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Extended-release calcifediol for secondary hyperparathyroidism in Chinese adults with stage 3 or 4 chronic kidney disease: a randomized trial

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Abstract

Background:

Vitamin D insufficiency (VDI) is a major driver of secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD). Extended-release calcifediol (ERC) is approved for SHPT in the United States, 11 European countries but not China. The present randomized controlled trial (RCT) evaluated ERC for Chinese adults with SHPT, stage 3–4 CKD and VDI.

Methods:

This RCT involved 100 adults with estimated glomerular filtration rate (eGFR) 15-<60 mL/min/1.73m², intact parathyroid hormone (iPTH) 85-<500 pg/mL and serum 25-hydroxyvitamin D (25D) 10-<30 ng/mL. Participants received daily ERC or placebo (randomized 2:1) for 26 weeks. Dosing started at 30 μg and increased, as needed, to 60 μg after 12 weeks. The primary efficacy endpoint was the proportion of participants attaining mean ≥ 30% decrease from baseline (BL) in iPTH during the last 6 weeks of treatment. A secondary efficacy endpoint was the proportion attaining mean 25D of ≥ 30 ng/mL. Safety endpoints included serum calcium and phosphorus, urine calcium:creatinine ratio and eGFR.

Results:

At BL, participants had mean age 52.6 years, body mass index 24.5 kg/m^2, 25D 17.4 ng/mL, eGFR 24.1 mL/min/1.73m^2; 84% had stage 4 CKD; 49% were female. More participants achieved the targeted ≥ 30% reduction in iPTH with ERC than with placebo (53.0% vs 6.3%; $p < 0.0001$) and the proportion achieving 25D of ≥ 30 ng/mL was higher with ERC (90.9% vs 9.4%; $p < 0.0001$). No clinically meaningful differences in safety parameters were observed between treatment groups.

Conclusion:

ERC was well tolerated and effective for treating SHPT in Chinese adults with stage 3–4 CKD and VDI.

Trial Registration:

Chinese Clinical Trial Registry ChiCTR2600126426; registration date: June 9, 2026. Retrospectively registered.

Introduction

Chronic kidney disease (CKD) is a growing global health concern that is projected to become the fifth-leading cause of premature death by 2050 [1]. Worldwide age-standardized prevalence has increased from 13.7% in 1990 to 14.2% in 2023, affecting approximately 800 million adults. China has an estimated 152 million adults with CKD, with an age-standardized prevalence of 12.3%, a proportion that has increased by 7.6% since 1990 [2, 3]. Hypertension, type 2 diabetes mellitus and glomerulonephritis are

major drivers of CKD mortality along with high body mass index (BMI), aging and secondary hyperparathyroidism (SHPT) [2, 4].

SHPT is a common complication of CKD which is associated with bone disease, vascular calcification, and increased cardiovascular risk. It is characterized by elevated parathyroid hormone (PTH) secretion and hyperplasia, and driven by phosphate retention, increased serum fibroblast growth factor 23 (FGF23), hypocalcemia, and impaired renal conversion of 25-hydroxyvitamin D (25D) to the active hormone 1,25-dihydroxyvitamin D (1,25D). Reduced 1,25D production occurs early in CKD and results in lower vitamin D receptor (VDR) activation in the parathyroids with consequent increases in PTH secretion. Concomitant vitamin D insufficiency (VDI) exacerbates SHPT by limiting substrate availability for 1,25D production [5] and is a modifiable component of SHPT pathophysiology [6, 7]. Various therapies are available for the treatment of VDI and SHPT in CKD patients but they differ substantially in pharmacological characteristics and clinical effects [8].

The prevalence of SHPT in Chinese patients with CKD is among the highest in the world, estimated to be 85% [4, 9]. High prevalence may be due to pervasive VDI, which remains poorly documented for the Chinese CKD population. A cross-sectional study conducted from 2013 to 2015 in Northern China reported serum 25D levels at or below 15 ng/mL in 79.7% of 207 adults with stage 1–5 CKD not receiving vitamin D supplementation [10]. Similarly, fewer than 10% of 2,706 adult outpatients in nephrology clinics in southeast China between 2019 and 2024 had serum 25D concentrations above 30 ng/mL while 63% had levels below 20 ng/mL [11]. Only 2 of 94 adult renal transplant recipients participating in a study in southern China [12] had 25D concentrations above 30 ng/mL while 44% had levels below 20 ng/mL. A control group comprised of 94 age- and gender-matched healthy volunteers had similar mean 25D concentrations indicating that vitamin D status following transplantation was consistent with that of the surrounding population. A meta-analysis of 43 studies conducted throughout mainland China involving 87,742 adults from the general population concluded that 63% had levels below 20 ng/mL [13]. Taken together, these data suggest that the high prevalence of SHPT in China is driven in part by low serum 25D concentrations.

Current clinical practice guidelines applicable to CKD patients in China [7, 14] suggest monitoring for VDI but rely on sufficiency thresholds of 20 or 30 ng/mL derived for the general population [15–17]. Data from randomized controlled trials (RCTs) conducted with extended-release calcifediol (ERC or Rayaldee®; NCT1651000; NCT0104079) in the United States (US) have demonstrated that clinically meaningful (≥ 30%) reductions in elevated PTH require substantially higher serum 25D concentrations in adults with stage 3 or 4 CKD [18–20] which are difficult to achieve with dietary vitamin D supplements (cholecalciferol or ergocalciferol) [21–23]. Whether higher 25D concentrations are required for similar suppression of elevated PTH in Chinese patients is unknown. This evidence gap is clinically relevant and warrants the present RCT which was conducted to evaluate the safety and efficacy of oral ERC in Chinese adults with SHPT, stage 3 or 4 CKD and VDI.

Materials and Methods

Study Design

This multi-center, randomized, double-blind, placebo-controlled, parallel group trial (Chinese Clinical Trial Registry ChiCTR2600126426; registration date June 9, 2026 [24]) was approved by the National Medical Products Administration (China; 2023LP00885) and conducted from August 28, 2023 to January 21, 2025 in compliance with the principles of the International Council for Harmonisation (ICH) good clinical practice, the Declaration of Helsinki, CONSORT guidelines and applicable regulatory requirements. All participants provided written informed consent prior to trial participation.

Participants

Non-dialysis CKD patients were screened at 38 clinical sites across mainland China. Eligible participants were adults (ages ≥ 18 years) with baseline (BL) estimated glomerular filtration rate (eGFR) of 15–60 mL/min/1.73m² (calculated with the CKD-EPI formula [25]), plasma intact parathyroid hormone (iPTH) of 85-<500 pg/mL, corrected serum calcium (Ca) of 8.4-<9.8 mg/dL, serum phosphorus (P) of 2.0-<5.0 mg/dL, serum total 25D of 10-<30 ng/mL, and stable renal function without anticipated dialysis or transplantation for 6 months post-enrollment. Exclusion criteria included spot urine Ca to creatinine (Cr) ratio of > 0.2 (200 mg/g), macroalbuminura (> 3 mg/mg creatinine), bisphosphonate therapy within 6 months of enrollment, and history of parathyroidectomy or renal transplantation.

Limitations on Concomitant Medications

Participants taking > 1,000 mg/day of elemental Ca reduced intake to ≤ 1,000 for the duration of the study and underwent a 2-week pre-treatment washout. Participants receiving ergocalciferol or cholecalciferol supplementation at doses > 1,600 IU/day underwent an 8-week washout, after which lower stable doses of ≤ 1,600 were maintained. Bone metabolism therapies potentially interfering with study endpoints (e.g., bisphosphonates) were discontinued for at least 4 weeks prior to treatment.

Screening and Randomization

Screening included up to three visits which allowed for protocol-defined washout of prohibited medications and dietary supplement intake above protocol limits. Eligible participants were randomized 2:1 by an interactive web response system (IWRS) to receive a daily bedtime dose of oral ERC (30 μg) or matching placebo for 12 weeks, followed by 14 weeks of either 30 or 60 μg/day of ERC (or placebo) according to titration rules intended to produce a ≥ 30% reduction in iPTH while minimizing safety concerns. At the end of the 26-week treatment period, participants completed a safety follow-up within 7 ± 3 days. Clinic visits during treatment were scheduled at biweekly or monthly intervals. The original protocol specified balanced stratification of eligible participants by CKD stage but this requirement was subsequently removed in a protocol amendment to facilitate enrollment. The amendment also required early termination of any participant who initiated regular dialysis due to CKD progression.

Study Blind

Study drugs had identical appearance and packaging. Participants and study personnel were blinded to the treatment assignments until database lock or until the blind was broken for a specific participant. All study personnel were also blinded to serum total 25D and plasma iPTH concentrations obtained during treatment. The randomization code was generated by an independent third-party using SAS software (version 9.4; SAS Institute Inc., Cary, NC, US) and uploaded into the IWRS. An independent medical monitor managed the IWRS and oversaw all drug allocation and dispensing procedures.

Laboratory Procedures

Biological specimens collected at each study visit underwent standardized processing and analysis at Teddy Clinical Research Laboratory (Shanghai). Serum Ca was corrected for low albumin (alb). Plasma iPTH and serum total 25D were quantified via electrochemiluminescence immunoassay (Roche Cobas e601 system), and total 1,25D was determined using liquid chromatography-tandem mass spectrometry (SCIEX 6500).

Data Analysis

Calculated sample size was 96 participants for 80% power with two-sided test ($\alpha = 0.05$), using a 2:1 allocation ratio between ERC and placebo treatment groups to detect a ≥ 25% difference in the percentages of participants achieving the primary efficacy endpoint, assuming a less than 20% drop-out rate.

All analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, US) according to a prespecified statistical analysis plan intended to demonstrate superior efficacy of ERC treatment compared to placebo. To reduce biological and assay variability, pre-treatment BL values were derived from averages across multiple visits (after washout, if needed) and endpoint values were defined as the mean of measurements obtained at 2-week intervals during the efficacy assessment period (EAP) defined as Weeks 20–26. The primary efficacy endpoint was the proportion of participants in the modified intent-to-treat (mITT) population achieving a mean ≥ 30% reduction from BL in plasma iPTH during the EAP, an accepted regulatory benchmark for therapeutic efficacy [18, 26, 27]. Participants with less than two iPTH measurements during the EAP were classified as non-responders since iPTH measurements have significant intra-participant variability. The mITT population, which included all participants who received at least one dose of study drug, was deemed more useful for analyzing the efficacy and safety of ERC.

Secondary efficacy endpoints included the proportions of participants in the mITT and per-protocol (PP) populations achieving during the EAP a mean ≥ 30% reduction from BL in plasma iPTH and a serum 25D level of ≥ 30 ng/mL, an operational definition for vitamin D sufficiency supported by the then-current clinical practice guideline [17]. The PP population was comprised of participants who had at least two iPTH measurements during the EAP and no major protocol deviations.

Safety endpoints included laboratory parameters (clinical chemistry, hematology, urine chemistry and urinalysis), physical examinations, vital signs, 12-lead electrocardiograms, eGFR, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and confirmed episodes of hypercalciuria (urinary Ca:Cr ratio > 0.2), hypercalcemia (serum Ca > 10.3 mg/dL) and hyperphosphatemia (serum P > 5.5 mg/dL with investigator-attributed drug relationship).

Time courses of key efficacy and safety parameters were evaluated during the course of the study. Comparisons between proportions of participants in the two treatment groups were accomplished with chi-square tests, while other comparisons were made with *t*-tests, all of which used a two-sided $\alpha = 0.05$ significance threshold. Missing values were not imputed. Differences between the following subgroups were estimated with Fisher's exact probability or Wald methods: CKD stage (3 versus 4), gender, age (< 65 versus ≥ 65 years) and BMI (< 24 versus ≥ 24 kg/m^2). Results for this study have not been previously published.

Results

Subject Disposition

A CONSORT diagram showing participant disposition is presented in Fig. 1. Non-dialysis patients (N = 306) were screened at 38 clinical sites in China and 100 eligible participants were randomized. Two participants (one in each treatment group) did not receive study drug.Eight participants (3 inthe ERC group, 5 in the placebo group) withdrew from treatment before reaching the EAP or did not have at least two iPTH measurements during the EAP. Two patients in the ERC group took prohibited drugs, leading to major protocol deviations. Ultimately, the PP population consisted of 61 participants in the ERC group and 27 in the placebo group. Most participants completed the study; reasons for early termination were comparable for groups, most commonly withdrawal of consent or discontinuation of treatment (ERC: 7.5%; placebo: 6.1%) and adverse events (ERC: 1.5%; placebo: 3.0%).

Study Population

Demographic and BL characteristics of the other 98 participants (mITT population) are summarized in Table 1 in aggregate and by treatment group (ERC, n = 66; placebo, n = 32). The two groups were balanced for gender and nationality, and had comparable CKD etiologies. Glomerulonephritis was the most common cause of CKD, observed in 44.9% of participants. No between-group differences were detected in age, height, weight, BMI, or key laboratory parameters. At BL, mean (SD) eGFR in all participants was 24.1 (8.03) mL/min/1.73 m^2, 16% had stage 3 CKD and 84% stage 4 CKD.

Table 1
Demographic and Baseline Characteristics (mITT Population)

Parameter	ERC (N = 66) n (%)/mean (SD)	Placebo (N = 32) n (%)/mean (SD)	All Participants (N = 98) n (%)/mean (SD)
Sex, n (%)			
Male	33 (50.0)	17 (53.1)	50 (51.0)
Female	33 (50.0)	15 (46.9)	48 (49.0)
Nationality, n (%)			
Han nationality	62 (93.9)	30 (93.8)	92 (93.9)
Other	4 (6.1)	2 (6.3)	6 (6.1)
Major causes of CKD, n (%)			
Diabetic kidney disease	7 (10.6)	3 (9.4)	10 (10.2)
Hypertensive nephropathy	9 (13.6)	7 (21.9)	16 (16.3)
Obstructive nephropathy	1 (1.5)	0	1 (1.0)
Glomerulonephritis	33 (50.0)	11 (34.4)	44 (44.9)
Polycystic kidney	2 (3.0)	1 (3.1)	3 (3.1)
Other	14 (21.2)	10 (31.3)	24 (24.5)
Characteristics, mean (SD)			
Age, years	53.6 (11.87)	50.7 (14.80)	52.6 (12.90)
Height, cm	162.9 (7.77)	164.6 (9.08)	163.4 (8.22)
Weight, kg	65.2 (12.64)	66.2 (13.88)	65.5 (13.00)
BMI, kg/m^2	24.5 (3.96)	24.5 (4.71)	24.5 (4.20)
Calcium, mg/dL	9.1 (0.29)	9.1 (0.23)	9.1 (0.27)
Phosphorus, mg/dL	3.8 (0.47)	4.0 (0.49)	3.9 (0.48)
iPTH, pg/mL	156.5 (66.69)	158.1 (76.42)	157.0 (69.62)
25-Hydroxyvitamin D, ng/mL	17.4 (4.80)	17.3 (5.08)	17.4 (4.87)
eGFR, ml/min/1.73 m^2	23.4 (7.64)	25.5 (8.74)	24.1 (8.03)

Vitamin D Metabolites

Mean (SD) serum total 25D increased gradually with ERC treatment from 17.4 (4.8) ng/mL at BL to a steady-state level of 93.9 (26.5) ng/mL during the EAP ($p < 0.001$), but was unchanged with placebo (Fig. 2). Differences between treatment groups became significant after 4 weeks of treatment and remained significant thereafter ($p < 0.001$). Nearly all participants treated with ERC attained serum 25D levels of at least 30 ng/mL in the mITT (90.9%) and PP (95.1%) populations versus 9.4% and 11.1%, respectively, of those receiving placebo ($p < 0.0001$). The efficacy of ERC to raise serum 25D was unaffected by CKD stage, gender, age or BMI. Mean serum total 1,25D increased with ERC treatment from 41.1 (17.7) pg/mL at BL to 67.4 (24.9) pg/mL during the EAP, whereas it decreased from 50.8 (28.9) to 38.8 (15.7) pg/mL with placebo.

Plasma iPTH

The primary efficacy endpoint was met as the proportions of participants who achieved at least a 30% reduction in plasma iPTH during the EAP were greater with ERC than with placebo in both the mITT and PP populations (mITT: 53.0% vs. 6.3%; PP: 55.7% vs. 7.4%; $p < 0.0001$). Mean (SD) plasma iPTH levels declined progressively with ERC treatment from 156.5 (66.7) pg/mL at BL to 118.9 (68.6) during the EAP, but increased from 158.1 (76.4) to 206.1 (146.6) with placebo treatment (Fig. 3). The efficacy of ERC to reduce iPTH was unaffected by CKD stage or other patient characteristics (Fig. 4).

Safety Parameters

Participants treated with ERC experienced a mean increase in the EAP from pre-treatment BL in serum Ca of 0.10 (0.25) mg/dL compared with a decrease of 0.16 (0.23) with placebo ($p < 0.005$; Fig. 5). The increase with ERC treatment primarily reflected upward correction of values that were in the low normal range at BL. Two participants (3%) in the ERC group, compared with none in the placebo group experienced confirmed hypercalcemia, one of whom had also exhibited hypercalcemia during screening. Both hypercalcemic episodes (one each in participants with stage 3 or 4 CKD) were deemed related to treatment.

No differences in mean serum P were observed between the treatment groups at any time (Fig. 5). One participant in the ERC group experienced confirmed hyperphosphatemia considered to be treatment related. Mean urine Ca:Cr ratios at BL were 24.5 (18.7) mg/g in the ERC group and 22.1 (15.5) in the placebo group and remained stable during the 26-week treatment period. Mean eGFR level trended downward ($p > 0.05$) similarly from BL in both groups, -3.59 (4.6) mL/min/1.73m^2 with ERC and − 2.25 (5.2) with placebo. No clinically significant differences between treatment groups were noted for other laboratory parameters, vital signs, or ECGs.

Adverse Events

The majority of participants experienced at least one TEAE (ERC: 77.3%; placebo: 81.3%) considered typical for the CKD population. The proportions of participants with treatment-related and serious TEAEs were comparable between groups and trended higher among those with stage 4 CKD. Most TEAEs were

mild to moderate (ERC: 84.8%; placebo: 65.6%) and considered unrelated to treatment (ERC: 81.8%; placebo: 84.4%).

SAEs were observed in 15.2% of participants in the ERC group, none of which were considered treatment-related, and 18.8% of those in the placebo group, one of which was considered treatment-related. TEAEs leading to dose interruption occurred in 6.1% and 9.4% of participants in the ERC and placebo groups, respectively. One death, not considered treatment-related, occurred in the ERC group.

Discussion

This 26-week multi-center, randomized, double-blind, placebo-controlled, parallel group trial demonstrated that ERC was well tolerated and effective for treating SHPT in Chinese patients with stage 3 or 4 CKD and VDI. The proportions of participants achieving a ≥ 30% reduction in plasma iPTH from BL (primary efficacy endpoint) and serum 25D concentrations ≥ 30 ng/mL (secondary efficacy endpoint) were greater with ERC treatment compared to placebo ($p < 0.0001$). Higher 25D concentrations achieved during ERC treatment were associated with greater iPTH-lowering responses consistent with the known continuous inverse relationship between serum 25D exposure (from ERC) and iPTH in non-dialysis CKD [19, 20]. Monitored safety parameters showed no clinically significant changes attributable to elevation of serum 25D with ERC treatment. Data from the current RCT are consistent with those previously reported from two phase 3 studies conducted with ERC in the US according to nearly identical protocols [18].

The current and prior US RCTs with ERC indicate that effective treatment of SHPT in CKD patients requires higher serum 25D exposures than recommended for the general population [15–17]. The higher 25D (substrate) requirement enables sufficient substrate-driven extra-renal 1,25D production that compensates for the progressive loss of renal cytochrome P450 25D-1α-hydroxylase (CYP27B1) with advancing CKD [5, 16]. CYP27B1 is broadly expressed beyond the kidneys, including in the parathyroid glands [5]. When renal CYP27B1 declines in advancing CKD, its extrarenal counterparts can be engaged therapeutically with ERC to become major alternative sources of 1,25D, thereby restoring normal vitamin D metabolism.

Extrarenal CYP27B1 receives 25D substrate largely by passive diffusion which requires a high concentration gradient across cell membranes [5]. Intracrine production of 1,25D increases with rising serum 25D concentrations and is not limited by feedback mechanisms regulating renal CYP27B1 [5, 16]. Data from the US RCTs with ERC in patients with stage 3 or 4 CKD suggest that raising serum 25D to ≥ 50 ng/ml is required to engage extrarenal CYP27B1, as the frequency of 30% reductions in elevated PTH became progressively higher as 25D rose above that level [19]. PTH-lowering response rates were agnostic to CKD stage indicating that comparable delivery of 1,25D to intracellular VDR in the parathyroids was achieved despite large differences in kidney function [19]. Elevation of serum 25D to an average of 84 ng/mL is associated with a mean reduction in elevated iPTH of ≥ 30% in non-dialysis CKD

patients, a degree of suppression associated with slower decline in kidney function [28, Poster #WCN26-AB-6077 presented at 2026 World Congress of Nephrology].

Effective management of SHPT in CKD has been constrained by the long-standing assumption that kidneys are the only meaningful source of 1,25D production [5] and by concerns regarding the potential toxicity of higher circulating 25D concentrations [15]. However, clinically meaningful increases in serum Ca, P or urine Ca:Cr ratio were not observed in the present or prior US studies with ERC despite elevations in serum 25D across the range of approximately 30–120 ng/mL [18–20].

Limitations of the current study include small sample size, short treatment duration and absence of monitoring for potential changes in serum FGF23. Larger clinical trials of longer duration will be needed to expand and refine the conclusions derived herein and to clarify the impact of iPTH reduction on clinical outcomes.

Data from this trial support the conclusion that oral ERC is well tolerated and effective for treating SHPT in Chinese adults with stage 3 or 4 CKD and VDI. The observed treatment responses were consistent with those observed previously in RCTs conducted with ERC in the US.

Declarations

Conflict of interest statement:

HT and HLi are employees of Nicoya Shanghai, LTD. JC, AA and CWB are employees of OPKO Health, Inc. There are no other conflicts of interest to disclose.

Ethics Approval and Consent to Participate:

The study (Chinese Clinical Trial Registry ChiCTR2600126426; registration date June 9, 2026) was approved by the National Medical Products Administration (China; 2023LP00885) conducted in compliance with the principles of the Declaration of Helinski and CONSORT guidelines. All participants provided advance written informed consent for their participation.

Competing Interests

HT and HLi are employees of Nicoya Shanghai, LTD. JC, AA and CWB are employees of OPKO Health, Inc. There are no other conflicts of interest to disclose.

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Author Contribution

HL, HLi and CWB contributed to the study design. JC, AA, CWB, HLi conducted the data analysis and prepared the table and figures, MF drafted the initial version of the manuscript. All authors critically reviewed, edited and approved the final version.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to applicable privacy restrictions.

References

1. World Health Organization. Reducing the burden of noncommunicable diseases through promotion of kidney health and strengthening prevention and control of kidney disease. May 27, 2025. https://apps.who.int/gb/ebwha/pdf_files/WHA78/A78_R6-en.pdf.
2. MarK PB, Stafford LK, Grams ME, et al. Global Burden of Disease. Global, regional, and national burden of chronic kidney disease in adults, 1990-2023, and its attributable risk factors: a systematic analysis for the Global Burden of Disease Study 2023. Lancet. 2025; doi:10.1016/S0140-6736(25)01853-7.
3. He G, Liu J, Lin Y, et al. Chronic kidney disease burden from 1990 to 2023 in China: national and provincial insights from the Global Burden of Disease study 2023. Lancet Regional Health – Western Pacific, 2025; doi:10.1016/j.lanwpc.2025.101776.
4. Wang Y, Liu J, Fang Y, et al. Estimating the global prevalence of secondary hyperparathyroidism in patients with chronic kidney disease. Front Endocrinol. 15:1400891. doi: 10.3389/fendo.2024.1400891.
5. Bishop CW, Ashfaq A, Choe J, et al. Managing dysregulated vitamin D metabolism in CKD: Time to update conventional wisdom? Kidney360. 2025;6: doi:10.34067/KID.0000000982.
6. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease: mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2009 Aug;(113):S1-130.
7. Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease: mineral and bone disorder. Kidney Int Suppl. 2017;7(1):1–59. doi:10.1016/j.kisu.2017.04.001.
8. Magagnoli L, Cassia M, Galassi A, et al. Vitamin D: are all compounds equal? Clin Kidney J. 2025;18 (Suppl 1):i61-i96.
9. Wei Y, Lin J, Yang F, et al. Risk factors associated with secondary hyperparathyroidism in patients with chronic kidney disease. Exp Ther Med. 2016:12:1206-1212. doi: 10.3892/etm.2016.3438.

10. Li M, Li Y. Prevalence and influencing factors of vitamin D deficiency in chronic kidney disease: A cross-sectional study. Int J Clin Pharmacol Ther. 2020. doi: 10.5414/CP203737.
11. Chen Y, Yu S, Ying W, et al. Investigation and analysis of vitamin D status in a coastal city population of southeast China. Hum Nutr Metab. 2026; doi.org/10.1016/j.hnm.2025.200352.
12. Ma, MKM, Mok, MMY, Yung S, et al. High prevalence of vitamin D insufficienty in southern China renal transplant recipients. Renal Fail, 2012; 34(8): 980-984.
13. Liu W, Hu J, Fang Y, et al. Vitamin D in mainland China: A systematic review and meta-analysis. E Clin Med. doi.org/10.1016/j.eclinm.2021.101017.
14. Liu Z-H, Li G, Zhang L, et al. Executive summaty: Clinical practice guideline of chronic kidney disease-mineral and bone disorder (CKD-MBD) in China. Kidney Dis 2019;5:197-203.
15. Ross AC, Manson JE, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011 Jan; 96(1): 53–58.
16. Jorgensen HS, Vervloet M, Cavalier E, et al. The role of nutritional vitamin D in CKD-MBD in children and adults with CKD, on dialysis and after kidney transplantation-a European consensus statement. Nephrol Dial Transplant. 2025; 40(4):797-822.
17. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.
18. Sprague SM, Crawford PW, Melnick JZ, Strugnell SA, Ali S,Mangoo-Karim R, et al. Use of extended-release calcifediol to treat secondary hyperparathyroidism in stages 3 and 4 chronic kidney disease. AmJ Nephrol. 2016;44:316-325.
19. Strugnell SA, Sprague SM, Ashfaq A et al. Rationale for raising current clinical practice guideline target for serum 25-hydroxyvitamin D in chronic kidney disease. Am J Nephrol. 2019;49(4):284-293.
20. Choe J, Ashfaq A, Bishop CW. Exposure-response analysis of extended-release calcifediol identifies a clinically-relevant serum 25-hydroxyvitamin D range in chronic kidney disease. Clin Kidney J. 2026; (submitted).
21. Bover J, Gunnarsson J, Csomor P, et al. Impact of nutritional vitamin D supplementation on parathyroid hormone and 25-hydroxyvitamin D levels in non-dialysis chronic kidney disease: a meta-analysis. Clin Kidney J. 2021;14(10):2177-86. https://doi.org/10.1093/ckf/sfab035.
22. Ekwaru JP, Zwicker JD, Holick MF, et al. The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxyvitamin D in healthy volunteers. PLoS ONE. 2014;9:e111265 https://doi.org/10.1371/journal.pone.0111265.
23. Bishop CW, Strugnell SA, Csomor P, et al. Extended-release calcifediol effectively raises serum total 25-hydroxyvitamin D even in overweight nondialysis chronic kidney patients with secondary hyperparathyroidism. Am J Nephrol. 2022;53:446-454 https:doi.org/10.1159/000524289.
24. Chinese Clinical Trial Registry ChiCTR2600126426: https://link.edgepilot.com/x/WQEkVNmFxD75ho49NwrgZDo?u=https://www.chictr.org.cn/

25. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Eng J Med. 2021;385:1737-1749. doi: 10.1056/NEJMoa2102953.
26. Block GA, Martin KJ, De Francisco ALM, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med. 2004:350:1516-1525.
27. Thadhani R, Applebaum E, Pritchett Y, et al. Vitamin D theraphy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. JAMA. 2012;307:674. https://doi.org/10.1001/jama.2012.120.
28. Bishop CW, Ashfaq A, Strugnell SA, et al. Sustained reduction of elevated intact parathyroid hormone concentrations with extended-release calcifediol slows kidney disease progression in secondary hyperparathyroidism patients. Am J Nephrol. 2024; 1-10. https://doi.org/10.1159/000541138.

Figures

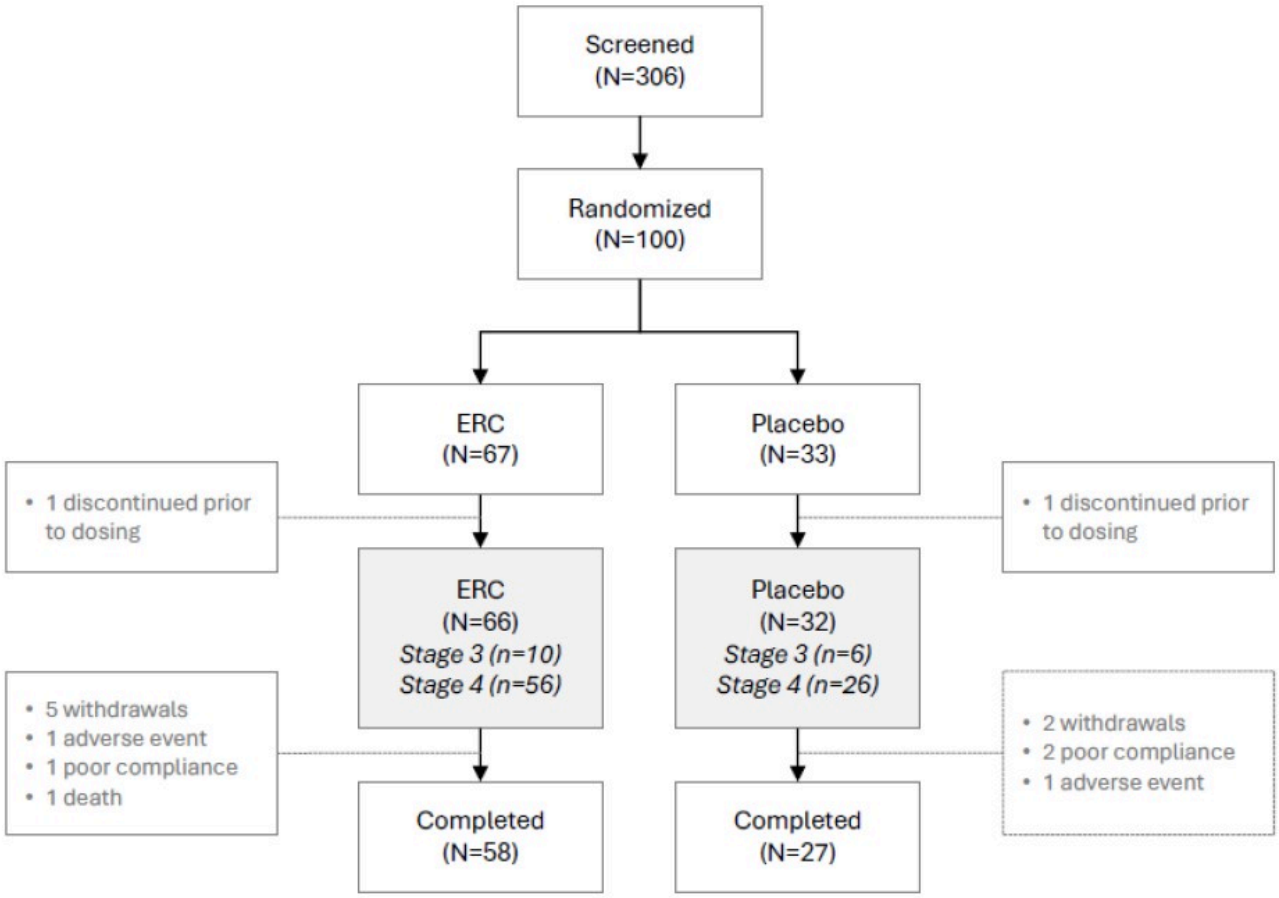


Figure 1

Consort Diagram

Consort diagram summarizing the disposition of study participants.

Alt text: A diagram summarizing the number of study participants who were screened (N=306), randomized (N=100) to treatment with extended-release calcifediol (ERC: N=67) or placebo (N=33), terminated from treatment prematurely (ERC: N=9; placebo: N=6), and completed the study (ERC: N=58; placebo: N=27).

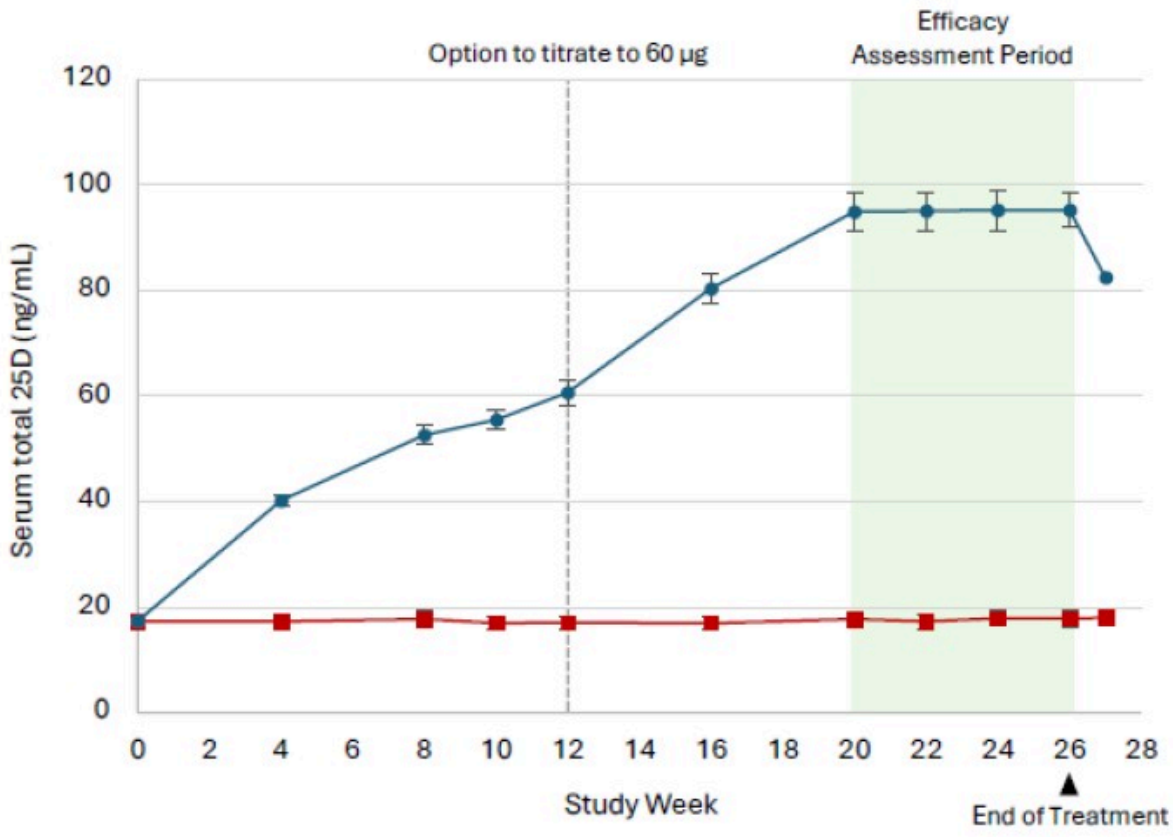


Figure 2

Time Courses of Mean Serum Total 25-hydroxyvitamin D

Time courses of mean (±SE) serum total 25-hydroxyvitamin D (25D) during 26 weeks of treatment with extended-release calcifediol (blue circles) or matching placebo (red squares) and the subsequent 1 week

of post-dosing observation in the modified intent-to-treat population.

Alt text: A graph showing elevation of mean (±SE) serum 25-hydroxyvitamin D (25D) concentrations during 26-weeks of treatment with extended-release calcifediol compared to stable 25D concentrations during placebo treatment in the modified intent-to-treat population.

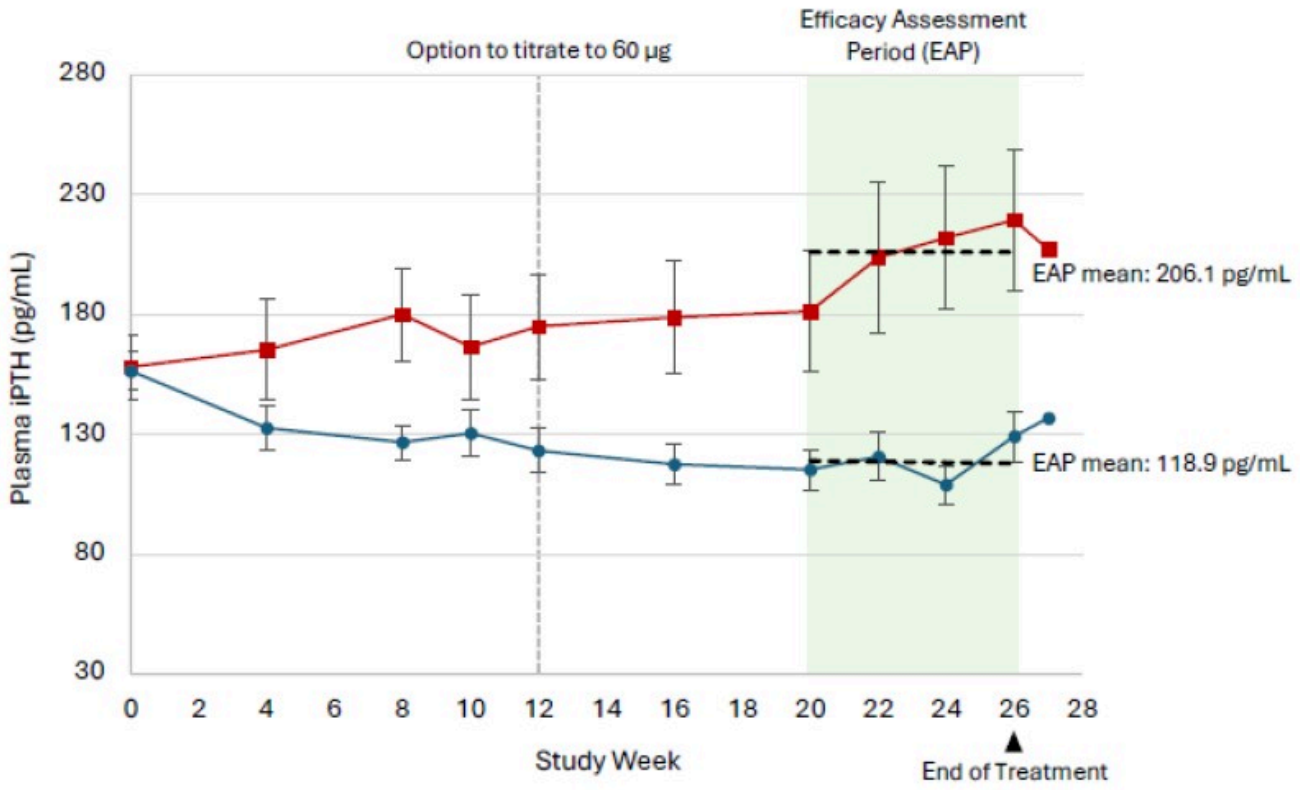


Figure 3

Time Courses of Mean Plasma iPTH

Time courses of mean (±SE) plasma intact parathyroid hormone (iPTH) during 26 weeks of treatment with extended-release calcifediol (blue circles) or matching placebo (red squares) and the subsequent 1 week of post-dosing observation in the modified intent-to-treat population.

Alt text: A graph showing significant reduction of mean (±SE) plasma intact parathyroid hormone (iPTH) concentrations during 26-weeks of treatment with extended-release calcifediol compared to progressively rising iPTH concentrations during placebo treatment in the modified intent-to-treat population.

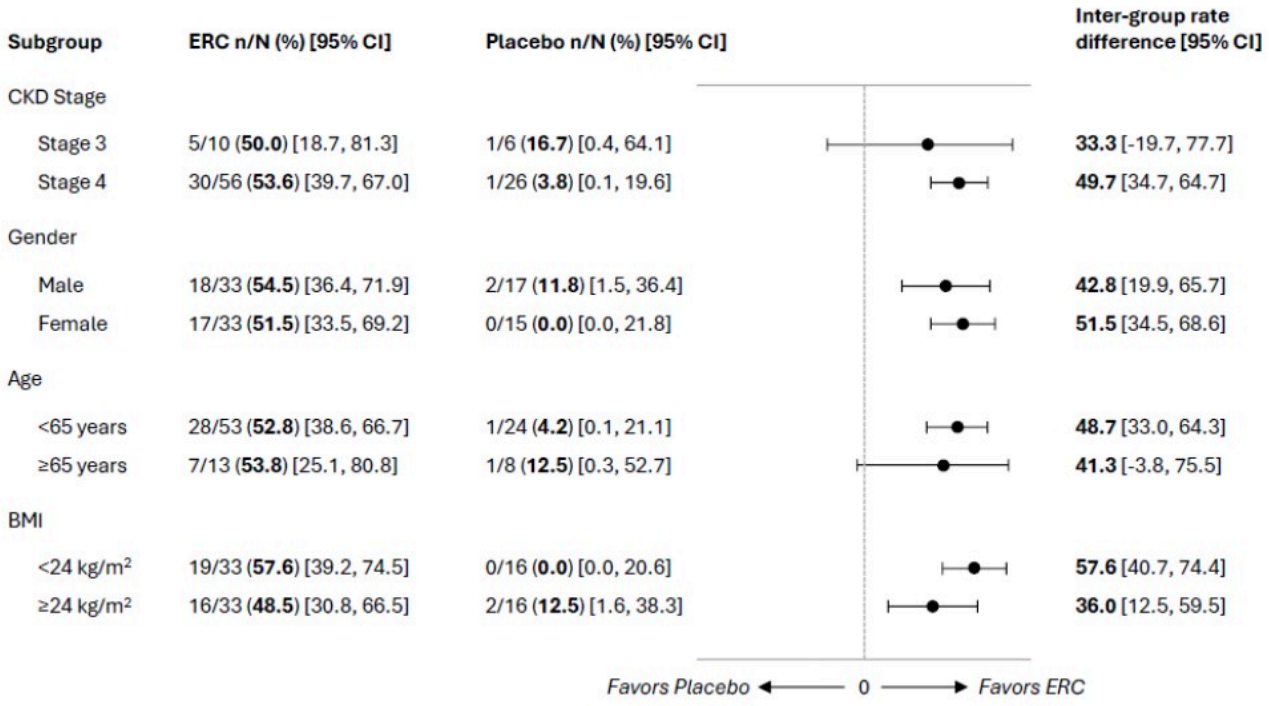


Figure 4

Forest Plot of Plasma iPTH Response Rates By Demographic Characteristics

Number (n) and percentages of participants in subgroups (N) of the modified intent-to-treat population achieving a ≥30% reduction in plasma intact parathyroid hormone from baseline in the efficacy assessment period during 26 weeks of daily treatment with extended-release calcifediol (ERC) or placebo. The analyzed subgroups were as follows: chronic kidney disease (CKD) stage (3 versus 4), gender, age (<65 versus ≥65 years) and body mass index (BMI; 24< versus ≥ 24 kg/m^2).

Alt text: A forest plot displaying differences in the number (n) and percentages of participants in subgroups (N) of the the modified intent-to-treat population achieving targeted plasma intact parathyroid hormone responses during 26 weeks of daily treatment with either extended-release calcifediol (ERC) or placebo. The analyzed subgroups were as follows: chronic kidney disease (CKD) stage (3 versus 4), gender, age (<65 versus ≥65 years) and bondy mass index (BMI; <24 versus ≥ 24 kg/m^2). The plotted differences consistently favored ERC treatment.

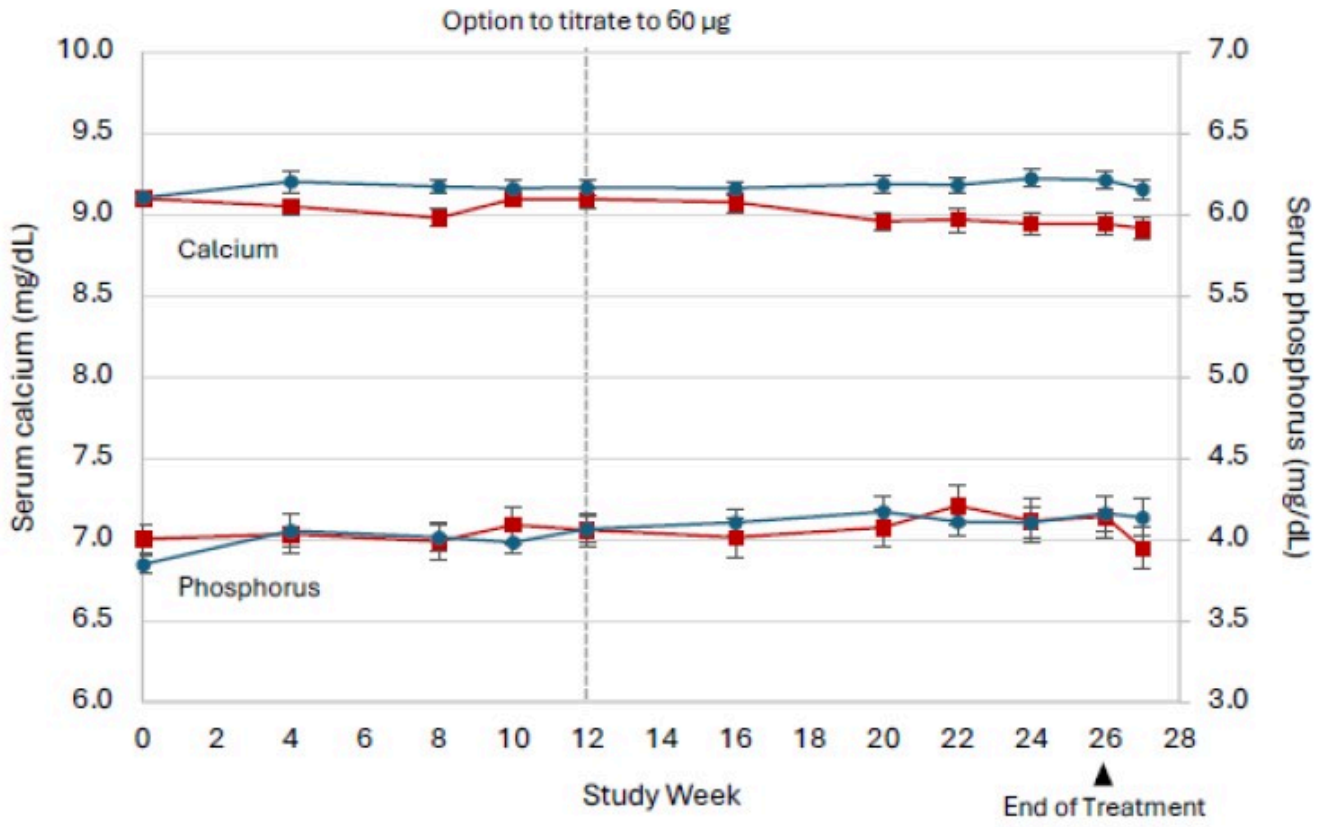


Figure 5

Time Courses of Mean Serum Calcium and Phosphorus

Time courses of mean serum calcium and phosphorus during 26 weeks of treatment with extended-release calcifediol (blue circles) or matching placebo (red squares) and the subsequent 1 week of post-dosing observation in the safety population.

Alt text: A graph showing minimal differences in mean (±SE) serum calcium and phosphorus concentrations during 26-weeks of treatment with extended-release calcifediol compared to placebo treatment in the modified intent-to-treat population.