A Randomized Trial of Cinacalcet versus Vitamin D Analogs as Monotherapy in Secondary Hyperparathyroidism (PARADIGM)

James B. Wetmore,* Konstantin Gurevich,† Stuart Sprague,‡ Gerald Da Roza,§ John Buierkt,¶ Maureen Reiner,$ William Goodman,* and Kerry Cooper¶

Abstract

Background and objectives Direct comparison of cinacalcet and vitamin D analogs as monotherapies to lower parathyroid hormone (PTH) levels has not been undertaken.

Design, setting, participants, & measurements This was a prospective, multicenter, phase 4, randomized, open-label study that enrolled participants from 2010 to 2012. Adult participants (n=312) on hemodialysis with PTH >450 pg/ml were randomized 1:1 to 12 months of treatment with either cinacalcet (n=155) or vitamin D analogs (n=157) to evaluate the mean percentage change in plasma PTH level (primary end point) and the proportion of participants achieving plasma PTH <300 pg/ml or a ≥30% decrease in PTH (secondary end points). A preplanned analysis to determine whether there were important region-by-treatment interactions was also undertaken.

Results Baseline mean PTH was 846 pg/ml (n=155) for cinacalcet and 816 pg/ml (n=157) for vitamin D analog therapy. The mean (95% confidence interval) percentage change from baseline in PTH was −12.1% (−20.0% to −4.1%) in the cinacalcet arm and −7.0% (−14.9% to 0.8%) in the vitamin D analog arm, a difference of −5.0% (−15.4% to 5.4%) (P=0.35). Similarly, there was no difference in achievement of secondary efficacy end points between arms (19.4% and 15.3% of participants with PTH >300 pg/ml and 42.6% and 33.8% of participants had a PTH reduction >30% in the cinacalcet and vitamin D analog arms, respectively). A prespecified analysis revealed a large treatment-by-region interaction, with nominally greater response to cinacalcet compared with vitamin D analogs in non–United States participants (US versus non-US participants, P<0.001). Hypocalcemia was more common in the cinacalcet arm, whereas hypercalcemia and hyperphosphatemia occurred more often in the vitamin D analog arm.

Conclusions Participants had similar modest reductions in PTH with either cinacalcet or vitamin D analog monotherapy over 52 weeks of treatment, but effects varied by region. Treatments differed with regard to effect on calcium and phosphorus levels.


Introduction

Therapies for the treatment of secondary hyperparathyroidism (SHPT) in patients receiving dialysis are often used in combination in an attempt to achieve clinically acceptable levels of parathyroid hormone (PTH) while maintaining control of calcium and phosphorus. Although numerous trials have documented the efficacy of cinacalcet (Sensipar/Mimpara; Amgen Inc., Thousand Oaks, CA) (1–10) and vitamin D analogs (11–17) in lowering PTH levels, no trial to date has directly compared these agents in the treatment of SHPT.

Although published data are lacking on the efficacy of cinacalcet as monotherapy, some participants in previous studies who were randomized to receive cinacalcet in addition to standard of care did not receive concomitant vitamin D analogs at the discretion of the investigator (2,18,19). As monotherapy in these participants, cinacalcet treatment resulted in PTH reductions comparable to those observed in patients who also received vitamin D analogs, suggesting that cinacalcet was effective when used without concomitant vitamin D analog treatment. This trial was designed to evaluate the efficacy, safety, and biochemical profiles of cinacalcet compared with vitamin D analogs used as monotherapies during the treatment of SHPT in patients receiving dialysis.

Materials and Methods

Participants

Participants aged ≥18 years treated with maintenance hemodialysis three times per week for ≥3 months before screening were eligible. Participants not receiving cinacalcet or vitamin D analogs within 60 days before
enrollment were eligible if they had a plasma PTH ≥450 pg/ml and a total corrected serum calcium ≥8.4 mg/dl and <10.2 mg/dl. Participants receiving cinacalcet and/or vitamin D analogs were eligible if they met these requirements after a 4- to 5-week washout period. Parathyroidectomy in the 12 weeks before the date of informed consent was an exclusion criterion. All participants provided written informed consent approved by each site’s institutional review board or ethics committee.

Study Design and Treatment
This was a prospective, phase 4, multicenter, randomized, open-label study conducted at 58 centers in the United States, Russia, Canada, and Australia from 2010 to 2012 (ClinicalTrials.gov identifier NCT01181531). Enrollment dates were September 8, 2010, to June 22, 2011, and the study completed August 14, 2012. Participants were randomized 1:1 to either cinacalcet or vitamin D analog therapy (oral or intravenous) (Figure 1) using a fixed permuted block design stratified by mode of vitamin D analog administration at a clinical site (oral vitamin D, intravenous vitamin D) was implemented by the RandGen system (a fully validated software package). Specialized Amgen staff, not otherwise involved in the study, produced the randomization. Treatment assignments were allocated sequentially upon enrollment from the fixed permuted block randomization list by the interactive response technology system. Cinacalcet was initiated at a dosage of 30 mg/d and titrated every 4 weeks to a maximum of 180 mg/d based on assessments of plasma PTH and serum calcium. An unplanned interim safety analysis showed a high prevalence of hypocalcemia (calcium <8.0 mg/dl) and hypocalcemia-related adverse events (AEs) in participants treated with cinacalcet, resulting in implementation of a protocol amendment that modified cinacalcet titration criteria (i.e., cinacalcet dose could be increased only if calcium was ≥8.4 mg/dl).

Participants randomized to vitamin D analog therapy were given an initial dosage approximately equivalent to an intravenous dosage of 2 μg paricalcitol three times weekly. Recommended equivalent dosages were 0.5 μg intravenous calcitriol three times weekly, 1 μg intravenous doxercalciferol or alfacalcidol three times weekly, 0.25 μg/d oral calcitriol, or 0.5 μg/d oral alfacalcidol. Doses were increased if plasma PTH was ≥300 pg/ml, serum calcium was ≥10.2 mg/dl, and serum phosphorus was ≤5.5 mg/dl, and were reduced or withheld in the presence of hypercalcemia (calcium >10.2 mg/dl) and hyperphosphatemia (serum phosphorus level >6.0 mg/dl). There was no maximum dose of vitamin D analogs, with final decisions at the discretion of the investigator. Participants randomized to cinacalcet could receive vitamin D analogs only when the investigator thought it was necessary to protect participant safety; the same principle applied to use of cinacalcet in those randomized to receive vitamin D analogs. Nutritional vitamin D supplementation was allowed at the discretion of the investigator in the cinacalcet arm, but it was not allowed in the vitamin D analog arm (consistent with package labeling for approved vitamin D therapies for SHPT). There were no restrictions on calcium supplements, the dialysate calcium concentration, or the type or dose of phosphate binders prescribed. Intact PTH (measured by a two-site sandwich immunoassay; ADVIA Centaur, Siemens/Bayer Healthcare Diagnostics, Tarrytown, NY) and all other analytes were measured at a central laboratory.

End Points
The primary end point was the mean percentage change from baseline in plasma PTH levels during the efficacy assessment phase (EAP; weeks 40–52). Secondary end points were the proportion of participants with plasma PTH <300 pg/ml during EAP and the proportion of participants with a ≥30% decrease from baseline in plasma PTH during EAP. Exploratory end points included mean serum calcium and phosphorus levels during the EAP and the incidence of hypercalcemia (calcium >10.2 mg/dl) and hyperphosphatemia (phosphorus >5.5 mg/dl) during the maintenance phase and EAP. Safety end points included the nature, frequency, severity, and relationship to treatment of all AEs, as well as the incidence of hypocalcemia (calcium <8.0 mg/dl). Alkaline phosphatase (AP) levels were determined at baseline and 52 weeks of treatment as part safety monitoring.

Figure 1. | Study schema. PTH, parathyroid hormone.
Statistical Analyses
A study size of 260 participants was estimated to provide 99% power to detect at least a 29% difference in the percentage reduction from baseline in mean PTH during the EAP at a two-sided significance level of $P=0.05$.

The percentage reduction from baseline in mean PTH during the EAP was compared between treatment arms using a mixed-model repeated-measures analysis with the randomization stratification factor for the specific type of vitamin D analog treatment at each site as a covariate. The Cochran–Mantel–Haenszel odds ratio (OR), adjusted for the route of vitamin D analog administration at each site, was calculated for both secondary end point results. Descriptive statistics were calculated to summarize the exploratory end points. Continuous measures were generally shown as means (SDs), except when skew was present when values were shown as medians. To estimate the treatment effect, a multivariate linear regression model was developed using purposeful selection methods for covariates. Variables were retained in the model at the $P=0.05$ level of significance. However, a variable, which was part of an interaction term with significance at the $P=0.05$ level, was retained in the model even if the significance of the main effect exceeded $P=0.05$.

Treatment-by-region interactions were evaluated as part of a prespecified multivariate analysis at study inception because dialysis practices and SHPT treatments differ by country; the specific contrast specified was United States versus the rest of the world. This analysis revealed a large treatment-by-region interaction with nominally superior PTH reduction in patients treated with cinacalcet compared with vitamin D analogs outside of the United States (US versus non-US participants, $P<0.001$). Two hypothesis-driven post hoc analyses were therefore undertaken to investigate the effect of regional differences in practice patterns, specifically use of low dialysate calcium concentrations (,<2.5 mEq/L) and of calcium-containing phosphate binders. The prevalence of AEs and hypocalcemia was also stratified by dialysate calcium concentration.

Results
Participant disposition and reasons for discontinuation are summarized in Figure 2. Of those randomized to the cinacalcet and vitamin D analog arms, 65% and 61% completed the study, respectively.

Demographics and Baseline Characteristics
Demographic and baseline clinical characteristics of the participants randomized to cinacalcet ($n=155$) and vitamin D analogs ($n=157$) were generally balanced (Table 1). Per protocol, washout of prior SHPT therapy was required in
92.9% and 87.7% of participants in the vitamin D analog and cinacalcet arms, respectively.

Baseline laboratory values, obtained after the washout period, showed that PTH levels were similar, with median (25th, 75th percentiles) PTH of 722 (528, 1046; mean 846 [431]) pg/ml in the cinacalcet arm and 684 (578, 861; mean 816 [428]) pg/ml in the vitamin D analog arm. Mean (SD) baseline serum calcium levels were 9.6 (0.5) mg/dl and 9.5 (0.5) mg/dl for the cinacalcet and vitamin D analog arms, respectively; phosphorus levels were 5.7 (1.6) mg/dl and 5.8 (1.5) mg/dl, respectively. These values are shown in Supplemental Table 1. Screening levels of AP were within the normal range, and did not differ between treatment arms at 112.1 (61.0) U/L and 107.6 (59.4) U/L, respectively.

**Treatments**

The mean (SD) durations of exposure were as follows: cinacalcet, 41.8 (16.8) weeks; intravenous vitamin D analogs, 40.6 (18.1) weeks; and oral vitamin D analogs, 36.6 (19.7) weeks. During the EAP, the mean (SD) dosages of cinacalcet were 83.1 (52.6) mg/d and 20.0 (12.3) mg/wk (in paricalcitol equivalents) for those receiving intravenous [Table 1. Participant demographics and baseline characteristics](#)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cinacalcet (n=155)</th>
<th>Vitamin D Analog (n=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>53 (21–81)</td>
<td>55 (22–86)</td>
</tr>
<tr>
<td>(min to max)</td>
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<tr>
<td>&lt;65</td>
<td>120 (77)</td>
<td>119 (76)</td>
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<tr>
<td>≥65</td>
<td>35 (23)</td>
<td>38 (24)</td>
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<td>≥75</td>
<td>12 (8)</td>
<td>11 (7)</td>
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<td>95 (61)</td>
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<tr>
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<td>86 (55)</td>
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</tr>
<tr>
<td>Hypertension</td>
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<td>19 (12)</td>
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<td>5 (3)</td>
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<tr>
<td>Median</td>
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<tr>
<td>(min to max)</td>
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<td></td>
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<td><strong>Type of vascular access</strong></td>
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<tr>
<td>Natural fistula</td>
<td>98 (63)</td>
<td>111 (71)</td>
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<tr>
<td>Graft</td>
<td>37 (24)</td>
<td>29 (18)</td>
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<tr>
<td>Permanent catheter</td>
<td>17 (11)</td>
<td>14 (9)</td>
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<tr>
<td>Other</td>
<td>3 (2)</td>
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</tr>
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<td><strong>Dialysate calcium, mEq/L</strong></td>
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<tr>
<td>Median (Q1, Q3)</td>
<td>2.50 (2.00, 2.50)</td>
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<td><strong>History of kidney transplant</strong></td>
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<td></td>
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<td>None reported</td>
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<td>3 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>≥2</td>
<td>5 (3)</td>
<td>3 (1)</td>
</tr>
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</table>

All data are shown as n (%) unless otherwise stated. min, minimum; max, maximum.

*Information missing in one participant in the vitamin D analog arm and two in the cinacalcet arm.
vitamin D analogs and 19.8 (14.0) μg/wk for oral vitamin D analogs; 81.5% of participants in the vitamin D analog arm received intravenous therapy. Of all participants randomized to vitamin D analogs, 38.7% received paricalcitol, 38.1% received doxercalciferol, 12.9% received alfacalcidol, and 10.3% received calcitriol. Overall, 91.7% of vitamin D analog–treated participants received phosphate binders during the study. Calcium-containing phosphate binders were used by 65.8% of participants in the cinacalcet arm and 49.0% of participants in the vitamin D analog arm. Sevelamer hydrochloride (carbonate), the predominant noncalcium-based binder, was received by 44.5% of cinacalcet-treated participants and 56.7% of vitamin D analog–treated participants. Administration of nutritional vitamin D supplementation was infrequent in either treatment arm, with 20.0% of cinacalcet-treated participants and 3.2% of vitamin D analog–treated participants receiving cholecalciferol or ergocalciferol during the trial. Ten participants in the vitamin D analog arm received proscribed cinacalcet and 14 participants in the cinacalcet arm received proscribed vitamin D analogs due to investigator-determined safety reasons.

There were significant regional differences in practice patterns related to choice of dialysate calcium concentrations and type of calcium-containing phosphate binders utilized: 39.7% of United States participants were treated with dialysate calcium concentration <2.5 mEq/L compared with 0.0% of non–United States participants (P<0.001), and 53.9% of United States participants were treated with calcium-containing binders compared with 73.1% of non–United States participants (P=0.02).

**Efficacy**

PTH levels over time in the cinacalcet and vitamin D analog treatment arms are shown in Figure 3. Table 2 shows that the mean (95% confidence interval [95% CI]) percentage change in intact PTH between baseline: The EAP was −12.1% (−20.0% to −4.1%) in the cinacalcet arm compared with −7.0% (−14.9% to 0.8%) in participants randomized to vitamin D analogs, a treatment difference of −5.0% (−15.4% to 5.4%; P=0.35). Similarly, there was no difference in achievement of secondary end points between arms. The proportion of participants who achieved a ≥30% reduction in PTH from baseline during the EAP was 42.6% and 33.8% in the cinacalcet and vitamin D analog arms, respectively (OR, 1.45; 95% CI, 0.92 to 2.29; P=0.11; Table 2). The proportion of participants with plasma PTH levels ≤300 pg/ml during the EAP was 19.4% in the cinacalcet arm and 15.3% in the vitamin D analog arm (OR, 1.33; 95% CI, 0.74 to 2.39; P=0.35). Of note, PTH levels at week 56, after a 4-week washout of vitamin D analogs and cinacalcet, were above baseline values in both treatment arms.

Changes in laboratory values from baseline to EAP are shown in Figure 4 and Table 3. Calcium and phosphorus levels decreased in the cinacalcet arm, whereas a modest increase in calcium was noted in the vitamin D analog arm.

The incidence of hypercalcemia ranged from 0.0% to 2.6% in participants treated with cinacalcet and from 20.5% to 30.0% in the vitamin D analog arm from week 20 through week 52. The incidence of hyperphosphatemia ranged from 30.3% to 43.9% in the cinacalcet arm and from 48.2% to 52.9% in the vitamin D analog arm from week 20 through week 52.

The results of a preplanned analysis demonstrated a significant interaction between randomized treatment and region, such that cinacalcet appeared to be nominally more effective than vitamin D analogs in participants outside the United States (P<0.001) and prompted further exploration. Testing two specific factors separately demonstrated a trend toward significance for the interaction with treatment in the mixed-effects model of the primary outcome: dialysate calcium concentration (P=0.06) and calcium-containing binders (P=0.05). Participants in the cinacalcet arm who were treated with dialysate calcium concentrations ≥2.5 mEq/L achieved nominally greater PTH reductions compared with participants in the vitamin D analog arm (mean [95% CI] change from baseline −18.9% [−28.0% to −9.9%] versus −6.0% [−15.1% to −1.0%]).

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**Figure 3.** Mean (SD) PTH over time by treatment arm. PTH, parathyroid hormone; PTWO, posttreatment washout phase.
to 3.1%; treatment difference of $\pm 12.9\%$ [$\pm 25.4\%$ to $\pm 0.5\%$]; nominal $P=0.04$; Table 4). PTH levels stratified by treatment are shown for the dialysate calcium concentrations in Supplemental Figure 1. Examined another way, PTH levels stratified by the different dialysate calcium concentrations are shown for both treatment arms in Supplemental Figure 2, along with the corresponding doses of cinacalcet and vitamin D analogs within the different dialysate calcium concentrations.

Participants who were treated with calcium-containing phosphate binders also had greater mean (95% CI) PTH change when treated with cinacalcet than when treated with vitamin D analogs ($\pm 16.1\%$ [$\pm 29.0\%$ to $\pm 3.3\%$] versus $1.2\%$ [$\pm 10.6\%$ to $13.0\%$], respectively; treatment difference of $\pm 17.3\%$ [$\pm 34.2\%$ to $\pm 0.4\%$]; nominal $P=0.04$; Table 4).

**Safety**

The frequency of AEs and serious AEs was balanced between treatment arms. Treatment-emergent AEs resulted in discontinuation of the investigational product in 7.8% and 5.8% of participants in the cinacalcet and vitamin D analog arms, respectively. There were 13 deaths in the cinacalcet arm (8.5%) and nine deaths in the vitamin D analog arm (5.8%). All deaths were determined to be unrelated to treatment, with the exception of one death in the cinacalcet arm that was determined by the investigator to be potentially treatment related. Hypercalcemia or hyperphosphatemia resulted in discontinuation of treatment in six vitamin D analog–treated individuals. Hypocalcemia and hypocalcemia-related AEs were more frequent among participants treated with cinacalcet. Over the course of the study, 69.9% of participants in the cinacalcet arm had at least one calcium level $<8.0$ mg/dl compared with 9.0% in the vitamin D analog arm. Although 17.6% of cinacalcet-treated participants had an AE of hypocalcemia, only one event was reported as serious and three participants discontinued cinacalcet treatment because of an event of hypocalcemia.

Overall, calcium levels and related AEs did not differ within treatment arms when stratified according to dialysate calcium concentration, with the exception that participants treated with cinacalcet were more likely to manifest consecutive calcium levels $<7.5$ mg/dl when they were also concomitantly treated with dialysate calcium $<2.5$ mEq/L. Levels of AP increased (baseline to week 52) by 51.7 U/L in the cinacalcet arm and 17.4 U/L in the cinacalcet arm and 17.4 U/L in the vitamin D analog arm (treatment difference of 34.3 U/L; $P<0.01$).

**Discussion**

In this study evaluating the relative efficacy of cinacalcet and vitamin D analogs as monotherapy for the treatment of SHPT in participants receiving chronic hemodialysis, there was no difference between treatment arms in the mean decrease in PTH (the primary end point), the percentage of participants achieving $\geq 30\%$ reduction in plasma parathyroid hormone (PTH) (95% CI) for cinacalcet/vitamin D analog combination.

### Table 2. PTH primary and secondary efficacy outcomes

<table>
<thead>
<tr>
<th>PTH Primary and Secondary Outcomes</th>
<th>Cinacalcet ($n=155$)</th>
<th>Vitamin D Analog ($n=157$)</th>
<th>Treatment Difference</th>
<th>Odds Ratio (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in PTH between baseline and EAP, %</td>
<td>$-12.1$ ($-20.0$ to $-4.1$)</td>
<td>$-7.0$ ($-14.9$ to $0.8$)</td>
<td>$-5.0$ ($-15.4$ to $5.4$)</td>
<td>1.15 (0.92 to 1.42)</td>
<td>0.11</td>
</tr>
<tr>
<td>Participants with $\geq 30%$ reduction in plasma PTH from baseline to EAP (%)</td>
<td>66 (42.6)</td>
<td>53 (33.8)</td>
<td>33 (21.2)</td>
<td>1.33 (0.74 to 2.39)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Data are presented as the mean (95% confidence interval) or n (%) unless otherwise indicated. PTH, parathyroid hormone; EAP, efficacy assessment phase; 95% CI, 95% confidence interval.

<sup>a</sup>Cochran-Mantel-Haenszel adjusted odds ratio (95% CI) for cinacalcet/vitamin D analog.

<sup>b</sup>P value for the difference between treatment arms for the primary study outcomes.
The unique finding of this trial was the limited ability of either agent to maintain substantial PTH reductions over the 12-month treatment period. This may be attributable to several study-specific factors, including (1) the 12-month duration of the trial, which was longer than that of most other studies; (2) the mandate for monotherapy in this population with severe disease; and (3) substantial variability in real-world practice patterns with regard to dialysate calcium concentrations and phosphate binders. Each of these factors is discussed below.

The relatively long treatment duration may have affected the efficacy of both therapies. PTH reductions in both treatment arms initially appeared to be more robust during the titration phase (first 20 weeks) of treatment. After treatment washout at the end of 52 weeks, PTH increased to levels higher than baseline in both arms, suggesting that underlying parathyroid disease severity may have worsened over time. Such a progression might be associated with a decrease in expression of the parathyroid calcium-sensing and vitamin D receptors (21,22), potentially resulting in treatment resistance; if so, the relatively long treatment duration compared with other trials (1,13) may have made it less likely that either agent could demonstrate effectiveness.

Another consequence of very advanced SHPT may be that monotherapy may be insufficient to control PTH levels. Although a high baseline PTH itself does not absolutely preclude responsiveness to cinacalcet as monotherapy, previous trials that have demonstrated the effectiveness of cinacalcet in reducing PTH in patients with severe SHPT have allowed concomitant vitamin D treatment (1,2). Therefore, a potential practice implication of this study may be that some patients with severe SHPT might be best served by treatment with multiple agents.
Finally, we hypothesize that concomitant SHPT treatment strategies, which affect calcium levels, might have affected study results. Because of a significant signal detected as part of the preplanned analysis examining regional differences, two factors were specifically explored, revealing that higher utilization of dialysate calcium concentration $\geq 2.5$ mEq/L and lower use of calcium-containing phosphate binders occurred in the United States participants. Based on the plausible hypotheses that dialysate calcium concentration and use of calcium-based binders might affect PTH reductions, we pursued these exploratory analyses despite only borderline nominal statistical significance in treatment interactions. We thought that this was clinically relevant in light of a previous report that suggested an interaction between dialysate calcium concentration and cinacalcet effectiveness (23). The post hoc exploratory analyses revealed that cinacalcet was nominally more effective than vitamin D analogs in reducing PTH levels when participants were also concomitantly treated with dialysate calcium $\geq 2.5$ mEq/L or calcium-based phosphate binders. Exposure to low dialysate calcium concentrations has been shown to result in acute reductions in ionized calcium levels and increases in intradialytic PTH levels (24). Conversion from dialysate calcium concentrations of 2.5 mEq/L to lower levels was shown to be associated with worsening of SHPT despite treatment intensification (25). In this study, PTH levels returned to levels above baseline after withdrawal of SHPT treatment, which is in contrast with other studies (26,27). This phenomenon was most prominent in cinacalcet-treated participants who were concomitantly exposed to low dialysate calcium concentrations, suggesting a possible effect on underlying disease progression.

Other differences during treatment with vitamin D analogs and cinacalcet were noted. Treatment with vitamin D analogs was associated with higher calcium and phosphorus levels and a higher prevalence of hypercalcemia and hyperphosphatemia. Cinacalcet treatment was associated with sustained phosphorus reductions, which was previously demonstrated (4,28). Cinacalcet therapy was also associated with lower calcium levels and a higher prevalence of hypocalcemia and hypocalcemia-related AEs. It is possible that the achievement of maximum effective doses of either cinacalcet or vitamin D analogs as monotherapies was limited by associated abnormal levels of calcium and/or phosphorus.

Although this study was not designed to assess the effect of cinacalcet or vitamin D analogs on bone turnover, total AP was noted to increase modestly in both treatment arms, more so in the cinacalcet arm. Differential responses to cinacalcet and vitamin D analog therapy with regard to total and bone-specific AP during the treatment of SHPT have been reported (29). Conversely, previous cinacalcet trials have demonstrated a 35% decrease in bone-specific AP over 26 weeks of treatment (1). More recently, treatment with 12 months of cinacalcet was demonstrated to improve bone histology in participants with high turnover bone disease associated with reductions in bone-specific AP and other markers of bone turnover (30).

**Study Limitations**

We acknowledge several important limitations. First, this was an open-label study. Second, a subset of participants in
### Table 4. Influence of dialysate calcium concentration and use of calcium-containing phosphate binders on PTH reduction mixed-effects model analysis

<table>
<thead>
<tr>
<th>Summary of Changes</th>
<th>Cinacalcet Mean change in PTH (%)</th>
<th>Vitamin D Analog Mean change in PTH (%)</th>
<th>Treatment Difference Mean change in PTH (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysate calcium ≥2.5 mEq/L</td>
<td>-18.9 (−28.0 to −9.9)</td>
<td>-6.0 (−15.1 to 3.1)</td>
<td>-12.9 (−25.4 to −0.5)</td>
<td>0.04</td>
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<tr>
<td>No. of participants</td>
<td>101</td>
<td>106</td>
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<td></td>
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<tr>
<td>Dosing during EAP</td>
<td>82.9 (53.69)</td>
<td>17.6 (10.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysate calcium &lt;2.5 mEq/L</td>
<td>4.8 (−21.0 to 30.5)</td>
<td>-7.6 (−33.2 to 18.0)</td>
<td>12.4 (−6.6 to 31.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>No. of participants</td>
<td>52</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing during EAP</td>
<td>83.6 (50.29)</td>
<td>23.5 (12.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-based phosphate binder used</td>
<td>61</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>-16.1 (−29.0 to −3.3)</td>
<td>1.2 (−10.6 to 13.0)</td>
<td>-17.3 (−34.2 to −0.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean change in PTH (%)</td>
<td>84</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-based phosphate binder not used</td>
<td>-9.2 (−19.4 to 0.9)</td>
<td>-14.3 (−25.1 to −3.5)</td>
<td>5.0 (−8.2 to 18.2)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Data are given as the mean (SD) or mean (95% confidence interval). PTH, parathyroid hormone; EAP, efficacy assessment phase.

* Cinacalcet dosage in milligrams per day.

* Vitamin D analog dosage expressed as paricalcitol equivalent units per week.


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## Supplementary Table 1. Summary of Differences between Cinacalcet and Vitamin D at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Vitamin D Mean (SD)*</th>
<th>Cinacalcet Mean (SD)*</th>
<th>Difference Cinacalcet – Vitamin D Analog (SD)</th>
<th>95% CI for Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/mL), Median (Q1, Q3)</td>
<td>684.0 (578.0, 861.0)</td>
<td>722.0 (528.0, 1046.0)</td>
<td>38.0</td>
<td>(-66, 112)**</td>
<td>0.79***</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.49 (0.54)</td>
<td>9.55 (0.46)</td>
<td>0.06 (0.50)</td>
<td>-0.05, 0.17</td>
<td>0.30</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>5.77 (1.49)</td>
<td>5.73 (1.62)</td>
<td>-0.04 (1.55)</td>
<td>-0.39, 0.30</td>
<td>0.80</td>
</tr>
<tr>
<td>Ca x P (mg^2, dL^2)</td>
<td>54.58 (14.16)</td>
<td>54.81 (15.86)</td>
<td>0.24 (15.03)</td>
<td>-3.14, 3.61</td>
<td>0.89</td>
</tr>
<tr>
<td>FGF-23 (ng/L)</td>
<td>348.2 (282.0)</td>
<td>336.0 (300.2)</td>
<td>-12.23 (291.4)</td>
<td>-82.67, 58.20</td>
<td>0.73</td>
</tr>
<tr>
<td>25(OH)D (ng/mL)</td>
<td>26.13 (14.12)</td>
<td>25.59 (13.97)</td>
<td>-0.55 (14.04)</td>
<td>-3.72, 2.62</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; CI, confidence intervals; PTH, parathyroid hormone; FGF-23, fibroblast growth factor-23.

*Except for PTH, where values are shown as medians and 25th/75th percentiles

** 95% bootstrap CI for difference of medians

*** P value from non-parametric Wilcoxon test, performed due to the skew of the PTH values.
Supplemental Material

Additional details on Results: analyses based on stratification of dialysate calcium concentration

**Supplementary Figure 1 (A, B)** Mean (SD) PTH (pg/mL) over time by treatment arm when dialysate calcium concentration was (B) ≥2.5 mEq/L or (C) <2.5 mEq/L. Abbreviations: DCC, Dialysate Calcium Concentration; PTH, parathyroid hormone; PTWO, posttreatment washout phase.

**Supplementary Figure 2 (A-D)** shows the levels of PTH and the doses of cinacalcet and vitamin D analogs over the course of the study when stratified according to dialysate calcium concentration. Figures 2A and 2B demonstrate that the increase in PTH after washout between weeks 52 and 56 in both treatment arms was greater in participants receiving low dialysate calcium concentrations, and that this was generally more pronounced in participants treated with cinacalcet. Mean cinacalcet dose (Figure 2C) did not vary according to dialysate calcium concentration (<2.5 mEq/L, 83.6 mg/d; ≥2.5 mEq/L, 82.9 mg/d), and reached the highest doses by week 20 with stable levels thereafter. Mean doses of vitamin D analogs increased progressively (Figure 2D) during the study, with higher doses used in participants treated with low dialysate calcium concentrations (<2.5 mEq/L, 23.5 µg paricalcitol equivalent units per week; ≥2.5 mEq/L, 17.6 µg [IV] and 18.5 µg [oral] paricalcitol equivalent units per week during the EAP).
Supplementary Figure 1A. Mean (SD) PTH (pg/mL) over time by treatment arm when dialysate concentration was ≥2.5 mEq/L.
Supplementary Figure 1B. Mean (SD) PTH (pg/mL) over time by treatment arm when dialysate calcium concentration was <2.5 mEq/L

- Cinacalcet
- Traditional Vitamin D
Supplementary Figure 2A. Mean (SD) PTH (pg/mL) over time by dialysate calcium concentration (mEq/L) for the cinacalcet treatment arm.

- Dialysate Ca < 2.5 mEq/L
- Dialysate Ca ≥ 2.5 mEq/L

Week
- Titration
- Maintenance
- Efficacy
- PTWO

PTH Mean (SD) (pg/mL)

<table>
<thead>
<tr>
<th>Week</th>
<th>Dialysate Ca &lt; 2.5</th>
<th>Dialysate Ca ≥ 2.5</th>
</tr>
</thead>
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<td>52</td>
<td>101</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
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<tr>
<td>56</td>
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<td>70</td>
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</tbody>
</table>
Supplementary Figure 2B. Mean (SD) PTH (pg/mL) over time by dialysate calcium concentration (mEq/L) for the vitamin D analog treatment arm.

- **Dialysate Ca < 2.5 mEq/L**
- **Dialysate Ca ≥ 2.5 mEq/L**

**Axis Details:**
- Y-axis: PTH Mean (SD) (pg/mL)
- X-axis: Week

**Legend:**
- Titration
- Maintenance
- Efficacy
- PTWO

**Data Values:**

<table>
<thead>
<tr>
<th>Week</th>
<th>Dialysate Ca &lt; 2.5</th>
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<tr>
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Supplementary Figure 2C. Mean (SD) cinacalcet dose over time by dialysate calcium concentration (mEq/L)

<table>
<thead>
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<th>Week</th>
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<th>Dialysate Ca ≥ 2.5</th>
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<tbody>
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</tbody>
</table>
Supplementary Figure 2D. Mean (SD) vitamin D analog dose over time by dialysate calcium concentration (mEq/L)

Traditional VD Mean (SD) (units)