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Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism
A Randomized Clinical Trial

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IMPORTANCE Secondary hyperparathyroidism contributes to extraskeletal calcification and is associated with all-cause and cardiovascular mortality. Control is suboptimal in the majority of patients receiving hemodialysis. An intravenously (IV) administered calcimimetic could improve adherence and reduce adverse gastrointestinal effects.

OBJECTIVE To evaluate the relative efficacy and safety of the IV calcimimetic etelcalcetide and the oral calcimimetic cinacalcet.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, double-dummy active clinical trial was conducted comparing IV etelcalcetide vs oral placebo and oral cinacalcet vs IV placebo in 683 patients receiving hemodialysis with serum parathyroid hormone (PTH) concentrations higher than 500 pg/mL on active therapy at 164 sites in the United States, Canada, Europe, Russia, and New Zealand. Patients were enrolled from August 2013 to May 2014, with end of follow-up in January 2015.

INTERVENTIONS Etelcalcetide intravenously and oral placebo (n = 340) or oral cinacalcet and IV placebo (n = 343) for 26 weeks. The IV study drug was administered 3 times weekly with hemodialysis; the oral study drug was administered daily.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was noninferiority of etelcalcetide at achieving more than a 30% reduction from baseline in mean predialysis PTH concentrations during weeks 20-27 (noninferiority margin, 12.0%). Secondary end points included superiority in achieving biochemical end points (>50% and >30% reduction in PTH) and self-reported nausea or vomiting.

RESULTS The mean (SD) age of the trial participants was 54.7 (14.1) years and 56.2% were men. Etelcalcetide was noninferior to cinacalcet on the primary end point. The estimated difference in proportions of patients achieving reduction in PTH concentrations of more than 30% between the 198 of 343 patients (57.7%) randomized to receive cinacalcet and the 232 of 340 patients (68.2%) randomized to receive etelcalcetide was −10.5% (95% CI, −17.5% to −3.5%, *P* for noninferiority, <.001; *P* for superiority, .004). One hundred seventy-eight patients (52.4%) to randomized etelcalcetide achieved more than 50% reduction in PTH concentrations compared with 138 patients (40.2%) randomized to cinacalcet (*P* = .001; difference in proportions, 12.2%; 95% CI, 4.7% to 19.5%). The most common adverse effect was decreased blood calcium (68.9% vs 59.8%).

CONCLUSIONS AND RELEVANCE Among patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism, the use of etelcalcetide was not inferior to cinacalcet in reducing serum PTH concentrations over 26 weeks; it also met superiority criteria. Further studies are needed to assess clinical outcomes as well as longer-term efficacy and safety.

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Supplemental content

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Secondary hyperparathyroidism is an important complication of chronic kidney disease (CKD) and end-stage renal disease, particularly among patients receiving dialysis. 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 the oral administration of intestinal phosphate binders, oral or intravenous (IV) calcitriol or active vitamin D analogs, and the oral calcimimetic agent cinacalcet.

Etelcalcetide (formerly AMG 416) is a synthetic peptide that comprises 7 D-amino acids linked to an L-cysteine via a disulfide bond and functions as an activator of the calcium sensing receptor. Recently, 2 phase 3 placebo-controlled clinical trials demonstrated efficacy of etelcalcetide in reducing PTH (above and beyond that achieved by conventional therapy) by 30% or more in 75% of treated patients compared with fewer than 10% of patients treated with placebo; asymptomatic reduced serum calcium was the most common (and expected) adverse effect.[3]

Cinacalcet is widely used in the management of moderate to severe secondary hyperparathyroidism in patients undergoing dialysis, particularly the sizeable fraction of patients with contraindications (eg, hypercalcemia) or refractory to therapy with calcitriol or active vitamin D analogs.[4] Persistent use of cinacalcet has been limited in clinical practice by a relatively high frequency of gastrointestinal adverse effects, particularly nausea and vomiting. We undertook the current trial to compare the relative efficacy and safety of etelcalcetide and cinacalcet, using a double-blind double-dummy design.

Key Points

Question What is the effect of the intravenous calcimimetic etelcalcetide compared with the oral calcimimetic cinacalcet on serum parathyroid hormone (PTH) concentrations in patients receiving hemodialysis?

Findings In a randomized clinical trial that included 683 adults receiving hemodialysis with PTH levels higher than 500 pg/mL, 68.2% of patients randomized to receive etelcalcetide vs 57.7% randomized to receive cinacalcet experienced more than a 30% reduction in mean PTH concentrations over 27 weeks, a significant difference.

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

Methods

Study Setting

The trial was conducted at 164 sites in United States, Canada, Europe, Russia, and New Zealand. The trial was approved by institutional review boards at participating study sites, and all participants signed informed consent (see trial protocol Supplement 1, protocol amendment 1 in Supplement 2, protocol amendment 1 changes in Supplement 3, protocol amendment 2 in Supplement 4, protocol amendment 2 changes in Supplement 5, protocol amend 3 in Supplement 6, protocol amendment 3 changes in Supplement 7 and statistical analysis plan in Supplement 8).

Participants

Patients receiving thrice weekly maintenance hemodialysis with moderate to severe secondary hyperparathyroidism (predialysis serum PTH >500 pg/mL; to convert to nanograms per liter, multiply by 0.1053) on stable doses of calcium supplements or phosphate binders and calcitriol or active vitamin D analogs with albumin-corrected serum calcium of 8.3 mg/dL or higher (to convert to millimoles per liter, multiply by 0.25) were eligible for randomization. A complete list of inclusion and exclusion criteria is available in Supplement 9. Race and ethnicity 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, American Indian or Alaska Native, and other). Eligible patients could not have received cinacalcet during the 3 months prior to the first screening laboratory assessments, and the use of commercial cinacalcet therapy was prohibited during the study.

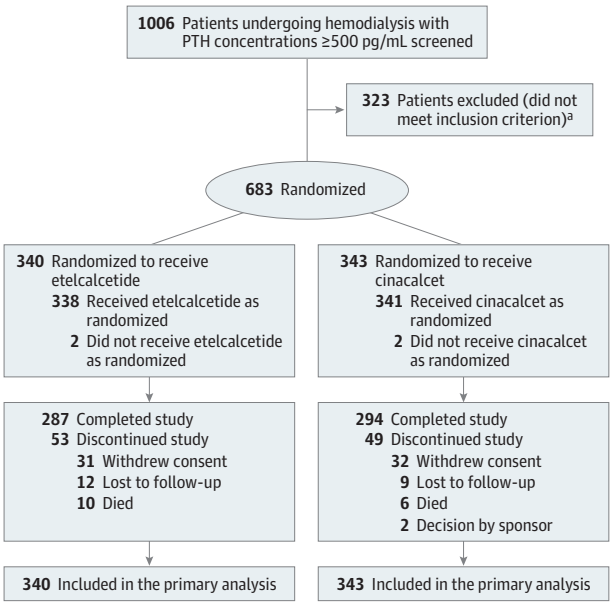
Study Design

This head-to-head comparison of etelcalcetide and cinacalcet was a phase 3, multinational, randomized, active control, double-blind, double-dummy, dose-titration trial with a 26-week treatment period to compare the therapeutic efficacy and safety of IV etelcalcetide and oral cinacalcet in patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism. All patients, regardless of treatment assignment, received standard care with phosphate binders and calcitriol or active vitamin D analogs, as prescribed by the individual investigator.

Procedures

Eligible patients were randomized 1:1 to receive either IV etelcalcetide and oral placebo or oral cinacalcet and IV placebo by an interactive voice or web response system. Permuted block randomization with a block size of 4 was used, stratified by region (North America and non-North America) and screening PTH (<900 and ≥900 pg/mL). Patients who were randomized to treatment with IV etelcalcetide and oral placebo received thrice weekly IV doses of etelcalcetide at the end of each hemodialysis session and daily oral doses of placebo tablets. Patients who were randomized to treatment with oral cinacalcet and IV placebo received daily oral doses of cinacalcet tablets, and thrice weekly IV doses of placebo at the end of each hemodialysis session. The IV study drug 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.

Figure 1. Flow Diagram of Patients Through the Trial



PTH indicates parathyroid hormone.

[a] Specific reasons were not available.

Dosing

The starting dose of IV etelcalcetide was 5 mg thrice weekly after hemodialysis and the starting dose of oral cinacalcet was 30 mg daily. Etelcalcetide (and corresponding IV placebo) could be titrated in increments of 2.5 mg or 5 mg (dose range, 2.5-15 mg) and cinacalcet (and corresponding oral placebo) in increments of 30 mg (dose range, 30-180 mg) at weeks 5, 9, 13, and 17, with the target serum PTH levels from 100 to 300 pg/mL. Dose titration was managed by an interactive voice or web response system; investigators were blinded to serum PTH results. Study drug was withheld for 2 consecutive PTH values less than 100 pg/mL, serum calcium less than 7.5 mg/dL, symptomatic hypocalcemia, or drug-related adverse events. Serum calcium, albumin, and PTH levels were monitored every 2 weeks.

Biochemical and Other Determinations

All biochemical data were analyzed in central laboratories. Parathyroid hormone was analyzed in serum samples using the Advia Centaur assay (Covance, population reference range, 14-72 pg/mL). In addition to serum calcium, phosphate, and albumin, intact phosphatonin fibroblast growth factor 23 (FGF23), serum bone-specific alkaline phosphatase, and collagen type 1 cross-linked C-telopeptide were measured at baseline and at weeks 12 and 27.

Self-reported Nausea and Vomiting

Patients were instructed to complete an instrument including (1) a visual analog scale assessing the presence and severity of nausea and (2) a single question on whether the patient had vomited that day, each evening using an electronic device.

End Points

The primary efficacy (noninferiority) end point was the proportion of patients with more than 30% reduction from baseline in mean PTH concentrations during the efficacy assessment phase (weeks 20-27). Key secondary end points included the proportion of patients with more than a 50% and more than a 30% reduction in PTH concentrations (superiority), and the mean weekly days of self-reported nausea and vomiting over the first 8 weeks. Relative effects on FGF23, bone-specific alkaline phosphatase, and collagen type 1 cross-linked C-telopeptide were considered exploratory end points. The assessment of all end points was blinded to allocation group.

Sample Size Determination

A noninferiority margin was determined based on data from the Evaluation of Cinacalcet Hydrochloride Therapy to Lower CardioVascular Events (EVOLVE) trial.[5] In the EVOLVE trial, 60% of patients in the cinacalcet group achieved at least 30% PTH concentrations reduction at 6 months. Assuming that 60% of patients achieve more than 30% reduction from baseline in mean predialysis PTH during the efficacy assessment phase, 300 patients per treatment group would provide 90% power to demonstrate noninferiority, using a margin of 12% for the upper bound of the 95% 2-sided CI for the treatment difference (ie, the proportion of cinacalcet-treated patients minus etelcalcetide-treated patients). For the test of superiority based on a more than 50% reduction in PTH concentration, 300 patients per treatment group would provide a 90% power to detect a statistically significant difference between treatment groups, assuming 60% and 45% response rates in patients randomized to etelcalcetide and cinacalcet, respectively. These assumptions were based on data from a phase 2 open-label etelcalcetide study[6] and EVOLVE, respectively.

Statistical Analysis

All data were analyzed according to the intention-to-treat principle. Where applicable, analyses were adjusted for randomization stratification factors. For the noninferiority analysis, the Mantel-Haenszel method was applied to compute the 2-sided 95% CI for the difference between the proportion of patients who achieved a more than 30% reduction from baseline in mean predialysis serum PTH concentrations during the efficacy assessment phase in the etecalcetide and cinacalcet groups. The proportion of patients achieving a reduction in PTH concentrations of more than 50% and more than 30% during the efficacy assessment phase was analyzed with the Cochrane-Mantel-Haenszel test. Missing data were handled as follows: For the primary (noninferiority) analysis, multiple imputation under the noninferiority null method[7] was used if patients had missing PTH data during the efficacy assessment phase. Under this imputation approach, a response rate of 60% was applied to impute response status in patients in the cinacalcet group with missing data. A response rate of 48% was applied to impute response status in patients in the etelcalcetide group with

Table 1. Baseline Patient Characteristics

	Etelcalcetide (n = 340)	Cinacalcet (n = 343)
Age, mean (SD), y	54.0 (13.81)	55.3 (14.41)
Women, No. (%)	148 (43.5)	151 (44.0)
Race/ethnicity, No. (%)		
White	261 (76.8)	277 (80.8)
Black (or African American)	54 (15.9)	52 (15.2)
Asian	9 (2.6)	7 (2.0)
Native Hawaiian or other Pacific Islander	6 (1.8)	3 (0.9)
American Indian or Alaskan Native	0 (0)	0 (0)
Other	10 (2.9)	4 (1.2)
Hispanic	38 (11.2)	41 (12.0)
Time since initiation of dialysis, median (IQR), y	4.4 (2.0-7.8)	4.1 (1.7-7.5)
Primary cause of ESRD, No. (%)		
Diabetes mellitus	77 (22.6)	66 (19.2)
Hypertension	70 (20.6)	80 (23.3)
Glomerulonephritis	78 (22.9)	61 (17.8)
Polycystic kidney disease	27 (7.9)	36 (10.5)
Urologic	19 (5.6)	16 (4.7)
Other	46 (13.5)	52 (15.2)
Unknown	23 (6.8)	32 (9.3)
History, No. (%)		
Kidney transplant	58 (17.1)	48 (14.0)
Cinacalcet use	80 (23.5)	92 (26.8)
Dialysis Modality, No. (%)		
Hemodiafiltration	85 (25.0)	79 (23.0)
Hemodialysis	255 (75.0)	264 (77.0)
Dialysate calcium, ≥3.0 mEq/L, No. (%)	149 (43.8)	154 (44.9)
Parathyroid hormone, pg/mL		
Median (IQR)	900 (685-1266)	930 (694-1327)
Mean (SD)	1092 (623)	1139 (707)
Calcium, albumin-corrected, mean (SD), mg/dL	9.67 (0.71)	9.58 (0.67)
Phosphate, mean (SD), mg/dL	5.81 (1.69)	5.82 (1.58)
FGF23, median (IQR), pg/mL	4033 (934-14 701)	2984 (877-12 160)
Bone-specific alkaline phosphatase, median (IQR), µg/L	29.3 (18.3-50.1)	30.0 (20.2-53.4)
Collagen type I cross-linked C-telopeptide, median (IQR), ng/L	3160 (2120-4600)	3310 (2290-4520)

Abbreviations: ESRD, end-stage renal disease; FGF23, fibroblast growth factor 23; IQR, interquartile range.

missing data. The imputation was performed 5 times to account for variability introduced by imputation. For the superiority analyses, patients who contributed no data during the efficacy assessment phase were considered to have not achieved the primary efficacy end point (ie, nonresponder imputation). Due to the difference in imputation methods, the estimated 95% CIs were slightly different between the noninferiority analysis and the superiority analysis of the end point of a reduction in PTH concentrations of more than 30%. The mean weekly number of days of vomiting or nausea in the first 8 weeks was compared using a generalized (Poisson) mixed-effects model. Since noninferiority was demonstrated, the 3 key secondary end points were tested sequentially in the order presented above to control family-wise type 1 error rate. All statistical analyses were conducted using SAS statistical software version 9.2 or above (SAS Institute Inc).

Results

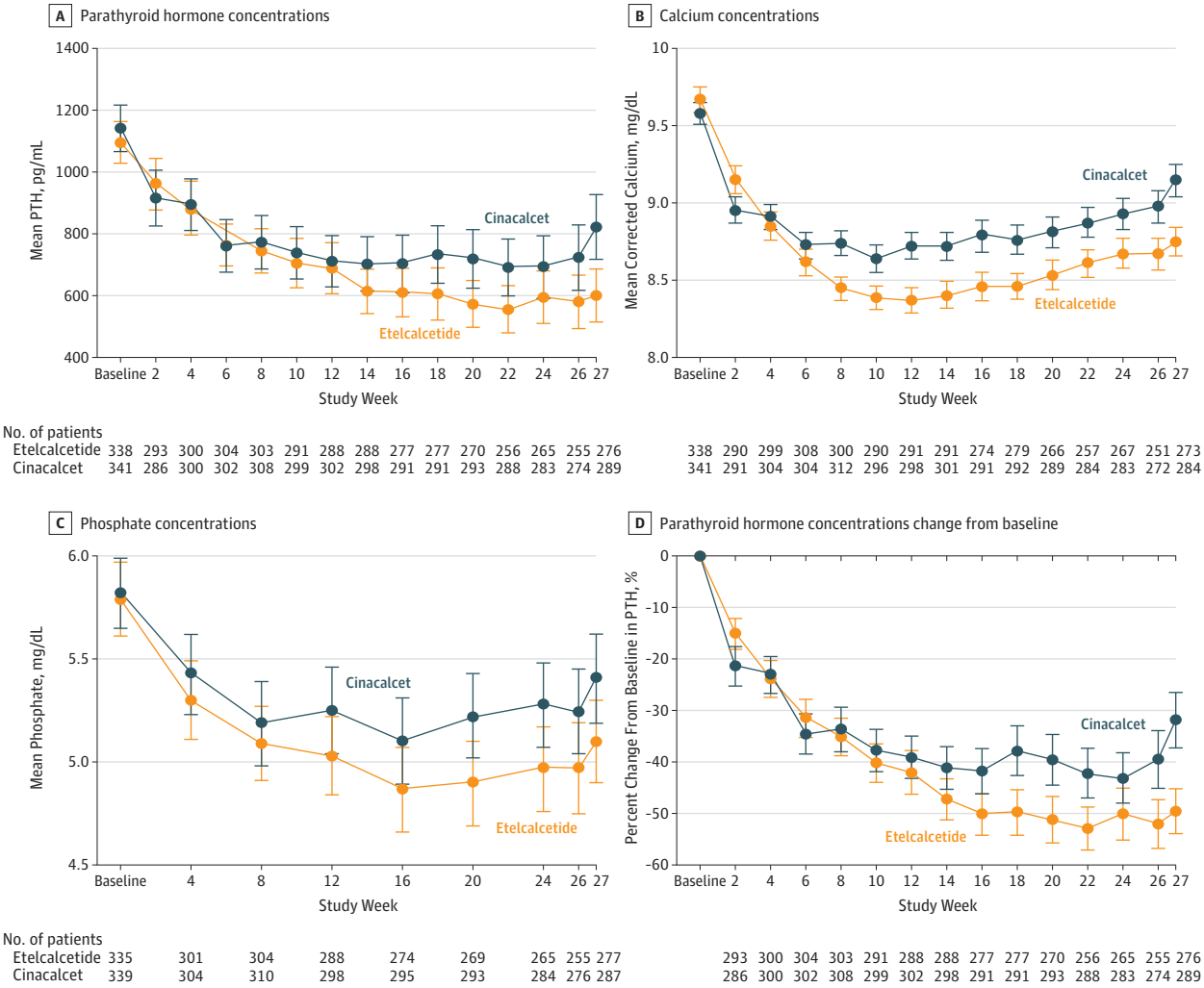
Enrollment

Six hundred eighty-three patients were enrolled (340 randomized to receive etelcalcetide and 343 to receive cinacalcet) from August 2013 to May 2014, with the end-of-participant follow-up in January 2015. The disposition of trial participants is shown in **Figure 1**. The proportion of randomized patients by country is shown in eTable 1 in Supplement 9.

Baseline Characteristics

Table 1 shows selected baseline demographic and clinical data for patients by randomized treatment group; eTable 2 in Supplement 9 shows additional detail. Baseline characteristics of patients randomized to etelcalcetide and cinacalcet were generally well balanced.

Figure 2. Parathyroid Hormone, Calcium, and Phosphate Concentrations in Patients Receiving Cinacalcet or Etelcalcetide by Study Week



Data markers indicate the mean and error bars, 95% confidence intervals.

Etelcalcetide and Cinacalcet Dosing

The median average weekly etelcalcetide dose during the efficacy assessment phase was 15.0 mg (interquartile range [IQR], 9.2-30.0 mg) and the median average daily cinacalcet dose was 51.4 mg (IQR, 26.4-80.4 mg).

Primary and Secondary Laboratory Determinations

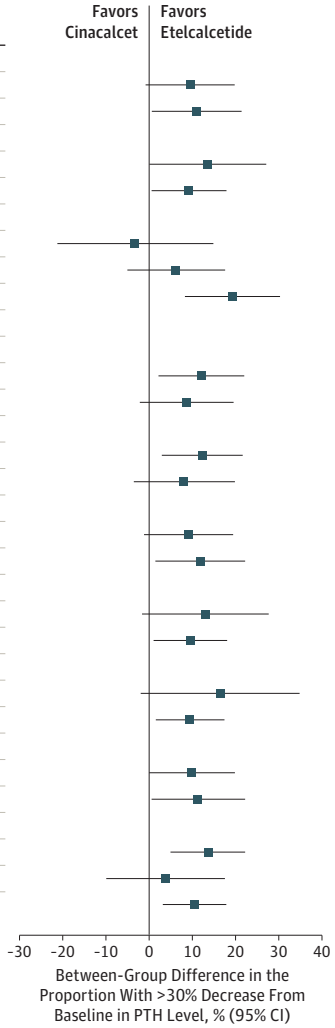
Mean serum PTH, calcium, and phosphate concentrations over time are shown in panels A through C and the percent change in PTH concentrations is shown in panel D of **Figure 2**. There were 42 patients (12.4%) in the group randomized to etelcalcetide and 33 patients (9.6%) in the group randomized to cinacalcet with no PTH data during the efficacy assessment phase. With respect to the primary end point (the proportion of patients achieving a reduction in mean PTH concentrations of >30% from baseline during weeks 20-27), the estimated difference between patients randomized to cinacalcet was 57.7% (198 of 343) and to etelcalcetide was 68.2% (232 of 340) in proportions achieving the end point was −10.5% (−17.5% to −3.5%; *P* for noninferiority, <.001; *P* for superiority, .004). Because the upper bound of the 95% CI was less than the prespecified noninferiority margin of 12%, the noninferiority criterion was met. One hundred seventy-eight patients (52.4%) randomized to etelcalcetide achieved a reduction in PTH concentrations of more than 50%, whereas 138 patients (40.2%) randomized to cinacalcet achieved a reduction in PTH concentrations of more than 50% (*P* = .001, difference in proportions, 12.2%; 95% CI, 4.7% to 19.5%) and for a reduction of more than 30%, the difference in proportions was 10.5% (95% CI, 3.3% to 17.7%). The relative proportion of patients achieving a reduction in PTH concentrations of more than 30% did not differ significantly across any of the patient subgroups examined (**Figure 3**).

Cointerventions

eFigure 1, panels A and B in Supplement 9 show increases in the proportion of patients in both groups using calcium

Figure 3. Forest Plot for Difference in Proportion With More Than 30% Decrease From Baseline in Parathyroid Hormone Levels

Subgroups	No./Total of Patients		Between-Group Difference in Proportion With >30% Decrease From Baseline in PTH Level, % (95% CI)
	Etelcalcetide	Cinacalcet	
Screening, PTH level, pg/mL			
<900	121/167	97/154	9.5 (-0.7 to 19.7)
≥900	110/171	97/182	11.0 (0.8 to 21.2)
Region			
North America	67/103	54/105	13.6 (0.3 to 26.9)
Non-North America	165/237	144/238	9.1 (0.6 to 17.7)
Time since initiation of dialysis, y			
0-≤1	33/46	36/48	-3.3 (-21.1 to 14.6)
>1-≤5	95/149	84/146	6.2 (-4.9 to 17.4)
>5	104/145	78/149	19.4 (8.5 to 30.2)
Baseline			
Dialysate calcium, mEq/L			
<3.0	128/191	104/189	12.0 (2.3 to 21.7)
≥3.0	104/149	94/154	8.8 (-1.9 to 19.4)
Vitamin D sterol use			
Yes	143/200	122/206	12.3 (3.1 to 21.5)
No	89/140	76/137	8.1 (-3.4 to 19.6)
Calcium-containing phosphate binder or calcium supplement use			
Yes	119/172	101/168	9.1 (-1.1 to 19.2)
No	113/168	97/175	11.8 (1.6 to 22.1)
Previous cinacalcet use			
Yes	53/80	49/92	13.0 (-1.5 to 27.5)
No	179/260	149/251	9.5 (1.2 to 17.8)
Race			
Black	38/54	28/52	16.5 (-1.7 to 34.7)
White or other	194/286	170/291	9.4 (1.6 to 17.2)
Sex			
Men	125/192	106/192	9.9 (0.2 to 19.6)
Women	107/148	92/151	11.4 (0.8 to 22.0)
Age, y			
<65	176/262	130/243	13.7 (5.2 to 22.1)
≥65	56/78	68/100	3.8 (-9.7 to 17.3)
Overall	232/340	198/343	10.5 (3.3 to 17.7)



PTH indicates parathyroid hormone. To convert PTH from pg/mL to ng/L, multiply by 0.1053.

supplements or calcium-containing phosphate binders and calcitriol or active vitamin D analogs, respectively. eTable 4 in Supplement 9 shows the proportion of patients treated with dialysate calcium concentrations of 2.5, more than 2.5 and less than 3.5, and 3.5 mEq/L at baseline and at the end of the study. In both groups, the proportion of patients using higher dialysate calcium concentrations was higher at the end of the study relative to the baseline, indicating a cointervention most likely prompted by relative reductions in serum calcium induced by both calcimimetic agents.

FGF23 and Markers of Bone Turnover

eFigure 2 in Supplement 9 shows the proportion of patients achieving a reduction in FGF23 of more than 30% from baseline to week 27 (panel A), the median percent change from baseline in FGF23 to weeks 12 and 27 (panel B), and the median percent change from baseline in bone-specific alkaline phosphate and collagen type 1 cross-linked C to weeks 12 and 27 (panel C). Etelcalcetide treatment yielded more pronounced reductions in FGF23 and in both markers of bone turnover.

Self-reported Nausea and Vomiting

The adjusted mean [SE] weekly days of vomiting or nausea in the first 8 weeks of treatment were not significantly different for patients randomized to etelcalcetide (0.4 [0.04]) and cinacalcet (0.3 [0.03]), corresponding to a rate ratio of 1.20 (95% CI, 0.89-1.49).

Adverse Events

Of the 338 patients treated with etelcalcetide, 62 (18.3%) reported nausea and 45 (13.3%), vomiting. Of the 341 patients treated with cincalcet, 77 (22.6%) reported nausea and 47 (13.8%), vomiting. Death occurred in 9 patients (2.7%) in the etelcalcetide-treated group and 6 (1.8%) in the cinacalcet-treated group; corresponding figures for heart failure events

Table 2. Treatment Emergent Adverse Events[a]

Preferred Term	Patients, No. (%) Etelcalcetide (n = 338)	Cinacalcet (n = 341)
Blood calcium decreased[b]	233 (68.9)	204 (59.8)
Nausea	62 (18.3)	77 (22.6)
Vomiting	45 (13.3)	47 (13.8)
Hypotension	23 (6.8)	10 (2.9)
Headache	22 (6.5)	24 (7.0)
Muscle spasms	22 (6.5)	20 (5.9)
Diarrhea	21 (6.2)	35 (10.3)
Hypertension	21 (6.2)	23 (6.7)
Anemia	17 (5.0)	15 (4.4)
Hypocalcemia	17 (5.0)	8 (2.3)
Pain in extremity	17 (5.0)	14 (4.1)
Bronchitis	5 (1.5)	17 (5.0)

[a] Adverse events occurring among 5% or more patients in either group. The term *treatment emergent* refers to a condition either not present before exposure to a study drug that develops after drug exposure or a condition present before exposure that worsens in frequency or severity. Adverse events occurring after the first dose of study drug and up to 30 days after the last dose of study drug were included. Counts and proportions refer to patients rather than to adverse events. In other words, patients may have one or more adverse event.

[b] Defined as an albumin-corrected serum calcium concentrations lower than 8.3 mg/dL (to convert to mmol/L, multiply by 0.25) that resulted in a medical intervention.

were 10 (3.0%) and 2 (0.6%), respectively, of which 5 and 1 were considered serious. Decreased blood calcium developed in 233 patients (68.9%) in the etelcalcetide-treated group and 204 patients (59.8%) in the cinacalcet-treated group. eFigure 3 in Supplement 9 shows time to first episode of albumin-corrected serum calcium of less than 7.5 mg/dL. A full listing of treatment emergent adverse events with a frequency of at least 5% in either treatment group is shown in **Table 2**. A more comprehensive listing of treatment emergent adverse events is provided in eTable 3 in Supplement 9.

Discussion

In this double-blind, double-dummy randomized head-to-head comparison of etelcalcetide and cinacalcet in patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism, PTH lowering was noninferior with etelcalcetide, the primary end point of the trial. Secondary superiority end points were also reached; 52.4% of patients randomized to etelcalcetide vs 40.2% of patients randomized to cinacalcet experienced a 50% reduction in PTH concentrations from baseline. Etelcalcetide also yielded more potent reductions in serum concentrations of the phosphatonin FGF23 and 2 markers of high-turnover bone disease. There was no significant difference in self-reported nausea and vomiting. Patients treated with etelcalcetide were more likely to experience reduced serum calcium, although there was similar use of interventions in both groups to counter this effect.

Etelcalcetide is an octapeptide type 2 calcimimetic that interacts with the calcium sensing receptor at a site distinct from cinacalcet.[8] Although the acute pharmacodynamic effects of etelcalcetide are similar to those of cinacalcet, the pharmacokinetic profile is distinct. Etelcalcetide is renally cleared, with a half-life allowing thrice weekly administration (concurrent with hemodialysis), yielded sustained reductions in PTH over the 48- to 72-hour dosing interval.[9] It is plausible that this pharmacokinetic difference contributes to the superior efficacy demonstrated over 27 weeks in reducing PTH, as well as the effects on serum calcium, phosphate, and FGF23 levels.

Data from the Dialysis Outcomes and Practice Pattern Study (DOPPS) suggest that PTH concentrations have been rising globally and that patients receiving dialysis with PTH levels higher than 600 pg/mL experience an increased risk of mortality.[2] Among patients with inadequately controlled PTH or phosphate concentrations, achieving reductions toward target values is associated with improved survival.[10,11] The primary analysis of the EVOLVE trial, an unadjusted intention-to-treat comparison of cinacalcet vs placebo, showed no significant difference.[5] However, accounting for baseline characteristics (mean age and the proportion of older patients were higher in the cinacalcet group), there were relative reductions in the primary composite end point (12%), mortality (14%), and clinical fracture (17%).[5,12]

Poorly controlled secondary hyperparathyroidism results in reduced bone mass and may contribute to the exaggerated (and increasing) risk of fracture evident in patients undergoing hemodialysis.[13,14] The more profound effect of etelcalcetide on biomarkers indicating high bone turnover would be expected to yield favorable effects on bone remodeling and a reduction in fracture risk. The effect of etelcalcetide on FGF23 levels is also noteworthy. Fibroblast growth factor 23 is profoundly elevated in patients with CKD[15,16] and has been causally linked to the development of left ventricular hypertrophy[17] and heart failure.[18] Treatment with calcitriol or active vitamin D analogs increases FGF23, whereas treatment with cinacalcet reduces FGF23. In the EVOLVE trial, a 30% reduction in FGF23 concentrations from baseline to week 20 was associated with significant reduction in risks of the primary composite end point, heart failure, and sudden death.[19]

Reduced corrected serum calcium was common with both treatments; however, it was more common with etelcalcetide than with cinacalcet. It is unclear if the occurrence of levels of low serum calcium is entirely attributable to superior PTH lowering. While symptomatic hypocalcemia was uncommon in both treatment groups, it should be emphasized that risks of adverse effects in clinical practice may exceed those in carefully conducted randomized trials. A sizeable fraction of patients taking etelcalcetide were prescribed oral calcium, calcitriol, or vitamin D analogs and had higher dialysate calcium concentrations. In the setting of profound lowering of PTH concentrations in secondary hyperparathyroidism, as occurs with parathyroidectomy, there may be enhanced skeletal uptake of calcium and phosphate ("hungry bone") resulting in remineralization and improved bone structure and strength. However, it is unclear

whether there are long-term adverse effects of inducing positive calcium balance in the setting of calcimimetic therapy.

We had anticipated that etelcalcetide would result in fewer gastrointestinal symptoms than cinacalcet, in part due to the IV route of administration. However, self-reported symptoms of nausea and vomiting were not significantly different between the 2 randomized groups. In several placebo-controlled trials, cinacalcet therapy resulted in higher rates of adverse gastrointestinal effects, principally nausea and vomiting.[3,20,21] In 2 large placebo-controlled trials of etelcalcetide, nausea was reported at rates 1.7-fold and vomiting at rates 1.5-fold higher than those of placebo.[3]

Overall safety and tolerability were similar between treatment groups. Although there were numerically more episodes of heart failure in the etelcalcetide group, overall event rates were similar to rates observed in the EVOLVE trial. Initially, there were concerns that cinacalcet might lead to heart failure and sudden death owing to the effects of reduced serum calcium on myocardial contractility and the QT interval, respectively. However, rates of heart failure and sudden death were reduced in patients randomized to cinacalcet in the EVOLVE trial.[22]

There are several important limitations to the trial. Although trial participants reflected patients in practice with moderate to severe secondary hyperparathyroidism (ie, relatively young in age, with several years of dialysis experience), we are unable to extrapolate efficacy and safety data to older patients, patients new to dialysis, or both. Although efficacy was sustained and relative safety demonstrated over 26 weeks, secondary hyperparathyroidism is a chronic condition often requiring life-long therapy; therefore, longer-term safety data will be required. The trial's major limitation was its focus on lowering PTH levels, a surrogate end point.

Conclusions

Among patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism, the use of etelcalcetide was not inferior to cinacalcet in reducing serum PTH concentrations over 26 weeks; it also met superiority criteria. 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 takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Block, Bushinsky, Cunningham, Dehmel, Drueke, Ketteler, Kewalramani, Silver, Chertow.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Block, Cunningham, Dehmel, Ketteler, Martin, Moe, Sun, Chertow.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Block, Sun, Hao, Chertow.
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Administrative, technical, or material support: Bushinsky, Dehmel, Ketteler, Kewalramani, Sun.
Supervision: Cheng, Dehmel, Ketteler, Kewalramani, Martin, Patel, Chertow.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Block reported receiving grants from Amgen and Kai Pharmaceutical, and medical director fees to his institution from Davita Inc. Dr Businshy reported receiving consulting fees from Amgen, Sanofi, Relypsa, Tricida, and OPKO and speaker fees from Sanofi; serving on the advisory board of Amgen; and owning stock options in Amgen, Relypsa, and Tricida. Dr Cheng reported being an employee of Amgen. Dr Cunningham reported receiving personal fees from and serving as a consultant to Amgen. Dr Demel reported being an employee of and owning stock in Amgen. Dr Kettler reported receiving honoraria for lecturing and consulting for Amgen, Medice, Pfizer, Sanofi, Shire, and Vifor Fresenius Medical Care Renal Pharma and receiving honoraria for consulting for Sanifit. Dr Kewalramani reported being an employee of and holding stock in Amgen. Dr Martin reported receiving consulting fees from Amgen, Diasorin, and OPKO. Dr Moe reported receiving consulting fees from Merck and UltraGenyx and grant support from the National Institutes of Health, the Veterans Administration, Novartis, and Chugai. Dr Patel reported receiving personal fees for serving on the clinical trial steering committee of Amgen, for serving on the advisory board of Reata Pharmaceuticals, Keryx Pharmaceuticals, and Gilead Sciences and for serving on the data safety monitoring boards of Gilead Sciences and Trevi Therapeutics; and receiving grant support from Amgen, Eli Lilly, Angion Biomedica Corp, CSL LTD, and GlaxcoSmithKline. Dr Silver reported receiving personal fees from Amgen. Ms Sun reported being an employee of Amgen. No other disclosures were reported.

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Role of the Funder/Sponsor: The sponsor participated in the design of the trial, and was responsible for coordinating the collection, management and analysis of the data. The academic authors were responsible for drafting, editing, and revising of the manuscript; sponsor coauthors participated in the writing process, although final decisions were the responsibility of the lead and senior authors. The academic authors were responsible for all decisions regarding submission and resubmission of the manuscript for publication. The sponsor did not have right to veto submission or publication of the study findings. 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.

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