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Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism
Two Randomized Clinical Trials

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IMPORTANCE Secondary hyperparathyroidism contributes to extraskeletal complications in chronic kidney disease.

OBJECTIVE To evaluate the effect of the intravenous calcimimetic etelcalcetide on serum parathyroid hormone (PTH) concentrations in patients receiving hemodialysis.

DESIGN, SETTING, AND PARTICIPANTS Two parallel, phase 3, randomized, placebo-controlled treatment trials were conducted in 1023 patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism. Trial A was conducted in 508 patients at 111 sites in the United States, Canada, Europe, Israel, Russia, and Australia from March 12, 2013, to June 12, 2014; trial B was conducted in 515 patients at 97 sites in the same countries from March 12, 2013, to May 12, 2014.

INTERVENTIONS Intravenous administration of etelcalcetide (n = 503) or placebo (n = 513) after each hemodialysis session for 26 weeks.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was the proportion of patients achieving greater than 30% reduction from baseline in mean PTH during weeks 20-27. A secondary efficacy end point was the proportion of patients achieving mean PTH of 300 pg/mL or lower.

RESULTS The mean age of the 1023 patients was 58.2 (SD, 14.4) years and 60.4% were men. Mean PTH concentrations at baseline and during weeks 20-27 were 849 and 384 pg/mL vs 820 and 897 pg/mL in the etelcalcetide and placebo groups, respectively, in trial A; corresponding values were 845 and 363 pg/mL vs 852 and 960 pg/mL in trial B. Patients randomized to etelcalcetide were significantly more likely to achieve the primary efficacy end point: in trial A, 188 of 254 (74.0%) vs 21 of 254 (8.3%; $P < .001$), for a difference in proportions of 65.7% (95% CI, 59.4%-72.1%) and in trial B, 192 of 255 (75.3%) vs 25 of 260 (9.6%; $P < .001$), for a difference in proportions of 65.7% (95% CI, 59.3%-72.1%). Patients randomized to etelcalcetide were significantly more likely to achieve a PTH level of 300 pg/mL or lower: in trial A, 126 of 254 (49.6%) vs 13 of 254 (5.1%; $P < .001$), for a difference in proportions of 44.5% (95% CI, 37.8%-51.2%) and in trial B, 136 of 255 (53.3%) vs 12 of 260 (4.6%; $P < .001$), for a difference in proportions of 48.7% (95% CI, 42.1%-55.4%). In trials A and B, respectively, patients receiving etelcalcetide had more muscle spasms (12.0% and 11.1% vs 7.1% and 6.2% with placebo), nausea (12.4% and 9.1% vs 5.1% and 7.3%), and vomiting (10.4% and 7.5% vs 7.1% and 3.1%).

CONCLUSIONS AND RELEVANCE Among patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism, use of etelcalcetide compared with placebo resulted in greater reduction in serum PTH over 26 weeks. Further studies are needed to assess clinical outcomes as well as longer-term efficacy and safety.

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Secondary hyperparathyroidism is an important complication of chronic kidney disease (CKD), particularly among patients receiving hemodialysis. Elevated serum concentrations of parathyroid hormone (PTH) contribute to bone and cardiovascular disorders (including osteitis fibrosa cystica and calcific cardiovascular disease, broadly referred to as CKD-mineral bone disorder), along with myopathy, neuropathy, anemia, and pruritus, and have been independently associated with all-cause and cardiovascular mortality.[1,2] Current treatment options consist of oral administration of intestinal phosphate binders, oral or intravenous calcitriol or active vitamin D analogs, and the oral calcimimetic agent cinacalcet. These interventions are often limited by undesirable off-target or adverse effects and several require adherence to daily or thrice-daily oral ingestion.

Etelcalcetide is a synthetic peptide composed of 7 D-amino acids linked to an L-cysteine via a disulfide bond that functions as an activator of the calcium-sensing receptor. Single doses of etelcalcetide have been shown to reduce PTH in healthy volunteers[3] and patients with end-stage renal disease receiving hemodialysis.[4] A single 12-week phase 2 dose escalation study of etelcalcetide in 37 patients receiving hemodialysis resulted in sustained reductions in PTH, calcium, and phosphate.[5]

Herein we report the combined results of 2 parallel, phase 3, randomized, placebo-controlled multinational trials designed to assess the safety and efficacy of etelcalcetide in patients receiving hemodialysis with inadequately controlled secondary hyperparathyroidism.

Key Points

Question What is the effect of the intravenous calcimimetic etelcalcetide compared with placebo on serum parathyroid hormone concentrations in patients receiving hemodialysis?

Findings In 2 randomized clinical trials that included 1023 adults receiving hemodialysis with moderate to severe secondary hyperparathyroidism, patients randomized to etelcalcetide compared with placebo were significantly more likely to have a greater than 30% reduction in mean parathyroid hormone concentrations over 26 weeks (74.0% vs 8.3% and 75.3% vs 9.6%).

Meaning Etelcalcetide was more effective than placebo in lowering parathyroid hormone concentration in patients receiving dialysis with secondary hyperparathyroidism, but further research is needed to assess clinical outcomes as well as longer-term efficacy and safety.

Methods

The trials were approved by institutional review boards at participating study sites and all patients provided written informed consent. Trial protocols are available in Supplement 1 and Supplement 2.

Participants

Patients receiving thrice-weekly maintenance hemodialysis with moderate to severe secondary hyperparathyroidism (PTH >400 pg/mL) with albumin-corrected serum calcium of 8.3 mg/dL or higher and taking stable doses of calcium supplements or phosphate binders and calcitriol or active vitamin D analogs were eligible for randomization. A complete list of inclusion and exclusion criteria is available in the eAppendix in Supplement 3. Race and ethnicity data were obtained to assess generalizability to clinical practice and were determined by self-report using fixed categories (white, black or African American, Asian, Native Hawaiian or Pacific Islander, and American Indian or Alaska Native). Eligible patients could not have received cinacalcet during the 4 weeks prior to the first screening laboratory assessments, and cinacalcet therapy was prohibited during the study.

Study Design

Both clinical trials were 26-week, phase 3, multicenter, randomized, double-blind, placebo-controlled trials. All patients, regardless of treatment assignment, received standard of care with phosphate binders and calcitriol or active vitamin D analogs as prescribed by the individual investigator. The trials were identical, as required for regulatory approval, with the exception that predialysis and postdialysis laboratory data and electrocardiograms were obtained in trial A, whereas only predialysis measurements were performed in trial B.

Procedures

Eligible patients were randomized 1:1 to receive either placebo or etelcalcetide by an interactive voice/web response system. Permuted block randomization with a block size of 4 was used, stratified by geographic region, prior cinacalcet use within 8 weeks of randomization, and screening PTH level. Study drug (etelcalcetide or placebo) was administered via bolus injection into the venous line of the dialysis circuit, immediately prior to or during rinse-back after each hemodialysis session for 26 weeks. The starting dose was 5 mg and could be increased in 2.5-mg or 5-mg increments at weeks 5, 9, 13, and 17 based on PTH and calcium results obtained during the prior week to achieve predialysis PTH of 300 pg/mL or lower, to a maximum dose of 15 mg. Investigators were blinded to PTH and phosphate results. Study drug was temporarily withheld for low PTH (<100 pg/mL on 2 consecutive measurements), low serum (albumin-corrected) calcium (<7.5 mg/dL), or symptomatic hypocalcemia and was subsequently resumed at a reduced dose. Investigators remained blinded to conditions that required etelcalcetide dose suspension, as the interactive voice/web response system algorithm randomly selected a matched patient receiving placebo in whom to suspend dosing. Sites were instructed to suspend routine local PTH monitoring during the study. Sites were not blinded to serum calcium levels to ensure the safety of trial participants.

Biochemical and Other Determinations

Biochemical data were collected prior to hemodialysis at baseline and periodically (eg, calcium and phosphate weekly, PTH every 2 weeks) through week 27 and analyzed in central

laboratories. Parathyroid hormone was analyzed in serum samples using the Advia Centaur assay (Covance; population reference range, 14-72 pg/mL). Serum bone-specific alkaline phosphatase, collagen type 1 cross-linked C-telopeptide, and intact fibroblast growth factor 23 (FGF23) were also measured, the latter using the Kainos ELISA kit (Medpace) on day 1 (before dosing) and at weeks 12 and 27. Triplicate electrocardiograms were acquired using standardized equipment and analyzed in a blinded fashion by an independent agency (eResearch Technology) at screening, day 1, and weeks 5, 13, and 26; QT intervals were corrected for heart rate using the formulas of Bazett (QTcB) and Fridericia (QTcF).

Outcomes

The primary efficacy end point was the proportion of patients with greater than 30% reduction from baseline in mean PTH during the efficacy assessment phase (weeks 20-27). The primary end point for these trials was chosen in agreement with the US Food and Drug Administration. Although no published data specifically document overt clinical benefits related to a 30% or greater reduction of PTH, several observational studies have shown that PTH concentrations greater than 600 pg/mL are associated with higher rates of death, cardiovascular events, and fracture than PTH concentrations in the range of 150 to 300 pg/mL.[6-9] Secondary end points included the proportion of patients with mean PTH levels of 300 pg/mL or lower and percentage reductions in PTH, calcium, calcium × phosphate, and phosphate. Exploratory end points included change in FGF23 and the bone turnover markers of bone-specific alkaline phosphatase and collagen type 1 cross-linked C-telopeptide.

Statistical Analysis

We estimated that treatment with placebo would result in a greater than 30% reduction in PTH in less than 20% of patients based on experience from an earlier phase 2 trial.[5] In the same phase 2 trial, the response rate for patients treated with etelcalcetide was 54%. For each trial, we assumed that 10% of randomized patients would not receive study drug and 25% of randomized patients would drop out before the efficacy assessment phase. We estimated response rates of 35% for etelcalcetide and 20% for placebo based on data from phase 2 clinical trials with etelcalcetide.[4,5] For a condition in which the majority of patients do not achieve control, a 15% absolute increase in the proportion of patients achieving control (corresponding to a 75% relative increase) was deemed clinically important. A sample size of 250 in each treatment group would yield at least 90% power to detect a difference in the primary efficacy end point using a χ^2 test with a 2-sided statistical significance level of .05.

All data were analyzed according to the intention-to-treat principle. Where applicable, analyses were adjusted for stratification factors. The primary and secondary efficacy end points for the proportion of patients achieving PTH levels of 300 pg/mL or lower were analyzed using the Cochran-Mantel-Haenszel χ^2 statistic. Patients with no PTH data during the efficacy assessment phase were included in all analyses and were considered to be nonresponders. Secondary efficacy end points for percentage change from baseline were analyzed using a repeated-measures mixed-effects model. To control for the study-wise type 1 error rate, the secondary efficacy end points were analyzed only after the primary efficacy end point reached the prespecified level of significance. Secondary efficacy end points were analyzed in the sequence listed above. Two-sided $P<.05$ was considered statistically significant. All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc).

Results

Trial A was conducted in 508 patients at 111 sites in the United States, Canada, Europe, Israel, Russia, and Australia from March 12, 2013, to June 12, 2014; trial B was conducted in 515 patients at 97 sites in the same countries from March 12, 2013, to May 12, 2014. The disposition of trial participants is shown in **Figure 1**. The proportion of randomized patients by country is described in eTable 1 in Supplement 3.

Table 1 shows selected baseline demographic and clinical data for patients by randomized treatment group. The mean age was 58.2 (SD, 14.4) years and 60.4% were men. Baseline characteristics were similar across trials except that in trial A, more patients were using hemodiafiltration rather than hemodialysis (16.1% vs 12.8%) and fewer patients were using low (<2.5 mEq/L) baseline dialysate calcium concentrations (6.1% vs 10.1%) relative to trial B. Baseline characteristics of the etelcalcetide and placebo groups were well balanced across both trials.

Mean percentage change in serum PTH and mean change in serum calcium and phosphate concentrations over time are shown in **Figure 2**. In trial A, mean PTH concentrations were 849 and 384 pg/mL at baseline and vs 820 and 897 pg/mL during the efficacy assessment phase in the etelcalcetide and placebo groups, respectively; corresponding values in trial B were 845 and 363 pg/mL vs 852 and 960 pg/mL. Patients randomized to etelcalcetide were significantly more likely than those in the placebo group, respectively, to achieve the primary efficacy end point (for trial A: 188/254 [74.0%] vs 21/254 [8.3%; $P < .001$]; difference in proportions, 65.7% [95% CI, 59.4%-72.1%]; for trial B, 192/255 [75.3%] vs 25/260 [9.6%; $P < .001$]; difference in proportions, 65.7% [95% CI, 59.3%-72.1%]). Sixty patients in trial A (11.8%) and 51 patients in trial B (9.9%) contributed no PTH data during the efficacy assessment phase and were considered nonresponders. A secondary PTH-based efficacy end point (the proportion of patients achieving mean PTH levels ≤300 pg/mL) was also achieved (for trial A: 126/254 [49.6%] with etelcalcetide vs 13/254 [5.1%] with placebo [$P < .001$]; difference in proportions, 44.5% [95% CI, 37.8%-51.2%]; for trial B: 136/255 [53.3%] with etelcalcetide vs 12/260 [4.6%] with placebo [$P < .001$]; difference in proportions, 48.7% [95% CI, 42.1%-55.4%]). More than half of etelcalcetide-treated patients achieved greater than 30% reduction in PTH in less than 6 weeks (eFigure 1 in Supplement 3). The difference in proportions of patients achieving greater than 30%

reduction in PTH was similar across all patient subgroups (eFigure 2 in Supplement 3). Median per-session dose of etelcalcetide during the efficacy assessment phase was 7.1 mg (interquartile range, 3.6-10.0 mg) in trial A and 5.0 mg (interquartile range, 2.5-10.0 mg) in trial B. The distribution of study drug dose received over the course of each trial is shown in eTable 2 in Supplement 3.

eFigure 3 in Supplement 3 shows changes in the use of calcium supplements or calcium-containing phosphate binders and calcitriol or active vitamin D analogs in both trials. The proportion of patients receiving calcium supplements or calcium-containing phosphate binders and the proportion of patients receiving active vitamin D analogs increased in the etelcalcetide group. eTable 3 in Supplement 3 shows dialysate calcium concentrations at baseline and end of study by randomized group; 37% and 51% of patients treated with etelcalcetide were treated with dialysate calcium concentrations greater than 2.5 mEq/L at the end of trials A and B, respectively.

Exploratory End Points

Treatment with etelcalcetide decreased serum intact FGF23. **Figure 3** shows serum intact FGF23 concentrations at baseline, week 12, and week 27 and **Figure 4** shows median percentage change in serum intact FGF23 at weeks 12 and 27 by randomized group within each trial.

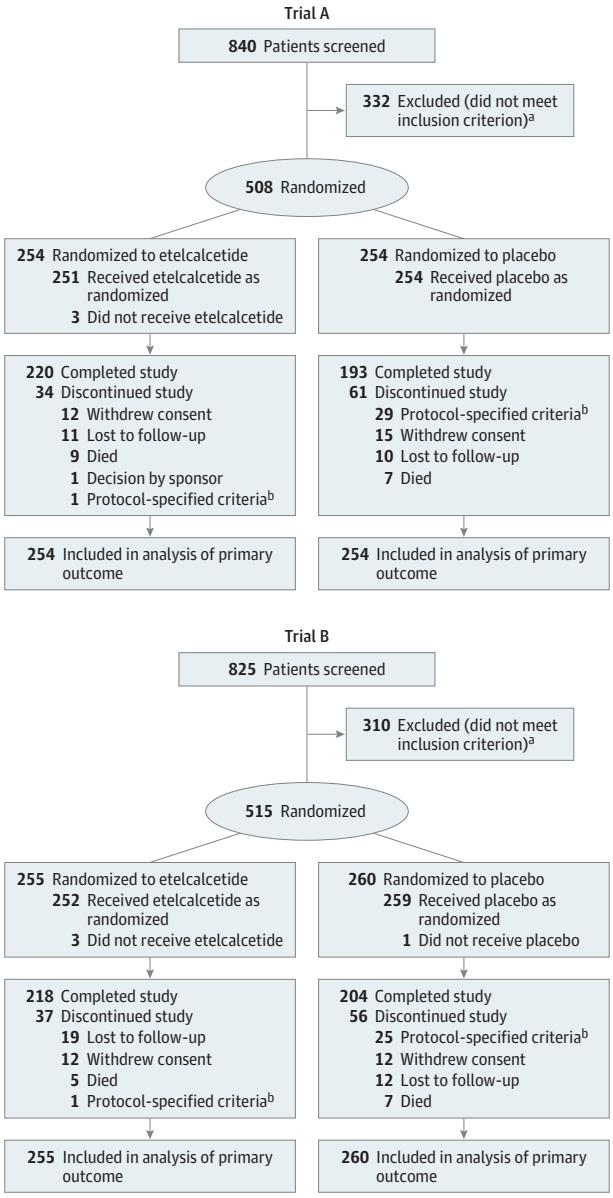
Treatment with etelcalcetide decreased bone-specific alkaline phosphatase and collagen type 1 cross-linked C-telopeptide. eTable 4 in Supplement 3 shows median absolute and percentage changes in bone-specific alkaline phosphatase and collagen type 1 cross-linked C-telopeptide at weeks 12 and 27 by randomized group within each trial.

Adverse Events

Reductions in serum calcium were the most frequent adverse events. eTable 5 in Supplement 3 shows the proportion of patients with serum calcium concentrations below 3 thresholds.

Treatment-emergent death occurred in 7 of 251 patients (2.8%) in trial A and 4 of 252 patients (1.6%) in trial B who received at least 1 dose of etelcalcetide vs 7 of 254 (2.8%) and 8 of 259 (3.1%) who received placebo, respectively. Among patients treated with etelcalcetide, adjudicated positive myocardial infarction occurred in 8 (3 [1.2%] in trial A and 5 [2.0%] in trial B), stroke in 2 (1 [0.4%] in each trial), and hospitalization for heart failure in 11 (7 [2.8%] in trial A and 4 [1.6%] in trial B). Among patients in the placebo group, adjudicated positive myocardial infarction occurred in 5 (2 [0.8%] in trial A and 3 [1.2%] in trial B), stroke in 3 (1 [0.4%] in trial A and 2 [0.8%] in trial B), and hospitalization for heart failure in 6 (2 [0.8%] in trial A and 4 [1.5%] in trial B). Confirmed seizures occurred in 4 patients (2 [0.8%] in each treatment group) in trial A and 6 (3 [1.2%] in each group) in trial B. **Table 2** shows a full list of adverse events with a frequency of at least 5% with at least a 1% difference between treatment groups. A more comprehensive list of adverse events is provided in eTable 6 in Supplement 3; eTable 7 shows baseline and maximal predialysis QTcB, QTcF, and maximal changes from baseline.

Figure 1. Participant Flow in 2 Trials Assessing the Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone Concentrations in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism



[a] Specific reasons not available.

[b] Participants met discontinuation criteria for increasing parathyroid hormone levels after week 12.

Discussion

These trials have several strengths. Participants were diverse in terms of age, sex, race, geographic region, and primary cause of end-stage renal disease and had a broad range of comorbidity and severity of secondary hyperparathyroidism. Few patients were lost to follow-up and relatively few stopped study drug for non-protocol-specified reasons. In aggregate, 74.7%

Table 1. Baseline Participant Characteristics

Characteristics	Trial A		Trial B	
	Etelcalcetide (n = 254)	Placebo (n = 254)	Etelcalcetide (n = 255)	Placebo (n = 260)
Age, mean (SD), y	58.4 (14.6)	57.1 (14.5)	58.4 (14.6)	59.0 (13.9)
Female, No. (%)	103 (40.6)	114 (44.9)	93 (36.5)	95 (36.5)
Race, No. (%)				
White	173 (68.1)	175 (68.9)	163 (63.9)	169 (65.0)
Black	72 (28.3)	69 (27.2)	64 (25.1)	80 (30.8)
Asian	5 (2.0)	3 (1.2)	13 (5.1)	6 (2.3)
Pacific Islander	0	2 (0.8)	7 (2.7)	3 (1.2)
American Indian or Alaska Native	0	0	0	0
Other or missing data	4 (1.6)	5 (2.0)	8 (3.2)	2 (0.8)
Hispanic, No. (%)	33 (13.0)	33 (13.0)	32 (12.5)	33 (12.7)
Time since initiation of dialysis, median (IQR), y	3.95 (1.95-8.36)	3.77 (1.65-6.85)	4.00 (2.17-7.10)	3.81 (2.00-6.77)
Primary cause of end-stage renal disease, No. (%)				
Diabetes mellitus	67 (26.4)	78 (30.7)	79 (31.0)	84 (32.3)
Hypertension	63 (24.8)	65 (25.6)	64 (25.1)	58 (22.3)
Glomerulonephritis	39 (15.4)	30 (11.8)	30 (11.8)	45 (17.3)
Polycystic kidney disease	19 (7.5)	20 (7.9)	16 (6.3)	22 (8.5)
Urologic	9 (3.5)	8 (3.1)	10 (3.9)	6 (2.3)
Other	46 (18.1)	44 (17.3)	39 (15.3)	32 (12.3)
Unknown	11 (4.3)	9 (3.5)	17 (6.7)	13 (5.0)
History of kidney transplant, No. (%)	30 (11.8)	34 (13.4)	28 (11.0)	30 (11.5)
History of cinacalcet use, No. (%)	103 (40.6)	109 (42.9)	137 (53.7)	126 (48.5)
Hemodiafiltration dialysis mode, No. (%)	41 (16.1)	41 (16.1)	31 (12.2)	35 (13.5)
Dialysate calcium <2.5 mEq/L, No. (%)	13 (5.1)	18 (7.1)	24 (9.4)	28 (10.8)
Albumin-corrected calcium, mean (SD), mg/dL	9.65 (0.66	9.61 (0.60	9.63 (0.65	9.70 (0.69
Phosphate, mean (SD), mg/dL	5.95 (1.59)	5.78 (1.60)	5.76 (1.60)	5.83 (1.45)
Parathyroid hormone, pg/mL				
Median (IQR)	706 (552-950)	706 (563-994)	740 (552-949)	726 (553-969)
Mean (SD)	849 (520)	820 (386)	845 (464)	852 (552)
Fibroblast growth factor 23, median (IQR), pg/mL	6134 (1210-16 439)	3355 (811-11 939)	3181 (969-12 771)	3311 (865-12 898)
Bone-specific alkaline phosphatase, median (IQR), µg/L	23.0 (15.2-33.9)	25.8 (17.4-38.2)	23.5 (15.4-35.0)	24.4 (16.7-36.5)
Collagen type I cross-linked C-telopeptide, median (IQR), ng/L	2960 (1990-4090)	3100 (2290-4340)	2940 (1970-4260)	3055 (2235-4100)

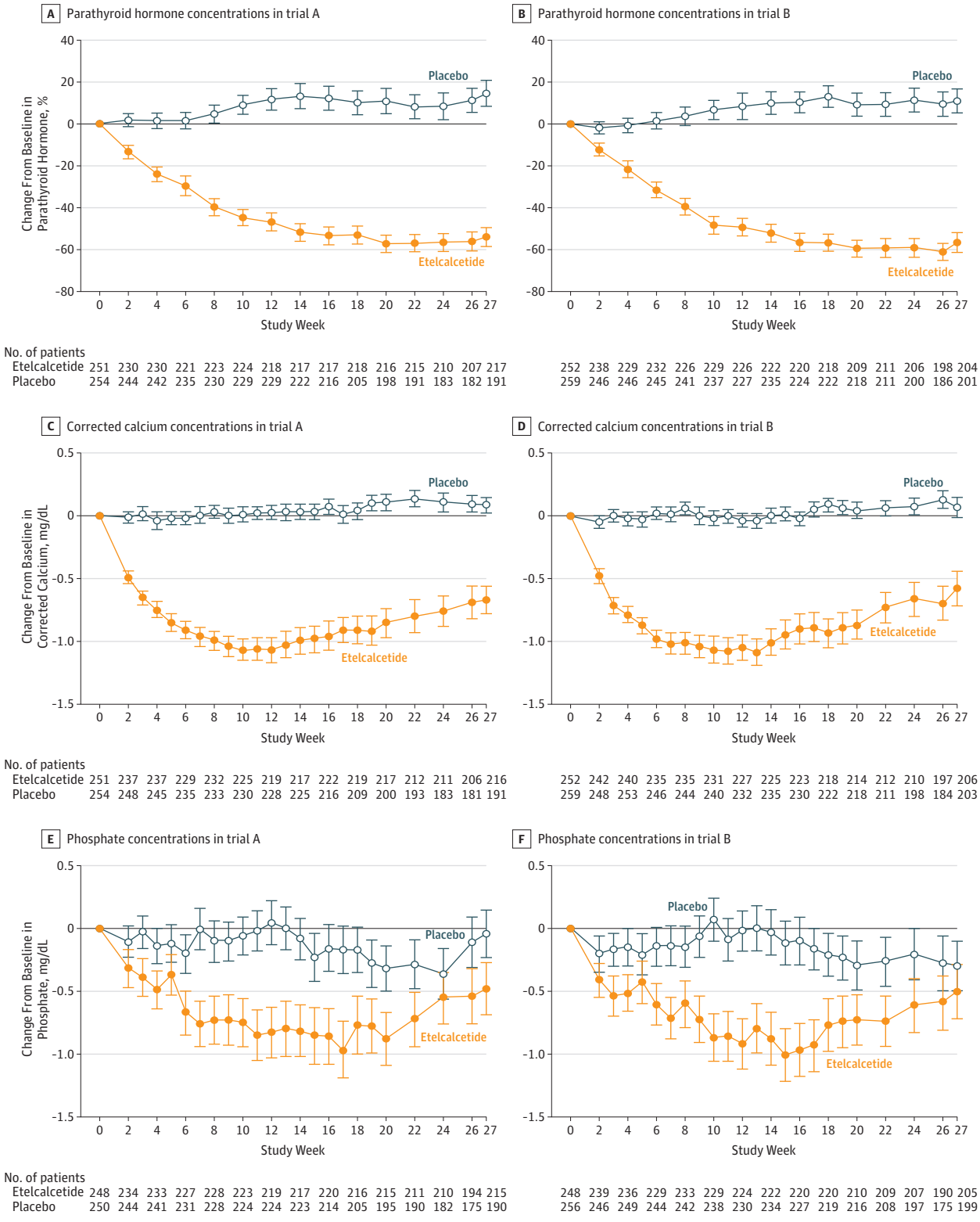
Abbreviation: IQR, interquartile range.

of patients randomized to receive the intravenous calcimimetic etelcalcetide thrice weekly after hemodialysis experienced greater than 30% reduction in serum PTH compared with less than 8.9% of patients randomized to placebo. The reduction in PTH was rapid, sustained over 26 weeks, and evident in all evaluated subgroups, with no apparent effect modification by age, sex, race, time since dialysis initiation, geographic region, baseline severity of secondary hyperparathyroidism, or use of vitamin D. The wide range of doses used in the trials demonstrates the importance of using a dose-titration strategy rather than a fixed dose for all patients. The efficacy results are particularly noteworthy given that patients were already receiving conventional therapy for secondary hyperparathyroidism.

The development of etelcalcetide followed a series of basic discoveries on calcium homeostasis by Brown et al,[10] who in 1993 reported on the cloning and characterization of the calcium-sensing receptor. The first calcimimetics, including cinacalcet, were allosteric activators of the calcium-sensing receptor. Etelcalcetide was found to act at a site on the calcium-sensing receptor distinct from that of cinacalcet and to induce a sharp decline in PTH and serum calcium in laboratory animals. Pharmacokinetic data suggested a sufficiently long terminal half-life,[4] making feasible the intermittent administration with thrice-weekly hemodialysis.

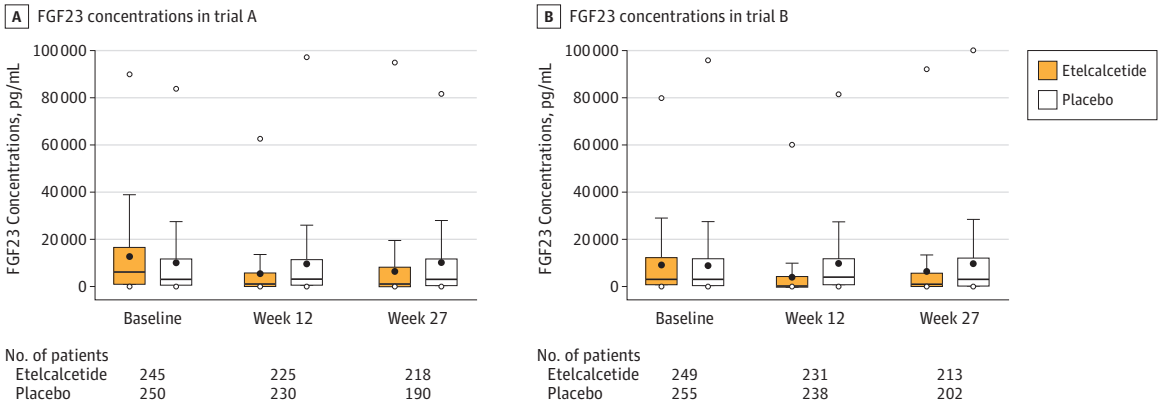
The ability to effectively reduce PTH while simultaneously reducing serum concentrations of calcium and phosphate is widely regarded as a key differentiating attribute of

Figure 2. Mean Percentage Change From Baseline by Study Week in Parathyroid Hormone, Corrected Calcium, and Phosphate Concentrations by Randomized Group in Each Trial



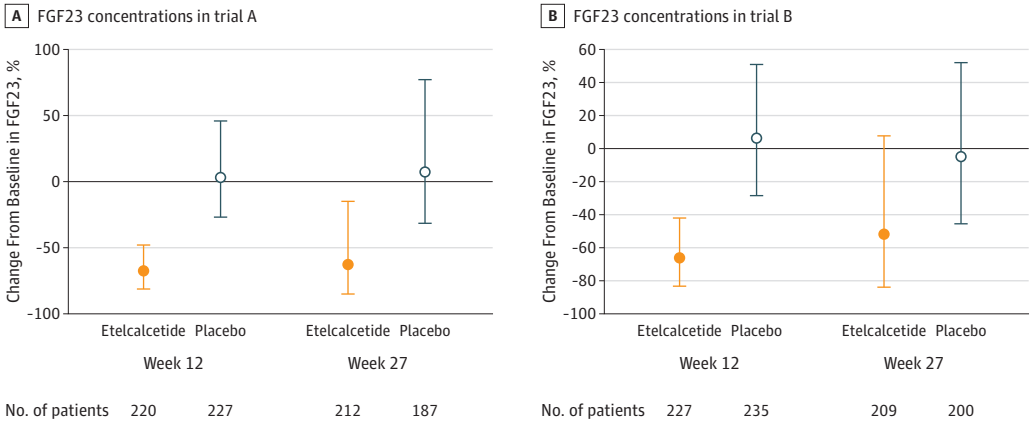
Error bars indicate 95% CIs. Week 27 was a posttreatment visit.

Figure 3. Serum Intact Fibroblast Growth Factor 23 (FGF23) Concentrations at Baseline, Week 12, and Week 27 by Randomized Group in Each Trial



Closed circles represent means; solid lines, medians; boxes, interquartile ranges; whiskers, 1.5 times interquartile ranges; and top and bottom open circles, maximum and minimum observations. The following values were excluded from the figure: in trial A, 1 (0.4%) etelcalcetide-treated and 2 (0.8%) placebo-treated patients had FGF23 values higher than 100 000 pg/mL at baseline, 1 (0.4%) etelcalcetide-treated and 5 (2.2%) placebo-treated patients had FGF23 values higher than 100 000 pg/mL at week 12, and 2 (0.9%) etelcalcetide-treated and 3 (1.6%) placebo-treated patients had FGF23 values higher than 100 000 pg/mL at week 27; in trial B, 2 (0.8%) etelcalcetide-treated and 10 (3.9%) placebo-treated patients had FGF23 values higher than 100 000 pg/mL at baseline, 0 etelcalcetide-treated and 5 (2.1%) placebo-treated patients had FGF23 values higher than 100 000 pg/mL at week 12, and 2 (0.9%) 2 etelcalcetide-treated and (1.0%) placebo-treated patients had FGF23 values higher than 100 000 pg/mL at week 27.

Figure 4. Median Percentage Change From Baseline in Serum Intact Fibroblast Growth Factor 23 (FGF23) at Weeks 12 and 27 by Randomized Group Within Each Trial



Error bars indicate interquartile ranges.

calcimimetics compared with calcitriol or active vitamin D analogs, which stimulate calcium and phosphate absorption from the gastrointestinal tract.[11]

Several observational studies have demonstrated higher rates of mortality, cardiovascular events, and fracture in patients with moderate to severe secondary hyperparathyroidism.[6-9] In an analysis of more than 40 000 patients receiving hemodialysis, Block et al[7] showed that PTH concentrations greater than 600 pg/mL were independently associated with a 15% higher risk of death relative to PTH concentrations either within the Kidney Disease Outcomes Quality Initiative target range of 150 to 300 pg/mL or 300 to 600 pg/mL; these findings were confirmed and extended by Kalantar-Zadeh et al.[8] in an even larger cohort examining time-varying PTH concentrations. Informed by these observational studies and safety data from a pooled analysis of short-term placebo-controlled clinical trials,[12] the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial assessed the safety and efficacy of the oral calcimimetic cinacalcet on death and major cardiovascular events in 3883 patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism.[13] Roughly two-thirds of patients in both groups discontinued oral study drug. Median PTH concentrations in cinacalcet-treated patients declined by more than 50% during the first 6 months of the trial; median differences in PTH of 30% or more were maintained throughout the trial despite reduced adherence. Among patients randomized to placebo, 14% of patients underwent parathyroidectomy and 21% started commercial cinacalcet because of poorly controlled secondary

Table 2. Treatment-Emergent Adverse Events[a]

	No. (%) of Participants			
	Trial A		Trial B	
Adverse Events	Etelcalcetide (n = 251)	Placebo (n = 254)	Etelcalcetide (n = 252)	Placebo (n = 259)
Blood calcium decrease[b]	153 (61.0)	21 (8.3)	168 (66.7)	31 (12.0)
Muscle spasms	30 (12.0)	18 (7.1)	28 (11.1)	16 (6.2)
Diarrhea	18 (7.2)	18 (7.1)	36 (14.3)	26 (10.0)
Nausea	31 (12.4)	13 (5.1)	23 (9.1)	19 (7.3)
Vomiting	26 (10.4)	18 (7.1)	19 (7.5)	8 (3.1)
Headache	18 (7.2)	20 (7.9)	20 (7.9)	11 (4.2)
Hypocalcaemia	18 (7.2)	1 (0.4)	17 (6.7)	0
Hypertension	12 (4.8)	17 (6.7)	19 (7.5)	12 (4.6)
Hypotension	16 (6.4)	10 (3.9)	14 (5.6)	16 (6.2)
Arteriovenous fistula site complication	13 (5.2)	14 (5.5)	16 (6.3)	12 (4.6)
Pain in extremity	17 (6.8)	11 (4.3)	7 (2.8)	9 (3.5)
Paresthesia	13 (5.2)	3 (1.2)	11 (4.4)	0
Back pain	8 (3.2)	8 (3.1)	14 (5.6)	11 (4.2)
Upper respiratory tract infection	8 (3.2)	10 (3.9)	13 (5.2)	16 (6.2)

[a] Events occurring in 5% or more of etelcalcetide-treated patients, with 1% or greater difference between groups in at least 1 study, based on patients who received at least 1 dose of investigational product. Some patients may have had more than 1 adverse event in each category.

[b] Blood calcium decrease defined as an albumin-corrected serum calcium level of less than 8.3 mg/dL that resulted in a medical intervention.

hyperparathyroidism. The unadjusted intention-to-treat analysis did not show a statistically significant reduction in the primary composite end point (relative hazard, 0.93; 95% CI, 0.85-1.02). Adjustment for baseline characteristics showed a 12% reduction in the relative hazard of the primary composite end point and a 14% reduction in the relative hazard of death, with more pronounced effects observed in older patients.[13] Clinical fractures were reduced,[14] as was the need for parathyroidectomy or the development of severe, unremitting hyperparathyroidism[15] and development of calcific uremic arteriolopathy (calciphylaxis).[16] In aggregate, EVOLVE suggested that correction of secondary hyperparathyroidism in patients receiving hemodialysis might be of clinical benefit yet highlighted the limitations of current calcimimetic therapy with respect to sustained adherence.

Parathyroidectomy can also be used to treat severe secondary hyperparathyroidism. A recent report on parathyroidectomy in 4435 patients receiving hemodialysis demonstrated a 2% perioperative mortality rate, a 24% rehospitalization rate within 30 days, a 39% increase in overall hospitalizations, and a 58% increase in hospital days in the subsequent year.[17] Thus, even among patients considered to be surgical candidates, morbidity associated with parathyroidectomy can be substantial. Elevated PTH is further recognized to contribute to sustained hyperphosphatemia, a potent risk factor consistently associated with cardiovascular events and mortality in patients receiving dialysis. Patients with adequate nutritional intake and PTH levels greater than 600 pg/mL are 3- to 5-fold more likely to have hyperphosphatemia[18]; thus, efforts aimed solely at reducing intestinal phosphate absorption are unlikely to be successful at managing hyperphosphatemia.

The phosphatonin FGF23 elevates early in the course of CKD[19] and increases with CKD progression, commonly reaching levels 2 orders of magnitude above normal in patients receiving dialysis. In CKD, elevated serum concentrations of FGF23 have been associated with incidence and progression of CKD, left ventricular hypertrophy, heart failure, cardiovascular events, and all-cause mortality.[20-23] Animal models support a causal role of FGF23 in the development of left ventricular hypertrophy.[24] Preclinical and clinical data suggest that calcium, phosphate, PTH, and vitamin D all upregulate FGF23.[25-27] Patients randomized to etelcalcetide were more likely to experience substantial lowering of FGF23 despite more frequent provision of calcium and vitamin D. The clinical significance of lowering FGF23 was supported by a post hoc analysis of EVOLVE by Moe et al.[28] Patients randomized to cinacalcet who experienced at least a 30% reduction in FGF23 from baseline to week 20 experienced nominally significant reductions in the primary composite end point (relative hazard, 0.82; 95% CI, 0.69-0.98), cardiovascular mortality (relative hazard, 0.66; 95% CI, 0.50-0.87), and heart failure (relative hazard, 0.69; 95% CI, 0.48-0.99).

Treatment with etelcalcetide lowered serum calcium in the majority of patients, with overt symptomatic hypocalcemia reported in 7%. The calcium-lowering effect of etelcalcetide was evident early after treatment initiation and reached a nadir at weeks 10 to 12 despite increased use of oral calcium and active vitamin D analogs, along with increases in dialysate calcium in a substantial fraction of patients. Concerns regarding excessive calcium intake and a large cumulative positive calcium balance in patients treated with calcimimetic agents are valid; additional studies are required to assess the effects of etelcalcetide on skeletal and vascular health. In an earlier randomized trial, patients receiving hemodialysis treated with cinacalcet and fixed-dose vitamin D compared with flexible doses of vitamin D alone suggested

an attenuation of vascular and cardiac valve calcification with calcimimetic therapy.[29]

Adverse events occurred in 92% of etelcalcetide-treated and 80% of placebo-treated patients. Nausea, vomiting, and diarrhea were more common in etelcalcetide-treated patients, as were symptoms potentially related to hypocalcemia, such as muscle spasms, headache, and paresthesia. Hyperkalemia was reported twice as often in etelcalcetide-treated patients; review of these events showed no consistent risk factors or associated events. It may not be possible to disentangle the effects of lower serum calcium and etelcalcetide itself on the QT interval. Nevertheless, physicians will need to exercise caution when using etelcalcetide in conjunction with other drugs that may prolong the QT interval. There were no notable differences in rates of death, myocardial infarction, stroke, or seizure between the etelcalcetide and placebo groups, and there was only a small numerical imbalance in heart failure requiring hospitalization, although the study was not adequately powered to detect differences in event rates.

These trials have several important limitations. Although the trials demonstrated biochemical control of secondary hyperparathyroidism compared with placebo, they were not designed to assess the effects of etelcalcetide on bone architecture or strength or the likelihood of fracture, an important consequence of secondary hyperparathyroidism. Moreover, the major limitation of these trials was that they were unable to determine whether etelcalcetide altered vascular calcification, cardiovascular structure or function, cardiovascular events, or other clinical outcomes, including mortality.

Conclusions

Among patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism, use of etelcalcetide compared with placebo resulted in greater reduction in serum PTH over 26 weeks. Further studies are needed to assess clinical outcomes as well as longer-term efficacy and safety.

ARTICLE INFORMATION

Author Contributions: Drs Block and Chertow had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Block, Bushinsky, Drueke, Kewalramani, Martin, Mix, Silver, Spiegel, Walsh, Chertow.
Acquisition, analysis, or interpretation of data: Block, Bushinsky, Cunningham, Drueke, Ketteler, Kewalramani, Martin, Mix, Moe, Patel, Spiegel, Sterling, Walsh, Chertow.
Drafting of the manuscript: Block, Cunningham, Ketteler, Moe, Sterling, Walsh, Chertow.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Block, Martin, Mix, Sterling, Walsh, Chertow.
Obtained funding: Kewalramani.
Administrative, technical, or material support: Kewalramani, Moe, Patel, Spiegel.
Study supervision: Block, Bushinsky, Kewalramani, Spiegel.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.
Dr Block reported steering committee fees from Amgen and advisory fees from Kai Pharmaceuticals. Dr Bushinsky reported equity in Amgen and Relypsa, personal fees from Sanofi/Genzyme and OPKO, and grants from the National Institutes of Health and the Renal Research Institute.
Dr Cunningham reported consulting fees from Amgen. Dr Drueke reported personal fees from Amgen, Fresenius Medical Care, Sanofi-Aventis, Hoffmann-LaRoche, Kyowa Hakko Kirin, and Vifor. Dr Ketteler reported speaker and consultancy honoraria from Amgen, Fresenius Medical Care, Sanofi/Genzyme, Vifor, and Abbvie. Dr Martin reported advisory board fees from Amgen and consultant fees from Diasorin. Dr Moe reported consulting fees from Merck and UltraGenyx, grants from the National Institutes of Health, the Veterans Administration, and Novartis, and personal fees from Novartis. Dr Patel reported grants or personal fees for clinical trial steering committees, clinical trial end point adjudication, data and safety monitoring boards, and advisory boards from Amgen, Lilly, Angion Biomedica, CSL Limited, Ablative Solutions, Kai Pharmaceuticals, Reata Pharmaceuticals, Keryx Pharmaceuticals, Gilead Sciences, GlaxoSmithKline, and Trevi Therapeutics. Dr Silver reported grants and personal fees from Amgen. Dr Chertow reported stock options and/or personal fees (advisory board, trial steering committee, board of directors) from Satellite Healthcare, Ardelyx, Durect, Outset Medical, Thrasos, Puracath Medical, Physiowave, DxNow, Cricket Health, Eliaz Therapeutics, Akebia, AMAG, AstraZeneca, Gilead, and Keryx Pharmaceuticals. No other disclosures were reported.

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Role of the Funder/Sponsor: The sponsor participated in the design of both trials and was responsible for coordinating the collection, management, and analysis of the data. The sponsor otherwise did not participate in preparation, review, or approval of the manuscript or decision to submit the manuscript for publication; the sponsor did not have the right to veto submission or publication of the study findings.

Additional Contributions: An independent data monitoring committee periodically reviewed safety and efficacy data. An independent events adjudication committee reviewed events of death, myocardial infarction, stroke, heart failure requiring hospitalization, and seizures in a blinded manner. The sponsor collected the trial data and analyzed them according to a predefined statistical analysis plan. We acknowledge the efforts of Gregory Bell, MD, whose work at Kai Pharmaceuticals informed the design of the trials. Dr Bell received no compensation in connection with these trials.

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