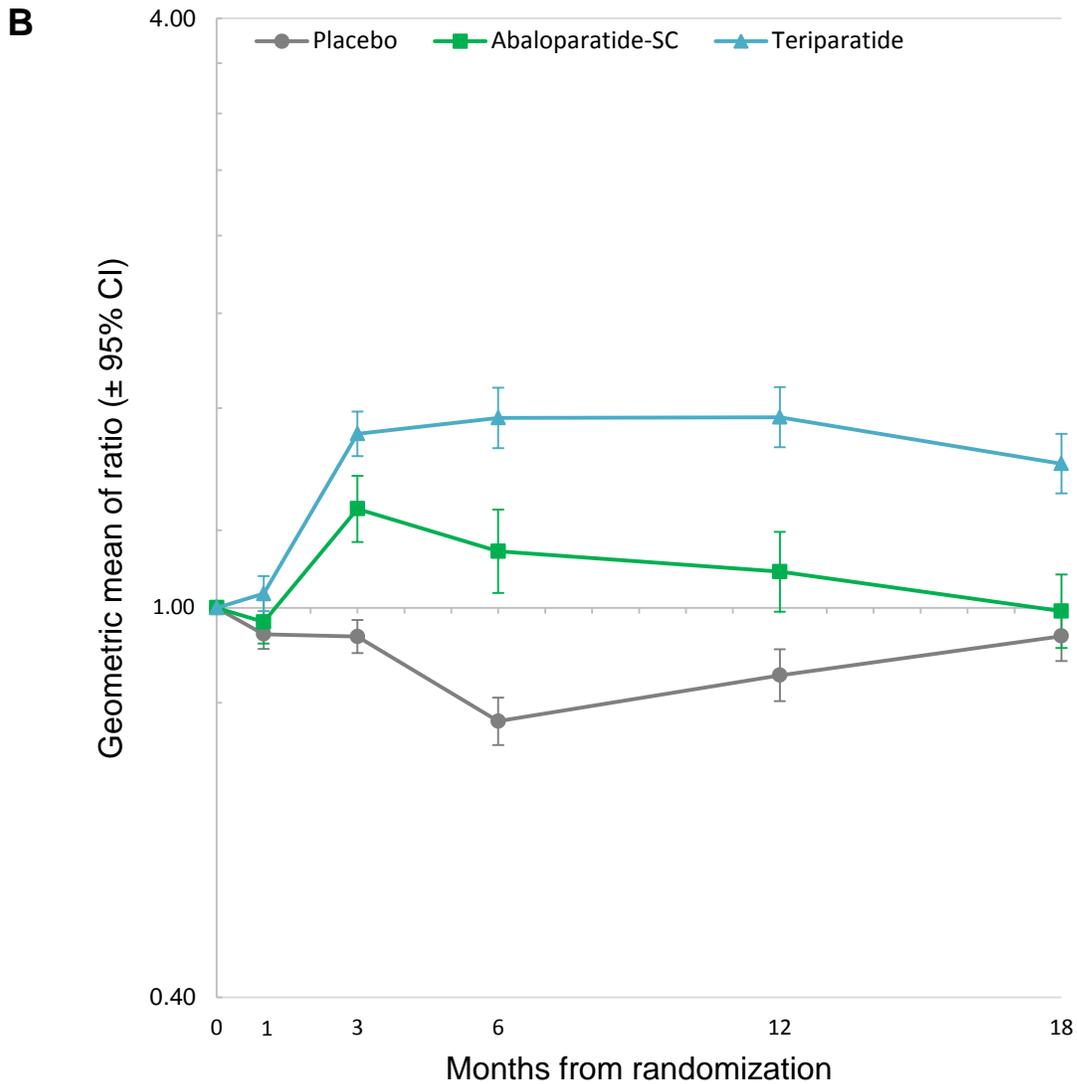
Mean ( $\pm 95\%$  CI) percent changes in bone mineral density at the (A) total hip, (B) femoral neck, and (C) lumbar spine were evaluated using dual-energy x-ray absorptiometry based on the ITT population. Values shown are mean percent change from baseline, using last observation carried forward (LOCF).  
 Abbreviations: BMD, bone mineral density; CI, confidence interval; ITT, intent to treat; SE, standard error.

**eFigure 2.** Geometric Mean of Ratio in Serum Bone Metabolism Markers Over Time by Treatment Group



Number of participants evaluated		1	3	6	12	18
Abaloparatide	189	187	187	189	189	189
Placebo	184	183	181	184	184	184
Teriparatide	227	227	227	227	227	227

continued **eFigure 2.**



**Number of participants evaluated**

Abaloparatide	189	187	187	189	189	189
Placebo	184	183	181	184	184	184
Teriparatide	227	227	227	227	227	227

Geometric mean ratios ( $\pm$  95% CI) for (A) s-PINP and (B) s-CTX after 1, 3, 6, 12, and 18 months of treatment over baseline are shown for a bone turnover marker population subset ( $n = 189$  abaloparatide,  $n = 184$  placebo, and  $n = 227$  teriparatide participants). All comparisons for s-PINP (A) of abaloparatide to placebo and of teriparatide to placebo,  $P < .001$ . Abaloparatide vs teriparatide at month 1,  $P = .131$ ; at month 3,  $P = .016$ ; at months 6, 12, and 18,  $P < .001$ . Comparisons for s-CTX (B) as follows: abaloparatide vs placebo at month 1,  $P = .395$ ; at 3, 6, and 12 months,  $P < .001$ ; at 18 months,  $P = .271$ . Teriparatide vs placebo,  $P < .01$  at all time points. Abaloparatide vs teriparatide,  $P < .001$  at all time points except for at month 1,  $P = .039$ . Abbreviations: BL, baseline; CI, confidence interval; s-CTX, serum carboxy-terminal cross-linking telopeptide of type 1 collagen; s-PINP, serum procollagen type I N-terminal propeptide.

## **eAppendix 5. References**

1. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology*. 1996;46(5):1470.
2. Lipsitz LA. Orthostatic hypotension in the elderly. *N Engl J Med*. 1989;321(14):952-957.
3. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006;296(24):2927-2938.