Once-Weekly Canvuparatide in Patients With Hypoparathyroidism: Interim Analysis of the Open-Label Extension to the Phase 2, Double-Blind, Placebo-Controlled Avail Study

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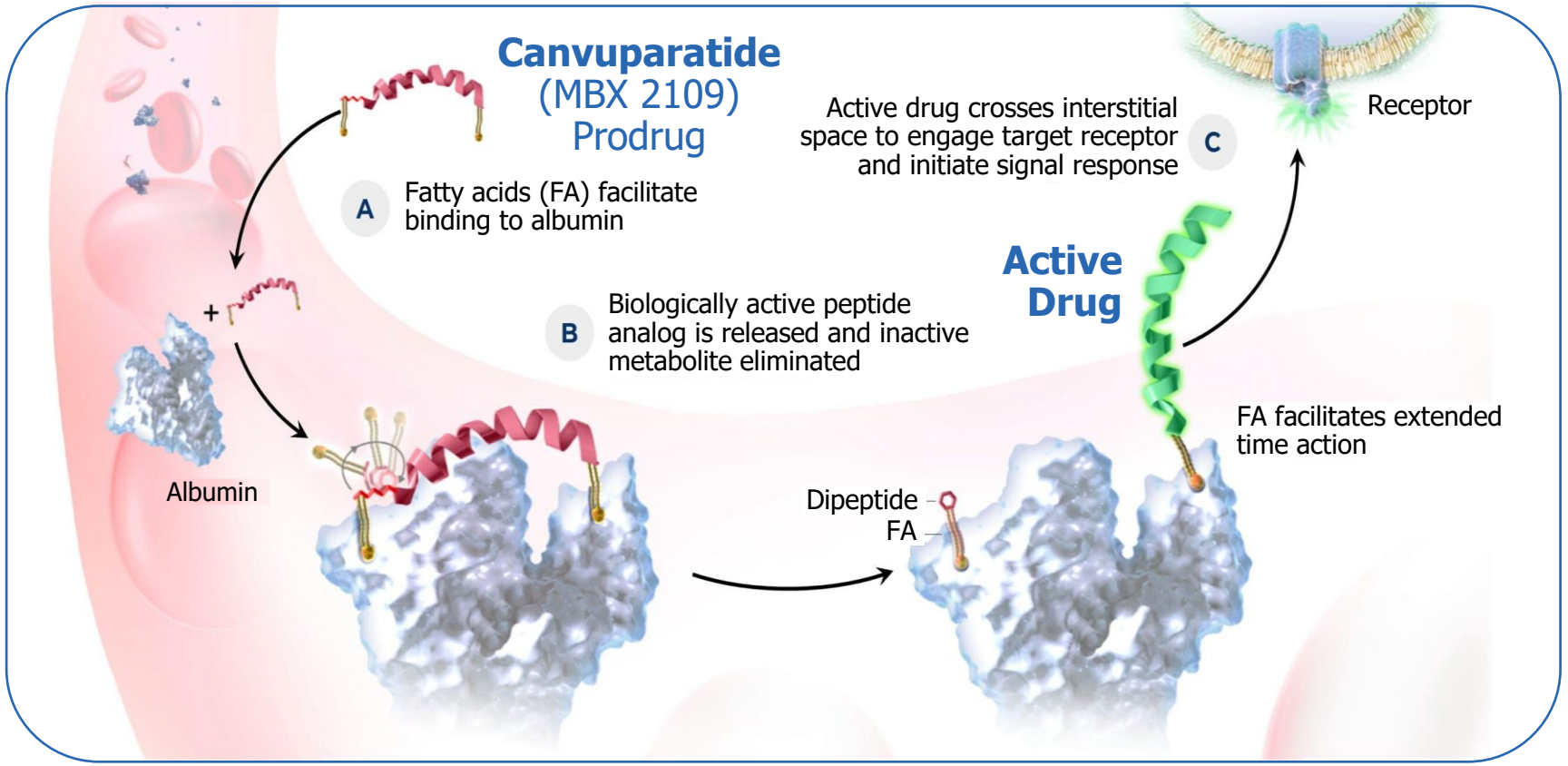
Disclosures

- This study was funded by MBX Biosciences, Inc.
- Dr Rubin has served as a consultant, advisor, and/or principal investigator for Alexion, Amolyt, Ascendis, Calcilytix, MBX Biosciences, Inc., and Takeda
- Medical writing support, funded by MBX Biosciences, Inc., was provided by Crystal Murcia, PhD, CMPP, MWC, and Ray Beck, Jr, PhD of JB Ashtin

Avail and Its OLE Are the First Studies to Evaluate the Efficacy and Safety of Canvuparatide in Patients With HypoPT

Canvuparatide (formerly MBX 2109):

- Is an investigational, fatty-acylated, long-acting prodrug of a **PTH analog**[1]
- Has a T_{max} of 2–3 days and a $T_{1/2}$ of 7.7–8.9 days for the active peptide, supporting **once-weekly dosing**[1]
- Has geometric mean peak-to-trough ratios in patients of 1.3[1]
- Is in development as a PTH replacement therapy in **patients with hypoPT**[1]

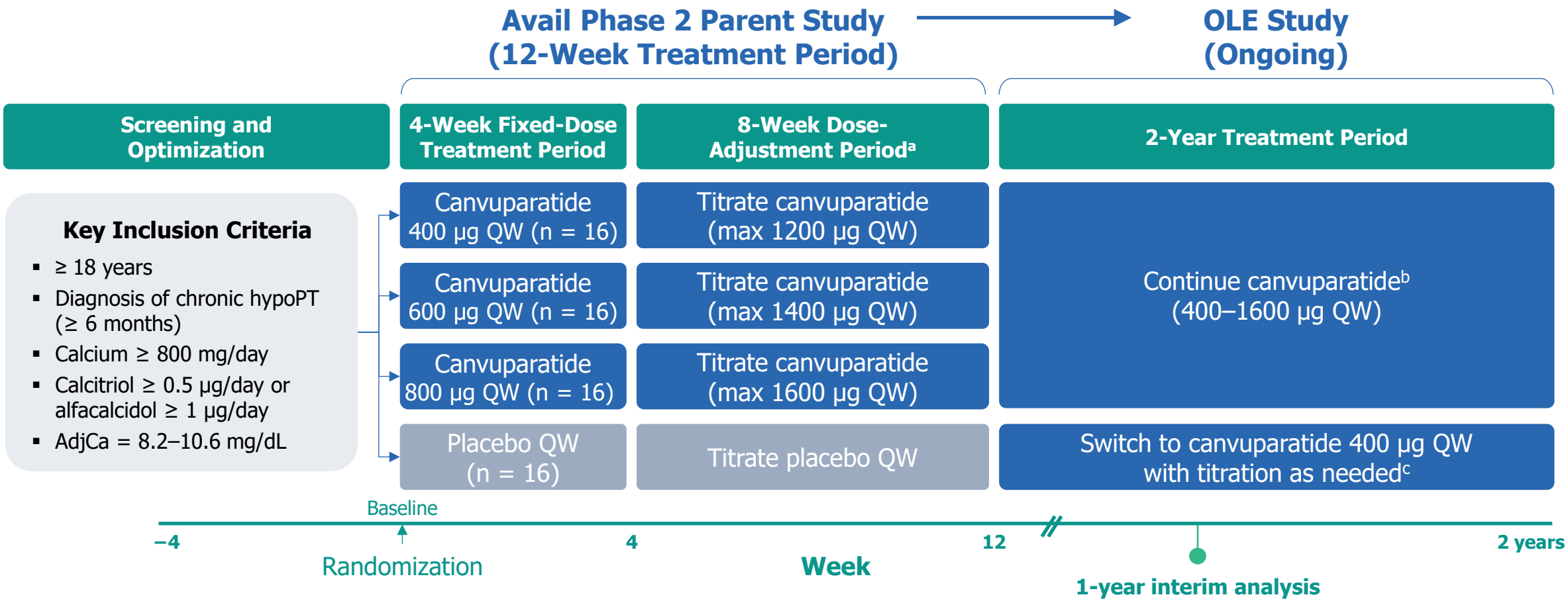


HypoPT, hypoparathyroidism; OLE, open-label extension; PTH, parathyroid hormone; T_{max}, time to maximum concentration; $T_{1/2}$, half-life.

1. Carney P, et al. *J Clin Endocrinol Metab*. 2025;110:940–950.

The OLE Study Is the Extension Trial of the Avail Phase 2 Study

OLE Is Designed to Evaluate the Long-Term Safety of Canvuparatide



AdjCa, albumin-adjusted calcium; hypoPT, hypoparathyroidism; OLE, open-label extension; QW, once weekly.

ClinicalTrials.gov Identifiers: NCT06465108 and NCT06531941. [a]Dose adjustments could be made in 200 µg increments, as needed, every 2 weeks during the dose-adjustment period. [b]Responders (patients could withdraw from active vitamin D and calcium in the parent study) continued the canvuparatide dose they received at week 11. Nonresponders had adjustments to the study drug dose and supplements according to the titration algorithm. [c]Patients initially randomized to placebo initiated canvuparatide 400 µg QW in the OLE, with dose adjustments made to maintain serum calcium 8.2–10.6 mg/dL after the titration algorithm.

The Avail Parent Study Evaluated the Efficacy and Safety of Canvuparatide for 12 Weeks

Primary Endpoint

- Proportion of patients meeting the following composite criteria at week 12:
  - Independence from active vitamin D supplements
  - Oral elemental calcium supplements ≤ 600 mg/day
  - Serum AdjCa concentration of 8.2–10.6 mg/dL

Secondary and Exploratory Endpoints

- Responders for each of the individual measures of the primary composite endpoint at week 12
- Change from baseline in AdjCa and 24-hour urine calcium
- Change from baseline in bone turnover markers (serum CTx, P1NP)
- Change from baseline in serum calcium, phosphorus, magnesium, 25(OH)D, 1,25(OH)2D, and calcium-phosphorus product
- Safety and tolerability

1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; AdjCa, albumin-adjusted calcium; CTx, C-telopeptide of type I collagen; P1NP, procollagen type 1 N-terminal propeptide.

The OLE Study Is Evaluating the Long-Term Safety of Canvuparatide

Primary Endpoint

- Treatment-emergent adverse events

Secondary and Exploratory Endpoints

- Proportion of patients meeting the composite criteria
- Proportion of patients meeting the individual components of the composite criteria
- 24-hour urine calcium
- Serum calcium, phosphorus, magnesium, 25(OH)D, 1,25(OH)2D, and calcium-phosphate product
- Bone biomarkers (serum CTx, P1NP)
- Bone mineral density
- Immunogenicity (ADA)

1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ADA, anti-drug antibodies; CTx, C-telopeptide of type I collagen; OLE, open-label extension; P1NP, procollagen type 1 N-terminal propeptide.

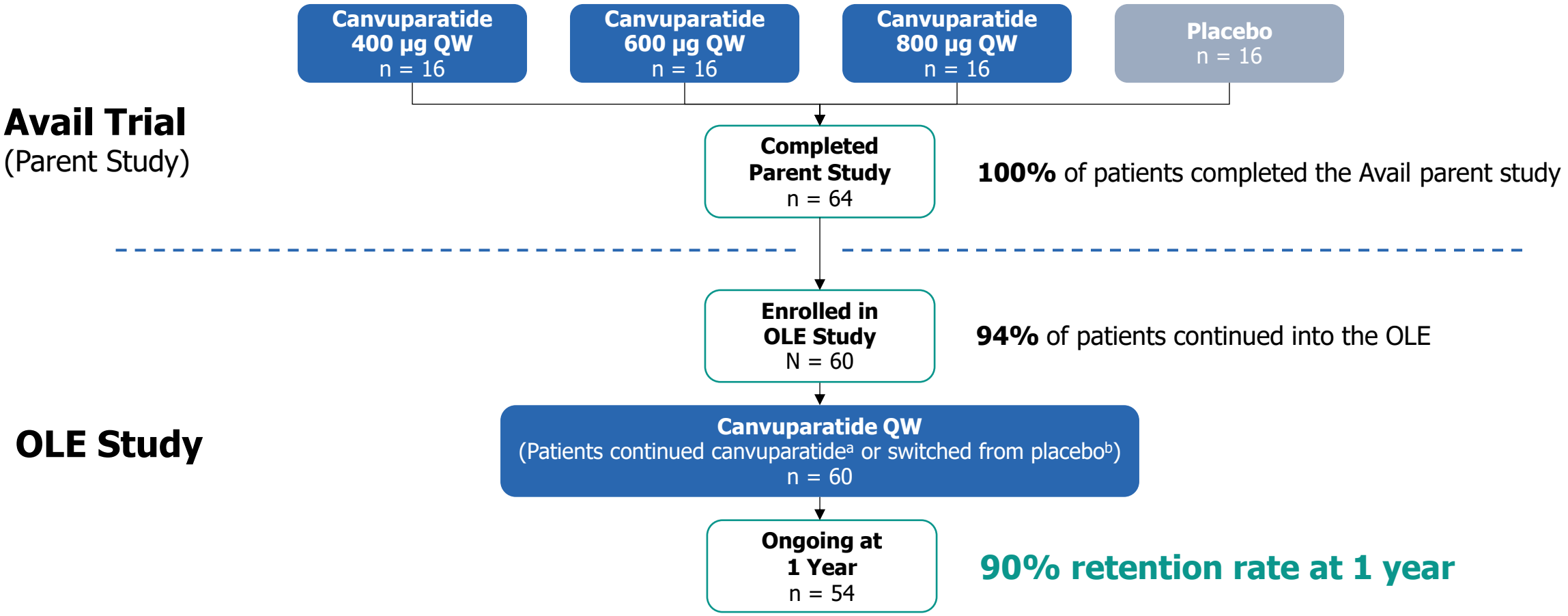
Baseline Characteristics Were Representative of the Population With HypoPT and Well Balanced Between Treatment Groups

Characteristic	Canvuparatide (n = 48)	Placebo (n = 16)
Age, years, median (range)	49.0 (23–72)	44.5 (19–63)
Female, n (%)	41 (85.4)	15 (93.8)
Race, n (%)		
White	43 (89.6)	13 (81.3)
Black or African American	4 (8.3)	2 (12.5)
Other	1 (2.1)	1 (6.3)
Hispanic or Latino, n (%)	29 (60.4)	9 (56.3)
BMI, kg/m^2, mean (SD)	31.3 (6.3)	30.2 (5.4)
Duration of hypoPT, years, mean (SD)	10.5 (9.0)	8.9 (4.8)

Characteristic	Canvuparatide (n = 48)	Placebo (n = 16)
Etiology of hypoPT, n (%)		
Postsurgical chronic	43 (89.6)	14 (87.5)
Nonsurgical[a]	5 (10.4)	2 (12.5)
Calcium dose, mg/day, mean (SD)	3208.0 (2872.3)	2455.3 (918.1)
Vitamin D dose, µg/day, mean (SD)	0.94 (0.52)	0.84 (0.39)
Serum PTH, ng/L, mean (SD)	10.2 (5.7)	12.1 (12.6)
Serum AdjCa, mg/dL, mean (SD)	9.3 (0.7)	9.0 (1.0)
Serum phosphorus, mg/dL, mean (SD)	4.6 (0.8)	4.6 (0.8)
Urine calcium, ≥ 250 mg/day, n (%)	22 (45.8)	7 (43.8)

AdjCa, albumin-adjusted calcium; BMI, body mass index; hypoPT, hypoparathyroidism; PTH, parathyroid hormone.
[a]Nonsurgical etiologies included idiopathic (canvuparatide, 6.3%; placebo, 12.5%), autoimmune (canvuparatide, 2.1%; placebo, 0%), and genetic (canvuparatide, 2.1%; placebo, 0%).

High Retention Rates Continued Across Avail and the OLE Study



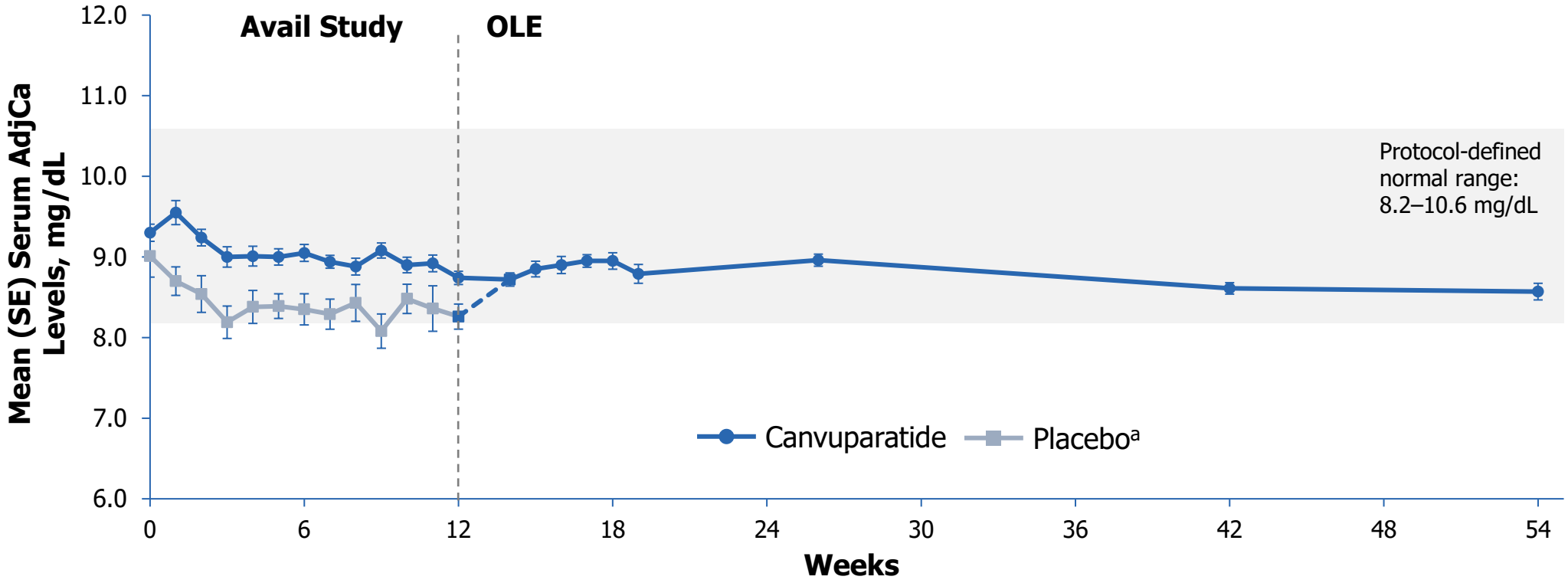
OLE, open-label extension; QW, once weekly.
[a]Patients randomized to canvuparatide in the parent study continued on the last dose they received in the parent study if they were able to be withdrawn from active vitamin D and calcium; if not, their dose was adjusted in accordance with the titration algorithm. [b] [c]Patients initially randomized to placebo initiated canvuparatide 400 µg QW in the OLE, with dose adjustments made to maintain serum calcium 8.2–10.6 mg/dL after the titration algorithm.

The Composite Endpoint and Each Component for Avail Was Also Maintained at 1 Year in the OLE Trial

Parameter, n (%)	Week 12 (Avail Study)	1 Year (OLE)
	Canvuparatide (n = 48)	Canvuparatide[a] (n = 54)
Proportion of patients meeting response criteria (responders), n (%)	30 (62.5)*	31 (57.4)
Proportion of patients meeting each component of response criteria, n (%)		
Independence from active vitamin D	47 (97.9)	46 (85.2)
Independence from oral calcium (≤ 600 mg/day)	36 (75.0)	39 (72.2)
Serum AdjCa within normal range (8.2–10.6 mg/dL)	39 (81.3)	41 (74.5)

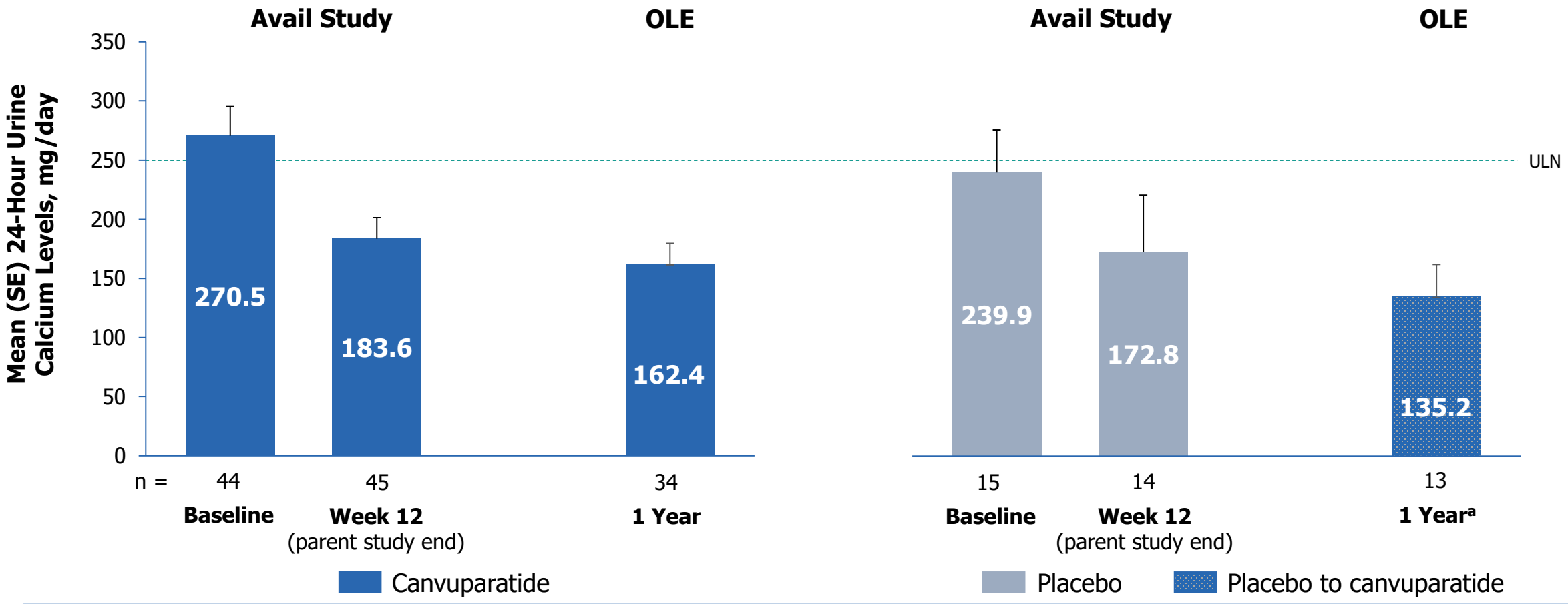
AdjCa, albumin-adjusted calcium; OLE, open-label extension.
*$P < .05$ vs placebo.
[a]The canvuparatide cohort at 1 year includes patients initially randomized to canvuparatide (n = 39) or placebo (n = 15) for 12 weeks in the parent study.

Mean Serum AdjCa Levels Remained in the Normal Range at All Visits With Canvuparatide Treatment



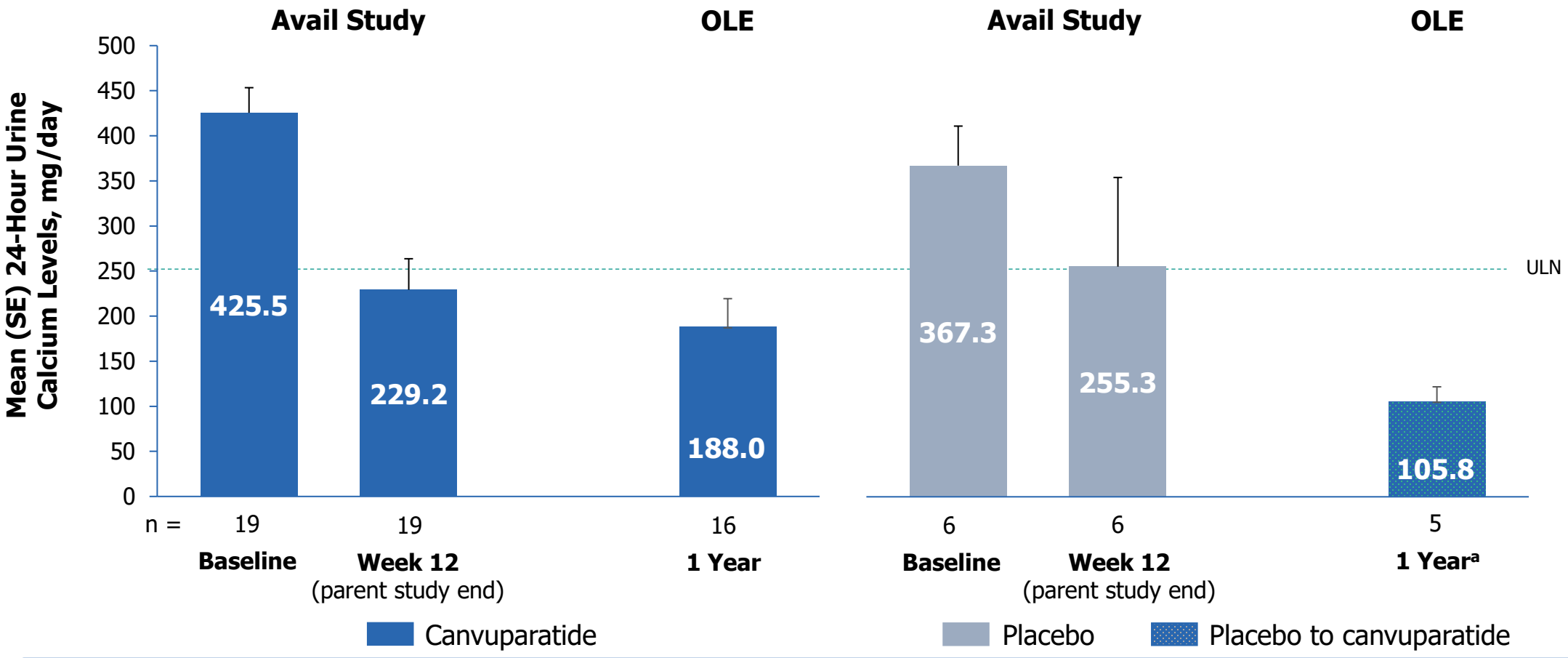
AdjCa, albumin-adjusted calcium; OLE, open-label extension.
[a]Starting after the baseline of the OLE (at week 12 overall), patients in the placebo group were switched to canvuparatide.

Urine Calcium Continued to Decrease Through 1 Year



OLE, open-label extension.
[a]Starting after the baseline of the OLE (at week 12 overall), patients in the placebo group were switched to canvuparatide.

Urine Calcium Continued to Decrease Through 1 Year in Patients With Elevated Urine Calcium



OLE, open-label extension.
[a]Starting after the baseline of the OLE (at week 12 overall), patients in the placebo group were switched to canvuparatide.

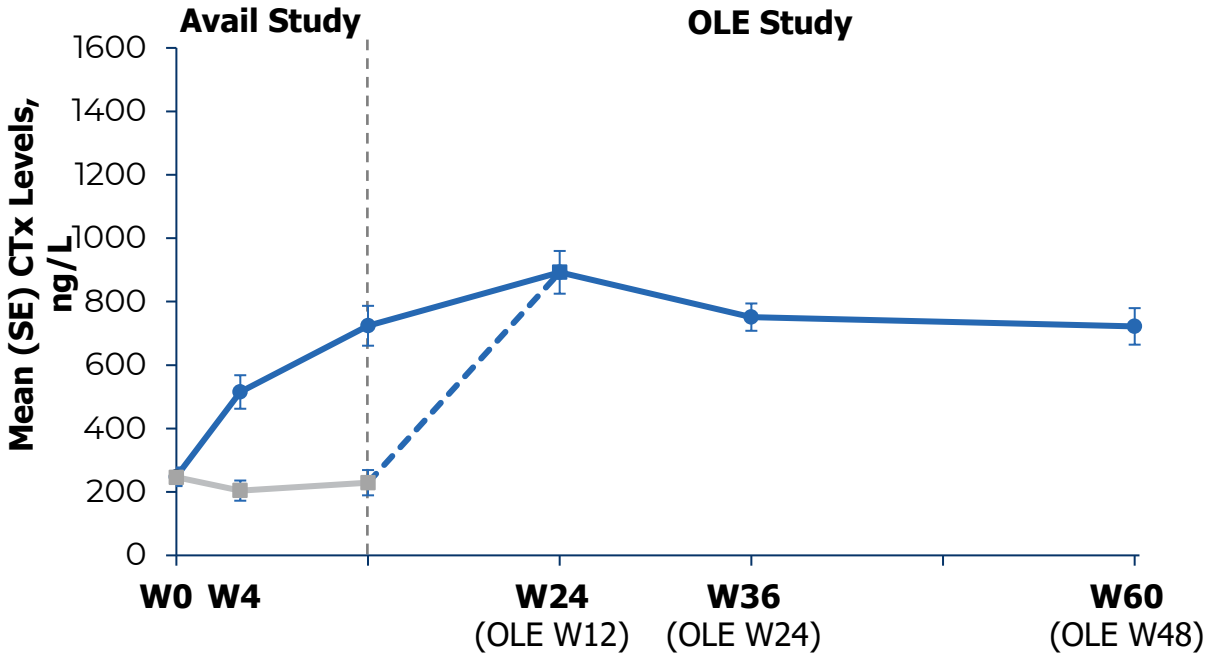
Once-Weekly Canvuparatide Demonstrated Expected Effects of PTH in the Kidney

Parameter, Mean (SE)	Change from Baseline at 1 Year (OLE)[a]
	Canvuparatide[b] (n = 54)
Phosphate, mg/dL	–0.4 (0.1)
Calcium-phosphorus product, mg^2/dL^2	–5.9 (0.8)[c]
1,25-Dihydroxyvitamin D3, ng/L	3.5 (3.6)
Estimated glomerular filtration rate, $mL/min/1.73m^2$	5.3 (2.1)

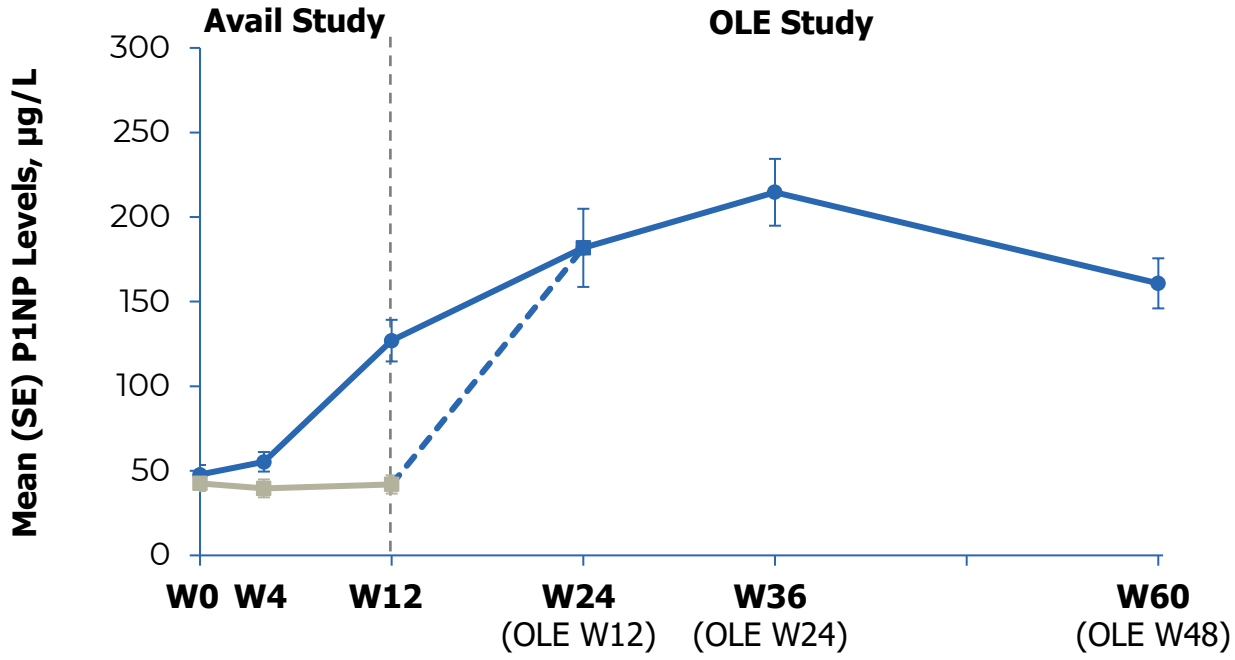
eGFR, estimated glomerular filtration rate; OLE, open-label extension; PTH, parathyroid hormone.
[a]1 year includes 12 weeks of the parent study and corresponds to week 48 of the OLE study.
[b]Starting after the baseline of the OLE (at week 12 overall), patients in the placebo group were switched to canvuparatide.
[c]n = 53.

Canvuparatide Restored Bone Metabolism

C-Telopeptide of Type I Collagen (CTx)



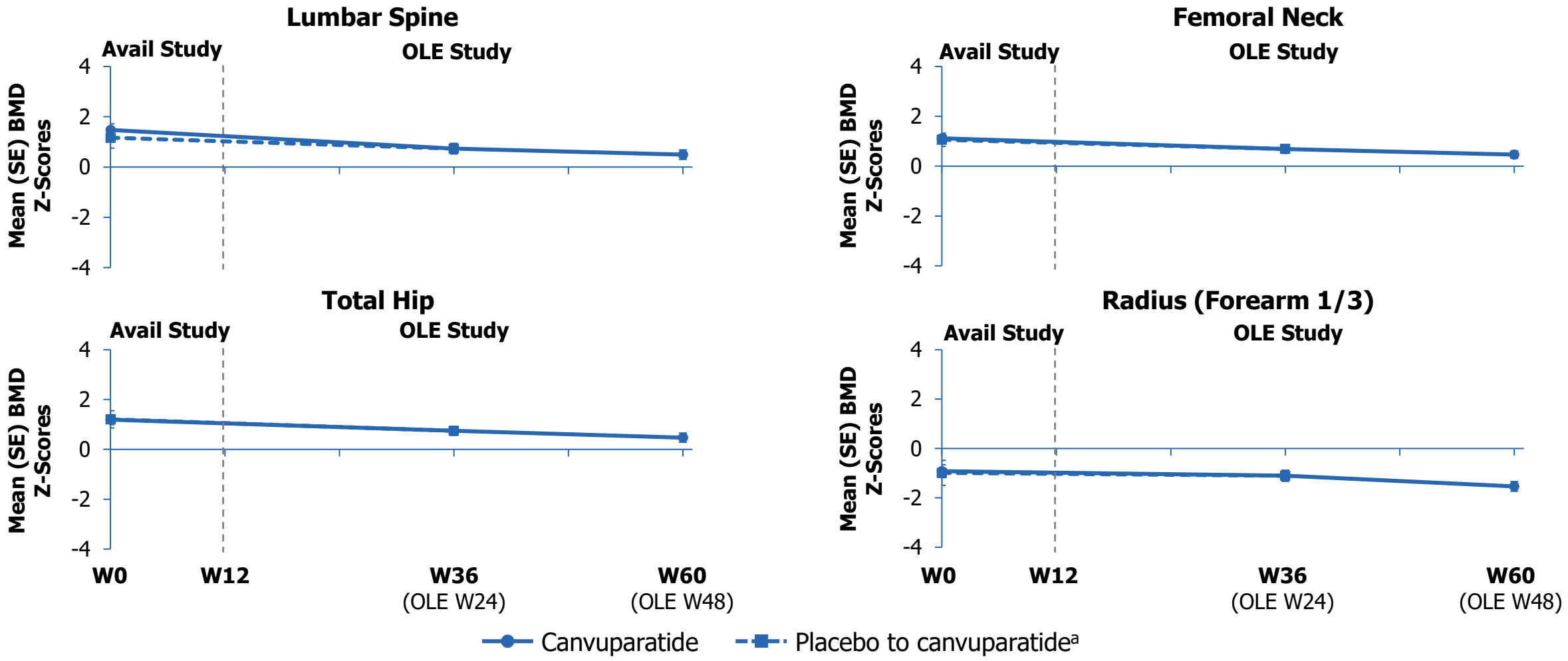
Procollagen Type 1 N-Terminal Propeptide (P1NP)



Canvuparatide Placebo Placebo to canvuparatide[a]

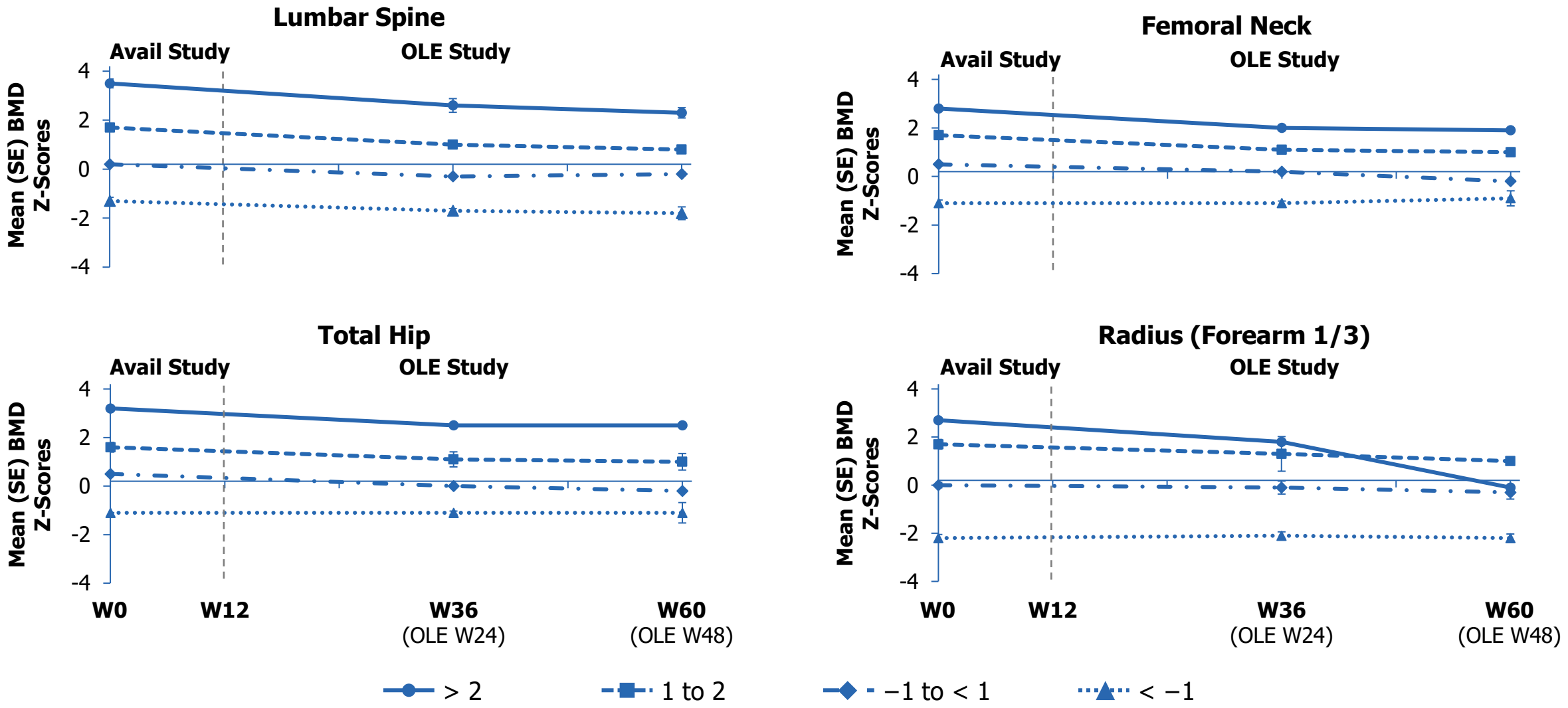
CTx, C-telopeptide of type I collagen; OLE, open-label extension; P1NP, procollagen type 1 N-terminal propeptide; W, week.
The reference ranges for CTx are 1008 ng/L (female high) and 854 ng/L (male high), and for P1NP are 14.3–97.0 µg/L (female) and 13.3–79.7 µg/L (male).
During the OLE (starting after week 12), patients in the placebo group received canvuparatide.

BMD Changes Correlated With the Bone Turnover Markers and Remained Within the Normal Range



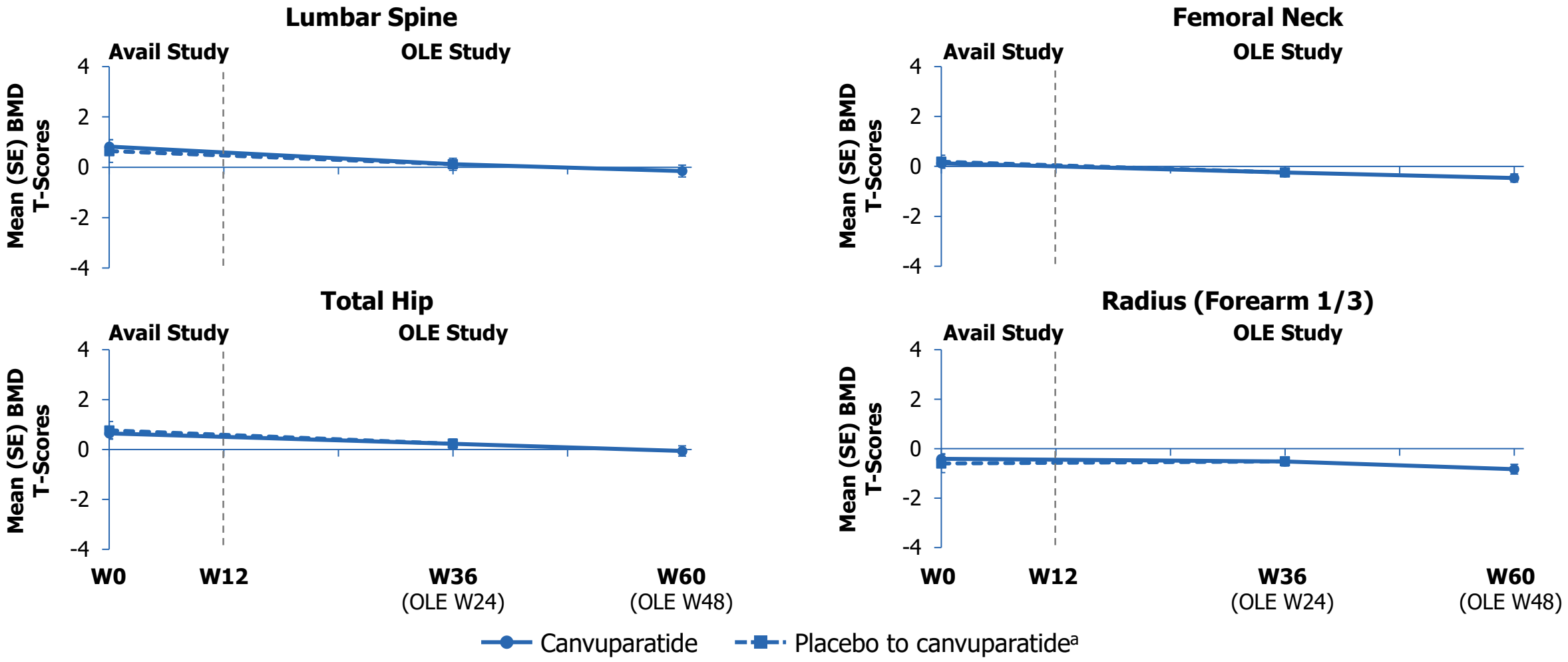
BMD, bone mineral density; OLE, open-label extension; W, week.
[a]Weeks 36 and 60 include 12 weeks of the parent study and corresponds to week 24 and 48, respectively, of the OLE study.

BMD Changes Were Driven by Patients With High BMD at Baseline



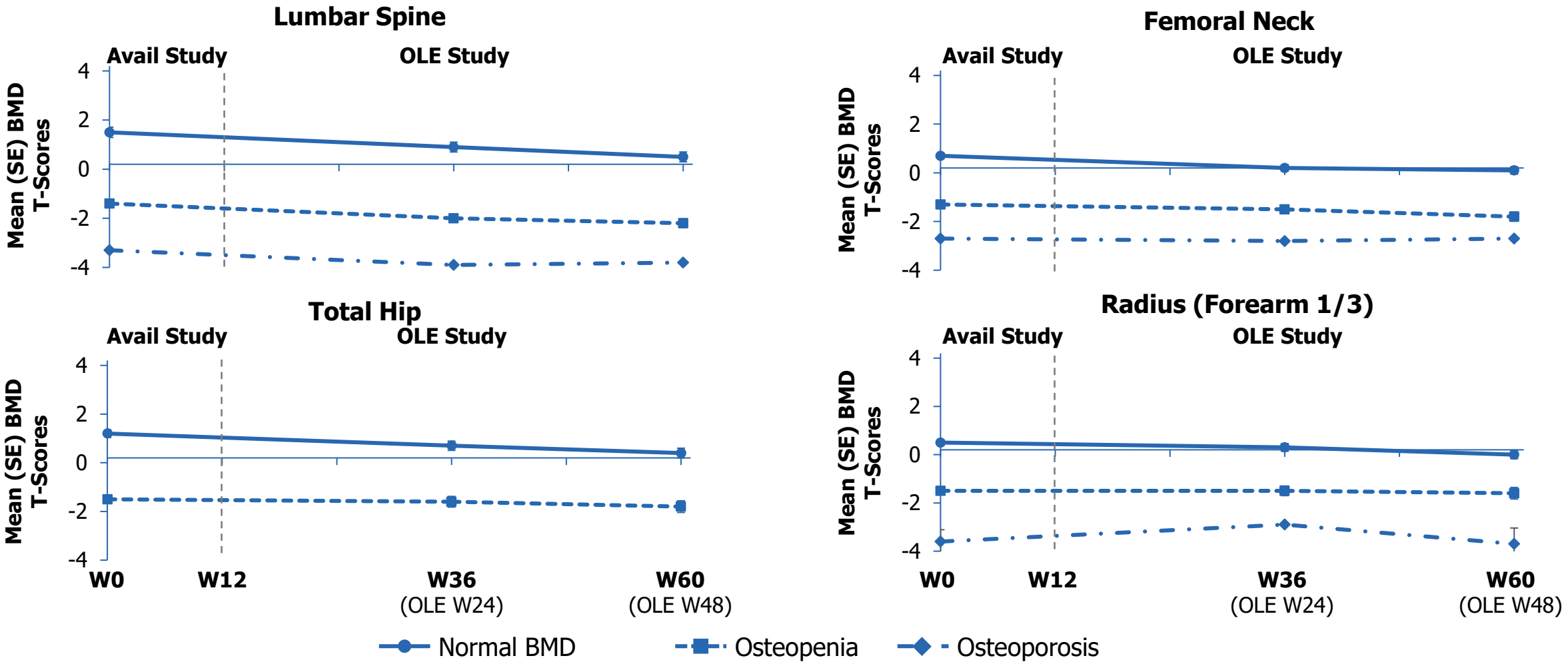
BMD, bone mineral density; OLE, open-label extension; W, week.

BMD Changes Correlated With the Bone Turnover Markers and Remained Within the Normal Range



BMD, bone mineral density; OLE, open-label extension; W, week.

A Slight BMD Reduction Was Driven by Patients With High BMD at Baseline Followed by Stabilization



BMD, bone mineral density; OLE, open-label extension; W, week.

Immunogenicity to Canvuparatide Was Minimal

Patients With Treatment-Induced ADAs, n (%)	Canvuparatide	
	ADA to Canvuparatide	ADA to Active Peptide
Week 12 (Avail parent trial)	0	0
Week 60 (OLE week 48)	1/59 (1.7)[a]	0

ADA, anti-drug antibodies; OLE, open-label extension.
[a]ADA occurred during 2 assessment time points and was detected at a low titer in a patient who was a treatment responder.

Treatment-Emergent Adverse Events and Adverse Events of Special Interest

TEAE,[a] n (%)	Canvuparatide (n = 60)
TEAE	48 (80.0)
Mild	22 (36.7)
Moderate	23 (38.3)
Severe	3 (5.0)
Treatment-related TEAE	23 (38.3)
SAE	5 (8.3)
Treatment-related SAEs	0
TEAE leading to study discontinuation	3 (5.0)
Deaths	0
AESI (>5% patients), n (%)	
Hypocalcemia[b]	12 (20.0)
Hypercalcemia[c]	7 (11.7)
All injection site reactions[d]	6 (10.0)

AESI, adverse events of special interest; SAE, serious treatment-emergent adverse events; TEAE, treatment-emergent adverse event.

[a]TEAEs included any adverse events that occurred during or after study drug dosing or began prior to receiving study drug but increased in severity after dosing.
[b]Symptomatic of greater intensity or duration than expected.
[c]Symptomatic or serum calcium level > 11.0 mg/dL.
[d]Injection site reaction preferred terms included injection site reaction (n = 3), injection site hematoma (n = 2), injection site erythema (n = 1), and injection site hemorrhage (n = 1).

Summary

- After 1 year of once-weekly canvuparatide treatment, patient retention remained high, reflecting the acceptability of long-term weekly injections
- The patients maintained long-term normal serum and urine calcium levels
- Bone turnover markers increased and plateaued consistent with restoration of bone metabolism with changes in BMD overall trending to age- and sex-matched normalization at the skeletal key sites evaluated
- Canvuparatide was generally well tolerated, with a safety profile characterized by predominantly mild to moderate TEAEs and few discontinuations
- Anti-drug antibody (ADA) incidence remained minimal
- Overall, these data support once-weekly canvuparatide as a PTH replacement therapy
- Based on these findings, once-weekly canvuparatide will be further evaluated in a Phase 3 randomized, placebo-controlled trial

BMD, bone mineral density; eGFR, estimated glomerular filtration rate; OLE, open-label extension; PTH, parathyroid hormone; TEAE, treatment-emergent adverse events.