Initial Evaluation of High-Dose Extended-Release Calcifediol (ERC) in Patients with Stage 5 Chronic Kidney Disease on Hemodialysis

Abstract TH-OR19, Session OR044 (Thurs 04 Nov 4:30-6:00 pm PDT)

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Disclosures

- Drs. Strugnell, Ashfaq and Bishop are salaried employees of OPKO Health Inc. Dr. Csomor is a salaried employee of Vifor Pharma Ltd. Options on company stock are part of their compensation packages.

- The clinical study presented in this talk was jointly funded by OPKO Health and Vifor Pharma.

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Background

- Extended-release calcifediol (ERC) has been FDA-approved since 2016 for the treatment of secondary hyperparathyroidism (SHPT) in adults with stage 3 or 4 CKD and vitamin D insufficiency.
- Approved doses are 30 mcg/day escalating, as needed, to 60 mcg/day (210 or 420 mcg/week).
- Conversion of calcifediol ($25(OH)D_3$) to calcitriol ($1,25(OH)_2D_3$) by CYP27B1 (1α-hydroxylase) occurs primarily in the kidney, in the consensus view of the scientific community, despite the enzyme's expression in other tissues. This view supports a belief that normal serum levels of $1,25(OH)_2D$ cannot be maintained with advancing CKD.

Background (Continued)

- A phase 2a study explored ERC treatment of end-stage renal disease (ESRD) patients with SHPT who required regular hemodialysis (HD).

- The goals of the study were to:

  1. Evaluate whether these patients could tolerate a high dose of ERC (900 mcg/wk) for 26 weeks;
  2. Ascertain whether ERC could normalize serum $1,25(OH)_2D$ in the absence of functional kidneys; and,
  3. Determine whether ERC has an impact on iPTH levels.

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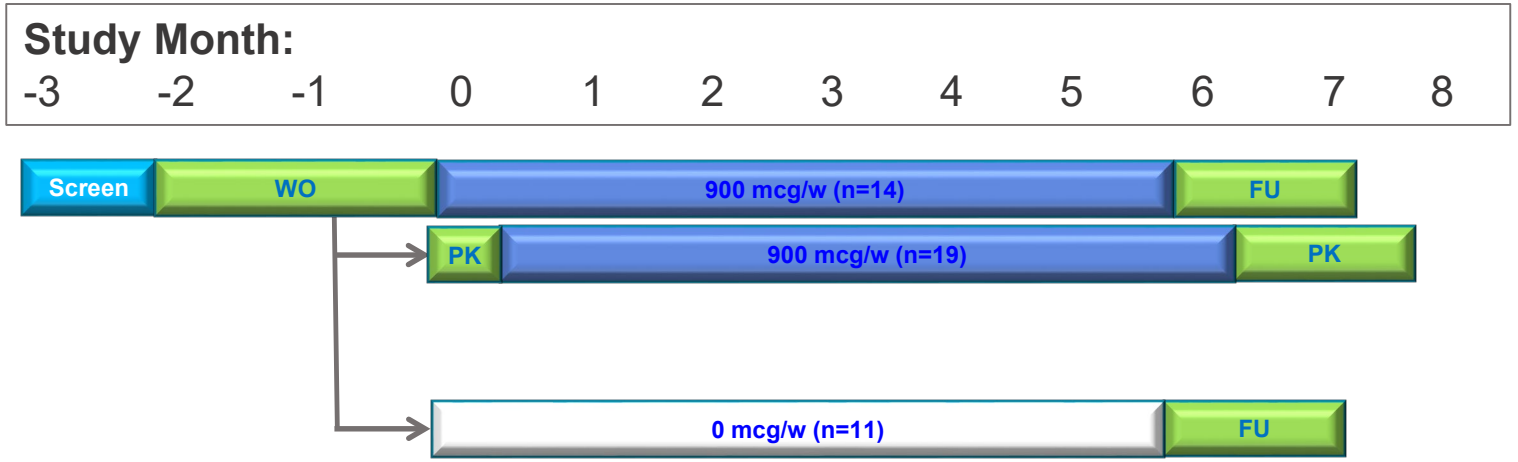
Methods

- Forty-four adults with ESRD on regular HD (for at least six months) were enrolled from 27 US dialysis centers.
- All subjects had iPTH ≥150 to <600 pg/mL and serum total 25(OH)D <50 ng/mL.
- Subjects underwent an 8-week washout from vitamin D and other PTH-lowering therapies and were then randomized to 26 weeks of single-blinded (subjects only) treatment with ERC (300 mcg 3x/week during HD) or matching placebo.
- Serum total 25(OH)D and $1,25(OH)_2D$, calcium (Ca), phosphorus (P) and plasma iPTH were monitored on a weekly or biweekly basis.

Study Design



WO = Washout
FU = Follow-up
PK = Pharmacokinetic evaluation

Pharmacokinetic (PK) observations were completed on 19/33 (58%) of ERC-treated subjects, per protocol. PK data will be presented elsewhere.

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Post-Washout Baseline Demographics

	ERC (n=33)	Placebo (n=11)
Sex	15F/18M	5F/6M
Race	1 Asian/23 Black/9 White	7 Black/4 White
Age†	57.6 (12.6)	58.5 (10.6)
Serum total 25(OH)D (ng/mL) †	24.4 (9.4)	38.4 (15.7)*
Serum calcium (Corr.)(mg/dL) †	8.9 (0.5)	8.8 (0.8)
Serum phosphorus (mg/dL) †	4.8 (1.2)	5.0 (1.2)
Plasma iPTH (pg/mL) †	526 (167)	544 (255)

†Data are Mean (SD)

*Significantly different from ERC, $p < 0.05$

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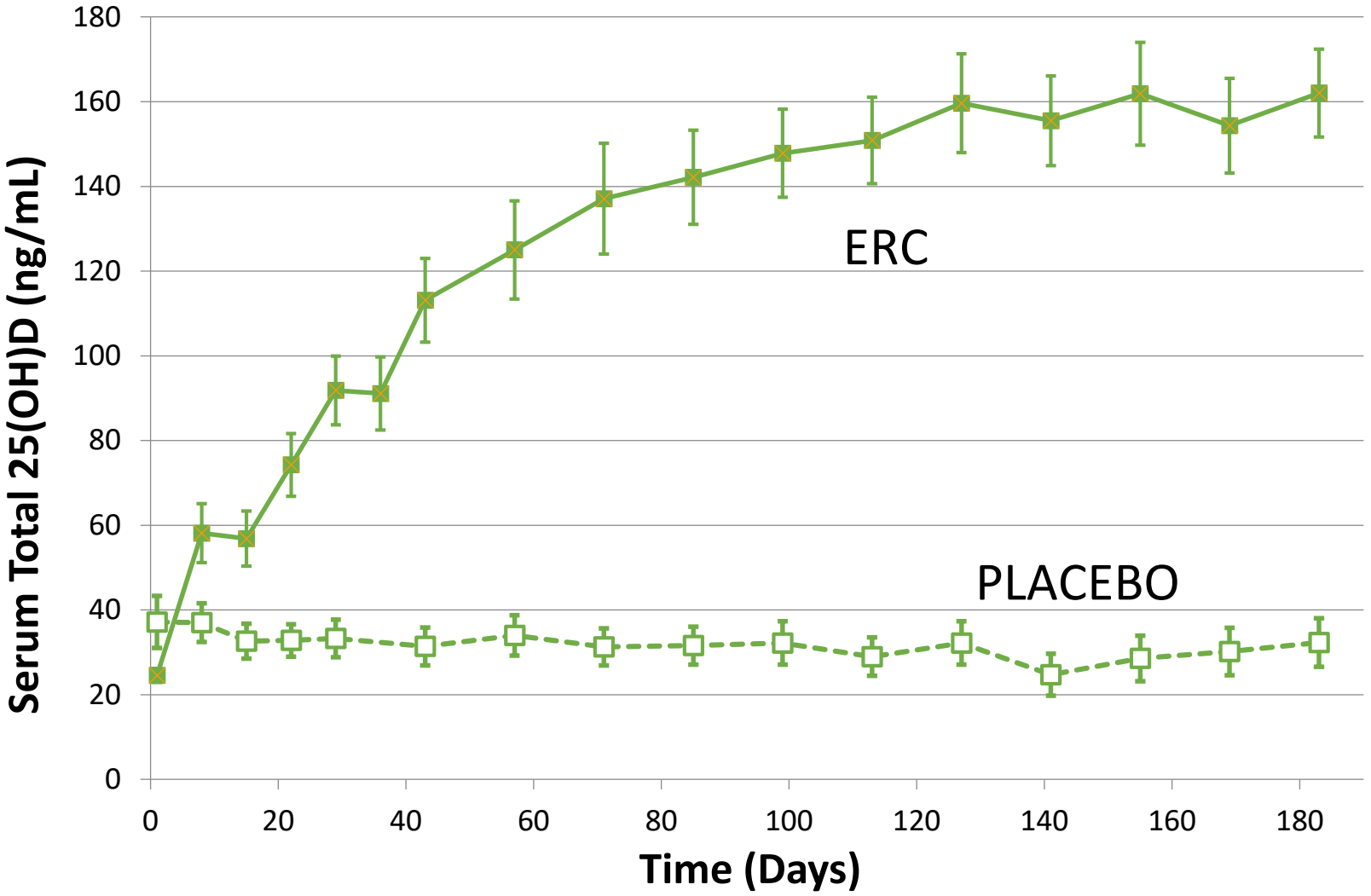
Changes in Serum Total 25(OH)D



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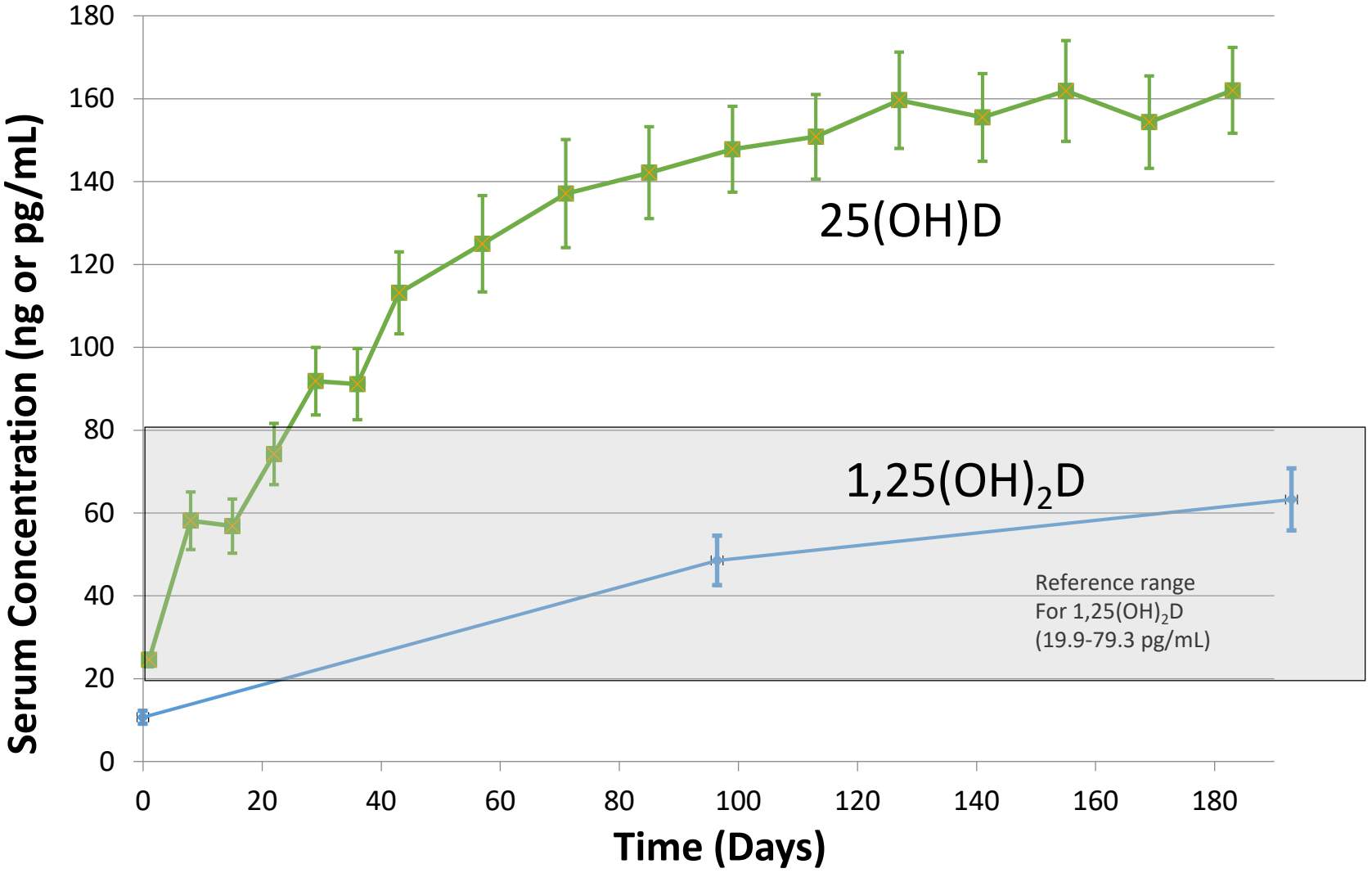
Changes in Serum Total $1,25(OH)_2D$ with ERC



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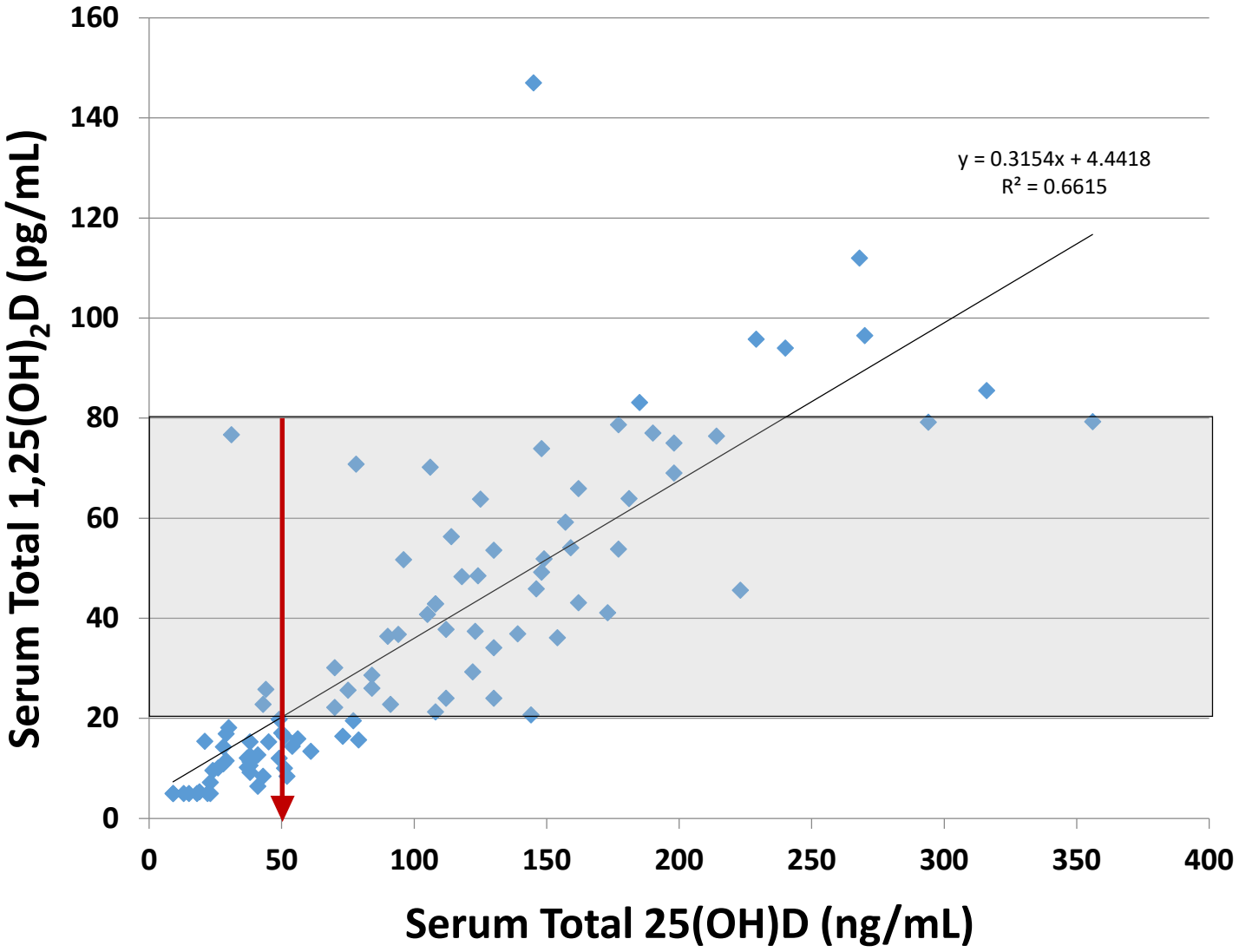
Serum Total $1,25(OH)_2D$ vs 25(OH)D



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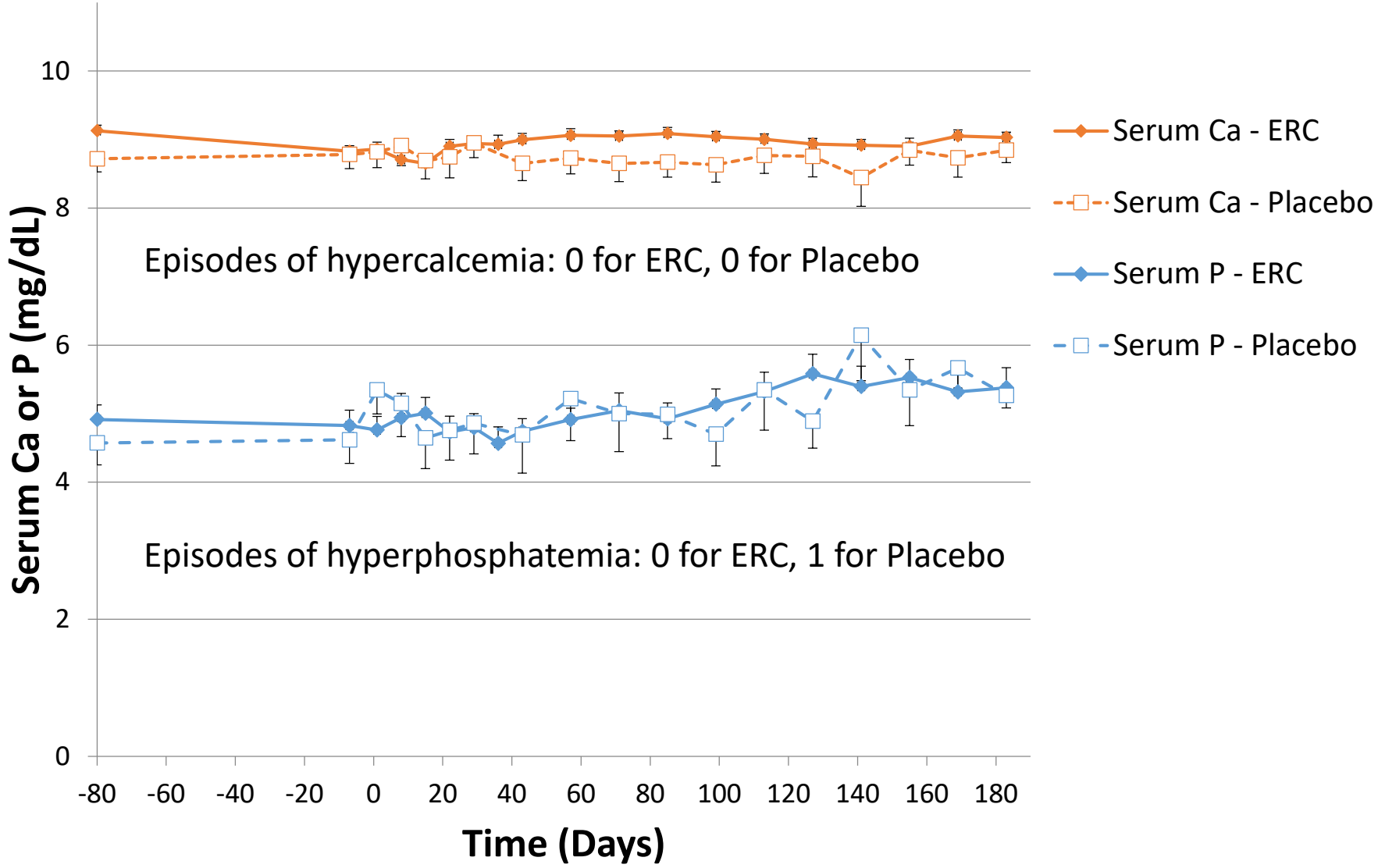
Changes in Serum Ca and P During Treatment



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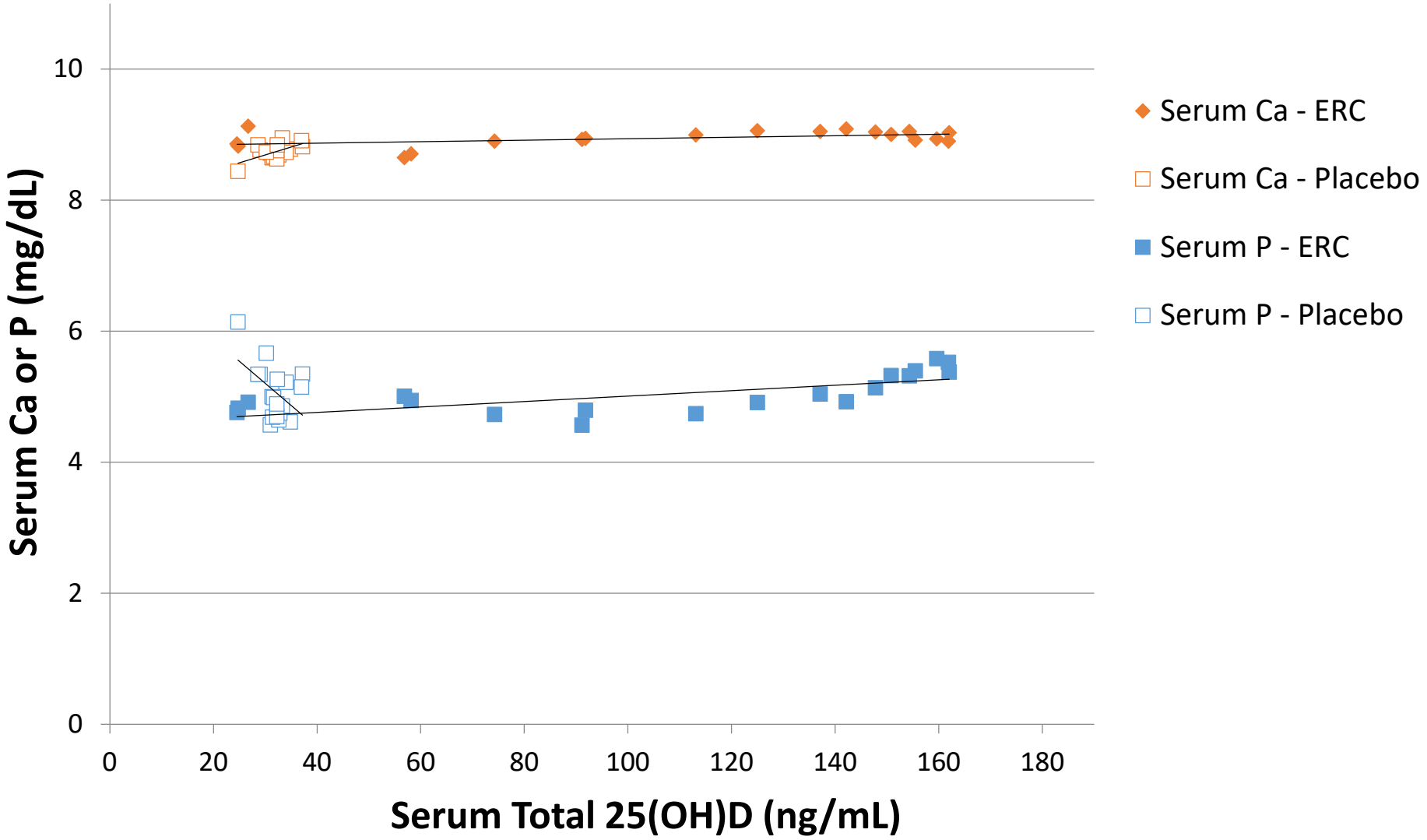
Changes in Serum Ca and P vs 25(OH)D



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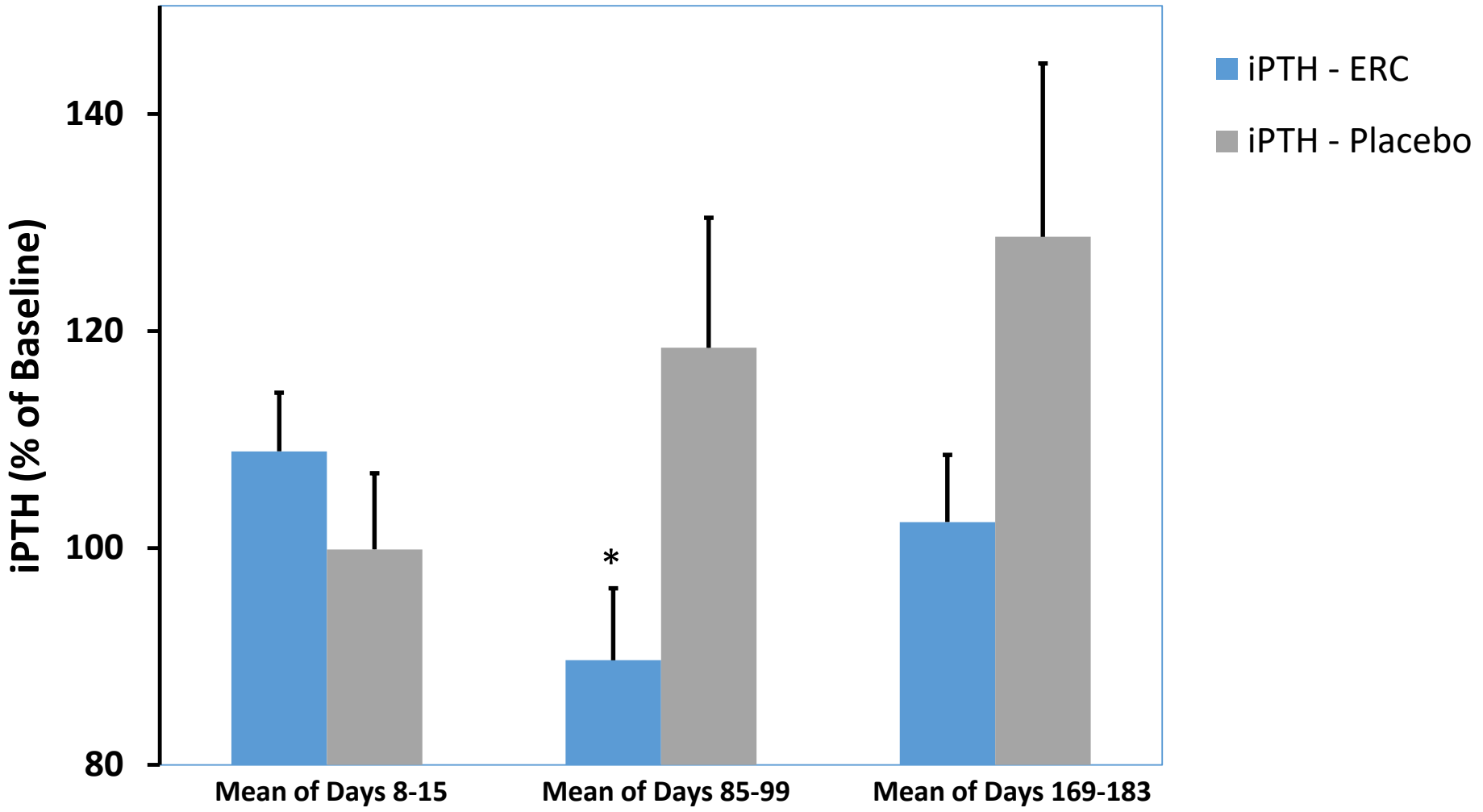
Changes in iPTH During Treatment



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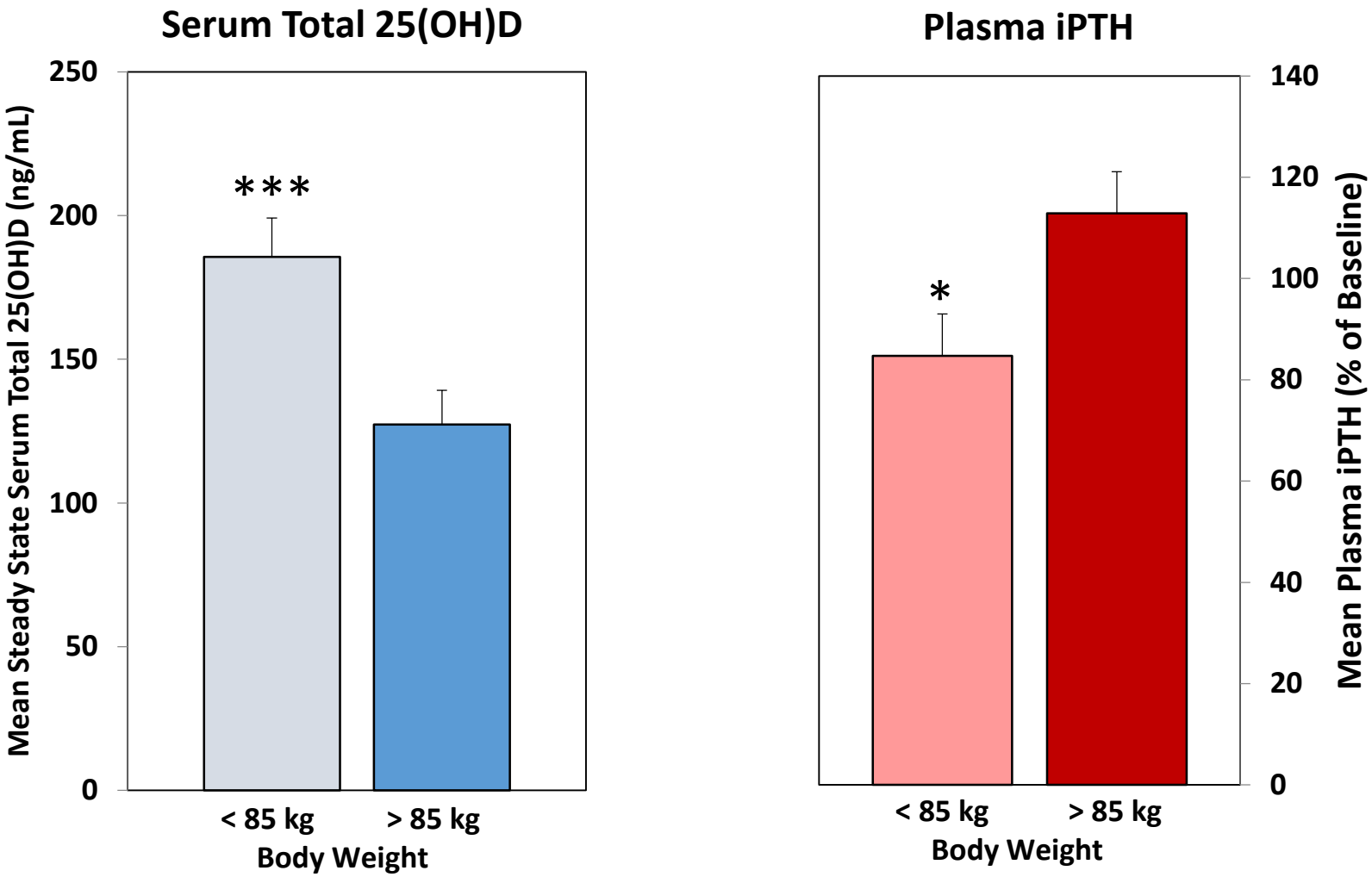
Effect of Weight and 25(OH)D on iPTH



* Significantly different from Body Weight >85 kg, $p < 0.05$
*** Significantly different from Body Weight >85 kg, $p < 0.001$

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Rates of Adverse / Serious Adverse Events

Protocol specified 3:1 randomization to active:placebo

Treatment Group (n)	Number of TEAEs*	Average Number of TEAEs per Subject	Number of SAEs	Average Number of SAEs per Subject
ERC (32)†	159	5.0	31	1.0
Placebo (11)	57	5.2	14	1.3

Most Common TEAEs	ERC	Placebo
Hypotension	6 (18.8%)	4 (36.4%)
Diarrhoea	5 (15.6%)	1 (9.1%)
Constipation	4 (12.5%)	0 (0.0%)

Most Common SAEs	ERC	Placebo
Atrial Fibrillation	0 (0.0%)	1 (9.1%)
Bradycardia	0 (0.0%)	1 (9.1%)

*TEAE = Treatment-Emergent Adverse Event; SAE =Serious Adverse Event

†One of the subjects in the ERC group was randomized to treatment but discontinued before receiving study drug.

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Summary of Results

- 44 subjects were enrolled – 33 ERC, 11 placebo.
- ERC-treated subjects attained mean (±SE) steady-state levels of 25(OH)D of 161 ± 11 ng/mL vs 30 ± 5.6 ng/mL with placebo.
- Mean serum total $1,25(OH)_2D$ rose into the normal range (62.0 ± 8.3 pg/mL) from low baseline levels (10.6 ± 1.5 pg/mL) with ERC.
- Normalization of $1,25(OH)_2D$ with ERC occurred with elevation of 25(OH)D to ≥ 50 ng/mL.

Summary of Results (Continued)

- Stabilization of iPTH was observed with ERC vs placebo, and significant decreases were observed with increasing 25(OH)D exposure.
- Greater reductions in iPTH may have been possible if better serum P control had been achieved during the treatment period.
- No clinically meaningful increases in serum Ca or P, or differences in the incidence of adverse events, were observed with ERC compared to placebo.

Conclusions

- ERC was:
  - Well tolerated at 900 mcg/week for 26 weeks
  - Readily activated to produce normal levels of $1,25(OH)_2D$ at 25(OH)D levels ≥ 50 ng/mL
  - Capable of stabilizing iPTH levels

- These data show that serum $1,25(OH)_2D$ can be normalized in HD patients by raising and maintaining serum 25(OH)D at levels of ≥ 50 ng/mL, despite the loss of kidney function.

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Thank you

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