Extended-Release Calcifediol Effectively Raises Serum Total 25-Hydroxyvitamin D Even in Overweight Nondialysis Chronic Kidney Disease Patients with Secondary Hyperparathyroidism

Charles W. Bishop a  Stephen A. Strugnell a  Philipp Csomor b  Edelgard Kaiser b  Akhtar Ashfaq a

a Renal Division, OPKO Health, Inc., Miami, FL, USA; b Vifor Pharma, Ltd., Zurich, Switzerland

Keywords
Extended-release calcifediol · Vitamin D · Secondary hyperparathyroidism · Chronic kidney disease · Obesity · Body mass index · Body weight

Abstract

Introduction: Obesity increases the risk of vitamin D insufficiency, which exacerbates secondary hyperparathyroidism in chronic kidney disease. Recent studies suggest that serum total 25-hydroxyvitamin D (25OHD) levels of ≥50 ng/mL are necessary to produce significant reductions in elevated parathyroid hormone levels in nondialysis patients. Data from real-world and randomized controlled trials (RCTs) involving these patients were examined for (1) relationships between vitamin D treatments and the achieved levels of serum 25OHD and between serum 25OHD and body weight (BW)/body mass index (BMI); and (2) the impact of BW/BMI on achieving serum 25OHD levels ≥50 ng/mL with extended-release calcifediol (ERC) treatment or vitamin D supplementation (cholecalciferol or ergocalciferol).

Methods: Data obtained from nondialysis patients participating in two real-world studies, one conducted in Europe (Study 1) and the other (Study 2) in the USA, and in two US RCTs (Studies 3 and 4) were analyzed for serum 25OHD outcomes after treatment with ERC, vitamin D supplements, or placebo. Results: More than 50% of subjects treated with vitamin D supplements in both real-world studies (Studies 1 and 2) failed to achieve serum 25OHD levels ≥30 ng/mL, a level widely viewed by nephrologists as the threshold of adequacy; only 7.3–7.5% of subjects achieved levels ≥50 ng/mL. Data from the European study (Study 1) showed that serum 25OHD levels had significant and nearly identical inverse relationships with BW and BMI, indicating that high BW or BMI thwarts the ability of vitamin D supplements to raise serum 25OHD. One RCT (Study 3) showed that 8 weeks of ERC treatment (60 μg/day) raised serum 25OHD levels to ≥30 and 50 ng/mL in all subjects, regardless of BW, while cholecalciferol (300,000 IU/month) raised serum 25OHD to these thresholds in 56% and 0% of subjects, respectively. The other RCT (Study 4) showed that ERC treatment (30 or 60 μg/day) successfully raised mean serum 25OHD levels to at least 50 ng/mL for subjects in all BW categories, whereas no increases were observed with placebo treatment.

Conclusion: Real-world studies conducted in Europe and USA in nondialysis patients (Studies 1 and 2) showed that vitamin D supplements (cholecalciferol or ergocalciferol) were unreliable in raising serum total 25OHD to targets of 30 or 50 ng/mL. In contrast, ERC was
demonstrated to be effective in one real-world study (Study 2) and two RCTs (Studies 3 and 4) conducted in US nondialysis patients in raising serum 25OHD to these targeted levels irrespective of BW.

Introduction

Inadequate levels of serum total 25-hydroxyvitamin D (25OHD) in chronic kidney disease (CKD) are associated with an increased risk of secondary hyperparathyroidism (SHPT) [1–4]. They can be difficult to raise sufficiently high to effectively lower elevated parathyroid hormone (PTH) levels especially in overweight patients [3, 5]. Obesity is common in CKD patients [6, 7] and requires attention when vitamin D repletion is considered.

Clinical practice guidelines for treating SHPT in CKD patients support the correction of vitamin D insufficiency (VDI) using treatment strategies recommended for the general population. These strategies target serum 25OHD levels of 20 or 30 ng/mL [1, 3, 8] and consist most frequently of oral administration of vitamin D supplements, either ergocalciferol (vitamin D$_2$) or cholecalciferol (vitamin D$_3$) in high bolus dose regimens, despite efficacy remaining unproven in randomized controlled trials (RCTs) [4, 9–11]. They focus on the administered dose, not exposure, ignoring factors which make it difficult to raise serum 25OHD to targeted levels, such as adipose-related dilution [12, 13], obesity-impaired hepatic activation of the administered supplement [14], and potentially increased catabolism due to upregulation of CYP24A1, the vitamin D catabolic enzyme [15].

To date, definitive guidance is lacking regarding the appropriate target for serum 25OHD in CKD as there is minimal consensus among the academic societies. In 2003, the National Kidney Foundation (NKF) recommended a target of 30 ng/mL for CKD patients in its Kidney Disease Outcomes Quality Initiative [1], and in 2011, the Endocrine Society defined vitamin D sufficiency as serum 25OHD concentrations between 30 and 100 ng/mL [3]. That same year, the National Academy of Medicine (NAM)/Institute of Medicine (IOM) concluded that clinicians should “classify 25OHD adequacy as concentrations >20 ng/mL without evidence of counter-regulatory hormone activity (i.e., elevated PTH).” In 2020, the Canadian Society of Nephrology recommended against routine vitamin D supplementation in patients with stage 3 CKD and made no recommendation for CKD stages 4–5 due to an inability to reach an internal consensus [18].

The lack of an established target for serum 25OHD in CKD makes it difficult to accurately assess the relative effectiveness of vitamin D repletion therapies and to choose the best option. Failure to provide effective SHPT management has the unwanted consequences of increased healthcare costs and risk of accelerated CKD progression [19, 20]. Recent clinical data suggest that a serum 25OHD target of 20 or 30 ng/mL is too low for effective management of SHPT in CKD patients. An RCT with extended-release calcifediol (ERC) in patients with CKD stages 2–4 demonstrated that reduction of PTH was directly proportional to increases in serum 25OHD [21] above 30 ng/mL. A large cross-sectional study in CKD patients reported that PTH levels became progressively lower as serum 25OHD levels rose up to 42–48 ng/mL [22]. A post hoc analysis of pooled data from two identical RCTs with ERC in patients with stage 3–4 CKD demonstrated that clinically meaningful reductions in PTH and serum bone turnover markers occurred only when serum 25OHD exceeded at least 50 ng/mL, and that gradual elevation of serum 25OHD to mean levels as high as 92.5 ng/mL had no adverse effects on safety parameters [23].

Recent studies suggest that vitamin D supplements do not reliably raise serum 25OHD or lower PTH in nondialysis CKD patients, even when administered at high doses [10, 24]. At high doses, cholecalciferol increased serum calcitriol levels but was unable to meaningfully increase the proportion of patients achieving a 30% decrease in PTH [25]. A meta-analysis of 14 RCTs showed only small, clinically irrelevant reductions in PTH in nondialysis CKD patients treated with vitamin D supplements [11]. Raising serum 25OHD with ergocalciferol or cholecalciferol is challenging in overweight patients [5], leading the Endocrine Society to recommend administration of two to three times more vitamin D than for patients with normal body weight (BW) [3]. VDI is highly prevalent in
obese patients [26–28] consistent with the known inverse relationship between serum 25OHD levels and increased BW and body mass index (BMI) [29, 30]. Some studies have reported that patients with severe VDI have the highest BMI values [31] and are more often morbidly obese [32]. Clinical data, presented herein, extend these observations to CKD patients and examine whether difficulties encountered in raising serum 25OHD in obese patients with supplements can be obviated by alternative treatment with ERC, enabling more effective SHPT management in nondialysis CKD.

**Methods**

Data from two real-world clinical studies (Studies 1 and 2) and two prospective RCTs (Studies 3 and 4) in CKD patients were analyzed to assess the influence of BW on the relative capabilities of vitamin D supplements and ERC to adequately raise 25OHD for effective management of SHPT. Real-world data were obtained from nondialysis patients with stage 3–5 CKD undergoing standard-of-care treatment at European facilities operated by Fresenius Medical Care (FMC) (Study 1) and from patients with stage 3–4 CKD, SHPT, and VDI from multiple USA clinics (Study 2; WIRB 1252915) [33]. Prospective data were obtained from two US RCTs conducted in patients with stage 3–4 CKD, SHPT, and VDI which examined short-term increases in serum 25OHD during ERC or cholecalciferol treatment (Study 3; NCT03588884; Advarra PRO00049450) or longer term increases in 25OHD with ERC as a function of BW (Study 4; NCT01651000, NCT01704079; Advarra PRO00007820) [34]. Baseline demographic and clinical laboratory data for these four studies are summarized in Table 1.

**Real-World Data**

Data were extracted from FMC’s EuCliD5 database between January 1, 2014, and December 1, 2020, for 2,459 adult nondialysis patients having estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m² (Study 1). These patients originated from the Czech Republic (56.7%), Hungary (1.3%), Italy (23.6%), Russia (1.6%), and Slovakia (16.8%) and had an average (SD) age of 69.6 (10.8) years, serum 25OHD of 23.2 (14.0) ng/mL, BW of 83.1 (18.6) kg, and BMI of 29.9 (14.0) kg/m². The majority (58.4%) had stage 3 CKD, and 34.4% and 7.2% had stage 4 or 5 CKD, respectively. Fifty-four percent of subjects were male, 66.3% white, and 33.7% others. The extracted data consisted of one measurement each of serum total 25OHD, BW, and BMI obtained within 90 days of the eGFR determination. Patients with a history of parathyroidectomy or renal transplantation were excluded. Patients received standard-of-care treatment including, if prescribed, ergocalciferol or cholecalciferol.

**Table 1. Baseline demographics and clinical laboratory data**

| Parameter | Real-world studies | RCTs |
|-----------|--------------------|------|
|           | Study 1 EU (n = 2,459) | Study 2 USA (n = 321) | Study 3 USA (n = 33) | Study 4 USA (n = 356) |
| Sex, n (%) | Female 1,132 (46.0) 166 (51.7) 15 (45.5) 178 (50.0) | Male 1,327 (54.0) 155 (48.3) 18 (54.5) 178 (50.0) |
| Race, n (%) | White 1,630 (66.3) 208 (64.9) 17 (51.5) 228 (64.0) | Black NR 65 (20.2) 16 (48.5) 117 (32.9) |
|          | Asian 1 (0.04) 1 (0.3) 0 5 (1.4) | Other/missing/not defined 828 (33.7) 47 (14.6) 0 6 (1.7) |
| Mean (SD) | Weight, kg 83.1 (18.6) 92.0 (25.3) 101.1 (27.2) 97.8 (24.3) | Age, years 69.6 (10.8) 69.2 (13.3) 66.9 (10.2) 65.4 (10.9) |
|          | BMI, kg/m² 29.9 (14.0) 33.4 (16.1) 34.4 (7.6) 34.7 (7.9) | eGFR, mL/min/1.73 m² 33.7 (12.8) 31.1 (12.7) 31.7 (8.4) 31.4 (10.2) |
|          | Ca, mg/dL 9.4 (0.6) 9.7 (4.0) 9.0 (0.6) 9.2 (0.3) | Ca, mg/dL 2.6 (0.7) 3.9 (2.0) 3.7 (0.6) 3.7 (0.5) |
|          | P, mg/dL 103.9 (191.1) 160.1 (93.5) 137.4 (76.0) 144.2 (55.2) | iPTH, pg/mL 23.2 (14.0) 19.6 (8.2) 20.4 (7.1) 19.6 (5.4) |
|          | 25-hydroxyvitamin D, ng/mL | EU, Europe. |
ERC Effectively Raises 25OHD in Overweight CKD Patients with SHPT

**Data from Prospective US RCTs**

A subset of data was analyzed from a prospective RCT investigating the influence of vitamin D therapies on serum 25OHD (Study 3). The subset consisted of 36 adult CKD patients enrolled into a prospective comparative trial from five US sites and randomized 1:1 (balanced for BW) to receive 6 weeks of open-label oral treatment with either ERC (60 μg/day) or cholecalciferol (300,000 IU/month). One subject in the ERC group completed treatment but was excluded due to a major protocol deviation, and 2 subjects in the cholecalciferol group were excluded because they withdrew from the study, leaving a per-protocol population of thirty-three (ERC: n = 17; cholecalciferol: n = 16). Eligible subjects had an eGFR of ≥15 and <60 mL/min/1.73 m², PTH of ≥65 and <500 pg/mL, serum total calcium (Ca) <9.8 mg/dL (corrected for albumin), and serum phosphorus (P) <5.5 mg/dL. On enrollment, subjects suspended use of any nonstudy vitamin D supplements or therapies and underwent at least 4 weeks of washout prior to randomization. No significant demographic or clinical differences were observed between treatment groups at baseline, with the exception that the cholecalciferol group included fewer women (25% vs. 59%, p < 0.05). Subjects were 45.5% female, 48.5% African-American or black, and 51.5% white, and 6.1% were Hispanic. Mean (SD) age at baseline was 66.9 (10.2) years, serum 25OHD was 20.4 (7.1) ng/mL, BW was 101.1 (27.2) kg, BMI was 34.4 (7.6), and eGFR was 31.7 (8.4) mL/min/1.73 m². ERC was provided as two 30 μg capsules (OPKO Pharmaceuticals, Miami), and cholecalciferol was provided as six 50,000 IU capsules (InVita, Plettenberg). Pre-treatment values of serum total 25OHD were defined as the average of post-washout measurements obtained prior to initiation of treatment on Day 1. End of treatment (EOT) values were defined as the average of two measurements, one obtained on Day 50 and the other on Day 57. Serum total 25OHD was determined at ACL Laboratories (West Allis) by chemiluminescence (DiaSorin). Further data (Study 4) were analyzed from two identical RCTs [34] investigating the efficacy and safety of ERC in treating adult nondialysis patients (n = 238) or placebo patients (n = 118) with eGFR of ≥15 and <60 mL/min/1.73 m², PTH ≥85 and <500 pg/mL, serum total 25OHD ≥10 and <30 ng/mL, serum total Ca ≥8.4 and <9.8 mg/dL (corrected for albumin), serum P ≥2.0 and <5.0 mg/dL, absence of nephrotic range proteinuria (>3 mg/mg creatinine), and no history of parathyroidectomy or renal transplantation. These subjects had mean (SD) age of 65.4 (10.9) years, serum 25OHD at baseline of 19.6 (5.4) ng/mL, BW of 97.8 (24.3) kg, and BMI of 34.7 (7.9) kg/m². Fifty percent were male, 64.0% white, 32.9% African-American or black, and 3.1% other, and 20% were Hispanic. The 356 subjects who completed a 20- to 26-week treatment period per protocol were included in the analysis. Enrolled subjects ingested one 30 μg capsule of ERC (OPKO Pharmaceuticals, Miami, FL, USA) daily for 12 weeks followed by one or two capsules (30 or 60 μg) daily for an additional 14 weeks. Control subjects received matching placebo. Subjects receiving supplementation with either ergocalciferol or cholecalciferol at the time of enrollment (66 on ERC and 31 on placebo) were required to maintain stable doses below 1,600 IU/day during the 26-week treatment period. Therapies modulating bone metabolism were disallowed. Observed changes in serum total 25OHD were analyzed as a function of BW. Serum total 25OHD was determined at PPD Global Central Labs (Highland Heights, KY, USA) by chemiluminescence (DiaSorin).

**Results**

**Real-World Data**

An analysis of serum 25OHD (Fig. 1) in European nondialysis patients with stage 3–5 CKD (Study 1) showed that 40.6% of patients treated with vitamin D supplements had levels of ≥30 ng/mL and only 7.3% had levels ≥50 ng/mL. In contrast, 24.4% of patients not treated with D supplements had levels of ≥30 ng/mL and only 3.3% had levels ≥50 ng/mL. Mean serum 25OHD levels showed significant and nearly identical inverse relationships to both mean BMI and mean BW (Fig. 2) that were unaffected by age or gender.

US patients with stage 3–4 CKD patients (Study 2) treated with weekly oral ergocalciferol (n = 97) or cholecalciferol (n = 50) achieved an average duration of supplementation of 21.1 weeks, and mean (SE) serum 25OHD rose from a baseline level of 18.8 (0.6) ng/mL by 9.7 ± 1.5 ng/mL (p < 0.001). Serum 25OHD levels reached at least 30 ng/mL in 37.0% of patients, and only 7.5% had levels of ≥50 ng/mL (Fig. 1); in contrast, 69.9% of patients receiving ERC achieved serum 25OHD levels of at least 30 ng/mL and 36.4% had levels ≥50 ng/mL. Greater 25OHD levels with ERC would likely have been observed with more frequent dose titration; administration of higher cholecalciferol doses would have been unwise. A total of 6.6% of patients not treated with D supplements had levels of ≥30 ng/mL, and only 0.3% had levels ≥50 ng/mL.

**Data from Prospective US RCTs**

In Study 3, mean (SD) serum 25OHD increased gradually in the ERC group, attaining 61.2 (13.6) ng/mL after 4 weeks of treatment and 82.9 (16.8) ng/mL after 8 weeks. ERC treatment achieved a serum total 25OHD response rate of 100% using a target of either 30 or 50 ng/mL. In the cholecalciferol group, mean 25OHD levels rose to 29.1 (11.4) ng/mL after 4 weeks and 30.3 (11.8) ng/mL.
after 8 weeks, leaving 56% of the subjects below this threshold; no subjects achieved serum 25OHD levels of ≥50 ng/mL. Serum 25OHD levels in both groups at the EOT showed significant inverse relationships with BW (Fig. 3). Serum 1,25(OH)2D levels for the ERC and cholecalciferol groups increased from mean (SD) values at baseline of 30.7 (3.4) and 24.9 (1.6) pg/mL, respectively, to 54.3 and 29.5 pg/mL, respectively. ERC treatment produced 10, 20, or 30% reductions in plasma iPTH from pre-treatment baseline in 76.5, 70.6, or 41.2% of subjects, respectively, compared with 56.3, 37.5, or 25.0% for cholecalciferol treatment.

Longer time course data (Study 4) for serum total 25OHD with daily ERC treatment were examined as a function of BW in 356 per-protocol subjects pooled from two identical, concurrent prospective US placebo-controlled RCTs. Mean serum 25OHD remained unchanged with placebo treatment, including in the 31 subjects who received ongoing supplementation with cholecalciferol or ergocalciferol at daily doses <1,600 IU (22.3 ng/mL in the treatment period vs. 19.3 ng/mL at baseline). Mean (SD) serum 25OHD rose progressively with ERC treatment to 67.1 (21.6) ng/mL (mean of weeks 20–26). The observed increases in serum 25OHD as a function of BW are shown in Figure 4 where it can be seen that mean serum 25OHD at EOT was inversely related to BW but exceeded 50 ng/mL in all BW categories. Side effects observed at these levels of exposure were similar to placebo, as delineated previously [34].

**Discussion**

The presented European and US real-world data show that serum total 25OHD levels are frequently inadequate in nondialysis CKD patients despite standard-of-care treatment. The observed negative inverse correlations of...
serum 25OHD levels with both BMI and BW suggest that obesity can prevent routine vitamin D supplementation from raising serum 25OHD to targeted levels in CKD.

Most CKD patients [6, 7] are overweight or obese, a problem which drives disease progression through the co-morbidities of type 2 diabetes and hypertension. Cholecalciferol and ergocalciferol are fat-soluble molecules which accumulate preferentially in adipose tissue [12, 13]. They have low affinities for the serum-based vitamin D binding protein, are poorly drawn out of adipose into circulation

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**Fig. 3.** Mean serum 25OHD levels versus BW in ERC- and cholecalciferol-treated subjects. Subjects with stage 3–4 CKD, SHPT, and VDI were treated with ERC or cholecalciferol for 8 weeks (Study 3). Serum 25OHD levels at the EOT (mean of last two measurements) were plotted versus baseline BW.

**Fig. 4.** Time course of mean serum 25OHD levels by BW category. Subjects with stage 3–4 CKD, SHPT, and VDI who were treated with ERC (30 escalating, as needed, to 60 μg/day) for 6 months in an RCT (Study 4) were divided by BW into six categories (>40–60 kg, >60–80 kg, >80–100 kg, >100–120 kg, >120–140 kg, and >140 kg), and the increases in mean serum 25OHD levels were plotted over time.
for hepatic activation [12, 35], and are prone to in situ catabolism by CYP24A1, the vitamin D catabolic enzyme that can be upregulated in CKD. Hepatic 25-hydroxylase activity is reduced in both obesity [14] and CKD [35, 36], blunting the intended elevation of serum total 25OHD. In contrast, calcifediol requires no hepatic activation, is more water soluble, and avidly binds D binding protein, reducing accumulation in adipose tissue and enabling its circulation to extra-renal tissues containing 25OHD-1α-hydroxylase (CYP27B1) and intracrine conversion to calcitriol (1,25-dihydroxyvitamin D3), the active hormone [37–40]. Gradual delivery of calcifediol (ERC) has been shown to cause minimal suppression of extra-renal CYP27B1 and minimal upregulation of CYP24A1 [41].

Extra-renal production of calcitriol depends on adequate supply of calcifediol, fostering an ongoing dialogue about the optimum level for serum total 25OHD in patients with stage 3–4 CKD. RCTs with ERC suggest that this target should be at least 50 ng/mL [23], not 20 or 30 ng/mL as endorsed by clinical practice guidelines [1, 3, 8], to enable intracrine production of calcitriol and control of SHPT despite the progressive loss of renal CYP27B1 in advancing CKD [42]. Extra-renal production of calcitriol at serum 25OHD levels ≥50 ng/mL has been documented in anephric patients [42].

Several meta-analyses of RCTs conducted in CKD patients have shown that ergocalciferol or cholecalciferol supplementation is unreliable in achieving a serum total 25OHD target of 30 ng/mL, let alone 50 ng/mL [9–11, 43]. One [11] concluded that supplementation produces such large variations in response that a precise evaluation of the true treatment effect is difficult.

It is time to reconsider the current paradigm [1, 2, 4] of treating SHPT in nondialysis patients. While cholecalciferol or ergocalciferol may seem intuitively appropriate for correcting VDI, these supplements have difficulty raising serum 25OHD to ≥30 ng/mL, especially in overweight patients. When PTH inevitably rises, patients are usually switched to calcitriol (or another 1α-hydroxylated vitamin D analogue) with the justification that too much renal CYP27B1 has been lost with advancing disease, preventing sufficient conversion of 25OHD to hormone.

Several things need to change in the current paradigm. First, the target for serum 25OHD of ≥30 ng/mL is too low and should be replaced with a higher one (≥50 ng/mL) to enable renal and extra-renal CYP27B1 to produce sufficient hormone for iPTH control by alternative intracrine and paracrine mechanisms. Second, cholecalciferol and ergocalciferol are poor initial choices for intervention as they cannot reliably and sufficiently raise serum 25OHD, a problem which adiposity can exacerbate. Alternatively, ERC should be initiated at a dose of 30 μg/day and the dose titrated upward to reliably achieve 25OHD levels of ≥50 ng/mL in both normal and overweight patients, overcoming the adverse impact of elevated BW/BMI on therapeutic efficacy. Third, in the absence of severe and progressive SHPT, patients with stage 3–4 CKD should not be switched to calcitriol or 1α-hydroxylated vitamin D analogues in view of the updated KDIGO clinical practice guideline which recommends against their regular use out of concern for hypercalcemia [4]. Instead, PTH control in nondialysis patients can be safely accomplished by raising serum 25OHD to ≥50 ng/mL with ERC, irrespective of CKD stage and obesity, allowing for physiologically controlled generation of sufficient 1,25(OH)2D to effectively treat SHPT.

The current findings have the following two strengths: (1) the conclusion that high BW/BMI have substantial negative impact on serum 25OHD levels achieved with vitamin D supplements in nondialysis CKD patients emanates from data obtained from both real-world studies and RCTs; and (2) successful elevation of serum 25OHD in these patients with ERC treatment has been demonstrated in this patient population with data from multiple RCTs. The weaknesses of the findings are as follows: (1) most of the presented data were not derived from studies specifically designed to evaluate the effects of BW and BMI on serum 25OHD elevation – rather, they derived from post hoc analyses; (2) the 300,000 IU monthly dose of cholecalciferol is not widely used in CKD patients and was chosen because few nephrologists would recommend a higher dosage; and (3) the recommended starting dose of ERC is 30 not 60 μg/day, as in one of the RCTs presented herein (Study 3). In this last regard, the higher starting dose was selected for research purposes only in order to accelerate the rise in serum 25OHD within an 8-week treatment period as ERC usually does not produce steady-state levels before 3 months of administration.

Conclusion

Clinical data presented herein from two real-world and two RCTs show that excessive BW, common in CKD patients, diminishes the abilities of cholecalciferol and ergocalciferol to adequately raise serum total 25OHD to target, making them unreliable therapeutic choices. The presented data from the US real-world and prospective RCTs demonstrate that ERC offers reliable elevation of serum 25OHD to levels above 30 and 50 ng/mL in CKD patients despite obesity.
Statement of Ethics

The European real-world study was an epidemiological retrospective cohort study which utilized existing secondary data from this database. All data were pseudonymized for scientific research purposes. The US real-world study was conducted in compliance with the principles of the Declaration of Helsinki. The protocol was reviewed and approved by the Western Institutional Review Board (WIRB). The US RCTs were also conducted in compliance with the principles of the Declaration of Helsinki. Their protocols were reviewed and approved by Advarra Institutional Review Board. All patients in the European and US real-world studies provided written informed consent for the use of their anonymized data for scientific research purposes. All patients in the US RCTs provided written informed consent for their participation in these studies.

Conflict of Interest Statement

Three authors (S.A.S., A.A., and C.W.B.) are full-time employees of OPKO Health and have no other conflicts of interest to disclose. Two authors (E.K. and P.C.) are full-time employees of Vifor Pharma and have no other conflicts of interest to disclose.

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Author Contributions

All authors designed the studies. S.A.S. carried out data analyses and preparation of the figures; S.A.S., A.A., C.W.B., E.K., and P.C. drafted and revised the paper; all authors approved the final version of the manuscript.

Data Availability Statement

The presented data were obtained from multiple sources where restrictions may apply. Data may be available from the corresponding author (S.A.S.) upon reasonable request and with the permission of all contributing sources.
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