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Modified-Release Calcifediol Effectively Controls Secondary Hyperparathyroidism Associated with Vitamin D Insufficiency in Chronic Kidney Disease

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Key Words

Chronic kidney disease (CKD) · Secondary hyperparathyroidism (SHPT) · Vitamin D · Vitamin D insufficiency · Calcifediol (25-hydroxyvitamin D_3) · Calcitriol (1,25-dihydroxyvitamin D_3) · Parathyroid hormone (PTH)

Abstract

Background/Aims: Vitamin D insufficiency drives secondary hyperparathyroidism (SHPT) and is associated with increased cardiovascular mortality in patients with chronic kidney disease (CKD). SHPT is poorly addressed by current vitamin D repletion options. The present study evaluated a novel investigational vitamin D repletion therapy: a modified-release (MR) formulation of calcifediol designed to raise serum 25-hydroxyvitamin D in a gradual manner to minimize the induction of CYP24 and, thereby, improve the SHPT control. ***Methods:*** This randomized, double-blind, placebo-controlled trial evaluated MR calcifediol in CKD subjects (n = 78) with plasma intact parathyroid hormone (iPTH) >70 pg/ml and serum total 25-hydroxyvitamin D <30 ng/ml. Subjects received daily treatment for six weeks with oral MR calcifediol (30, 60 or 90 μg) or a placebo. ***Results:*** More than 90% of subjects treated with MR calcifediol achieved serum 25-hydroxyvitamin D levels ≥30 ng/ml versus 3% of subjects treated with placebo ($p < 0.0001$). Mean plasma iPTH decreased from baseline (140.3 pg/ml) by 20.9 ± 6.2% (SE), 32.8 ± 5.7 and 39.3 ± 4.3% in the 30, 60 and 90 μg dose groups, respectively, and increased 17.2 ± 7.8% in the pooled placebo group ($p < 0.005$). No clinically significant safety concerns arose during MR calcifediol treatment. ***Conclusion:*** Oral MR calcifediol appears safe and highly effective in treating SHPT associated with vitamin D insufficiency in CKD.

Introduction

Vitamin D insufficiency afflicts more than 20 million adults in the United States (US) having stage 1 through 4 chronic kidney disease (CKD) [1]. The prevalence of vitamin D insufficiency increases with CKD severity and is associated with low serum total 1,25-dihydroxyvitamin D, secondary hyperparathyroidism (SHPT) and metabolic bone disease, suggesting that vitamin D insufficiency has a causal role in these related disorders [2, 3].

Multiple factors drive vitamin D insufficiency in CKD including nutritional inadequacy, decreased sunlight exposure, proteinuric loss and decreased hepatic synthesis of 25-hydroxyvitamin D, and increased expression of

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CYP24, the cytochrome P-450 enzyme that specifically catabolizes vitamin D and its metabolites [4–6]. Adequate production of 1,25-dihydroxyvitamin D by renal and extra-renal 1α-hydroxylase (CYP27B1) requires sufficient 25-hydroxyvitamin D supply. Consequently, vitamin D insufficiency can cause reduced vitamin D hormone production and its sequelae of decreased intestinal absorption of dietary calcium (Ca), increased secretion of parathyroid hormone (PTH), and metabolic bone disease. Inadequate 1,25-dihydroxyvitamin D production is exacerbated by increased fibroblast growth factor 23 (FGF23), which causes progressive decreases in renal CYP27B1 activity with advancing CKD [7, 8].

The K/DOQI and KDIGO Clinical Practice Guidelines for the treatment of metabolic bone disease in CKD recommend regular screening for elevated PTH beginning in stage 3 CKD [9, 10]. They also recommend testing for vitamin D insufficiency as soon as elevated PTH is encountered, and correcting it with oral ergocalciferol or cholecalciferol supplementation. Consensus is lacking on the definition of vitamin D insufficiency with K/DOQI, for example, defining it as <30 ng/ml and the Institute of Medicine (IOM) favoring <20 ng/ml [11]. Supplementation with vitamin D has been found to be inconsistently effective and often inadequate in patients with predialysis CKD, leaving SHPT largely uncorrected [12]. Thus, therapy with vitamin D receptor activators (VDRAs) is required to treat SHPT in many predialysis CKD patients. Although VDRAs lower plasma PTH, they also can raise FGF23 and CYP24-mediated vitamin D catabolism, as evidenced by elevated 24,25-dihydroxyvitamin D [13]. Clearly, improved vitamin D repletion therapy is needed.

An overlooked vitamin D repletion therapy is calcifediol (25-hydroxyvitamin D_3). Oral calcifediol was approved in the United States in 1980 for the treatment for metabolic bone disease in dialysis patients and was withdrawn from the market in 2001–2002 for commercial reasons; it was displaced by VDRAs. Calcifediol is more readily absorbed in the intestine than ergocalciferol or cholecalciferol due to its increased polarity and resulting lack of reliance on adequate bile secretion [14–16]. Many clinical studies have shown that immediate-release (IR) calcifediol boosts serum 25-hydroxyvitamin D more effectively than ergocalciferol or cholecalciferol [17–19]. However, IR calcifediol produces only clinically meaningful reductions in PTH (≥30% from pre-treatment levels) in CKD patients when administered at doses that raise serum 25-hydroxyvitamin D to supra-physiological levels (>100 ng/ml) [20, 21]. High doses of IR calcifediol cause surges in serum 1,25-dihydroxyvitamin D which, in turn, induce the expression of CYP24 in target tissues such as the parathyroid glands, attenuating the desired inhibition of PTH secretion [22].

The present study evaluated a modified-release (MR) formulation of calcifediol, designed to raise serum 25-hydroxyvitamin D in a gradual manner to physiological levels (≥30 to ≤100 ng/ml), avoiding excessive induction of CYP24. In this study, the efficacy and safety of a 6-week course of daily MR calcifediol was compared to placebo in elevating serum 25-hydroxyvitamin D to ≥30 ng/ml (adequacy) and in reducing elevated plasma intact PTH (iPTH) in predialysis CKD patients with SHPT and vitamin D insufficiency.

Methods

Study Design

This randomized, double-blind, placebo-controlled trial involved 78 subjects recruited from 16 US sites into two cohorts studied sequentially. Subjects in each cohort were randomized to 6 weeks of daily treatment with either MR calcifediol or a matching placebo, followed by 6 weeks of post-treatment monitoring. In Cohort 1, a total of 51 subjects were assigned to three treatment groups (n = 17) receiving MR calcifediol (60 or 90 μg) or placebo. In Cohort 2, 27 subjects were assigned to two treatment groups receiving 30 μg of MR calcifediol (n = 13) or placebo (n = 14). Plasma iPTH and serum Ca, phosphorus (P), calcifediol, total 25-dihydroxyvitamin D and total 1,25-dihydroxyvitamin D were measured weekly. Routine blood chemistries, hematologic parameters, fasting spot urine Ca and creatinine (Cr) levels, and serum FGF23, bone-specific alkaline phosphatase (BAP), C-reactive protein (CRP) and bone natriuretic protein (BNP) were measured monthly. An independent Data Safety Monitoring Board (DSMB) monitored patient safety throughout the study. The primary efficacy endpoints were the proportion of subjects that achieved (a) serum 25-hydroxyvitamin D levels of ≥30 ng/ml and (b) mean percent reductions of plasma iPTH of ≥30% from pre-treatment baseline at the end of treatment (EOT).

Subject Selection

Eligible subjects had ages between 18 and 85 (inclusive) and CKD (not requiring regular dialysis) as evidenced by an estimated glomerular filtration rate (eGFR) of ≥25 and <70 ml/min/1.73 m^2. Other eligibility criteria included serum total 25-hydroxyvitamin D between 10 and 29 ng/ml (inclusive), plasma iPTH above 70 pg/ml, serum Ca of ≥8.4 to <10.0 mg/dl and serum P of ≥2.0 to <5.0 mg/dl. Exclusion criteria included spot urine Ca:Cr ratio >0.2, nephrotic range proteinuria (>3 mg/mg Cr), and history of parathyroidectomy or renal transplantation. Subjects taking more than 1,000 mg/day of elemental Ca reduced their intake for the duration of the study and underwent a 14-day pre-treatment washout. Subjects receiving supplementation with ergocalciferol or cholecalciferol maintained a stable dose below 1,600 IU/day. Any bone metabolism therapy (with the exception of bisphosphonates) that could potentially interfere with study endpoints was discontinued for the duration of the study and a 28-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.

Drug Products and Dosing

Calcifediol was purchased from the Dishman Group (Veenendaal, the Netherlands) and formulated in MR capsules containing 30, 60 or 90 μg by Catalent Pharma Solutions (Clearwater, Fla., USA). The capsules gradually released calcifediol over a 12-hour period during in vitro dissolution testing. Placebo capsules had the same formulation except for the omission of calcifediol. Subjects were instructed to take one capsule by mouth every day at bedtime (with liquid). Subjects discontinued dosing if they had confirmed plasma iPTH <30 pg/ml, serum Ca >10.5 mg/dl, serum p >5.5 mg/dl (only if deemed to be study drug related), or serum 25-hydroxyvitamin D >100 ng/ml.

Subject Disposition

Nine subjects terminated study participation prematurely: 2 withdrew consent (1 each in the placebo and 30 μg groups); 2 experienced an adverse event requiring study termination (1 in the placebo group and 1 in the 90 μg group); 3 reached laboratory safety parameters (1 in the 60 μg group exhibited serum Ca of 10.6 to 10.7 mg/dl, 1 in the 90 μg group developed serum 25-hydroxyvitamin D >100 ng/ml, and 1 in the 90 μg group exhibited plasma iPTH <30 pg/ml); and 2 were lost to follow-up (both in the 90 μg group). Four of these subjects terminated during the post-treatment observation period.

Laboratory and Clinical Procedures

Blood samples were shipped for analysis to SpectraEast Laboratory (Rockleigh, N.J., USA). Plasma iPTH levels were determined by two-site sandwich immunochemiluminescence. Serum total 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, BAP and BNP were determined by chemiluminescence. CRP was analyzed using a turbidometric assay. Serum samples were forwarded to PharmaNet (Quebec City, Que., Canada) for analysis of calcifediol by high-performance liquid chromatography with tandem mass spectrometry detection, and to Queens University (Kingston, Ont., Canada) for analysis of intact FGF23 by ELISA (Immunotopics, San Clemente, Calif., USA). A 12-lead electrocardiogram (ECG) and the Beck Depression Inventory Questionnaire [23] were obtained from each subject prior to and after the 6-week treatment period.

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 (MDRD) equation [24]. Pre-treatment 'baseline' values for all parameters were defined as the average of three determinations obtained at (a) the two latest screening visits and (b) prior to dosing on the day that treatment was initiated. EOT values were defined as the average of three determinations obtained at ~12 h after the last administered dose in the 5th week of treatment and at ~12 and ~36 h after the last administered dose in the 6th week of treatment. Efficacy endpoints were analyzed in the intent-to-treat (ITT) and per-protocol (PP) populations, but results of only the PP analyses are reported herein, since there were no material differences between the two analyses. The PP population was defined as the 73 subjects who completed the 6-week treatment period.

The pharmacokinetic (PK) parameters for baseline-corrected serum calcifediol and total 1,25-dihydroxyvitamin D were derived using non-compartmental analysis. Area under the serum concentration-time curve (AUC) was estimated using the linear trapezoid rule. The $t_{1/2}$ was calculated by determination of the elimination rate constant from concentration values in the follow-up period.

Results

Study Population

Demographic and baseline characteristics of the 78 randomized subjects are summarized in table 1, by treatment group. No significant differences in these characteristics were detected between the two placebo groups, or between the pooled placebo group and any of the three active treatment groups. No significant differences were observed among the treatment groups for prior or concomitant medications. Key baseline and EOT characteristics of the 73 subjects comprising the PP population are shown in table 2.

Serum Total 25-Hydroxyvitamin D

The mean baseline 25-hydroxyvitamin D for all 78 subjects was 21.3 ng/ml. The 6-week course of daily MR calcifediol effectively treated vitamin D insufficiency as more than 90% of subjects in the 30, 60 and 90 μg dose groups achieved adequate serum 25-hydroxyvitamin D levels (≥30 ng/ml) by EOT compared with only 3% in the pooled placebo group ($p < 0.0001$). Daily MR calcifediol increased mean serum 25-hydroxyvitamin D approximately in proportion to the administered dose (fig. 1). The 30 and 90 μg doses increased mean serum 25-hydroxyvitamin D at EOT to 37.3 ± 2.0 (SE) ng/ml and to 84.8 ± 5.5 ng/ml, respectively. A mean decrease of 1.9 ± 0.7 ng/ml was observed in the pooled placebo group. Differences between the three MR calcifediol groups and the placebo group were all significant ($p < 0.0001$).

Serum Calcifediol

Mean serum calcifediol concentrations gradually increased during treatment in a dose-dependent fashion and then decreased thereafter (fig. 2). Mean peak concentrations (Cmax), after adjustment for baseline values, were 27.8 ± 2.4 (SE), 60.3 ± 4.7 and 85.7 ± 7.2 ng/ml for the 30, 60 and 90 μg groups, respectively. Calcifediol exposures, calculated as mean background adjusted area-under-the-curve (AUC 0–6 weeks), were dose proportional and the median terminal elimination half-life ($t_{1/2}$) was 24 to 36 days. Linear regression analyses of slopes between each 2 consecutive PK time points indicated that

Table 1. Subject demographic and baseline characteristics (all randomized subjects)

Characteristic	Placebo			MR calcifediol				Total (n = 78)
	Cohort 1 (n = 17)	Cohort 2 (n = 14)	Total (n = 31)	30 μg (n = 13)	60 μg (n = 17)	90 μg (n = 17)	Total (n = 47)	
Sex								
Female	13 (76.5)	7 (50.0)	20 (64.5)	7 (53.8)	7 (41.2)	9 (52.9)	23 (48.9)	43 (55.1)
Male	4 (23.5)	7 (50.0)	11 (35.5)	6 (46.2)	10 (58.8)	8 (47.1)	24 (51.1)	35 (44.9)
Race								
White	10 (58.8)	6 (42.9)	16 (51.6)	8 (61.5)	14 (82.4)	10 (58.8)	32 (68.1)	48 (61.5)
Black or African-American	7 (41.2)	8 (57.1)	15 (48.4)	4 (30.8)	3 (17.6)	7 (41.2)	14 (29.8)	29 (37.2)
Other	0	0	0	1 (7.7)	0	0	1 (2.1)	1 (1.3)
Ethnicity								
Hispanic or Latino	2 (11.8)	1 (7.1)	3 (9.7)	2 (15.4)	2 (11.8)	1 (5.9)	5 (10.6)	8 (10.3)
Not Hispanic or Latino	15 (88.2)	13 (92.9)	28 (90.3)	11 (84.6)	15 (88.2)	16 (94.1)	42 (89.4)	70 (89.7)
Age, years	61.9±17.79	63.9±11.47	62.8±15.06	58.2±16.14	64.7±9.20	65.4±11.41	63.1±12.34	63.0 (13.39)
BMI, kg/m^2	35.2±7.63	32.0±7.73	33.7±7.73	33.5±8.76	35.5±6.74	36.7±6.84	35.4±7.33	34.7 (7.48)
Ca, mg/dl	9.4±0.31	9.4±0.31	9.4±0.31	9.3±0.44	9.3±0.36	9.3±0.30	9.3±0.36	9.3 (0.34)
P, mg/dl	3.6±0.43	3.4±0.48	3.5±0.46	3.8±0.55	3.5±0.58	3.8±0.52	3.7±0.55	3.6 (0.52)
iPTH, pg/ml	160.6±65.90	127.6±69.04	145.7±68.27	150.8±58.87	115.3±28.30	147.4±58.56	136.7±51.41	140.3 (58.44)
eGFR, ml/min/1.73 m^2	36.9±14.04	40.9±11.37	38.7±12.86	36.7±11.00	42.6±9.13	37.2±10.22	39.5±9.80	39.2 (11.04)
25-hydroxyvitamin D, ng/ml	18.9±5.49	20.6±5.50	19.7±5.47	21.7±6.56	23.4±4.52	21.8±4.81	22.3±5.20	21.3 (5.43)
1,25-dihydroxyvitamin D, pg/ml	23.4±12.20	22.7±12.55	23.1±12.16	18.8±7.70	21.7±7.02	20.9±7.81	20.6±7.43	21.6 (9.60)

Values are presented as n (%) or mean ± SD.

Table 2. Subject end of treatment characteristics (per protocol subjects)

Characteristic	Placebo			MR calcifediol			
	Cohort 1 (n = 17)	Cohort 2 (n = 14)	Total (n = 31)	30 μg (n = 12)	60 μg (n = 16)	90 μg (n = 14)	Total (n = 42)
Baseline							
Ca, mg/dl	9.4±0.31	9.4±0.31	9.4±0.31	9.3±0.46	9.3±0.34	9.3±0.33	9.3±0.37
P, mg/dl	3.6±0.43	3.4±0.48	3.5±0.46	3.8±0.58	3.6±0.58	3.8±0.55	3.7±0.57
iPTH, pg/ml	160.6±65.90	127.6±69.04	145.7±68.27	156.3±57.92	118.5±25.89	155.9±58.51	141.7±50.72
25-hydroxyvitamin D, ng/ml	18.9±5.49	20.6±5.50	19.7±5.47	21.1±6.49	23.6±4.54	21.1±5.02	22.1±5.33
Ca/Creatinine, mg/g	22.7±25.75	29.2±20.03	25.5±23.29	19.6±12.59	40.8±39.80	38.3±46.44	34.1±37.57
FGF23, pg/ml	22.2±12.29	20.6±13.05	21.5±12.45	37.5±30.33	23.8±16.18	28.8±18.07	29.4±21.85
eGFR, ml/min/1.73 m^2	36.9±14.04	40.9±11.37	38.7±12.86	35.6±10.69	42.6±9.42	36.0±10.59	38.9±10.01
End-of-treatment							
Ca, mg/dl	9.4±0.40	9.4±0.28	9.4±0.35	9.4±0.45	9.4±0.33	9.4±0.29	9.4±0.35[a]
P, mg/dl	3.7±0.54	3.5±0.54	3.6±0.55	4.0±0.74	3.9±0.78	4.0±0.63	4.0±0.70
iPTH, pg/ml	187.1±86.04	139.6±72.64	165.7±82.54	123.6±57.39[b]	78.8±31.33[b]	93.4±41.10[b]	96.5±46.03[c]
25-hydroxyvitamin D, ng/ml	18.3±5.22	18.7±5.69	18.5±5.35	37.3±6.95[c]	66.9±17.72[c]	84.8±20.49[c]	64.4±24.90[c]
Ca/Creatinine, mg/g	56.7±66.65	53.33±98.50	55.0±82.27	40.9±62.07	45.1±47.32	44.6±61.95	43.8±54.41
FGF23, pg/ml	28.7±23.35	24.5±33.56	26.8±27.99	36.9±26.31	27.9±14.60	36.6±24.92	33.4±22.28
eGFR, ml/min/1.73 m^2	36.7±12.82	41.1±12.15	38.7±12.52	36.1±13.08	37.8±10.24	37.3±11.39	37.2±11.22

End of treatment (EOT) values were compared to baseline values using a mixed effect model: [a] $p < 0.05$; [b] $p < 0.001$; [c] $p < 0.0001$. Values are mean ± SD.

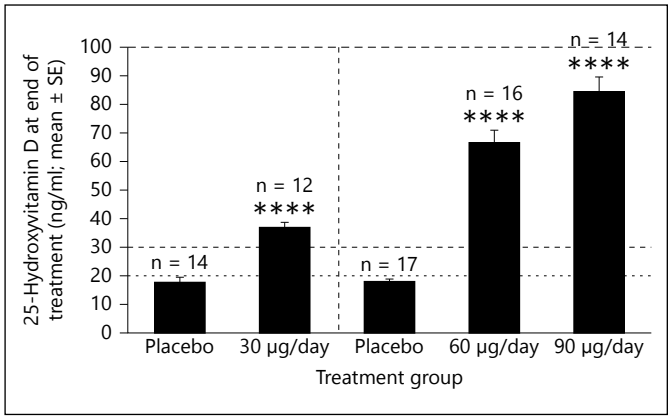

Fig. 1. Changes in serum 25-hydroxyvitamin D. Serum total 25-hydroxyvitamin D (ng/ml) at the end of the 6-week treatment period increased approximately in proportion to the administered dose (30, 60 or 90 µg/day) in all groups receiving MR calcifediol and relative to the placebo groups, with all differences between each active and corresponding placebo group reaching significance. The three horizontal dashed lines indicate the lower limit of normal per the IOM (fine) and K/DOQI (medium), and the upper limit of the laboratory reference range (coarse). **** Significantly different from placebo, $p < 0.0001$.

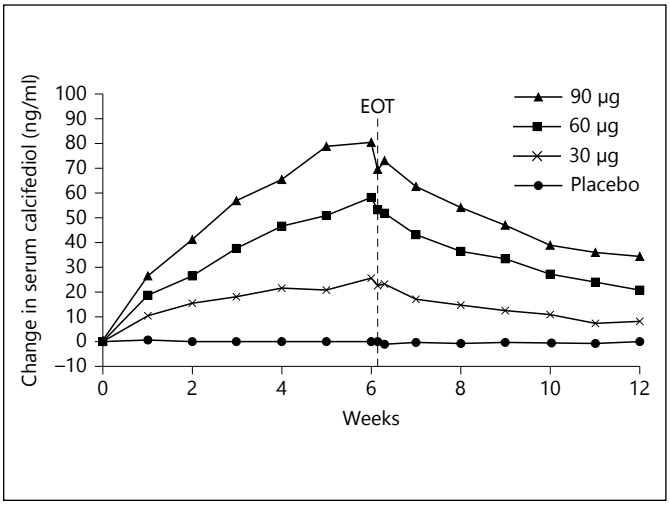

Fig. 2. Changes in calcifediol (25-hydroxyvitamin D_3). Serum calcifediol concentrations (ng/ml) gradually increased during the 6-week treatment period from pre-treatment baseline in proportion to the administered dose (30, 60 or 90 µg/day) in all groups receiving MR calcifediol, and declined after the end of treatment (EOT). Plotted values have been corrected for differences in baseline.

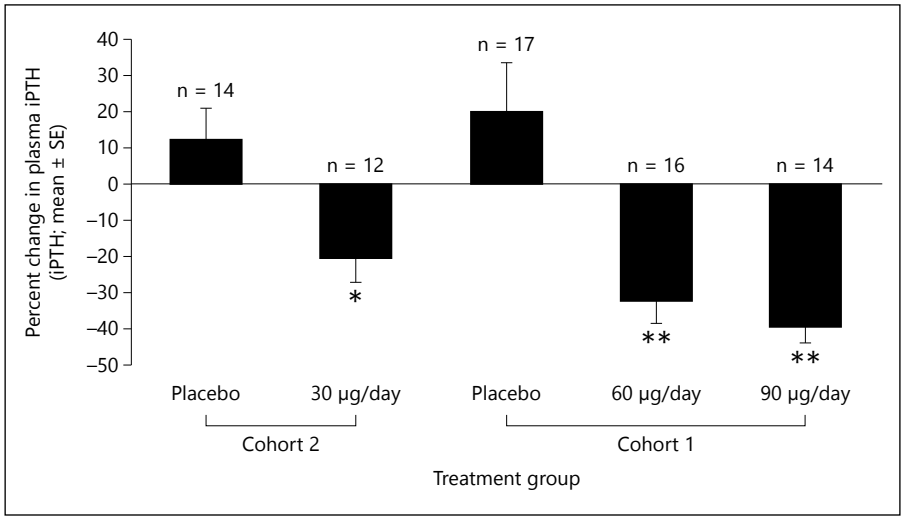

Fig. 3. Changes in plasma iPTH. Percent changes in plasma iPTH at the end of the 6-week treatment period from pre-treatment baseline were negative and approximately proportional to the administered dose (30, 60 or 90 µg/day) in all groups receiving MR calcifediol and positive in the placebo groups, with differences between each active and corresponding placebo group reaching significance. * Significantly different from placebo, $p < 0.05$; ** Significantly different from placebo, $p < 0.001$.

steady state levels of calcifediol would have been achieved after 8 to 9 weeks of dosing. Racial differences in serum calcifediol levels at EOT were not detected.

Plasma iPTH

Mean baseline iPTH concentration for the study population was 140.3 pg/ml. Daily MR calcifediol therapy progressively reduced the mean iPTH from baseline approximately in proportion to the administered dose (fig. 3). The mean percent changes from baseline at EOT were –20.9 ± 6.2% (SE), –32.8 ± 5.7% and –39.3 ± 4.3% for the 30, 60 and 90 µg dose groups, respectively, compared to +17.2 ± 7.8 in the pooled placebo group ($p < 0.005$). The proportion of subjects treated with MR calcifediol who achieved a mean reduction of at least 20% increased progressively with dose reaching 93% in the 90 µg group, and

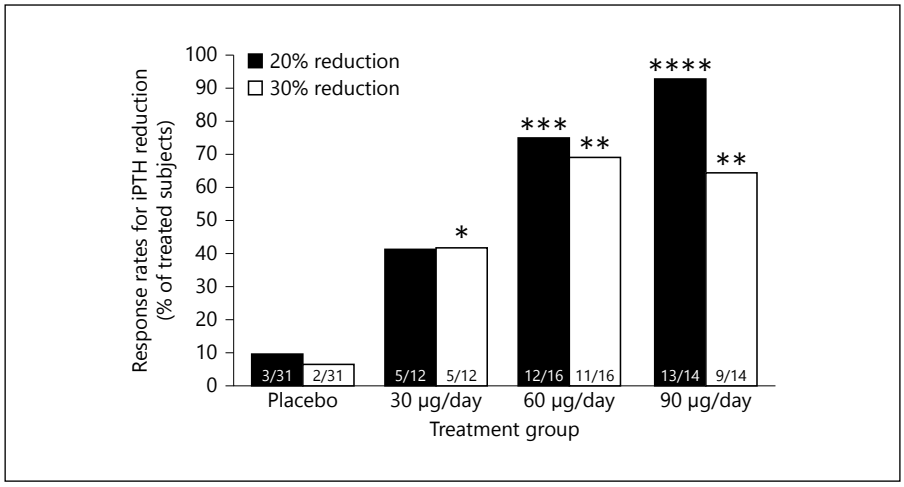

Fig. 4. Response rates for plasma iPTH reduction. The portion of subjects attaining a reduction in plasma iPTH of at least 20 or 30% is shown for three groups receiving MR calcifediol (30, 60 or 90 µg/day) and the pooled placebo group, with significance noted for differences between active and placebo treatment. * Significantly different from placebo, $p < 0.05$; ** Significantly different from placebo, $p < 0.01$; *** Significantly different from placebo, $p < 0.001$; **** Significantly different from placebo, $p < 0.0001$.

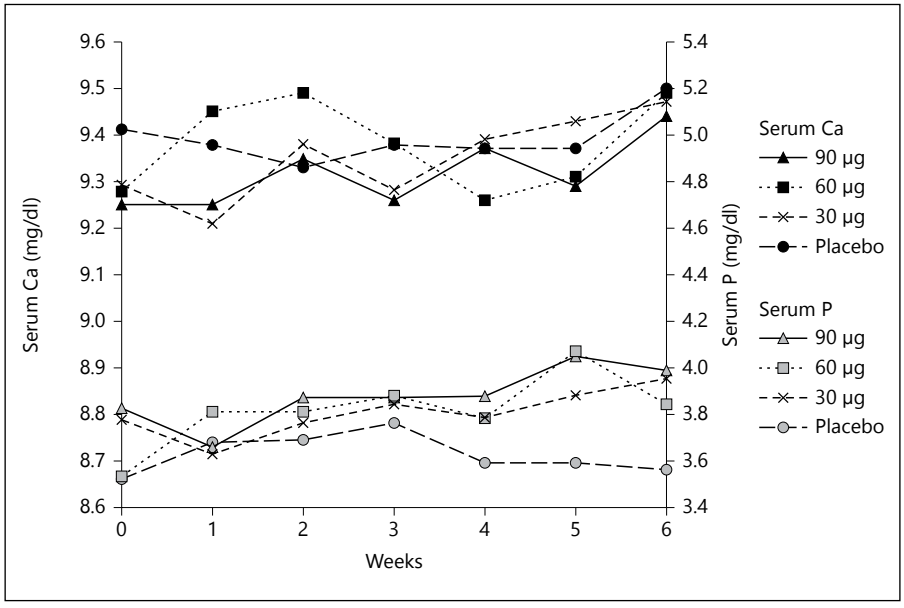

Fig. 5. Changes in serum calcium and phosphorus. Weekly corrected serum Ca and serum P values (mg/dl) from the intent-to-treat population are shown for the 6-week treatment period for groups receiving 30, 60 or 90 µg/day of MR calcifediol and for the pooled placebo group. Data at week 0 represent pre-treatment baseline values. Serum Ca values are shown in black and are plotted according to the scale on the left axis; serum P values are shown in gray and are plotted according to the scale on the right axis. Significant differences from baseline are indicated.

the proportion of subjects who achieved a reduction of 30% increased with dose to 64–69% (fig. 4). Differences in the observed response rates for a mean 30% iPTH reduction were significant between all 3 MR calcifediol groups and the corresponding placebo groups ($p < 0.05$). Racial differences in iPTH reduction at EOT were not detected.

Serum Ca and P, and Urine Ca

Mean serum Ca and P concentrations during the 6-week treatment period are shown in figure 5. The only change reaching statistical significance occurred in the 60 µg group where mean serum Ca rose from a baseline value of 9.3 ± 0.09 (SE) to a week 6 value of 9.5 ± 0.11 ($p < 0.05$). The EOT value for the 60 ug group (average of 3 determinations including the week 6 value) was unchanged from baseline (see table 2). The change in mean serum Ca from baseline to EOT (~0.1 mg/dl) in all subjects treated with MR calcifediol was significant ($p < 0.05$). No differences were detected between treatment groups regarding changes in urinary Ca excretion, expressed as a ratio to Cr excretion, from baseline ($p > 0.05$). One instance of hypercalcemia (confirmed serum Ca >10.5 mg/dl) was observed in one subject in the 60 µg group. Hyperphosphatemia (confirmed serum P >5.5 mg/dl related to study drug administration) and hypercalciuria (>200 mg Ca/g Cr) were not observed.

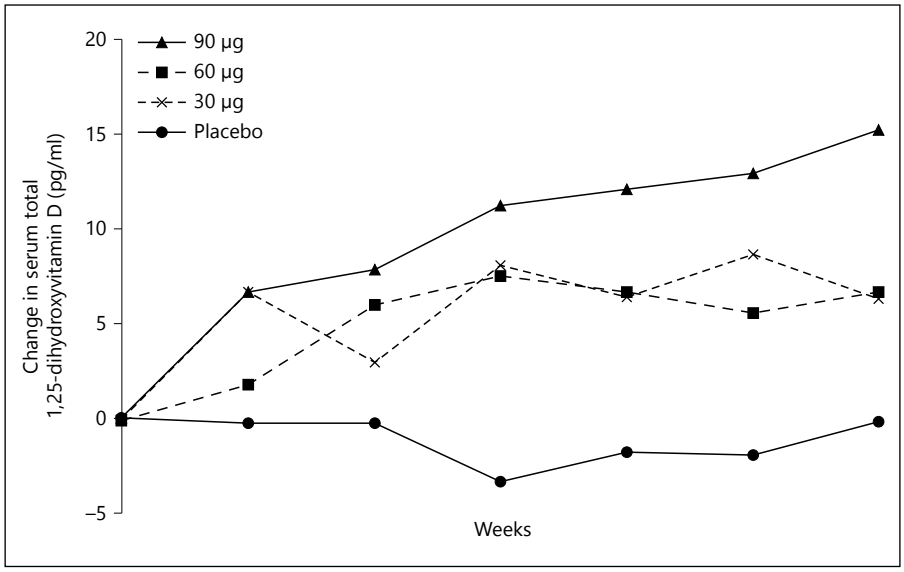

Fig. 6. Changes in serum total 1,25-dihydroxyvitamin D. Serum 1,25-dihydroxyvitamin D (pg/ml) showed gradual increases during the 6-week treatment period from pre-treatment baseline in all groups receiving MR calcifediol. Plotted values have been corrected for differences in baseline.

Table 3. Overall summary of treatment-emergent adverse events (all randomized subjects)

Characteristic	Placebo (n = 31)	MR calcifediol			
		30 µg (n = 13)	60 µg (n = 17)	90 µg (n = 17)	Total (n = 47)
Subjects with no TEAE	8 (25.8)	4 (30.8)	5 (29.4)	6 (35.03)	15 (31.9)
Subjects with at least one TEAE	23 (74.2)	9 (69.2)	12 (70.6)	11 (64.7)	32 (68.1)
Subjects with related TEAE	6 (19.4)	3 (23.1)	4 (23.5)	5 (29.4)	12 (25.5)
Subjects with severe TEAE	1 (3.2)	0 (0.0)	1 (5.9)	1 (5.9)	2 (4.3)
Subjects with serious TEAE	1 (3.2)	1 (7.7)	1 (5.9)	1 (5.9)	3 (6.4)
Subjects discontinued due to TEAE	1 (3.2)	0 (0.0)	0 (0.0)	1 (5.9)	1 (2.1)

Serum Total 1,25-Dihydroxyvitamin D

Mean baseline-adjusted serum total 1,25-dihydroxyvitamin D concentrations gradually increased with daily MR calcifediol during the 6-week treatment period (fig. 6). No change was observed in subjects administered placebo. Differences in exposure (AUC 0–6 weeks) to serum 1,25-dihydroxyvitamin D between all groups receiving MR calcifediol and placebo were significant ($p < 0.05$).

Other Parameters

No significant changes from baseline or differences between treatment groups were observed at the end of the 6-week treatment period for eGFR, serum FGF23, BNP, BAP, or CRP, hematology and coagulation parameters, vital signs, ECG evaluations, or the Beck Depression Inventory II.

Adverse Events

No deaths occurred during the study, no serious adverse events were deemed related to study drug, and no significant differences were observed between the MR calcifediol and placebo groups regarding nonserious adverse events attributed to study drug. Overall, comparable proportions of subjects reported treatment-emergent adverse events (TEAEs) across the treatment groups (table 3). A TEAE was defined as any adverse event, regardless of relationship to study drug, which occurred during or after receiving study drug. No dose-dependent patterns were observed with the exception that more subjects in the 90 µg group reported gout (n = 4, 23.5%), which was considered unrelated to study drug. Two of these 4 subjects reported gout before starting treatment. Table 4 summarizes all TEAEs deemed related to study drug by the site investigators.

Table 4. Summary of related treatment-emergent adverse events (all randomized subjects)

System organ class preferred term	Placebo, n (%) (n = 31)	MR calcifediol, n (%)			
		30 μg (n = 13)	60 μg (n = 17)	90 μg (n = 17)	Total (n = 47)
Subjects with at least 1 drug-related TEAE	5 (16.1)	2 (15.4)	4 (23.5)	4 (23.0)	10 (21.2)
Cardiac disorders	0	0	0	1 (5.9)	1 (2.1)
Edema peripheral	0	0	0	1 (5.9)	1 (2.1)
Endocrine disorders	0	0	1 (5.9)	0	1 (2.1)
Hyperglycemia	0	0	1 (5.9)	0	1 (2.1)
Gastrointestinal disorders	4 (12.9)	2 (15.4)	1 (5.9)	0	3 (6.4)
Abdominal discomfort	0	1 (7.7)	0	0	1 (2.1)
Abdominal distension	1 (3.2)	0	0	0	0
Constipation	1 (3.2)	0	1 (5.9)	0	1 (2.1)
Dry mouth	0	1 (7.7)	0	0	1 (2.1)
Dysgeusia	0	1 (7.7)	0	0	1 (2.1)
Frequent bowel movements	0	1 (7.7)	0	0	1 (2.1)
Nausea	1 (3.2)	0	0	0	0
Vomiting	1 (3.2)	0	0	0	0
General disorders and administration site conditions	0	1 (7.7)	1 (5.9)	0	2 (4.2)
Fatigue	0	1 (7.7)	0	0	1 (2.1)
Hot flush	0	0	1 (5.9)	0	1 (2.1)
Investigations	1 (3.2)	0	0	2 (11.8)	2 (4.2)
Blood LDH increased	1 (3.2)	0	0	0	0
Vitamin D increased	0	0	0	2 (11.8)	2 (4.3)
Metabolism and nutrition disorders	1 (3.2)	0	0	0	0
Decreased appetite	1 (3.2)	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (3.2)	0	0	0	0
Muscle spasms	1 (3.2)	0	0	0	0
Pain in extremity	1 (3.2)	0	0	0	0
Nervous system disorders	0	0	1 (5.9)	1 (5.9)	2 (4.2)
Dizziness	0	0	0	1 (5.9)	1 (2.1)
Headache	0	0	1 (5.9)	0	1 (2.1)

Discussion

Many studies have evaluated vitamin D (either cholecalciferol or ergocalciferol) as a treatment for vitamin D insufficiency or SHPT in adults with predialysis CKD [25–42]. Most were open-label studies and some were conducted in patients exhibiting SHPT. Only 9 were conducted with concurrent placebo or untreated control groups [34–42]. Vitamin D therapy produced modest or transient increases in serum 25-hydroxyvitamin D (generally 10–15 ng/ml), leaving a considerable proportion of the treated patients (up to ~50%) showing no clinically meaningful increases in serum 25-hydroxyvitamin D or decreases in plasma iPTH. The overall conclusion from this body of work has been well summarized: *'Most of these studies have shown either no or minimal to inadequate changes in PTH levels, usually only in some stages of CKD, or changes that still would not satisfy the K/DOQI recommended target ranges for PTH'* [12].

Only three studies have evaluated calcifediol therapy in adults with stage 3 or 4 CKD and SHPT [43–45]. They showed IR calcifediol to be highly effective in raising serum 25-hydroxyvitamin D but ineffective in reducing elevated PTH (by ≥30% from pre-treatment baseline) at doses that maintained mean serum 25-hydroxyvitamin D between 30 and 100 ng/ml, a range considered appropriate for CKD patients.

Data from the current study showed that a 6-week course of therapy with 30, 60 or 90 μg/day of MR calcifediol increased 25-hydroxyvitamin D levels to ≥30 ng/ml in more than 90% of subjects and reduced plasma iPTH by ≥30% from pre-treatment baseline in more than 60%

of subjects at dosages ≥60 μg/day. The mean 25-hydroxyvitamin D level in the 30 μg dose group at EOT was 37.3 ng/ml, only modestly higher than the K/DOQI-specified minimum adequate level (30 ng/ml), indicating that this was the minimum effective dose for correcting vitamin D insufficiency. Mean 25-hydroxyvitamin D rose dose-responsively to 84.8 ng/ml in the 90 μg group, far higher than routinely achieved with ergocalciferol or cholecalciferol supplementation. The mean iPTH levels decreased in a similar fashion, reaching 39.3% below pretreatment baseline in the 90 μg group and 56.5% below the pooled placebo group. The mean serum calcifediol did not quite reach steady-state levels during 6 weeks of treatment with MR calcifediol and, at EOT, had risen in the 60 and 90 μg groups to levels above 50 ng/ml for which the IOM has stated there 'may be reason for concern' [11]. Consequently, further research will focus on the 30 and 60 μg doses and longer observation in larger numbers of CKD patients will be needed to establish the safety of these dose levels.

The pharmacodynamic effect of MR calcifediol on plasma iPTH coincided with increased exposures to calcifediol and serum total 1,25-dihydroxyvitamin D. The iPTH reductions observed with 6 weeks of MR calcifediol therapy compared favorably to those previously observed in pre-dialysis patients during treatment with vitamin D hormone therapies. Doxercalciferol, for example, reduced the mean iPTH levels by approximately 30–32% after 12 weeks of treatment [46, 47]. Paricalcitol produced a mean decrease in iPTH of about 29–52% after 12–24 weeks [48–50]. Alfacalcidol treatment over 2 years produced no significant change in PTH from starting levels [51]. In the most recent study, calcitriol reduced the mean iPTH by 46% [50].

The safe upper limit for serum total 25-hydroxyvitamin D remains poorly defined in the general population and in patients with CKD. While the laboratory reference range is approximately 30 to 100 ng/ml, the threshold for acute toxicity has been estimated at values above 100 ng/ml [52], 150 ng/ml [53] and >150–200 ng/ml [54, 55]. The threshold for long-term toxicity may be lower. The 2010 report by the IOM set the safe upper limit for serum 25-hydroxyvitamin D at 30–48 ng/ml in healthy normal individuals, with levels of 50–60 ng/ml as the toxicity threshold [11]. This lower limit was based on observational studies of mortality in elderly subjects [56, 57] and in the general population [58] or on the incidence of cancer [59–61] and cardiovascular disease [62]. OPKO Health recently completed a carcinogenicity evaluation of calcifediol in a rodent model, as requested by the US Food and Drug Administration, which showed no carcinogenicity potential at the highest dose tested (33 μg/kg/day) [unpublished data]. Other studies cited in the same IOM report failed to support these lower ranges [63, 64]. Recent observational studies in CKD patients reported increased mortality with vitamin D insufficiency [65–70] suggesting that a higher serum 25-hydroxyvitamin D is associated with improved clinical outcomes. As some authors have noted [27, 47], serum 25-hydroxyvitamin D levels of 30 ng/ml may not be adequate for PTH control in CKD patients, and the optimum level may be higher in CKD patients compared with the general population. The safety of serum total 25-hydroxyvitamin D levels in the range of 30 to 100 ng/ml is being further investigated in ongoing larger and longer-term studies of MR calcifediol.

In conclusion, the present double-blinded placebo-controlled trial indicates that oral MR calcifediol administered in daily doses of 30, 60 or 90 μg is safe and highly effective in raising serum total 25-hydroxyvitamin D concentrations to ≥30 ng/ml and reducing plasma iPTH concentrations in adult CKD patients with eGFRs ranging from approximately 20 to 70 ml/min/1.73 m^2. Additional trials with more prolonged periods of treatment are needed to define the long-term efficacy and safety of MR calcifediol as a vitamin D repletion therapy in CKD.

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