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Use of Extended-Release Calcifediol to Treat Secondary Hyperparathyroidism in Stages 3 and 4 Chronic Kidney Disease

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Key Words

Chronic kidney disease · Secondary hyperparathyroidism · Vitamin D · Vitamin D insufficiency · Calcifediol (25-hydroxyvitamin D_3) · Parathyroid hormone

Abstract

Background/Aims: Vitamin D insufficiency and secondary hyperparathyroidism (SHPT) are associated with increased morbidity and mortality in chronic kidney disease (CKD) and are poorly addressed by current treatments. The present clinical studies evaluated extended-release (ER) calcifediol, a novel vitamin D prohormone repletion therapy designed to gradually correct low serum total 25-hydroxyvitamin D, improve SHPT control and minimize the induction of CYP24A1 and FGF23. ***Methods:*** Two identical multicenter, randomized, double-blind, placebo-controlled studies enrolled subjects from 89 US sites. A total of 429 subjects, balanced between studies, with stage 3 or 4 CKD, SHPT and vitamin D insufficiency were randomized 2:1 to receive oral ER calcifediol (30 or 60 μg) or placebo once daily at bedtime for 26 weeks. Most subjects (354 or 83%) completed dosing, and 298 (69%) entered a subsequent open-label extension study wherein ER calcifediol was administered without interruption for another 26 weeks. ***Results:*** ER calcifediol normalized serum total 25-hydroxyvitamin D concentrations (>30 ng/ml) in >95% of per-protocol subjects and reduced plasma intact parathyroid hormone (iPTH) by at least 10% in 72%. The proportion of subjects receiving ER calcifediol who achieved iPTH reductions of ≥30% increased progressively with treatment duration, reaching 22, 40 and 50% at 12, 26 and 52 weeks, respectively. iPTH lowering with ER calcifediol was independent of CKD stage and significantly greater than with placebo. ER calcifediol had inconsequential impact on serum calcium, phosphorus, FGF23 and adverse events. ***Conclusion:*** Oral ER calcifediol is safe and effective in treating SHPT and vitamin D insufficiency in CKD.

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Introduction

Chronic kidney disease (CKD) is a worldwide public health problem with steadily increasing patient numbers and cost. Prevalence exceeds 10% globally [1] and has risen to 14% in the United States (US) [2]. Key factors driving the growth of CKD in developed countries include aging populations and the increasing incidence of obesity, with its associated complications of hypertension and adult-onset diabetes. Stages 3 and 4 CKD afflict more than 6% of the US population, or approximately 20 million individuals [2].

Secondary hyperparathyroidism (SHPT) is a major facet of CKD mineral and bone disorder (CKD-MBD), the broader clinical syndrome of mineral, bone and calcific cardiovascular abnormalities that develop as a complication of CKD. SHPT is characterized by excessive secretion of parathyroid hormone (PTH) and arises from a combination of vitamin D insufficiency, phosphate retention, elevated FGF23 and reduced serum total 1,25-dihydroxyvitamin D and calcium (Ca) concentrations. SHPT affects 40 and 82% of patients with stages 3 and 4 CKD [3], respectively, and requires prompt and effective treatment. In the absence of effective treatment, SHPT becomes progressively more severe and ultimately unresponsive to medical treatment [4], leading ultimately to parathyroidectomy.

Vitamin D insufficiency affects an estimated 71–83% of patients with stage 3 or 4 CKD [5, 6]. It is defined in clinical practice guidelines applicable to CKD as serum total 25-hydroxyvitamin D <30 ng/ml [7, 8] and it arises from nutritional inadequacy, decreased sunlight exposure, proteinuric loss and decreased hepatic synthesis of 25-hydroxyvitamin D and increased expression of CYP24A1, the cytochrome P450 enzyme that specifically catabolizes 25-hydroxyvitamin D to 24,25-dihydroxyvitamin D and more polar catabolites [9, 10]. There is general agreement amongst nephrologists and endocrinologists that vitamin D insufficiency should be corrected [7, 8, 11]. However, no dosing regimen with ergocalciferol or cholecalciferol has been shown to be effective for reliably correcting vitamin D insufficiency and significantly reducing elevated PTH levels in CKD [12, 13].

In contrast, extended-release (ER) calcifediol has been shown in a 6-week randomized, double-blind, placebo-controlled trial to reliably correct vitamin D insufficiency and to effectively suppress elevated plasma intact PTH (iPTH) in CKD patients while maintaining normal serum total 25-hydroxyvitamin D concentrations [10]. We report herein additional studies that examine the safety and efficacy of ER calcifediol administered for periods of up to 52 weeks in patients with stage 3 or 4 CKD.

Methods

Study Design

Two identical studies (studies A and B) with multicenter, randomized, double-blind, placebo-controlled designs enrolled 429 subjects with CKD stage 3 or 4, SHPT and vitamin D insufficiency from 89 US sites. A total of 213 subjects were randomized in study A (72 received placebo and 141 received ER calcifediol), and 216 subjects were randomized in study B (72 received placebo and 144 received ER calcifediol). Subjects were stratified equally by CKD stage and were randomized in a 2:1 ratio to receive a once daily 30 μg oral dose of ER calcifediol (or matching placebo) for 12 weeks at bedtime followed by an additional 14 weeks of treatment with once daily bedtime doses of either 30 or 60 μg of ER calcifediol (or placebo). The dose was increased to 60 μg at the start of week 13 if plasma iPTH remained >70 pg/ml (the upper limit of the laboratory reference range), serum total 25-hydroxyvitamin D was <65 ng/ml and serum Ca was <9.8 mg/dl.

A total of 354 subjects (83%) completed studies A or B, and 298 (69%) entered a single 6-month open-label extension study during which dosing continued unchanged with the exceptions that (a) subjects who had been receiving placebo switched to 30 μg of ER calcifediol (once daily at bedtime), and (b) all subjects could titrate to 60 μg at week 38 if plasma iPTH was >70 pg/ml and serum Ca was <9.8 mg/dl, with no restriction on the level of serum 25-hydroxyvitamin D. A total of 84 subjects who had been receiving 60 μg daily at week 38 and met dose titration criteria were randomized (1:1) to continue daily ER calcifediol (a) alone or (b) with daily additional adjunctive therapy. Data collected from 42 subjects randomized to additional adjunctive therapy have been excluded from this analysis to focus solely on the effect of ER calcifediol.

Plasma iPTH and serum Ca, phosphorus (P) and total 25-hydroxyvitamin D were measured every 2 or 4 weeks in studies A and B and in the subsequent extension. Serum total 1,25-dihydroxyvitamin D (includes both 1,25-dihydroxyvitamin D_2 and D_3) and 24,25-dihydroxyvitamin D_3 were measured at the same intervals in studies A and B only. Routine blood chemistries, hematologic parameters, spot urine Ca, P and creatinine (Cr) levels and serum FGF23 were measured before initiating treatment, titrating the dose and at the end of treatment. An independent Data Safety Monitoring Board monitored patient safety throughout the study.

The sole primary efficacy end point in all 3 studies was the number (n, %) of subjects in the intent-to-treat (ITT) population that attained a mean decrease of ≥30% in plasma iPTH from pretreatment baseline in the efficacy assessment period (EAP), defined as the last 6 weeks of the 26- and 52-week treatment periods.

The primary safety end points included adverse event (AE) rates, laboratory parameters (clinical chemistry, hematology, urine chemistry and urinalysis), physical examinations, vital signs, 12-lead electrocardiograms and assessments of estimated glomerular filtration rate (eGFR), all of which were evaluated at regular intervals.

Subject Selection

Eligible subjects were ≥18 years of age and had CKD (not requiring regular dialysis) with eGFR ≥15 and <60 ml/min/1.73 m^2. Other eligibility criteria included serum total 25-hydroxyvitamin D ≥10 and <30 ng/ml, plasma iPTH ≥85 and <500 pg/ml, serum Ca ≥8.4 and <9.8 mg/dl and serum P ≥2.0 and <5.0 mg/dl. Exclusion criteria included a spot urine Ca:Cr ratio >0.2, nephrotic range proteinuria (>3 mg/mg Cr) and history of parathyroidectomy for SHPT or renal transplantation. Subjects taking >1,000 mg/day of elemental Ca reduced intake for the duration of the study and underwent a 14-day pre-treatment washout. Subjects receiving supplementation with ergocalciferol or cholecalciferol maintained stable doses below 1,600 international units (IU)/day and 1,600 IU/dose. Any bone metabolism therapy (with the exception of bisphosphonates) that could potentially interfere with study end points was discontinued for the duration of the study, and a 56-day pre-treatment washout was imposed. In the case of bisphosphonates, subjects had to be on a stable dose for >6 months prior to enrollment and maintain that dose for study duration.

Study Blind

All subjects and staff were blinded as to whether a given subject was assigned to ER calcifediol or placebo treatment until the study database was locked or until a decision was made to break the blind for that subject (e.g., as a result of an emergent AE). For subjects enrolling into the extension study, treatment assignments remained blinded until 8 weeks after the end of studies A or B at which time the study database was locked for that subject. All subjects took 1 capsule per day from a single bottle starting at day 1 for 12 weeks, and 2 capsules per day from 2 bottles (1 capsule from each bottle) starting after 12 weeks, unless dose reduction (to 1 capsule thrice weekly) or suspension was warranted (these were rare events). The switch from 1 to 2 bottles after 12 weeks in all subjects allowed the ER calcifediol dose to be increased, as necessary, from 30 to 60 μg/day for selected subjects without breaking the blind.

All subjects and staff were also blinded to serum total 25-hydroxyvitamin D and plasma iPTH concentrations obtained during treatment. Serum total 25-hydroxyvitamin D and plasma iPTH data were maintained blinded for any subject enrolling into the subsequent extension study until that subject had completed another 8 weeks of treatment and the subject's data from the preceding study had been locked.

Drug Products and Dosing

Calcifediol was purchased from the Dishman Group (Veenendaal, Netherlands) and formulated in ER capsules containing 30 μg by Catalent Pharma Solutions (Clearwater, Fla., USA). Placebo capsules had the same formulation, except for the omission of calcifediol, and had identical appearance and packaging. Both active and placebo capsules underwent full quality control analysis prior to use in the studies, and were monitored for stability during the period of use. The active capsules gradually released calcifediol over a 12-hour period during in vitro dissolution testing. A single-dose study of 450 and 900 μg ER calcifediol in subjects with stage 3 or 4 CKD produced maximum serum calcifediol concentrations in the range of 13.1–13.6 h after dosing in the fasted state [14].

Subjects were instructed to take 1 or 2 capsules by mouth every day at bedtime (with any non-alcoholic liquid). Subjects discontinued dosing if they had confirmed plasma iPTH <30 pg/ml, serum Ca >10.3 mg/dl, serum P >5.5 mg/dl (only if deemed to be study drug related) or serum total 25-hydroxyvitamin D >100 ng/ml.

Laboratory and Clinical Procedures

Blood and urine samples were shipped on dry ice for analysis to PPD Global Central Labs (Highland Heights, KY, USA). Plasma iPTH levels were determined by 2-site sandwich immunochemiluminescence (Roche Elecsys). Serum total 25-hydroxyvitamin D was determined by chemiluminescence (DiaSorin), serum total 1,25-dihydroxyvitamin D was determined by radioimmunoassay (IDS) and intact FGF23 was determined by ELISA (Millipore). Samples were forwarded to InVentiv Health (Quebec, Canada) for analysis of serum 24,25-dihydroxyvitamin D_3 by LC-MS/MS.

Analysis of Data

Serum Ca values were corrected for albumin below 4.0 g/dl. eGFR was calculated with the Modification of Diet in Renal Disease equation [15]. Pre-treatment 'baseline' values for all parameters were defined as the average of the measurements obtained at (a) the 2 screening visits and (b) immediately prior to dosing on the day when treatment was initiated. EAP values were defined as the average of all (minimum of 2) measurements in weeks 20, 22, 24 and 26 for studies A and B as well as the average of all (minimum of 2) measurements in weeks 46, 50 and 52 for the extension study. Efficacy end points were analyzed in the ITT and per-protocol (PP) populations according to a pre-specified statistical analysis plan, but results of only the PP analyses are reported herein, except where noted, since there were no material differences between the 2 analyses.

Results

Study Population

Demographic and baseline characteristics of the 429 subjects are summarized in table 1 by study and treatment group. No significant differences were detected among the 2 treatment groups for both the individual studies A and B and for the pooled data. The subjects' mean age was 66 years (range 25–85), 50% were male, 65% White, 32% African-American or Black, 21% Hispanic and 3% Other. At baseline, subjects had SHPT and stage 3 (52%) or stage 4 (48%) CKD. The most common causes of CKD were diabetes and hypertension and the mean eGFR was 31 ml/min/1.73 m^2. Mean baseline plasma iPTH was 130 pg/ml for subjects with stage 3 disease (n = 222) and 166 pg/ml for subjects with stage 4 disease (n = 207). Also, at baseline, mean serum Ca was 9.2 mg/dl, mean serum P was 3.7 mg/dl and mean serum total 25-hydroxyvitamin D was 20 ng/ml. Nutritional vitamin D therapy was used concomitantly by 14.4% of subjects randomized to ER calcifediol treatment and by 13.2% of subjects randomized to placebo treatment. Only one subject (randomized to placebo treatment) used concomitant bisphosphonate therapy.

Table 1. Subject demographics and baseline characteristics

Parameter	Pooled data from placebo-controlled studies A and B					
	study A		study B		total	
	placebo (n = 72)	ER calcifediol (n = 141)	placebo (n = 72)	ER calcifediol (n = 144)	placebo (n = 144)	ER calcifediol (n = 285)
Sex, n (%)						
Female	33 (45.8)	71 (50.4)	39 (54.2)	71 (49.3)	72 (50.0)	142 (49.8)
Male	39 (54.2)	70 (49.6)	33 (45.8)	73 (50.7)	72 (50.0)	143 (50.2)
Race, n (%)						
White	48 (66.7)	85 (60.3)	46 (63.9)	98 (68.1)	94 (65.3)	183 (64.2)
Black	22 (30.6)	50 (35.5)	23 (31.9)	43 (29.9)	45 (31.3)	93 (32.6)
Other	2 (2.7)	6 (4.2)	3 (4.2)	2 (1.4)	5 (3.4)	8 (2.8)
Ethnicity, n (%)						
Hispanic or Latino	16 (22.2)	28 (19.9)	15 (20.8)	29 (20.1)	31 (21.5)	57 (20.0)
Not Hispanic	56 (77.8)	113 (80.1)	57 (79.2)	115 (79.9)	113 (78.5)	228 (80.0)
Cause of CKD, n (%)						
Diabetes mellitus	34 (47.2)	55 (39.0)	30 (41.7)	74 (51.4)	64 (44.4)	129 (45.3)
Hypertension	24 (33.3)	54 (38.3)	31 (43.1)	49 (34.0)	55 (38.2)	103 (36.1)
Polycystic kidney disease	2 (2.8)	4 (2.8)	0 (0.0)	4 (2.8)	2 (1.4)	8 (2.8)
Glomerulonephritis	2 (2.8)	1 (0.7)	0 (0.0)	1 (0.7)	2 (1.4)	2 (0.7)
Weight, kg, mean (SD)	96.3 (25.55)	96.2 (25.84)	97.4 (18.47)	97.5 (24.13)	96.9 (22.2)	97.1 (25.1)
Age, years, mean (SD)	64.4 (12.74)	65.1 (10.33)	65.3 (10.06)	66.8 (10.90)	64.9 (11.5)	66.0 (10.6)
BMI, kg/m^2, mean (SD)	34.2 (7.66)	34.1 (8.33)	35.0 (7.34)	34.7 (7.93)	34.6 (7.5)	34.4 (8.1)
eGFR, ml/min/1.73 m^2, mean (SD)	32.3 (11.02)	30.3 (11.07)	31.8 (9.61)	30.9 (9.90)	32.0 (10.3)	30.6 (10.5)
Ca, mg/dl, mean (SD)	9.2 (0.28)	9.2 (0.29)	9.3 (0.28)	9.3 (0.35)	9.2 (0.28)	9.2 (0.32)
P, mg/dl, mean (SD)	3.8 (0.59)	3.7 (0.55)	3.7 (0.47)	3.8 (0.56)	3.8 (0.53)	3.7 (0.55)
iPTH, pg/ml, mean (SD)	142.2 (46.11)	146.8 (56.01)	155.6 (63.09)	147.6 (64.21)	148.9 (55.5)	147.2 (60.2)
25-Hydroxyvitamin D, ng/dl, mean (SD)	19.2 (5.43)	20.2 (5.08)	19.4 (5.51)	19.7 (5.56)	19.3 (5.5)	19.9 (5.3)

Subject Disposition

Most (83%) enrolled subjects completed the 26-week placebo-controlled treatment period. Comparable proportions of subjects in the 2 treatment groups and studies terminated early for various reasons, the most frequent of which were withdrawal of consent (6%), followed by discontinuations due to a non-serious (1.8%) or serious (3.5%) treatment emergent AE (TEAE).

Serum Total 25-Hydroxyvitamin D

Mean serum total 25-hydroxyvitamin D increased gradually and comparably with ER calcifediol treatment in both studies (fig. 1) but was unchanged with placebo treatment ($p < 0.0001$). In studies A and B, 80 and 83% of the ITT subjects treated with ER calcifediol attained serum 25-hydroxyvitamin D levels of at least 30 ng/ml versus 3 and 7% of subjects treated with placebo ($p < 0.001$), respectively. More than 95% of the PP subjects in each study attained at least 30 ng/ml. At the start of week 13, 74% of subjects treated with ER calcifediol increased the dose to 60 μg/day. Steady-state serum total 25-hydroxyvitamin D levels were reached after 12 weeks of dosing and averaged 50 and 56 ng/ml for subjects receiving 30 μg daily, and 69 and 67 ng/ml for subjects receiving 60 μg daily, in the 2 studies, respectively. The levels remained stable throughout the 52-week treatment period.

Plasma iPTH

In studies A and B, mean plasma iPTH levels declined gradually, but progressively, with ER calcifediol treatment and tended to increase with placebo treatment (fig. 2). Differences between the treatment groups in the EAP were significant in both studies ($p < 0.001$). During

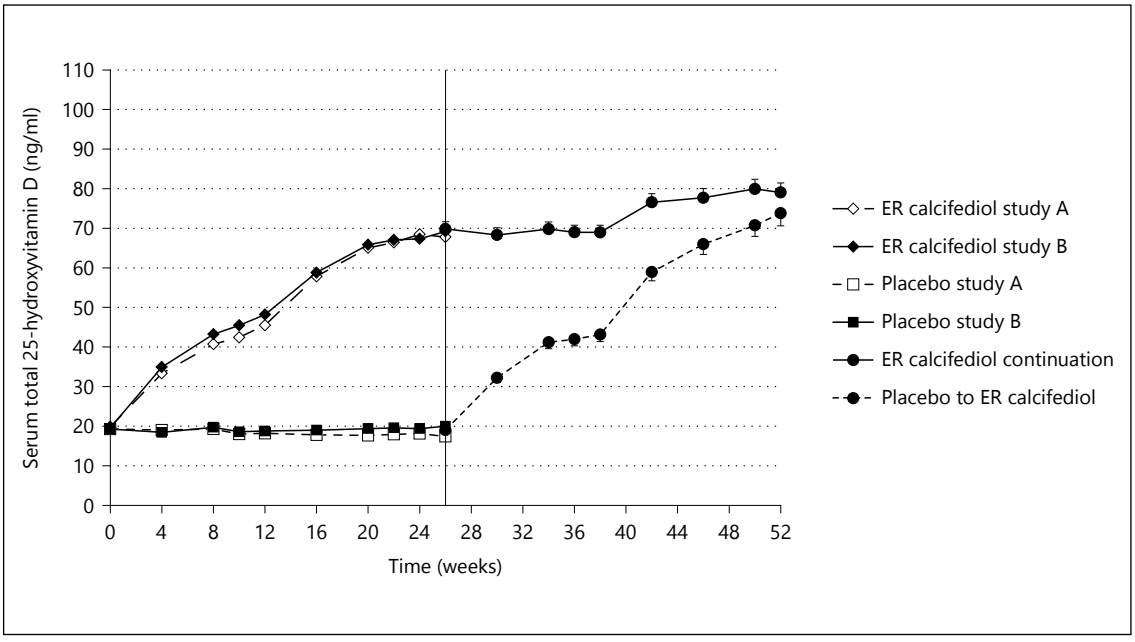

Fig. 1. Mean (SE) change over time in serum total 25-hydroxyvitamin D in the pooled PP population. Data points from 0 to 26 weeks represent mean values for individual time points from placebo-controlled studies A and B. Error bars in this portion of the figure are omitted for clarity. Data points from 26 to 52 weeks represent mean ± SE values for data from the open-label extension study. SE values for weeks 0–26 weeks were of similar magnitude to those in the open-label extension.

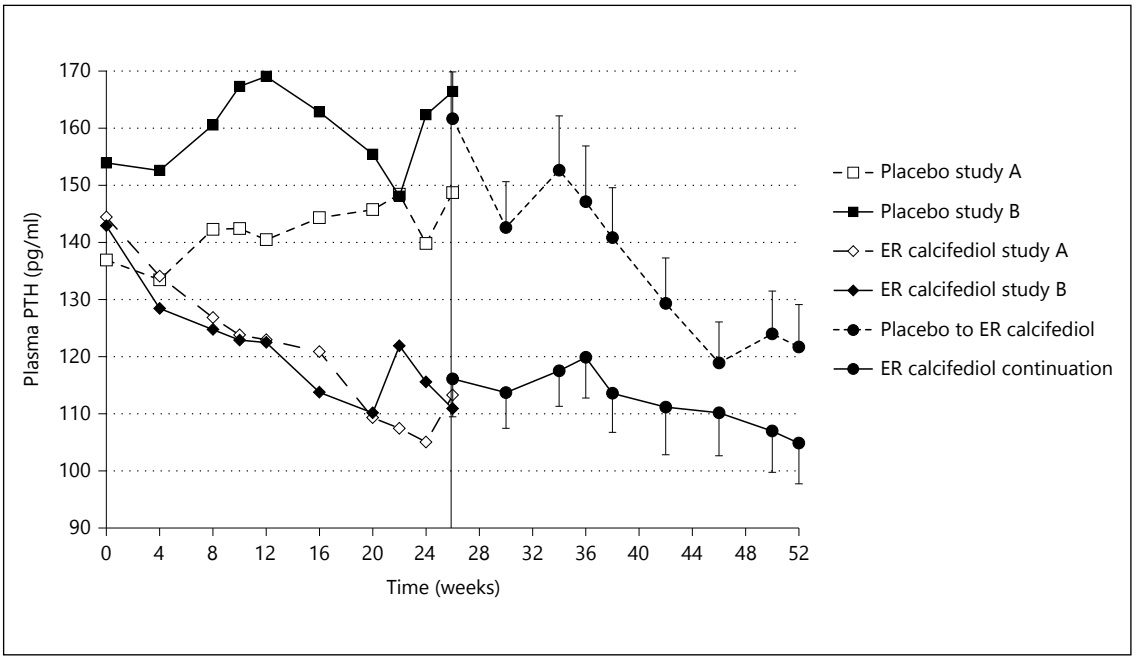

Fig. 2. Mean (SE) change over time in plasma iPTH in the pooled PP population. Data points from 0 to 26 weeks represent mean values for individual time points from placebo-controlled studies A and B. Error bars in this portion of the figure are omitted for clarity. Data points from 26 to 52 weeks represent mean ± SE values for pooled data from the open-label extension study.

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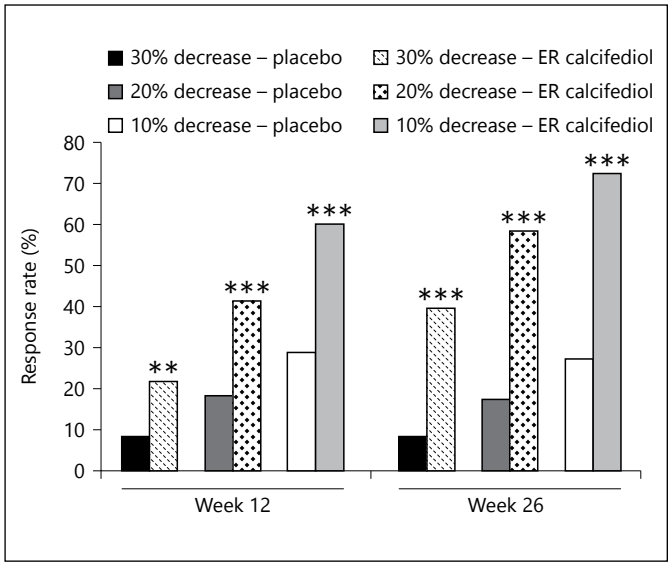

Fig. 3. Response rates for plasma iPTH reductions of ≥30, ≥20 and ≥10% by treatment group and duration of treatment in the pooled PP population. Data for each subject at weeks 12 and 26 represent the mean of up to 3 values obtained in the periods of weeks 8–12 and 20–26, respectively. ** $p < 0.005$ vs. placebo, *** $p < 0.0001$ vs. placebo.

the open-label extension study, the gradual decrease in plasma iPTH continued for subjects receiving ER calcifediol. For subjects switching from placebo to ER calcifediol, plasma iPTH declined in a manner similar to that observed previously with active treatment in the 2 blinded studies.

In the ITT population, the proportion of subjects who achieved at least a 30% reduction in plasma iPTH in the EAP was greater with ER calcifediol than with placebo treatment in both studies (33 vs. 8% in study A ($p < 0.001$) and 34 vs. 7% in study B ($p < 0.001$)) irrespective of whether the CKD stages were combined or analyzed separately. In the pooled PP population, response rates rose with duration of ER calcifediol therapy, reaching 22% after 12 weeks, 40% after 26 weeks and 50% after 52 weeks, compared with <8% for placebo ($p < 0.001$). Response rates were higher in the PP analysis because subjects who terminated prematurely were deemed to be non-responders in the ITT analysis, irrespective of observed changes in plasma iPTH. Figure 3 shows that more (72%) subjects in the pooled PP population treated with ER calcifediol achieved reductions in plasma iPTH of at least 10% in the EAP (weeks 20–26) than subjects (27%) treated with placebo ($p < 0.01$).

Serum Total 1,25-Dihydroxyvitamin D and 24,25-Dihydroxyvitamin D_3

Mean (SE) serum total 1,25-dihydroxyvitamin D and 24,25-dihydroxyvitamin D_3 levels at baseline were 34.4 (0.9) pg/ml and 1.0 (0.04) ng/ml, respectively, in the pooled ER calcifediol group compared to 36.0 (1.3) pg/ml and 1.0 (0.04) ng/ml in the pooled placebo group. Mean serum levels of these 2 metabolites increased gradually with ER calcifediol treatment versus both placebo treatment and baseline to 46.7 (1.0) pg/ml and 3.8 (0.1) ng/ml after 26 weeks ($p < 0.05$), respectively. No changes were observed with placebo treatment.

Serum Ca and P

Subjects randomized to ER calcifediol experienced a slightly greater mean (SE) increase in serum Ca than those randomized to placebo (fig. 4). This increase was 0.2 (0.02) mg/dl for ER calcifediol versus 0.1 (0.03) mg/dl for placebo ($p < 0.001$), and resulted primarily from upward correction of a subset of serum Ca values that were in the low normal range at baseline. Six subjects (2%) in the ER calcifediol treatment group and no subjects (0%) in the placebo group required dose reductions for protocol-defined hypercalcemia (2 consecutive serum Ca values >10.3 mg/dl). All but one of these subjects exhibited a tendency toward elevated serum Ca before treatment, as evidenced by occasional serum Ca values ≥9.8 mg/dl during the screening period. The only exception was a patient who developed hypercalcemia as a consequence of prolonged high doses with a thiazide diuretic. A total of 4.2% of active-treated subjects and 2.1% of placebo-treated subjects experienced at least 1 elevation in serum Ca above the upper limit of normal (10.5 mg/dl), none of which were clinically significant.

Patients randomized to ER calcifediol also experienced a slightly greater mean (SE) increase in serum P than patients randomized to placebo, namely 0.2 (0.03) vs. 0.1 (0.04) mg/dl. One subject (0.4%) in the active treatment group met protocol-defined hyperphosphatemia (2 consecutive serum P values >5.5 mg/dl deemed to be study drug related) compared to no subjects in the placebo group. A total of 45% of active-treated subjects and 44% of placebo-treated subjects experienced at least one elevation in serum P above the upper limit of normal (4.5 mg/dl)

Urine Ca/Cr

Mean (SE) ratios of urine Ca:Cr were 0.04 (0.003) in the ER calcifediol group and 0.04 (0.005) in the placebo treatment group at baseline, and were unchanged after 26 weeks of treatment.

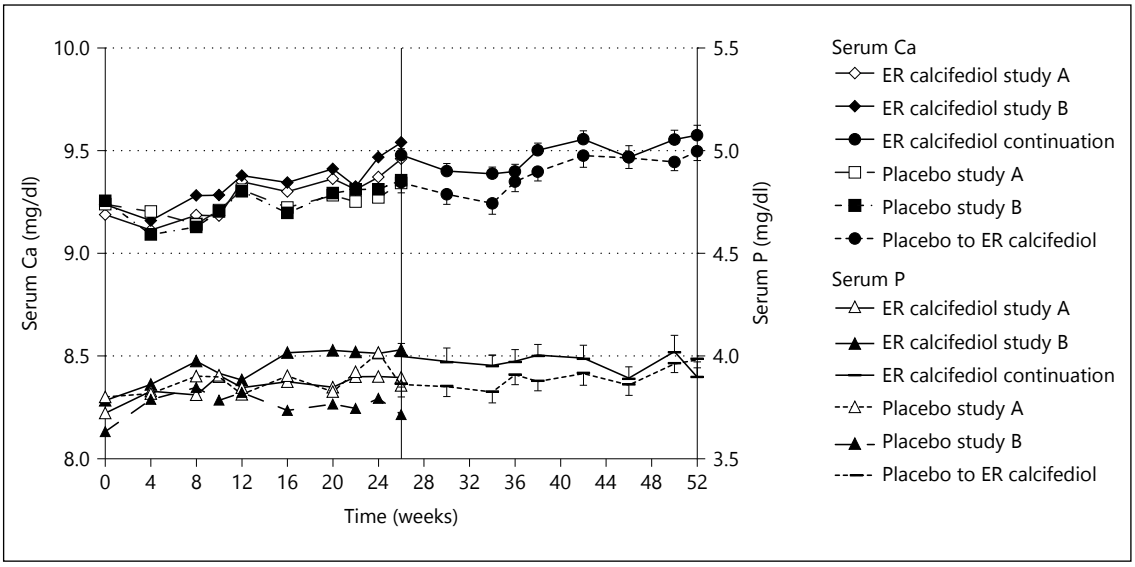

Fig. 4. Mean (SE) change over time in serum Ca and P in the pooled PP population. Data points from 0 to 26 weeks represent mean values for individual time points from placebo-controlled studies A and B. Error bars in this portion of the figure are omitted for clarity. Data points from 26 to 52 weeks represent mean ± SE values for data from the open-label extension study.

Serum FGF23

Mean (SE) serum FGF23 levels showed similar trends in the pooled ER calcifediol group (from 41.4 (3.5) to 54.9 (5.2) ng/ml) and in the pooled placebo group (from 38.3 (3.6) to 53.4 (7.1) ng/ml) after 26 weeks of treatment (p = NS). No significant differences in serum FGF23 levels were noted between treatment groups at any time point.

Estimated Glomerular Filtration Rate

Pooled data from studies A and B showed that the ER calcifediol and placebo groups experienced identical percentage declines (–2.2%) in mean eGFR over the 26-week treatment period. Mean (SE) serum Cr was slightly higher at baseline in the ER calcifediol treatment group (2.2 ± 0.05 vs. 2.1 ± 0.06 mg/dl, respectively), and both treatment groups experienced a 0.1 mg/dl increase over the 26-week treatment period.

Adverse Events

The percentages of subjects that experienced at least one TEAE were comparable in the pooled placebo (69.4%) and ER calcifediol (67.4%) groups. Most TEAEs were not serious (84.0% with placebo vs. 81.8% with ER calcifediol) and were mild or moderate in severity (87.0% with placebo vs. 85.4% with ER calcifediol). The most common TEAEs that were observed in at least 4% of placebo subjects and more frequently than in ER calcifediol subjects were urinary tract infection (9.0 vs. 4.9%), diarrhea (8.3 vs. 4.2%), hypertension (7.6 vs. 6.3%), back pain (5.6 vs. 2.5%), pain in extremity (5.6 vs. 2.1%), peripheral edema (5.6 vs. 4.6%), arthralgia (4.9 vs. 2.8%), chest pain (4.9 vs. 2.5%), gout (4.9 vs. 3.5%), upper respiratory tract infection (4.9 vs. 2.5%), nausea (4.2 vs. 3.2%), vomiting (4.2 vs. 1.4%), hypokalemia (4.2 vs. 1.4%) and metabolic acidosis (4.2 vs. 1.1%). The most common TEAEs that were observed in at least 4% of ER calcifediol subjects and more frequently than in the placebo subjects were anemia (4.9 vs. 3.5%), nasopharyngitis (4.9 vs. 2.8%), increased blood Cr (4.9 vs. 1.4%) and dyspnea (4.2 vs. 2.8%). ER calcifediol was well tolerated based on the low rate of discontinuations due to TEAEs (5.7% compared with 2.8% for placebo in study A, and 4.9 vs. 5.6% in study B).

Discussion

Supplementation with ergocalciferol or cholecalciferol is recommended for SHPT associated with vitamin D insufficiency by the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Bone Metabolism and Disease in CKD [8], the more recent Kidney Disease: Improving Global Outcomes Guideline for CKD-MBD [11] and the Endocrine Society's Guideline for the Treatment and Prevention of vitamin D Deficiency [7]. None of these clinical practice guidelines provides guidance on how supplements should best be administered. Published

studies have reported daily vitamin D doses of 700–4,000 IU, weekly doses of 5,000–50,000 IU and monthly doses of 50,000–300,000 IU. Recent reviews, however, have concluded that there is little, if any, benefit of nutritional vitamin D replacement in CKD [12, 13].

In current clinical practice, therapy with a VDRA is initiated in CKD patients when vitamin D supplements are found ineffective in lowering PTH [8, 11]. Although VDRAs effectively lower plasma PTH, they leave serum 25-hydroxyvitamin D uncorrected (and potentially lower) [16], depriving tissues with CYP27B1 of adequate substrate for local hormone production. Bolus oral or intravenous administration of VDRAs produces supraphysiological surges in blood vitamin D hormone levels, causing unwanted elevation of FGF23 and CYP24A1-mediated vitamin D catabolism, both of which are implicated in the observed development of resistance to vitamin D therapy [17].

Published clinical studies [18–20] have shown that immediate-release (IR) calcifediol failed to produce clinically meaningful reductions in PTH (≥30% from pre-treatment levels) in patients with stage 3 or 4 CKD unless administered at doses that sustained serum 25-hydroxyvitamin D at levels well above the upper limit of the normal range (100 ng/ml). In one study [18], subjects were treated with oral calcifediol (10–50 μg/day) or calcium carbonate (control) for 2 years. The PTH responses in the 2 treatment groups were reported as 'comparable' and, in aggregate, decreased by 4%. Another study [19] reported that a much higher dose (160 μg orally per day) reduced PTH by 6%. A third study [20] reported a mean decrease in PTH of 21% at 200 μg/day orally or 500 μg given intravenously every 1–5 days. Although blood 25-hydroxyvitamin D levels were not reported, such high doses would have been expected to produce sustained serum total 25-hydroxyvitamin D levels far above 100 ng/ml, based on the published dose–response data [21].

ER calcifediol increases serum total 25-hydroxyvitamin D at a slower rate than IR formulations. A single-dose comparative study conducted in vitamin D-deficient rats [14] demonstrated that IR calcifediol produced surges in serum calcitriol that triggered substantial CYP24A1 and FGF23 induction, whereas ER calcifediol produced similar but more gradual hormonal exposure with only minimal effects on CYP24A1 and FGF23. A single-dose comparative clinical study showed that ER calcifediol was more effective than IR calcifediol in lowering elevated plasma iPTH in CKD patients with vitamin D insufficiency [14]. A 6-week randomized, double-blind placebo-controlled study in CKD patients demonstrated that daily bedtime doses of 30, 60 or 90 μg of ER calcifediol increased serum 25-hydroxyvitamin D levels to ≥30 ng/ml in more than 90% of treated subjects and dosages of ≥60 μg/day reduced plasma iPTH by ≥30% from pre-treatment baseline in more than 60% of subjects without meaningful impact on serum Ca, P or FGF23 [10].

The present studies have extended these findings by examining the safety and efficacy of 30–60 μg/day of ER calcifediol in treating SHPT in patients with stage 3 or 4 CKD over a treatment period of up to 52 weeks. The two 26-week studies (studies A and B), with identical randomized, double-blind and placebo-controlled designs, demonstrated that ER calcifediol reproducibly raised both serum total 25-hydroxyvtiamin D and 1,25-dihydroxyvitamin D and reduced mean plasma iPTH by at least 30% from pre-treatment baseline in a greater proportion of subjects than matching placebo ($p < 0.0001$), using a pre-specified analysis. Pooled data from all 3 studies showed that iPTH suppression became progressively greater with continuing ER calcifediol treatment, reaching 50% after 52 weeks. The majority of subjects (72%) treated with ER calcifediol experienced a PTH-lowering benefit of at least 10% after 26 weeks.

The proportion of subjects in the ITT population of each 26-week study achieving a serum total 25-hydroxyvitamin D level of at least 30 ng/ml in the EAP (weeks 20–26) was greater with ER calcifediol (≥80%) than with placebo treatment (≤7%; $p < 0.0001$). Response rates with ER calcifediol were similarly high in both studies and >95% in the PP population. These data showed that ER calcifediol, unlike any commonly prescribed regimen of nutritional vitamin D, reliably raised serum total 25-hydroxyvitamin D to levels (mean of 50–67 ng/ml) required for plasma iPTH suppression. The observation that serum 25-hydroxyvitamin D levels >30 ng/ml are required for iPTH control in CKD has been previously reported [22]. The small rise in serum total 25-hydroxyvitamin D observed between 38 and 42 weeks of treatment with ER calcifediol (fig. 1) resulted in dose titration from 30 to 60 μg/day without the restriction that pre-titration 25-hydroxyvitamin D levels be <65 ng/ml. Patients with massive proteinuria were excluded from participation in these 2 studies. It is, therefore, unknown if ER calcifediol therapy could overcome proteinuric loss of 25-hydroxyvitamin D in these patients. A significant inverse relationship was observed in the pooled data between serum total 25-hydroxyvitamin D and proteinuria in subjects treated with ER calcifediol.

Data from the 3 trials presented herein, and from one previous controlled study [10], have all demonstrated

that ER calcifediol is well tolerated at higher 25-hydroxyvitamin D levels within the normal range and that subjects' compliance with the prescribed doses is excellent. The incidences of TEAEs in studies A and B were similar between subjects treated with ER calcifediol and placebo, and there was a low rate of discontinuations due to TEAEs (5.3% for ER calcifediol compared with 4.2% for placebo). The 6 observed episodes of hypercalcemia (2 consecutive serum Ca values >10.3 mg/dl) with ER calcifediol were not related to dose, serum total 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D level, or use of elemental Ca or Ca-based phosphate binder, supporting an etiology related to an extrinsic (diet or drug) or intrinsic (intestinal transport) factor. No data from these studies have suggested that ER calcifediol has an adverse effect on renal function; mean serum Cr increase and mean eGFR decline were similar in the active and placebo groups. High serum concentrations of 25-hydroxyvitamin D_3 (>300 ng/ml) have been reported to exacerbate tubular interstitial injury in CYP27B1 knockout mice [23], but these levels were much greater than those recorded in the present studies. Mean adherence to study drug was over 95% in all studies.

Conclusions

These data presented from the two 26-week randomized, double-blind, placebo-controlled trials and a subsequent 26-week extension study show that oral ER calcifediol administered in daily bedtime doses of 30 or 60 μg is safe and effective in treating SHPT and correcting the underlying vitamin D insufficiency in adult patients with stage 3 or 4 CKD. They indicate that ER calcifediol may provide a more reliable and standardized approach to vitamin D repletion than any commonly used regimens of nutritional vitamin D and may reduce dependency on the more calcemic VDRA therapies for controlling SHPT in CKD patients not requiring regular dialysis.

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