Effect of Baseline Serum Calcium on Responses to Extended-Release Calcifediol (ERC) in Stage 3 - 4 CKD

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Introduction

- Calcitriol and its 1α-hydroxylated analogs frequently increase serum calcium (Ca) and the risk of vascular calcification in patients with stage 3-4 CKD. For this reason, the revised KDIGO Guideline for CKD-MBD suggests that these agents not be routinely used in this population.[1]
- Secondary hyperparathyroidism (SHPT) is commonly associated with CKD as a result of vitamin D insufficiency (VDI) and other factors.[2,3]
- Randomized clinical trials (RCTs) with oral extended-release calcifediol (ERC), an FDA-approved therapy for SHPT, demonstrated effective control of elevated plasma intact parathyroid hormone (iPTH) with minimal changes in serum Ca in stage 3-4 CKD.[4]
- Data from these RCTs were examined post-hoc to assess the potential impact of baseline serum Ca on end-of-treatment (EOT) serum Ca, phosphorus (P), total 25-hydroxyvitamin D (25D) and total 1,25-dihydroxyvitamin D (1,25D), and on plasma iPTH in ERC- and placebo-treated subjects.

Objective

- The objective of this analysis was to determine the impact of baseline serum Ca on EOT parameters in patients with stage 3-4 CKD.

Methods

- This was a post-hoc analysis of pooled data from 2 identical, randomized, multisite, double-blind, placebo-controlled 26-week trials in 429 subjects.
- Eligible subjects had stage 3 or 4 CKD, SHPT, and VDI; were aged ≥18 years, with urinary albumin excretion ≤3000 mcg/mg creatinine (Cr); estimated glomerular filtration rate ≥15–<60 mL/min/1.73 m^2, plasma iPTH >85–<500 pg/mL; serum Ca ≥8.4–<9.8 mg/dL; serum P ≥2.0–<5.0 mg/dL; serum 25D ≥10–<30 ng/mL; elemental Ca intake ≤1000 mg/day and vitamin D intake ≤1600 IU/day; and spot urine Ca:Cr ratio ≤0.2 (≤200 mg/g).
- Subjects were randomized in a 2:1 ratio to receive oral once-daily bedtime doses of ERC (30 mcg) or placebo.
  - The ERC dose was increased to 60 mcg daily at Week 13 in subjects with serum 25D <65 ng/mL, serum Ca <9.8 mg/dL, and plasma iPTH >70 pg/mL (averaged over weeks 8–10).
- Post-hoc analyses were conducted of per-protocol data on the comparative efficacy of ERC vs placebo for increasing serum total 25D and reducing iPTH.
- Time course data for the per-protocol ERC and placebo populations were ranked by baseline serum Ca and divided into tertiles. Selected data for each tertile are presented for three time points (baseline, Week12 and EOT) along with mean changes from baseline, by treatment group. EOT was defined as the Efficacy Assessment Period (EAP, mean of weeks 20-26).
- Statistical differences between placebo - and ERC-treated subjects for each tertile, at baseline and for changes from baseline, were assessed by t-test.

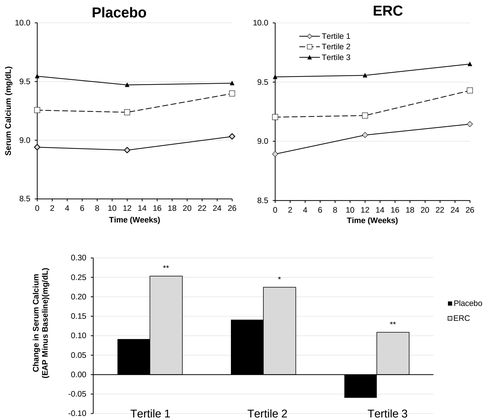
Results

Table 1. Subject demographics at baseline

Variable	Placebo			ERC		
	Tertile 1 n (%)	Tertile 2 n (%)	Tertile 3 n (%)	Tertile 1 n (%)	Tertile 2 n (%)	Tertile 3 n (%)
Number of subjects	41	40	41	78	78	78
Gender						
Female	15	23	22	29	42	47
Male	26	17	19	49	36	31
	Tertile 1 Mean (SE)	Tertile 2 Mean (SE)	Tertile 3 Mean (SE)	Tertile 1 Mean (SE)	Tertile 2 Mean (SE)	Tertile 3 Mean (SE)
Weight, kg	98.0 (3.3)	92.1 (3.3)	99.6 (3.8)	98.0 (2.6)	96.3 (3.0)	101.0 (3.0)
BMI , kg/m^2	34.9 (1.2)	34.0 (1.2)	34.8 (1.2)	33.6 (0.8)	34.4 (0.9)	36.5 (1.0)
Age, y	62.2 (1.8)	67.3 (1.8)	63.0 (1.8)	66.4 (1.2)	65.8 (1.3)	65.8 (1.1)
Serum Ca, mg/dL	8.9 (0.02)	9.3 (0.01)	9.5 (0.02)	8.9 (0.02)	9.2 (0.01)**	9.5 (0.02)
Serum P, mg/dL	3.7 (0.1)	3.7 (0.1)	3.7 (0.1)	3.8 (0.1)	3.7 (0.1)	3.7 (0.1)
Total 25D, ng/mL	19.5 (0.9)	20.1 (1.0)	18.2 (0.8)	19.8 (0.6)	19.2 (0.6)	20.2 (0.6)*
Total 1,25D (pg/mL)	37.5 (2.8)	34.4 (1.9)	36.0 (2.0)	32.3 (1.5)	33.9 (1.5)	37.2 (1.5)
iPTH, pg/mL	146.5 (7.1)	148.5 (10.8)	140.8 (5.6)	156.5 (5.5)	138.4 (6.9)	136.0 (6.9)
eGFR, mL/min/1.73 m^2	31.3 (1.5)	33.2 (1.6)	34.3 (1.7)	28.5 (1.1)	30.9 (1.2)	32.3 (1.2)

1,25D, 1,25-dihydroxyvitamin D; 25D, 25-hydroxyvitamin D; BMI, body mass index; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; SE, standard error.

Figure 1. Changes in mean serum Ca



* Significantly different from placebo, p < 0.05
** Significantly different from placebo, p < 0.01

Figure 2. Changes in mean serum P

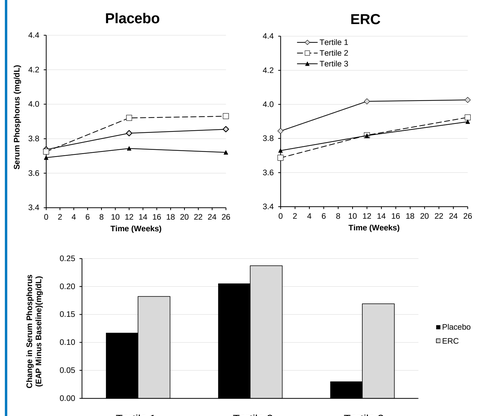
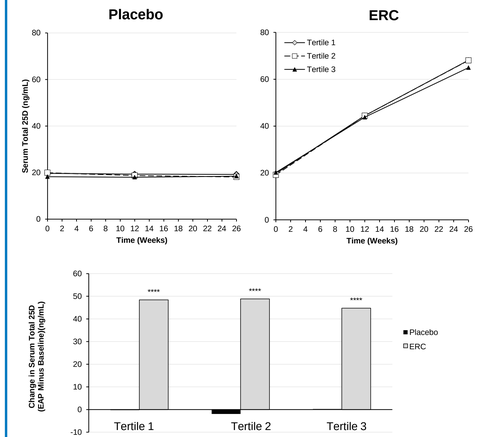
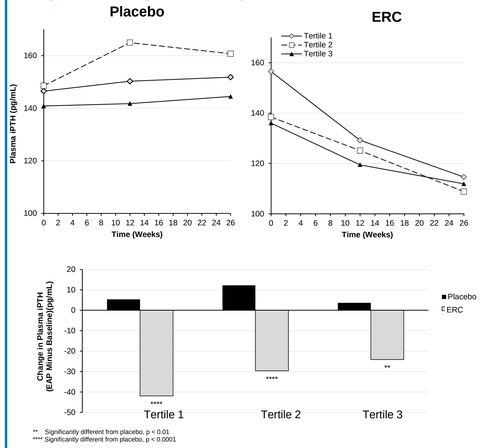


Figure 3. Changes in mean serum total 25D



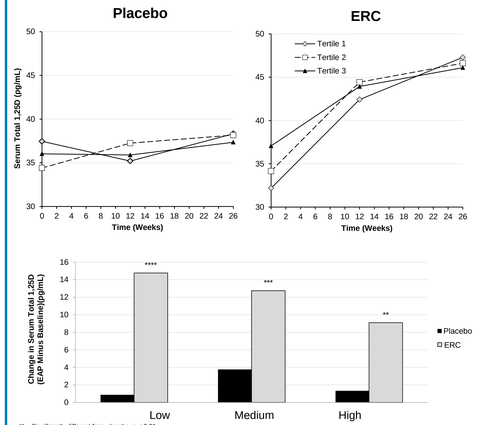
**** Significantly different from placebo, p < 0.0001

Figure 4. Changes in mean plasma iPTH



** Significantly different from placebo, p < 0.01
**** Significantly different from placebo, p < 0.0001

Figure 5. Changes in mean serum total 1,25D



** Significantly different from placebo, p < 0.01
*** Significantly different from placebo, p < 0.001
**** Significantly different from placebo, p < 0.0001

Results Summary

- Significant differences in baseline demographic characteristics between active and placebo subjects in each tertile are as marked (Table 1). More men were included in Tertile 1 and more women in Tertiles 2 and 3. Plasma iPTH trended higher with decreasing baseline serum Ca.
- Mean serum Ca levels (Figure 1) increased with ERC treatment in all tertiles ($p < 0.05$ or less), with greater changes at lower baseline Ca.
- Mean serum P (Figure 2) was not significantly affected by ERC treatment, relative to placebo (p = ns).
- Mean serum 25D (Figure 3) increased similarly with ERC treatment in all tertiles ($p < 0.0001$).
- Mean plasma iPTH (Figure 4) decreased with ERC treatment in all tertiles, with greater changes at lower baseline serum Ca ($p < 0.01$ or $p < 0.0001$).
- ERC treatment increased mean serum 1,25D in all tertiles (Figure 5), with levels converging at EOT and larger increases at lower baseline serum Ca ($p < 0.01$ or less).

Conclusions

- ERC treatment effectively increased mean serum total 25D and 1,25D, and reduced mean plasma iPTH, in all tertiles.
- Baseline serum Ca affected serum 1,25D and plasma iPTH responses to ERC treatment. ERC-induced increases in 1,25D and decreases in iPTH were greatest in subjects with the lowest baseline Ca.

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Disclosures

Dr. Strugnell, Dr. Ashfaq, and Dr. Bishop are employees of OPKO Renal Division. Dr. Kopyt and Dr. Petkovich have served as consultants for OPKO Renal Health Division.

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