

## Original Article

## Combined therapy with cinacalcet and low doses of vitamin D sterols in patients with moderate to severe secondary hyperparathyroidism

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### Abstract

**Background.** Adequate control of all four KDOQI™ biochemical targets for chronic kidney disease, bone and mineral disorder (CKD-MBD), which include parathyroid hormone (PTH), calcium (Ca), phosphorus (P) and Ca × P, remains difficult and is accomplished in <6% of patients receiving haemodialysis. The objective of the current study was to determine whether treatment with cinacalcet combined with low doses of vitamin D sterols improves control of both PTH and Ca × P among haemodialysis patients with secondary hyperparathyroidism (sHPT).

**Methods.** This multicentre, open-label study enrolled haemodialysis subjects ( $N = 444$ ) with moderate to severe sHPT (mean serum biPTH > 160–430 pg/mL) (~iPTH 300–800 pg/mL or ng/L). Cinacalcet was titrated sequentially (30–180 mg/day) during an 8-week dose-titration phase to achieve biPTH ≤ 160 pg/mL (~iPTH 300 pg/mL or ng/L) and efficacy was assessed over 8 weeks. At week 2 of the study, subjects receiving vitamin D sterols had doses reduced to the equivalent of 2 mcg of paricalcitol three times a week or 6 mcg/week. Among the efficacy endpoints were the proportion of subjects with mean biPTH ≤ 160 pg/mL (~iPTH 300 pg/mL or ng/L), with mean Ca × P ≤ 55 mg<sup>2</sup>/dL<sup>2</sup> (4.4 mmol<sup>2</sup>/L<sup>2</sup>) and with both simultaneously during the assessment phase.

**Results.** The majority of subjects ( $n = 375$ ) reached the assessment phase of the study and were included in efficacy analyses; 39 subjects withdrew due to adverse events. Sixty-two percent of subjects achieved the biPTH target, 83% achieved the Ca × P target and 54% reached both targets. Treatment reduced biPTH by 35% ( $P < 0.0001$ ), calcium by 11% ( $P < 0.0001$ ), phosphorus by 7% ( $P < 0.0001$ ) and Ca × P by 17% ( $P < 0.0001$ ). The proportion of subjects with values for biPTH, for Ca × P and for both biPTH and Ca × P within the target range during the assessment phase

did not differ between subjects who received cinacalcet together with vitamin D sterols, and those who received cinacalcet alone.

**Conclusion.** Among subjects with moderate to severe sHPT undergoing haemodialysis, combined therapy with cinacalcet and low doses of vitamin D sterols improved achievement of the biochemical targets for CKD-MBD recommended by the KDOQI™ guidelines.

**Keywords:** cinacalcet; KDOQI™; PTH; secondary hyperparathyroidism; vitamin D

### Introduction

Vitamin D sterols and phosphate-binding agents are used commonly to treat secondary hyperparathyroidism (sHPT) among patients with chronic kidney disease (CKD) [1]. Managing the biochemical consequences associated with these therapeutic agents is challenging, particularly among patients with end-stage renal disease (ESRD). Vitamin D sterols promote intestinal calcium [2] and phosphorus [3] absorption, and their use to manage sHPT raises serum calcium and phosphorus concentrations [4–7]. The concurrent administration of calcium-containing phosphate-binding agents further increases the likelihood of developing hypercalcaemia [8]. As a result, <6% of haemodialysis patients achieve adequate control of all four biochemical parameters for chronic kidney disease-mineral and bone disorder (CKD-MBD) as set forth in the KDOQI™ guidelines [9]. Accordingly, therapeutic strategies that lower parathyroid hormone (PTH) while limiting the risks of hyperphosphataemia and/or hypercalcaemia are of considerable interest.

Data from several large clinical trials indicate that the calcimimetic cinacalcet hydrochloride (Sensipar®/Mimpara®) substantially lowers plasma PTH levels and concurrently lowers serum calcium and phosphorus concentrations when given either alone or together with

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relatively large doses of vitamin D sterols to dialysis patients with sHPT that are inadequately controlled despite conventional therapy [10,11]. More recently, cinacalcet was shown to lower serum calcium and phosphorus concentrations while maintaining control of plasma PTH levels when used together with low doses of vitamin D sterols [12]. Accordingly, treatment strategies that utilize cinacalcet together with low doses of vitamin D sterols may be able to modify parathyroid gland function favourably through two distinct, yet complementary, pathways while serving to maintain serum calcium and phosphorus levels. The current open-label study was designed to determine whether combined therapy enhances achievement of the KDOQI™ biochemical targets for CKD-MBD in a cohort of subjects unable to achieve target values with conventional therapy.

## Subjects and methods

### Study design

This open-label study consisted of three phases: a 30-day screening period, an 8-week dose-titration phase and an 8-week assessment phase. Study visits occurred at 2-week intervals throughout. Adult haemodialysis patients were eligible for inclusion if they had received dialysis regularly for  $\geq 3$  months, if their albumin-adjusted serum calcium level was  $\geq 8.4$  mg/dL (2.1 mmol/L) and if their mean plasma PTH (bio-intact PTH or biPTH) exceeded 160 pg/mL but was not  $>430$  pg/mL or ng/L values that correspond approximately to intact PTH levels in the range of 300–800 pg/mL or ng/L [13]. Key exclusion criteria were ongoing use of oral vitamin D sterols, the use of drugs that are potent inhibitors or inducers of cytochrome P450 (CYP) 3A4 and the use of therapeutic agents metabolized predominantly by CYP2D6 and that have a narrow therapeutic index within 21 days the start of the study. Additional exclusion criteria included pregnancy, women who were breastfeeding, a history of myocardial infarction or parathyroidectomy within the previous 12 weeks or an unstable medical condition during the previous 30 days. The study was conducted in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the appropriate Institutional Review Boards/Independent Ethics Committees at each study site, and all subjects provided written informed consent.

### Interventions

During the dose-titration phase, treatment with cinacalcet was begun using a dose of 30 mg/day. Doses were increased subsequently in increments to 60, 90, 120 and 180 mg/day if biPTH values were  $>160$  pg/mL ( $\sim$ iPTH 300 pg/mL or ng/L). The dose of cinacalcet was increased until the maximum dose was achieved unless subjects experienced an adverse event that precluded a dosage increase. Doses could be decreased if biPTH values on two consecutive study visits were  $<80$  pg/mL ( $\sim$ iPTH 150 pg/mL or ng/L) and treatment with vitamin D sterols had already been discontinued.

All study subjects continued to receive their previously prescribed doses of phosphate-binding agents. Those receiving vitamin D sterols upon entering the trial continued to receive the same agent throughout the study, but doses were reduced during the second week of the dose-titration phase to an amount considered to be approximately equivalent to the endogenous production rate for calcitriol among persons with normal renal function. For the current clinical trial, doses of 2 mcg of paricalcitol, the most commonly used vitamin D sterol, given three times a week with each dialysis treatment were considered to be equivalent to doses of either 1 mcg of doxercalciferol or 0.5 mcg of calcitriol three times a week. For the remainder of the study, the doses of vitamin D sterols could be increased only if serum calcium levels were  $<8.4$  mg/dL (2.1 mmol/L), if symptoms of hypocalcaemia developed or if biPTH values remained  $>270$  pg/mL ( $\sim$ iPTH 500 pg/mL or ng/L) and  $\text{Ca} \times \text{P}$  were  $<70$  mg<sup>2</sup>/dL<sup>2</sup> (5.6 mmol<sup>2</sup>/L<sup>2</sup>) among subjects receiving the maximum dose of cinacalcet. Doses of vitamin D sterols could be decreased if biPTH values were  $<80$  pg/mL ( $\sim$ iPTH 150 pg/mL or ng/L) on two consecutive study visits. Changes in the type and dose of phosphate-binding agents were permitted at the discretion of each investigator throughout the study. A dialysate calcium concentration of 2.5 mEq/L was used in all subjects.

### Outcomes measured

Biochemical determinations were done using blood samples collected before dialysis and before daily doses of cinacalcet, usually 24 h after the preceding dose. Plasma PTH (biPTH) was measured using a second-generation immunometric assay (Nichols Advantage® Bio-Intact PTH (1–84), Nichols Institute Diagnostics, San Clemente, CA, USA). The doses of vitamin D sterols and phosphate-binding agents and occurrences of adverse events were recorded at each study visit.

### Statistical analysis

The safety population included all enrolled subjects who received at least one dose of cinacalcet, and safety analyses were based upon all data obtained from the time of the first dose of cinacalcet until 30 days after the last dose. The efficacy population comprised all subjects included in the safety analysis who had at least one biochemical measurement during the assessment phase. Efficacy analyses were based upon all measurements gathered during the assessment phase. Changes from baseline in values obtained during the assessment phase for biPTH,  $\text{Ca} \times \text{P}$ , serum calcium and serum phosphorus were assessed using Student's *t*-tests.

Among the primary efficacy endpoints were the proportion of subjects with a mean biPTH  $\leq 160$  pg/mL ( $\sim$ iPTH 300 pg/mL or ng/L), proportion of subjects with a mean  $\text{Ca} \times \text{P}$  value  $\leq 55$  mg<sup>2</sup>/dL<sup>2</sup> (4.4 mmol<sup>2</sup>/L<sup>2</sup>) and proportion of study participants who achieved both biochemical endpoints during the assessment phase. Because of methodological differences in PTH assays, the targeted range for plasma PTH levels in the current clinical trial differs from that recommended in the KDOQI™ guidelines. It should

be recognized, however, that the current study protocol was developed before the KDOQI™ guidelines were published.

Other biochemical parameters examined included absolute values and the percentage change from baseline levels during the assessment phase for plasma biPTH, serum calcium and phosphorus and calculated values for  $\text{Ca} \times \text{P}$ . *Post hoc* analyses were done to determine the proportion of subjects who achieved results that fell within the biochemical target ranges recommended by the KDOQI™ guidelines for all four biochemical parameters using biPTH rather than iPTH [13,14]. Safety endpoints included the incidence of all adverse events, including hypocalcaemia as defined separately by serum calcium levels  $<8.4$  mg/dL [2.1 mmol/L] or  $<7.5$  mg/dL [1.9 mmol/L] and hypercalcaemia as defined by values  $>10.2$  mg/dL [2.55 mmol/L]. The average doses of vitamin D sterols and of phosphate-binding compounds during the assessment phase were determined, and the change in dose of each therapeutic agent from baseline values was calculated.

## Results

### Study population

The study was conducted between 30 June 2003 and 5 July 2004. Of the 444 subjects who received cinacalcet and thus were included in safety analyses, 375 (84.5%) reached the assessment phase and were included in the efficacy analyses. A total of 329 (74.1%) subjects completed the assessment phase. The leading causes for early discontinuation from the study were adverse events in 39 (8.8%), withdrawal of consent in 22 (5.0%), administrative decision in 14 (3.2%) and death in 9 (2.0%) cases. Other reasons for discontinuation included protocol-specified criteria in eight cases (1.8%), loss to follow-up in two cases (0.5%) and ineligibility in one case (0.2%). An additional 20 subjects (4.5%) withdrew for a variety of other reasons (Figure 1).

At baseline, 334 of 444 subjects (75%) were receiving vitamin D sterols, and 419 of 444 (94%) were treated with phosphate-binding agents. The demographic features, clinical characteristics and use of concomitant medications did not differ between subjects entering the trial initially and those included in efficacy analyses (Table 1).

### Efficacy endpoints

The primary efficacy endpoint as defined by a mean plasma biPTH concentration  $\leq 160$  pg/mL ( $\sim$ iPTH 300 pg/mL or ng/L) was achieved in 62% of subjects, and 83% achieved a  $\text{Ca} \times \text{P} \leq 55$  mg<sup>2</sup>/dL<sup>2</sup> (4.4 mmol<sup>2</sup>/L<sup>2</sup>). The combined study endpoint of a mean plasma biPTH level  $\leq 160$  pg/mL ( $\sim$ iPTH 300 pg/mL or ng/L) and a  $\text{Ca} \times \text{P}$  value in serum  $\leq 55$  mg<sup>2</sup>/dL<sup>2</sup> (4.4 mmol<sup>2</sup>/L<sup>2</sup>) was attained in 54% of study participants (Figure 2). Of the 375 subjects who reached the assessment phase, the mean biPTH concentration decreased by 35% from a baseline value of  $268 \pm 93.3$  pg/mL ( $\sim$ iPTH 496 pg/mL) (ng/L) to  $160 \pm 93.2$  pg/mL ( $\sim$ iPTH 300 pg/mL or ng/L) during the assessment phase ( $P < 0.0001$ ) (Figure 3a). The mean serum calcium concentration decreased by 11% from  $9.5 \pm 0.8$  to  $8.4 \pm 0.7$  mg/dL

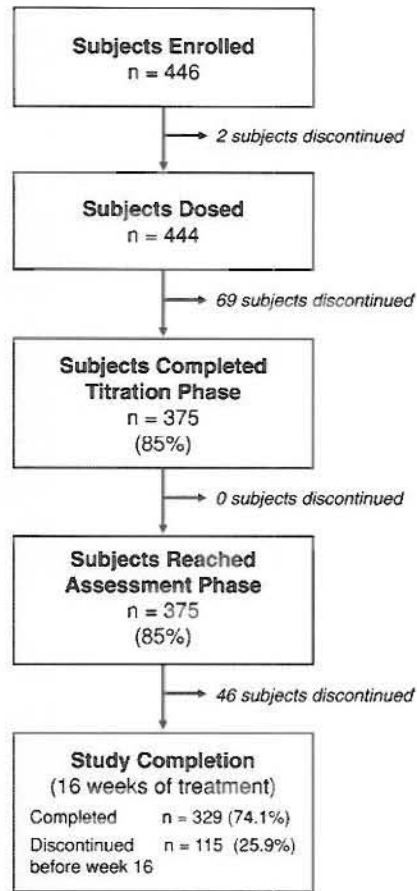


Fig. 1. Subject disposition.

(2.4 to 2.1 mmol/L) ( $P < 0.0001$ ) (Figure 3b), and the mean serum phosphorus concentration decreased by 7% from  $5.7 \pm 1.6$  to  $5.2 \pm 1.5$  mg/dL (1.8 to 1.7 mmol/L) ( $P < 0.0001$ ) (Figure 3c) between baseline and the assessment phase of the study. Mean values for  $\text{Ca} \times \text{P}$  also decreased from  $54.5 \pm 15.4$  to  $43.6 \pm 13.3$  mg<sup>2</sup>/dL<sup>2</sup> (4.4 to 3.5 mmol<sup>2</sup>/L<sup>2</sup>), or by 17% ( $P < 0.0001$ ), during the same interval (Figure 3d).

### Medication use

At the end of the assessment phase, 62% of subjects were receiving daily doses of either 30 or 60 mg of cinacalcet, and 70% of these subjects achieved a biPTH  $\leq 160$  pg/mL ( $\sim$ iPTH 300 pg/mL or ng/L). The average dose of cinacalcet was 69.5 mg/day. Vitamin D sterols were used by 76% of subjects at baseline and by 80% during the assessment phase (Table 2). The mean dose of vitamin D sterols, expressed as microgram equivalents of paricalcitol, was 51% lower during the assessment phase, 10.2 mcg/week, than at baseline, 21.0 mcg/week (Table 2). The use of sevelamer as a phosphate-binding agent decreased from 65% of subjects at baseline to 54% during the assessment phase, and the mean dose of sevelamer decreased from 9231 to 8627 mg/day (−7%) (Table 2). Conversely, the use of calcium-based phosphate binders among study participants increased from

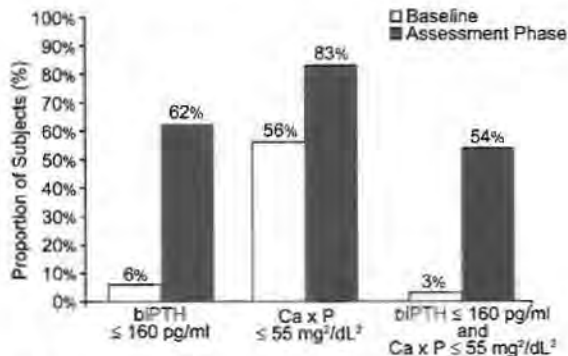
**Table 1.** Baseline demographic and clinical characteristics

Characteristic	Randomized population ( <i>n</i> = 444)	Assessment phase population ( <i>n</i> = 375)
Sex, <i>n</i> (%)		
Male	247 (56)	215 (57)
Female	197 (44)	160 (43)
Race, <i>n</i> (%)		
Black	199 (45)	171 (46)
White	173 (39)	145 (39)
Other	72 (16)	59 (16)
Age (years), mean ± SD	55.5 ± 13.9	54.9 ± 13.5
Dialysis vintage (months) median (interquartile range)	41.4 (20.7, 75.1)	41.2 (19.8, 70.5)
Activated vitamin D therapy, <i>n</i> (%)	334 (75)	285 (76)
Phosphate binder use, <i>n</i> (%)	419 (94)	356 (95)
biPTH (~iPTH) (pg/mL), mean ± SD median [interquartile range]	266 ± 92 (493 ± 170)	268 ± 93 (496 ± 172)
mean ± SD median [interquartile range]	249 [192, 327] (461 [356, 606])	255 [189, 331] (472 [350, 613])
Serum calcium (mg/dL), mean ± SD	9.5 ± 0.7	9.5 ± 0.8
Serum phosphorus (mg/dL), mean ± SD	5.7 ± 1.6	5.7 ± 1.6
Ca × P (mg <sup>2</sup> /dL <sup>2</sup> ), mean ± SD	54.2 ± 15.3	54.5 ± 15.4

To convert biPTH in pg/mL to ng/L, multiply by 1; corrected serum calcium in mg/dL to mmol/L, multiply by 0.2495; serum phosphorus in mg/dL to mmol/L, multiply by 0.3229; calcium-phosphorus product in mg<sup>2</sup>/dL<sup>2</sup> to mmol<sup>2</sup>/L<sup>2</sup>, multiply by 0.0806.

biPTH = bio-intact parathyroid hormone.

Dialysate calcium concentration 2.5 mEq/L was used.



**Fig. 2.** Proportion of subjects with mean biochemical values reaching the primary endpoint. biPTH = bio-intact parathyroid hormone; Ca × P = calcium phosphorus product.

43% at baseline to 69% during the assessment phase, and the average daily oral intake of elemental calcium in the form of phosphate-binding medications increased by 16% from 1427 to 1694 mg (Table 2).

Forty-three subjects (12%) received no vitamin D sterols during the entire 4-month study period. Nevertheless, mean decreases for plasma biPTH, serum calcium, serum phosphorus and serum Ca × P were 35%, 8%, 8% and 15%, respectively, in this group, and the results were similar to those observed among 332 subjects who received both cinacalcet and low doses of vitamin D sterols.

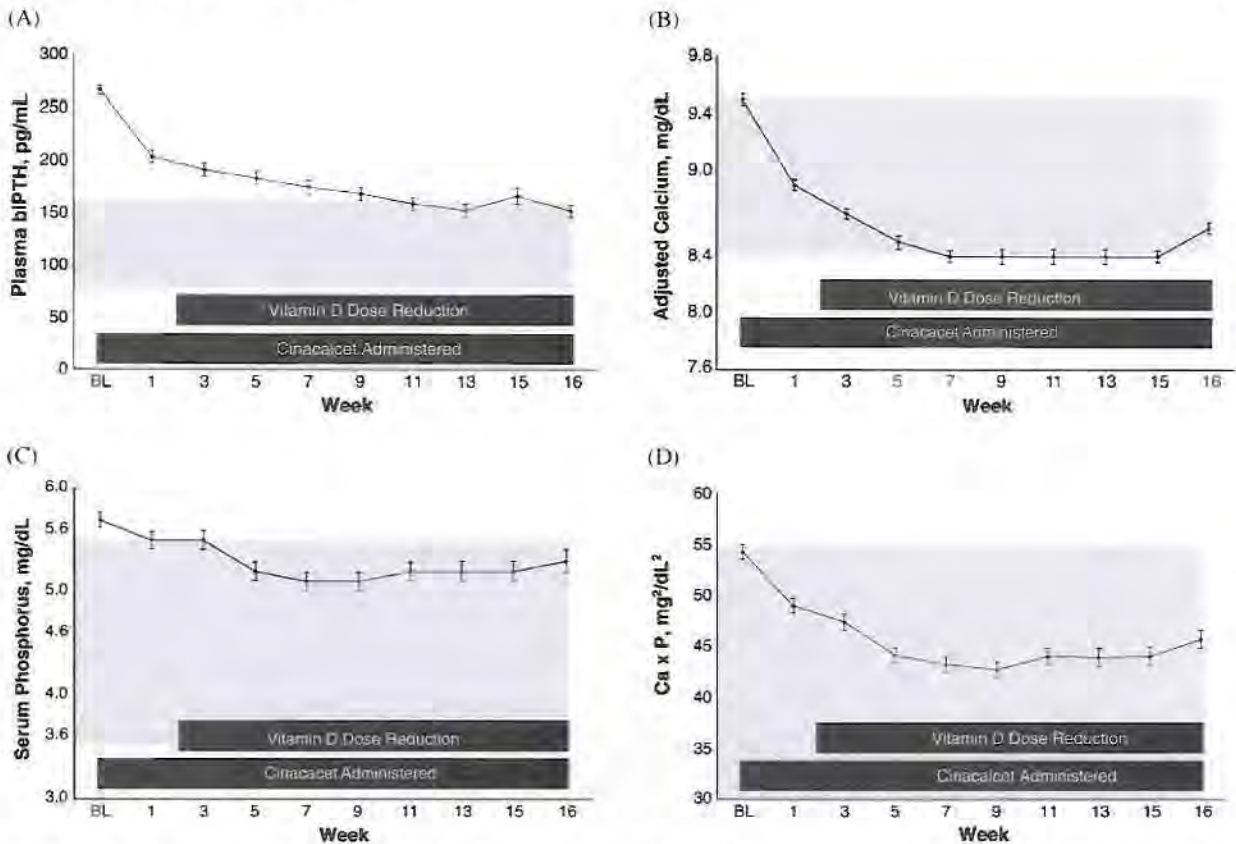
#### Achievement of KDOQI™ goals

Additional analyses were done to assess the ability of subjects given cinacalcet and low doses of vitamin D sterols to achieve the recommended KDOQI™ biochemical goals for CKD-MBD during the assessment phase of the study. At baseline, only 6% of subjects had biPTH concentrations ≤ 160 pg/mL (~iPTH 300 pg/mL) (ng/mL) and 56% had

Ca × P ≤ 55 mg<sup>2</sup>/dL<sup>2</sup> (4.4 mmol<sup>2</sup>/L<sup>2</sup>). In contrast, these two biochemical targets were attained in 62% and 83%, respectively, during the assessment phase. At baseline, calcium and phosphorus concentrations were within the recommended KDOQI™ target ranges in 49% and 43% of subjects, respectively. During the assessment phase, serum calcium levels were in the target range of 8.4–9.5 mg/dL (2.1–2.4 mmol/L) in 42% of subjects, whereas serum phosphorus levels were in the target range of 3.5–5.5 mg/dL (1.1–1.8 mmol/L) in 53%. Study target values for both biPTH and Ca × P were achieved in only 3% of subjects at baseline while receiving conventional treatments for sHPT but in 54% of subjects during the assessment phase when given cinacalcet and low doses of vitamin D sterols. The proportion of subjects with values for biPTH, for Ca × P and for both biPTH and Ca × P within the target range during the assessment phase did not differ between subjects who received cinacalcet together with vitamin D sterols (63%, 84%, and 54%, respectively) and those who received cinacalcet alone (57%, 79%, and 53%, respectively).

#### Safety

Overall, 405 of 444 subjects (91%) experienced at least one adverse event during the study. The most commonly reported adverse events included nausea (28%), vomiting (23%), diarrhoea (19%), headache (11%) and dizziness (11%). Adverse events were generally mild to moderate in severity. Thirty-nine (8.8%) subjects withdrew from study due to adverse events. Causes for early discontinuation (>1 subject) included nausea in 11 subjects (2.5%), diarrhoea in 9 subjects (2.0%), vomiting in 6 subjects (1.4%), rash in 5 subjects (1.1%), headache in 4 subjects (1.0%) and abdominal pain, hypotension, myalgia or tremor in 2 subjects each (0.5%). Hypercalcaemia occurred in two subjects (0.5%) and hyperphosphataemia developed in one subject



**Fig. 3.** (A) Bio-intact parathyroid hormone (biPTH); (B) serum calcium; (C) serum phosphorus and (D) calcium phosphorus product ( $\text{Ca} \times \text{P}$ ) by study week. Mean values are compared with the KDOQI<sup>TM</sup> goal ranges for dialysis patients with secondary HPT (iPTH 150–300 pg/mL corresponding to biPTH 80–160 pg/mL or ng/L), serum calcium 8.4–9.5 mg/dL [2.1–2.4 mmol/L], serum phosphorus 3.5–5.5 mg/dL [1.1–1.8 mmol/L] and  $\text{Ca} \times \text{P} < 55 \text{ mg}^2/\text{dL}^2$  [4.4 mmol<sup>2</sup>/L<sup>2</sup>] [18].

**Table 2.** Use of concomitant medications for secondary hyperparathyroidism

	Baseline ( <i>n</i> = 375)	Assessment phase ( <i>n</i> = 375)
Activated vitamin D sterol use		
Subjects, <i>n</i> (%)	285 (76)	299 (80)
Paricalcitol dose equivalents <sup>a</sup> (mcg/week), mean ± SD	20.7 ± 20.8	10.2 ± 9.3
Sevelamer use		
Subjects, <i>n</i> (%)	244 (65)	203 (54)
Sevelamer dose (mg/day), mean ± SD	9231 ± 6319	8627 ± 6750
Calcium-based phosphate binder use		
Subjects, <i>n</i> (%)	161 (43)	257 (69)
Elemental calcium dose (mg/day)	1427 ± 927	1694 ± 986

<sup>a</sup>2 mcg paricalcitol = 1 mcg doxercalciferol = 0.5 mcg calcitriol.

(0.2%). There were nine deaths (2.0%) during the study, but none of these was attributed to cinacalcet.

Over the entire data collection period, seven subjects (1.6%) experienced seizures, two of whom had reported a history of seizures in the past. No definitive relationship could be established between seizure episodes and serum calcium concentrations, but information was not available in all cases. The serum calcium concentration within 24 h of the seizure was <8.4 mg/dL (2.1 mmol/L) in two cases with

calcium values of 6.5 mg/dL and 7.9 mg/dL (1.6 mmol/L and 2.0 mmol/L), respectively. In a third case, the serum calcium level was within the range of normal at 9.3 mg/dL (2.3 mmol/L). Additional confounding factors at the time of seizure included West Nile encephalitis and hypertensive crisis in one subject each.

Of the 444 subjects in the safety population, 347 (78%) had at least one serum calcium <8.4 mg/dL (2.1 mmol/L) during the study, and 216 (49%) had two consecutive values

**Table 3.** Low serum albumin-adjusted calcium

Event	n/N (%)
One serum calcium value <8.4 mg/dL	347/444 (78)
Action taken for any serum calcium <8.4 mg/dL within 2 weeks	
None	181/347 (52)
Vitamin D dose increased	81/347 (23)
Calcium-based phosphate binder dose increased	67/347 (19)
Both vitamin D and calcium-based binder dose increased	18/347 (5.2)
Two serum calcium values <8.4 mg/dL	216/444 (49)
Two serum calcium values <7.5 mg/dL	40/444 (9.0)
Study withdrawal due to low serum calcium	1/444 (0.2)

To convert corrected serum calcium in mg/dL to mmol/L, multiply by 0.2495.

below this level (Table 3). No action was taken by the investigator to correct serum calcium in 52% (181/347) of subjects with at least one serum calcium concentration <8.4 mg/dL (2.1 mmol/L), whereas the doses of active vitamin D sterols, calcium-based phosphate binders or both were increased in other subjects. Only one subject (0.2%) was withdrawn from the study due to hypocalcaemia.

## Discussion

The concurrent sustained achievement of KDOQI™ recommended target values for biochemical parameters that are important in the clinical management of CKD-MBD has proven to be among the most difficult of challenges for nephrologists. This is due in part to the reliance on large doses of vitamin D sterols as the primary therapeutic option for sHPT. Vitamin D acts through genomic mechanisms [15] to reduce PTH production and to lower plasma PTH levels, but it also promotes intestinal calcium and phosphorus absorption [2,3], changes that increase serum calcium and phosphorus levels [7]. In contrast, calcimimetic agents inhibit PTH secretion and lower plasma PTH levels by acting directly on the calcium-sensing receptor [16,17] while simultaneously reducing serum calcium and phosphorus concentrations [10,11]. Accordingly, treatment strategies that utilize cinacalcet together with low doses of vitamin D sterols may be able to modify parathyroid gland function favourably through two distinct, yet complementary, pathways while serving to maintain serum calcium and phosphorus levels.

The results of the current trial indicate that combined therapy with cinacalcet and low doses of vitamin D sterols effectively lowered plasma PTH and Ca × P levels among subjects with moderate to severe sHPT who were refractory to conventional therapy. This therapeutic approach reduced the weekly dose of vitamin D sterols by 51% while increasing the proportion of subjects who achieved recommended target values for PTH and Ca × P. Both the impact of treatment with cinacalcet on serum calcium and phosphorus levels and the clinical safety profile of cinacalcet in the current study were similar to that described previously in larger, placebo-controlled phase 3 clinical trials [10,11].

Overall, 62% of subjects given cinacalcet and low doses of vitamin D sterols achieved adequate control of plasma PTH as defined by values <160 pg/mL (~iPTH 300 pg/mL or ng/L) and 83% of subjects had Ca × P values ≤55 mg<sup>2</sup>/dL<sup>2</sup> (4.4 mmol<sup>2</sup>/L<sup>2</sup>) during the assessment phase of the study.

The KDOQI™ guidelines for CKD-MBD recommend that vitamin D therapy be withheld if albumin-adjusted serum calcium concentrations exceed 10.2 mg/dL (2.5 mmol/L) or if serum phosphorus levels exceed 6.0 mg/dL (1.9 mmol/L) [18]. These constraints often require interruptions in treatment that may lead to inadequate or unsustained control of plasma PTH levels and to substantial short-term variations in serum calcium and phosphorus concentrations. In contrast, episodes of hypercalcaemia and hyperphosphataemia were uncommon (<1% of subjects each) in the current study using combined therapy with cinacalcet and low doses of vitamin D sterols. Such an approach may make it possible to achieve long-term sustained control of plasma PTH levels by simultaneously affecting PTH gene transcription [19] and PTH secretion [16,17] while avoiding the clinically important and potentially detrimental biochemical side effects commonly associated with vitamin D therapy.

Several observational studies and retrospective analyses of data gathered from large dialysis providers have suggested that treatment with vitamin D sterols is associated with a survival benefit among patients undergoing haemodialysis regularly [20]. The mechanisms responsible are not understood, and the impact of treatment with vitamin D sterols on specific outcomes such as cardiovascular events has not been consistent among studies. Indeed, some reports have failed to document a relationship between the therapeutic use of vitamin D sterols and dialysis survival [21]. Apart from the issue of confounding by indication, a legitimate concern for any observational study, issues of vitamin D nutrition may be involved. Nevertheless, many clinicians are inclined to use vitamin D sterols regularly in the clinical management of patients receiving dialysis because of perceived benefits apart from those related to the treatment of sHPT. In this context, the use of low doses of vitamin D analogues in conjunction with cinacalcet to manage sHPT may facilitate the control of plasma PTH levels while diminishing the risk of adversely affecting serum calcium and phosphorus levels and the risks associated with hypercalcaemia and hyperphosphataemia. Furthermore, although 49% of subjects exhibited low serum calcium levels (two consecutive values <8.4 mg/dL), only one subject discontinued from the trial as a result of hypocalcaemia, suggesting that in most cases, it was tolerable and manageable.

The current study has several limitations. This was an open-label study without an active control group due to the hypothesis that patients refractory to conventional therapy would have biochemical improvement with simultaneous use of cinacalcet and vitamin D sterols. One key biochemical endpoint for this clinical trial was a plasma biPTH level ≤160 pg/mL (~iPTH 300 pg/mL or ng/L) as determined by a biPTH assay. It was not defined by a range of biPTH values between 80 and 160 pg/mL (~iPTH 150–300 pg/mL or ng/L) as recommended by the KDOQI™ guidelines [18].

Accordingly, the proportion of subjects who achieved the PTH goal (62%) as defined in the study protocol was not the same as the fraction who had values that fell within the KDOQI™ target range (46%). Also, only biochemical outcomes were measured. No assessments of bone-related outcomes or indices of cardiovascular health were made in this relatively short 16-week trial. Studies of much longer duration will be required to examine the impact of various treatment strategies for sHPT on bone mass, bone quality, skeletal fracture rates, cardiovascular calcification and ultimately, cardiovascular events and mortality. Several such studies are currently underway.

The nature of the response of investigators to reductions in serum calcium concentrations during treatment with cinacalcet is important clinically and deserves comment. The KDOQI™ guidelines recommend that patients undergoing dialysis receive no more than 1500 mg per day of elemental calcium as part of a phosphate-binding regimen and that the total daily intake of calcium from dietary and medicinal sources does not exceed 2000 mg [18]. In the current trial, the average intake of elemental calcium exceeded this threshold during the maintenance phase of the study, in part because investigators were allowed to increase the doses of oral calcium-containing phosphate binders if serum calcium level decreased during cinacalcet therapy. Because calcimimetic agents fundamentally alter parathyroid gland function by modifying the set-point for calcium-regulated PTH secretion [16], treatment with cinacalcet renders parathyroid tissue more sensitive to the inhibitory actions of calcium on PTH release. Interventions designed to offset the calcium-lowering effect of cinacalcet and to raise serum calcium concentrations, such as the administration of large oral doses of calcium, may thus lead to further reductions in PTH secretion, cause plasma PTH levels to decrease below recommended values, and result in inadvertent calcium loading with the attendant risk of soft-tissue and vascular calcification. The long-term safety and efficacy of oral calcium supplementation among patients receiving cinacalcet thus remains uncertain, and such measures should be undertaken with caution.

The current KDOQI™ guidelines state that no therapeutic intervention is required to correct low serum calcium levels unless patients have a secondary, compensatory increase in plasma PTH levels or have clinical symptoms attributable to hypocalcaemia [18]. Symptomatic hypocalcaemia has generally not been observed in clinical trials with cinacalcet when therapy is initiated and doses are adjusted according to established guidelines, but reductions in serum calcium concentration are an expected and predictable biochemical response to treatment [10,11]. Downward adjustments to the dose of cinacalcet rather than additional amounts of calcium given orally may thus be a more prudent intervention to correct hypocalcaemia if it develops among patients receiving cinacalcet. Clinical trials designed to assess the impact of treatment with cinacalcet on vascular calcification and arterial function among patients managed with calcium-containing phosphate binders are currently underway.

In conclusion, this study finds that the combined use of cinacalcet and low doses of vitamin D sterols in patients unable to achieve target values with conventional therapy

improves the control of sHPT and enhances the ability to reach KDOQI™ target values for biochemical parameters of CKD-MBD.

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## Appendix

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