secondary HPT in the United States. There is no evidence that age or race had any effect on safety or efficacy outcomes.

X. Conclusions and Recommendations

Efficacy

The National Kidney Foundation recently updated the treatment guidelines for patients with CKD and secondary HPT. Per these guidelines, patients on dialysis should strive for iPTH levels of 150 pg/ml to 300 pg/ml and pre-dialysis patients . The Ca x P ion product in dialysis patients should be below 55 $(mg/dl)^2$. These treatment goals aim primarily to reduce the risk for osteitis fibrosa while avoiding iatrogenic adynamic bone disease, and reduce the occurrence of soft tissue calcification, including that involving the coronary arteries and cardiac valves. Effective management of secondary HPT is presumed to reduce the risks for cardiovascular disease and fractures, though no controlled trials have been conducted to verify this assumption.

Data from three randomized, double-blind, placebo-controlled, 6-month trials of more than 1000 patients with CKD and secondary HPTH receiving dialysis, indicate that cinacalcet, when initiated at 30 mg QD and titrated to a dose as high as 180 mg QD, reduces serum iPTH by approximately 50% relative to placebo. A much higher percentage of cinacalcet-treated patients (40%) compared with placebo-treated subjects (5%) were able to achieve a serum iPTH level $\leq$ 250 pg/ml, and nearly twice as many cinacalcet as placebo patients attained a serum Ca x P ion product of less than 55 mg/dl^2. Cinacalcet's calcimimetic action allows for the simultaneous reductions of serum iPTH and the Ca x P ion product – a duel treatment effect that is rarely achieved with current vitamin D and phosphate-binder therapies. For example, whereas 5% of placebo subjects had concurrent reductions of iPTH to 150 to 300 pg/ml and Ca x P < 55 mg/dl^2, almost 25% of cinacalcet patients achieved these therapeutic goals.

Based on the favorable changes in these biomarkers, it's not unreasonable to speculate that a treatment regimen that includes cinacalcet might decrease cardiovascular morbidity and mortality. While evidence of such a benefit is lacking, the Division nevertheless accepts these biochemical changes as demonstration of efficacy for cinacalcet in this population.

[redacted]

High doses of cinacalcet had marginal efficacy in lowering serum calcium levels in 10 patients with parathyroid carcinoma. At the end of a 16-week, open-label, titration phase, 7 out of the 10 patients had reductions in serum calcium of $\geq$ 1.0 mg/dL. None of the patients, however, normalized their serum calcium levels.

To state the obvious, the data upon which Amgen is requesting approval for the treatment of parathyroid carcinoma are very limited. Yet, parathyroid carcinoma is a rare disease and patients

have few treatment options for the hypercalcemia associated with the condition. Cinacalcet offers the potential to satisfy an unmet medical need in this population of seriously ill patients.

In addition to the indications for the treatment of secondary HPT and the hypercalcemia of parathyroid carcinoma, Amgen is seeking approval for the treatment of patients with primary hyperparathyroidism for whom parathyroidectomy is not a treatment option. To the best of my knowledge, the original NDA submission contains data on 3 patients for whom this indication may be applicable. Not only are 3 patients inadequate to judge the efficacy and safety of cinacalcet for this proposed indication, but Amgen has not even made it clear what criteria were used to make the determination that parathyroidectomy was not a treatment option for these patients. In short, the company has not provided sufficient information upon which to assess the efficacy or safety of cinacalcet's use in patients with primary hyperparathyroidism for whom parathyroidectomy is not a treatment option.

Safety

Nausea and vomiting were the two most commonly reported adverse events and the most frequent reasons for premature withdrawal from the trials. Vomiting was dose-related, nausea was not.

The risk of hypocalcemia (< 8.4 mg/dL) is clearly increased in patients treated with cinacalcet. The risk does not appear to be dose-related, but is does appear higher in pre-dialysis vs. dialysis patients. This is particularly true in pre-dialysis patients with relatively mild elevations in iPTH who are aggressively treated (i.e., goal iPTH < 65 pg/ml). In one study, nearly 50% of the cinacalcet patients developed serum calcium levels less than 7.4 mg/dl, whereas none of the placebo subjects became hypocalcemic. Because calcium levels were monitored weekly in the trials and low levels were managed with supplemental calcium and/or vitamin D, it would seem appropriate for the labeling to recommend frequent, perhaps even weekly, measurement of serum calcium levels in patients at particular risk for hypocalcemia because of relatively mild hyperparathyroidism until a stable dose of cinacalcet is achieved.

There was an imbalance between the cinacalcet and placebo groups in the number of patients who reportedly suffered a "seizure" during the studies of patients with CKD who were receiving dialysis. It is unknown if this imbalance is a chance finding or reflects a true drug-induced risk, perhaps by way of hypocalcemia. At this point the most appropriate action would be to include the seizure information in the labeling, reinforce the need to regularly measure serum calcium levels, and closely monitor ongoing clinical trial and post-approval data for reports of seizures. Insofar as several of the patients who had seizures while treated with cinacalcet had histories of epilepsy and two were on anticonvulsant therapy it would also be worthwhile for Amgen to conduct *in vitro* enzyme induction studies to rule out the possibility that cinacalcet enhances the activity of enzymes responsible for the metabolism of common anti-seizure medications.

Regarding cardiac repolarization, limitations of the preclinical and clinical data do not allow for a comprehensive assessment of cinacalcet's potential to significantly prolong the QT interval. It is unclear if the minor QT prolongation observed in the phase-3 trials is due to lowering of serum calcium levels or to direct effects of cinacalcet or its metabolites. Given this degree of

uncertainty, a thorough QT would provide valuable information regarding the overall risk – benefit relationship of this drug. While admittedly a conservative approach, until a thorough QT study is completed, it would be prudent to limit approval of cinacalcet to patients with secondary HPT and CKD receiving dialysis and to patients with parathyroid carcinoma – the populations who stand to benefit the most from the drug and for which a small risk for QT prolongation would therefore be acceptable.

Not only do patients with pre-dialysis CKD have less severe hyperparathyroidism than those CKD requiring dialysis, and therefore in theory have a less favorable benefit-to-risk profile, but they may also be at greater risk for cinacalcet-induced hypocalcemia – itself a potential trigger of a malignant arrhythmia. This is yet another reason to thoroughly characterize the QT-prolonging potential of cinacalcet before approving it for patients with less serious forms of disease.

Conclusions

Based upon the data presented in this NDA, we conclude that the benefit-to-risk profile of cinacalcet supports approval for the treatment of secondary HPT in patients with CKD receiving dialysis and the treatment of hypercalcemia associated with parathyroid carcinoma. We consider the following two indications approvable, pending review of additional data: (1) The treatment of secondary HPT in pre-dialysis CKD patients and, (2) The treatment of primary hyperparathyroidism when parathyroidectomy is not a treatment option. [redacted]

Regulatory Recommendations

- Approval of cinacalcet for the indication: The treatment of secondary HPT in patients in patients with CKD receiving dialysis.
- Approval of cinacalcet for the indication: The treatment of hypercalcemia associated with parathyroid carcinoma.
- Approvable for the indication: The treatment of secondary HPT in patients in patients with pre-dialysis CKD, [redacted]
- Approvable for the indication: The treatment of patients with primary hyperparathyroidism for whom parathyroidectomy is not an option, [redacted]

XI. Appendix

XI.A. Other Relevant Materials

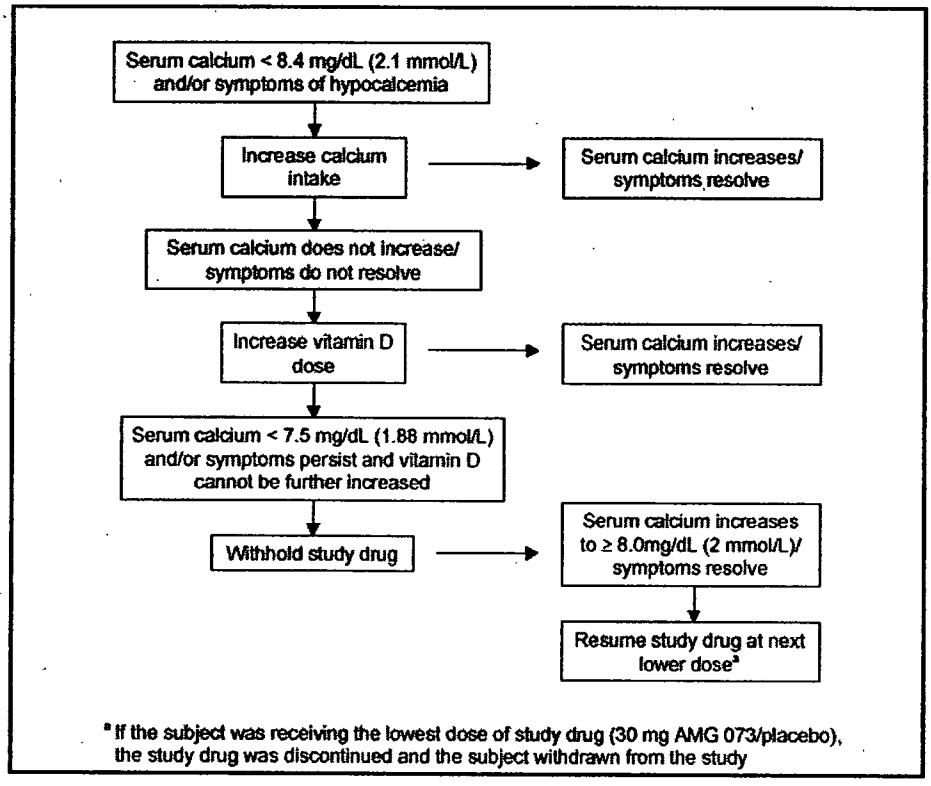
XI.A.1. Incidence of Adverse Events, Pooled Phase 3 Safety data

Table 13. Subject Incidence of Common (≥ 5%) Adverse Events by Preferred Term in Descending Order of Frequency (Phase 3 ESRD Safety Subjects - 6 Month Exposure)

Preferred Term	Placebo (N = 470) n (%)	Cinacalcet (N = 656) n (%)
Nausea	91 (19)	204 (31)
Vomiting	69 (15)	178 (27)
Diarrhea	94 (20)	136 (21)
Headache	82 (17)	106 (16)
Myalgia	64 (14)	98 (15)
Pain Abdominal	66 (14)	81 (12)
Infection Upper Respiratory	62 (13)	77 (12)
Dizziness	36 (8)	64 (10)
Dyspnea	44 (9)	60 (9)
Pain Limb	49 (10)	59 (9)
Dyspepsia	36 (8)	50 (8)
Arthralgia	41 (9)	46 (7)
Fever	45 (10)	45 (7)
Fatigue	35 (7)	45 (7)
Hypertension	23 (5)	45 (7)
Hypotension	55 (12)	44 (7)
Edema Peripheral	34 (7)	44 (7)
Asthenia	17 (4)	44 (7)
Cough	32 (7)	40 (6)
Pruritus	31 (7)	40 (6)
Anorexia	19 (4)	40 (6)
Thrombosis Vascular Access	32 (7)	39 (6)
Pain Chest, Non-Cardiac	20 (4)	37 (6)
Access Infection	21 (4)	36 (5)
Constipation	28 (6)	28 (4)
Pain Back	32 (7)	21 (3)

XI.A.2. Guidelines for treating hypercalcemia, Phase 3 studies.

Figure 7-2. Guidelines for Treating Hypocalcemia



XI.A.3. Adverse events associated with low serum calcium levels.

Adverse Events Possibly Associated with Low Serum Calcium in ESRD Subjects

Preferred Term
Anxiety
Arrhythmia
Arrhythmia Atrial
Asthenia
AV Block
Bradycardia
Bronchospasm
Bundle Branch Block
Convulsions
Convulsions Local
Fatigue
Hyperesthesia
Hypertonia
Hypoesthesia
Hypotension
Hypotension Postural
Malaise
Muscle Contractions Involuntary
Muscle Weakness
Myalgia
Nervousness
Pain Musculo-Skeletal
Palpitation
Paresthesia
Status Epilepticus
Tachyarrhythmia
Tachycardia
Tachycardia Supraventricular
Tachycardia Ventricular
Throat Tightness

XI.A.4. Subjects in the cinacalcet clinical program who experienced seizures

Subject	Study No.	History of Seizures	Confounding Factors	Calcium[a] (mg/dL)	Dose level (mgs)	Treatment Relationship[b]
Cinacalcet						
30608	20010240		isoniazid	11.8 / 10.2	30	No
33510	20000183	X	subdural hematoma	8.6 / —	60	No
31602	20000183	X	HTN, tramadol	8.0 / 10.0	120	Yes
30202	20000183		VP shunt, UTI	9.1 / 7.8	120	No
34204	20000183		cefazolin	9.6 / 8.0	60	Yes
10602	20000172		HTN	8.6 / 9.5	30	No
10706	20000172/ 20010240	X		8.3 / 8.6 7.3 / 9.2	180 180	Yes
20511	20000188	X	low phenytoin level	7.4 / 9.7 9.7 / 8.8	60 60	No
10911	20000188			9.0 / 8.5 9.6 / 10.7	60 90	Yes
16708	20010240			9.4 / 11.0	90	No
13107	20000188	X		7.8 / 9.3	90	No
Placebo						
14302	20000172			8.2 / 8.9	90	Yes
13105	20000172	X	promethazine	9.0 / 8.6	90	No

[a] Nearest on-study serum calcium values before and after event
[b] Investigator's assessment

XI.B. Individual More Detailed Study Reviews

Study 20000172: A Phase 3 Study to Assess the Efficacy and Safety of an Oral Calcimimetic Agent (AMG 073) in Secondary Hyperparathyroidism of End Stage Renal Disease Treated with Hemodialysis

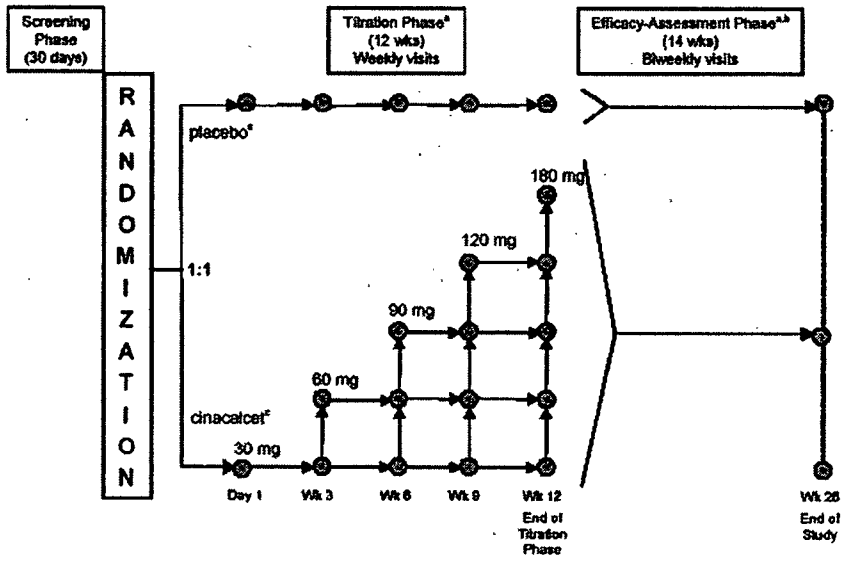
This was a randomized, double-blind, placebo-controlled, multicenter study of the efficacy and safety of cinacalcet in patients with secondary hyperparathyroidism of end stage renal disease treated with hemodialysis.

Objectives: The primary objective of this study was to investigate the efficacy of cinacalcet compared with placebo by determining the proportion of subjects with a mean plasma intact parathyroid hormone (iPTH) value ≤ 250 pg/mL during the efficacy - assessment phase.

Study Design: This was a randomized, double-blind, placebo-controlled, parallel-group, 26-week study. Sixty three centers in North America participated in the study. After a 30-day screening period, subjects who qualified for the study were randomized in a 1:1 ratio to cinacalcet or placebo within 1 of 6 strata defined by baseline mean iPTH and Ca x P concentrations. Throughout the study, investigators could prescribe concomitant therapy considered necessary.

The study consisted of 2 phases: a 12-week dose-titration phase followed by a 14-week efficacy-assessment phase. Possible sequential daily doses during the treatment period were 30, 60, 90, 120, and 180 mg cinacalcet or placebo. Visits occurred weekly during the titration phase and biweekly during the efficacy-assessment phase. At the Week 3, 6, 9, 12, 16, 20, and 24 study

visits, subjects could be titrated up to the next sequential dose level of cinacalcet/placebo based on iPTH response and safety monitoring (see figure below).



Population: The study population consisted of subjects with end stage renal disease who were maintained on hemodialysis. Subjects were stratified as follows:

- iPTH ≥ 300 pg/mL (31.8 pmol/L) to ≤ 500 pg/mL (53 pmol/L) and Ca x P ≤ 70 $(mg/dL)^2$ (5.65 $[mmol/L]^2$)
- iPTH ≥ 300 to ≤ 500 pg/mL and Ca x P > 70 $(mg/dL)^2$
- iPTH > 500 to ≤ 800 pg/mL (84.8 pmol/L) and Ca x P ≤ 70 $(mg/dL)^2$
- iPTH > 500 to ≤800 pg/mL and Ca x P > 70 $(mg/dL)^2$
- iPTH > 800 pg/mL and Ca x P ≤ 70 $(mg/dL)^2$
- iPTH > 800 pg/mL and Ca x P > 70 $(mg/dL)^2$

A maximum of 20% of subjects with baseline iPTH > 800 pg/mL were allowed in the study.

Inclusion Criteria

- ≥ 18 years of age at the start of screening
- Agreed to use, in the opinion of the principal investigator, highly effective contraceptive measures throughout the study
- Mean of 3 central laboratory iPTH values ≥ 300 pg/mL obtained within 30 days before Day 1
- Mean of 3 central laboratory serum calcium values ≥ 8.4 mg/dL (2.1 mmol/L) obtained within 30 days before Day 1
- Prescribed hemodialysis 3 times weekly for ≥ 3 months before Day 1
- Signed the IRB-approved informed consent document before any study-specific procedures were initiated

Exclusion Criteria

- Had an unstable medical condition, defined as having been hospitalized, other than for dialysis vascular access revision, within 30 days before day 1, or were otherwise unstable in the judgment of the investigator
- Pregnant or nursing
- Parathyroidectomy in the 3 months before day 1
- Received vitamin D sterol therapy for < 30 days before day 1 or required a change in vitamin D sterol brand or dose within 30 days before day 1 (for subjects prescribed vitamin D)
- Changed the brand or dose of phosphate binder or oral calcium supplement in the 30 days before Day 1
- Changed dialysate calcium concentration in the 30 days before day 1
- Received, within 21 days before day 1, therapy with flecainide, lithium, thioridazine, haloperidol, or tricyclic antidepressants (e.g., imipramine or desipramine) (except the tricyclic antidepressant amitriptyline was permitted)
- Experienced a myocardial infarction within 3 months before day 1
- Enrolled in, or not yet completed < 30 days before day 1, other invasive investigational device or drug trials, or were receiving other investigational agents (experimental dialysis machines were acceptable)
- GI disorder that may have been associated with impaired absorption of orally administered drugs or an inability to swallow tablets
- Disorder that would have interfered with understanding and giving informed consent or compliance with protocol requirements
- Participated in other studies with cinacalcet

COMMENT: The inclusion and exclusion criteria appear appropriate.

Study Medication: All medications were administered orally with a starting dose of 30mg cinacalcet or placebo. Tablets were taken with food or shortly after a meal if feasible and were swallowed whole without biting or chewing. The study drug was provided as light green film-coated tablets of 30-, 60-, and 90-mg free-base equivalents or placebo, which were graduated in size, smallest to largest. Possible sequential doses during the study were 30, 60, 90, 120, and 180 mg cinacalcet or placebo. Combinations of the tablets were used for the 120- and 180-mg doses (two 60-mg and two 90-mg tablets, respectively). Except during the screening phase, changes in phosphate binders/oral calcium supplements were permitted throughout the study. The prescribed dialysate calcium concentration was not to change in the 30 days before day 1 or during the study. Changes in vitamin D therapy were only permitted based on protocol-specified guidelines.

COMMENT: Dosing instructions appear appropriate, as drug absorption is improved with food.

Efficacy Measures A reduction in iPTH to ≤ 250 pg/mL was chosen as the primary endpoint for the phase 3 program. In patients with ESRD, relatively normal bone histology has been observed with PTH concentrations of approximately 2 to 4 times the upper limit of normal, corresponding to approximately 100 to 250 pg/mL. A reduction in iPTH ≥ 30% is also considered clinically meaningful by many nephrologists and has been used as the primary endpoint in trials for vitamin D sterols in treatment of secondary HPT.

The Nichols first generation immunometric iPTH assay has been considered the current gold-standard assay for PTH measurement and was used in the cinacalcet phase 3 program for titration of study medication and efficacy evaluation. It is now recognized that the Nichols assay detects a PTH fragment (amino acids 7-84) in addition to the full-length molecule (1-84). Recently, the bio-intact PTH (biPTH) assay, which detects only the full-length molecule, has become available. In this study, duplicate plasma samples were collected to allow comparison of results obtained with the iPTH and biPTH assays.

COMMENT: The primary endpoint target range of iPTH is appropriate. K/DOQI guidelines[4] list the target range of iPTH in dialysis patients as 150 – 300 pg/mL.

Primary Efficacy Endpoint

- Proportion of subjects with a mean iPTH value ≤ 250 pg/mL during the efficacy-assessment phase.

Secondary Efficacy Endpoints

- Proportion of subjects with a reduction from baseline in mean iPTH of ≥ 30%
- Percentage change from baseline in mean Ca x P
- Change from baseline in self-reported cognitive functioning scale score

Tertiary Efficacy Endpoints

- Percentage changes from baseline in mean iPTH, serum calcium, and serum phosphorus
- Proportion of subjects with both a mean iPTH ≤ 250 pg/mL and a reduction from baseline in mean Ca x P

Exploratory Bio-intact PTH Analyses: Exploratory analyses comparing the results obtained with the 2 PTH assays included the following:

- Correlation analysis of iPTH and biPTH values at baseline (all subjects)
- Correlation analysis of efficacy-assessment phase iPTH values and biPTH values by treatment group (to address whether cinacalcet changes the relationship between intact and bio-intact PTH)
- Mean absolute value and mean percentage change from baseline in biPTH at each measurement time point

[4] K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003, Oct. 42 (4) Supplement 3.

- Proportion of subjects who had ≥ 30% reduction from baseline in biPTH during the efficacy-assessment phase

Safety Measures: Safety was assessed by adverse events, laboratory measurements, electrocardiograms (ECGs), vital signs, and physical exams.

Study Methods: [redacted] was used to analyze the samples for the primary, secondary and safety endpoints. All iPTH levels were obtained utilizing the manual IRMA methodology.

Dose Titration: Subjects could be titrated up to the next sequential dose level of study drug at the week 3, 6, 9, 12, 16, 20, and 24 study visits. For each of these visits, a site representative called the IVRS within 5 days before and 3 days after the scheduled visit in order for a subject to receive the next bottle number(s). The site personnel were asked for subject information that included central laboratory iPTH and serum calcium values and safety information.

If any of the following criteria applied, a subject's dose was NOT increased:

For weeks 3, 6, 9 and 12:

- The mean of the 2 central laboratory iPTH values from the preceding 2 weeks was ≤ 200 pg/mL (21.2 pmol/L), with any missing values excluded from calculation.

For weeks 16, 20, and 24:

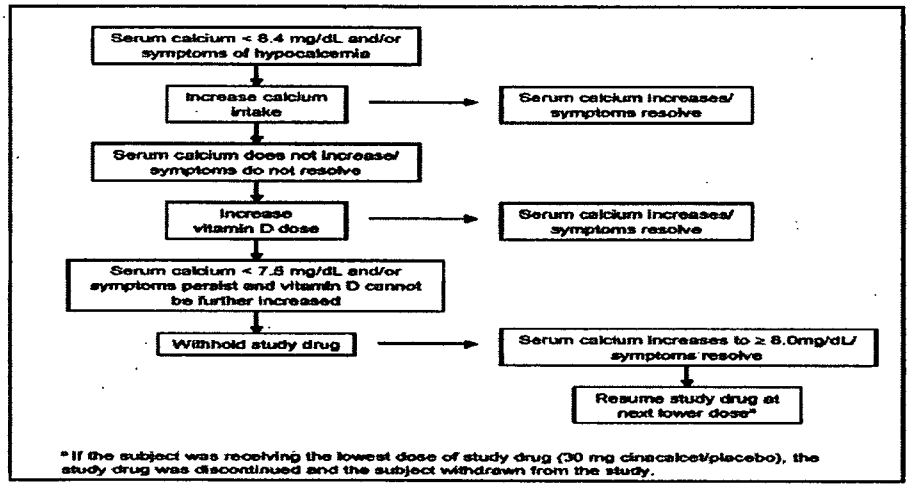
- The central laboratory iPTH value from the preceding study visit was ≤ 200 pg/mL (21.2 pmol/L) with any missing value replaced by the most recent past value.

For weeks 3, 6, 9, 12, 16, 20, and 24:

- The highest dose of study medication was reached.
- The serum calcium was < 7.8 mg/dL (1.95 mmol/L) or the subject was experiencing symptoms of hypocalcemia.
- The subject was experiencing an adverse event that precluded a dose increase.

If iPTH values were < 100 pg/mL (10.6 pmol/L) for 3 consecutive study visits, study medication was reduced to the next lower dose. If the subject was already receiving the lowest dose of study drug, vitamin D therapy could be decreased.

Treatment of Hypocalcemia: If a subject experienced symptoms of hypocalcemia and/or a serum calcium < 8.4 mg/dL, calcium supplements and/or phosphate binders may have been increased to resolve these symptoms (if present) or to increase serum calcium to ≥ 8.4 mg/dL. If these measures were insufficient, the vitamin D dose could be increased. Guidelines used for management of hypocalcemia are outlined in the figure below:



Protocol Specified Guidelines for Changes in Vitamin D therapy: If a subject's iPTH concentration increased ≥ 50% from baseline for 3 consecutive study visits, vitamin D therapy was increased. If a subject's serum calcium concentration was ≥ 11 mg/dL (2.75 mmol/L), or serum phosphorus concentration was ≥ 6.5 mg/dL (2.1 mmol/L), and/or Ca x P was ≥ 70 $(mg/dL)^2$ (5.65 $[mmol/L])^2$, the investigator could modify diet and/or change dose or brand of phosphate binders. If these measures were not sufficient, vitamin D could be withheld or the dose reduced until the serum calcium, phosphorus, and Ca x P were below these levels. If vitamin D sterol was withheld, it was restarted at the investigator's discretion.

Withdrawal criteria: Any subject had the right to withdraw from the study at any time and for any reason. Subjects could be withdrawn from the study in the event of kidney transplant, parathyroidectomy or pregnancy. Withdrawn patients were not replaced.

Statistical Analyses: It was hypothesized that the results of this study would demonstrate the following:

- Cinacalcet decreases mean iPTH concentrations to ≤ 250 pg/mL in a significantly greater proportion of subjects with ESRD and secondary HPT compared with placebo.
- Cinacalcet reduces mean iPTH concentrations by ≥ 30% in a significantly greater proportion of subjects compared with placebo.
- Cinacalcet causes a significantly greater mean percentage reduction in Ca x P compared with placebo.
- Cinacalcet significantly improves cognitive functioning compared with placebo.

The sample size calculation was based on a χ^2 test of equal proportions of subjects with a mean iPTH value ≤ 250 pg/mL during the efficacy-assessment phase, with a statistical significance level of 0.05 (2-sided). The placebo response was predicted on the basis of previous cinacalcet phase 2 studies to be ≤ 15%. With a cinacalcet response rate of 35% assumed for the purpose of sample size considerations, the planned 400 subjects (200 cinacalcet, 200 placebo) yielded 98% power.

A 4-stage hypothesis testing procedure was performed for the primary and secondary endpoints. The primary endpoint was tested at a significance level of 0.05. The first secondary endpoint, the proportion of subjects with a reduction from baseline in mean iPTH $\geq$ 30% during the efficacy-assessment phase, was to be tested only if statistical significance was achieved for the primary endpoint. The key secondary endpoint, percentage change from baseline in mean Ca x P, was to be tested only if statistical significance was achieved for the first secondary endpoint. Similarly, the final secondary endpoint, the change from baseline in PRO cognitive functioning scale score, was to be tested only if statistical significance was achieved for the key secondary endpoint.

Descriptive statistics were used to summarize each efficacy endpoint at each measurement time point during the dose-titration and efficacy-assessment phases. Descriptive statistics included mean, median, SE, 25th and 75th percentiles, minimum, and maximum for continuous variables and number and percent for categorical variables. For continuous efficacy variables, 95% 2-sided confidence intervals (CIs) were provided for the means. For categorical efficacy variables, the odds ratio of achieving the endpoint under consideration and the difference between the treatment groups were presented with the associated 95% CIs.

The statistical analysis plan was amended once (15 April 2003). The amendment included the following changes:

- redefinition of the primary iPTH dataset and addition of sensitivity analyses for iPTH-related endpoints after identification of inconsistencies in the acceptability criteria for iPTH assays at [redacted] and affiliates
- inclusion of analyses of ECG interval data
- addition of exploratory analyses of biPTH data
- clarification regarding analyses if subjects had been randomized to an incorrect iPTH and Ca x P stratum
- redefinition of the conversion factor for paricalcitol equivalents.

Protocol Amendments: The protocol was amended twice with changes noted below:
Amendment 1 (19 November 2001)

- Lengthened the study from 18 to 26 weeks by extending the efficacy-assessment phase from 6 to 14 weeks
- Added an ECG assessment at week 14
- Added a PRO assessment at week 20
- Added a statistical sensitivity analysis to assess the primary endpoint at the final 2 visits of the efficacy-assessment phase

Amendment 2 (04 April 2002)

- Added an additional 80 subjects to the study
- Changed the tertiary endpoint, proportion of subjects with a reduction from baseline in mean iPTH of $\geq$ 30%, to a secondary endpoint

Results

Patient Disposition: As shown in the table below, 772 subjects were screened and 410 subjects were enrolled and randomized this study. Approximately 77% of placebo-treated and 71% of cinacalcet-treated subjects completed the 26-week trial. Adverse events were the most common reason for early withdrawal, with the rates balanced between the two groups.

20000172: Patient Disposition

	Placebo	Cinacalcet
Enrolled	205	205
No treatment	1	5
At least one dose	204	200
Withdrew - Total	46 (22)	54 (27)
Withdrew - AE	19 (9)	19 (10)
Deaths	5 (2)	6 (3)
Withdrew - Parathyroidectomy	2 (1)	0 (0)
Withdrew – Renal Transplant	5 (2)	7 (4)
Withdrew - Other	15 (7)	22 (11)
Completed Titration Phase (Weeks 1-16)	174 (85)	170 (83)
Completed Study	158 (77)	146 (71)

Protocol Violations: Thirty seven (9%) subjects had eligibility deviations in this study, which were discovered after subjects were enrolled. The most common eligibility deviation was a change in vitamin D sterol dose during the 30 days before day 1. Major protocol deviations occurred in 33% of subjects overall (29% of the placebo-treated group and 38% of the cinacalcet-treated group). Compliance with study drug was >90% and similar in both treatment groups.

Subject Incidence of Major Protocol Deviations by Treatment Group and Baseline Randomization Strata (Phase 3 ESRD Studies)

	Placebo	Cinacalcet
	n/N (%)	n/N (%)
Study 20000172		
iPTH 300 to 500 and Ca x P 70	21/70 (30%)	26/70 (37%)
iPTH 300 to 500 and Ca x P > 70	8/23 (35%)	7/22 (32%)
iPTH 501 to 800 and Ca x P 70	17/51 (33%)	20/52 (38%)
iPTH 501 to 800 and Ca x P > 70	6/21 (29%)	10/21 (48%)
iPTH > 800 and Ca x P 70	7/26 (27%)	9/26 (35%)
iPTH > 800 and Ca x P > 70	0/14 (0%)	5/14 (36%)

COMMENT: Protocol violations were numerous and varied. The predominant major violation was missed doses, occurring in 13% of the placebo-treated group and 21% of the cinacalcet-treated group. If anything, the disparity between groups of subjects missing doses would underestimate the reported efficacy of cinacalcet. .

Demographics: Baseline subject demographics were well balanced across the treatment groups (see table below). Fifty-eight percent of enrolled subjects were Black, which is consistent with the increased prevalence of ESRD and severity of secondary HPT in African-Americans in the United States. Approximately 27% of enrolled subjects were ≥ 65 years of age. The duration of dialysis ranged from 1 to 290 months, with a mean of 64 months. Randomization within each

baseline stratum was balanced between treatment groups. At baseline, mean iPTH, Ca x P, serum calcium, and serum phosphorus were similar in the cinacalcet and placebo groups. At study entry, vitamin D and phosphate binder use were similar in the 2 treatment groups.

Study 20000172: Demographics

	Placebo	Cinacalcet
N	205 (%)	205 (%)
Age (yrs.)	54.2 ± 14.6	53.3 ± 14.2
≥ 65 years	57 (28)	52 (25)
≥ 75 years	18 (9)	18 (9)
Sex		
Male	124 (60)	124 (60)
Female	81 (40)	81 (40)
Race		
Caucasian	69 (34)	62 (30)
Black	118 (58)	121 (59)
Other	18 (9)	22 (11)
Randomization Strata		
PTH 300 – 500, Ca x P ≤ 70	70 (34)	70 (34)
PTH 300 – 500, Ca x P > 70	23 (11)	22 (11)
PTH 500 – 800, Ca x P ≤ 70	51 (25)	52 (25)
PTH 500 – 800, Ca x P > 70	21 (10)	21 (10)
PTH > 800, Ca x P ≤ 70	26 (13)	26 (13)
PTH > 800, Ca x P > 70	14 (7)	14 (7)
Baseline Labs		
iPTH (pg/mL)	651.1 ± 397.8	635.7 ± 340.7
Serum Ca (mg/dL)	9.90 ± 0.81	9.84 ± 0.81
Ca x P (mg/dL)[2]	61.14 ± 16.06	62.05 ± 16.22
Serum Phos (mg/dL)	6.18 ± 1.59	6.33 ± 1.72
Baseline Vitamin D use		
Yes	139 (68)	144 (70)
No	66 (32)	61 (30)
Baseline Phosphate Binder use		
Yes	195 (95)	193 (94)
No	10 (5)	12 (6)

Primary Efficacy Outcomes

iPTH Proportion of subjects with a mean iPTH value ≤ 250 pg/mL during the efficacy-assessment phase: The primary analyses of the efficacy endpoints were based on the ITT analysis set. The mean baseline iPTH was 651 pg/mL in the placebo-treated group and 636 pg/mL in the cinacalcet-treated group. Significantly more subjects in the cinacalcet group (41%) compared with the placebo group (4%) achieved a mean iPTH concentration ≤ 250 pg/mL during the efficacy-assessment phase ($p < 0.001$). More cinacalcet-treated subjects in the lowest baseline iPTH strata achieved an iPTH concentration ≤ 250 pg/mL than subjects in the higher baseline iPTH strata: 52% in the ≥ 300 and ≤ 500 pg/mL stratum, 41% in the > 500 and ≤ 800 pg/mL stratum, and 15% in the > 800 pg/mL stratum. The iPTH response in the cinacalcet group was similar regardless of baseline Ca x P strata. In the placebo group, the proportions of subjects within each baseline iPTH and Ca x P stratum who achieved the primary endpoint ranged from 0% to 7%. The primary endpoint was also analyzed separately by age (< 65 , > 65 years), sex,

and race (black, white, other). Results were similar for all subgroups and were comparable to the primary analysis.

Study 20000172: Proportion of Subjects With a Mean iPTH Concentration ≥ 250 pg/mL

iPTH Stratum [pg/mL]	Ca x P Stratum [mg/dL][2]	Placebo (N = 205) n/N1(%)	Cinacalcet (N = 205) n/N1(%)
≥ 300 and ≤ 500	≤ 70	5/70 (7)	39/70 (56)
	> 70	0/23 (0)	9/22 (41)
	All	5/93 (5)	48/92 (52)
> 500 and ≤ 800	≤ 70	2/51 (4)	20/52 (38)
	> 70	1/21 (5)	10/21 (48)
	All	3/72 (4)	30/73 (41)
> 800	≤ 70	0/26 (0)	4/26 (15)
	> 70	0/14 (0)	2/14 (14)
	All	0/40 (0)	6/40 (15)
All	≤ 70	7/147 (5)	63/148 (43)
All	> 70	1/58 (2)	21/57 (37)
Overall		8/205 (4)	84/205 (41)

Test Statistics:

CMH Statistic (χ^2)		Odds Ratio (Cinacal/Plac)		Difference (Cinacal-Plac)	
Value	P-value	Value	95% CI	Value	95% CI
83.41	< 0.001	15.70	(7.64, 32.27)	37%	(30%, 44%)

Analysis by Dose Level: Cinacalcet treatment was titrated based on an individual subject's iPTH response and tolerability. At the end of the study (Week 26), subjects were distributed across all dose levels of cinacalcet, with 45% of subjects receiving 180 mg (see table below). In the placebo group, 96% of subjects were at the 180-mg placebo dose level.

Study 20000172: Summary of Study Drug Dose Level

	Placebo (N=204)	Cinacalcet (N=200)
Daily dose (mg) at end of titration (week 14) - n(%)		
30	1/174 (1)	21/169 (12)
60	1/174 (1)	22/169 (13)
90	5/174 (3)	44/169 (26)
120	29/174 (17)	29/169 (17)
180	138/174 (79)	53/169 (31)
Daily dose (mg) at end of study (week 26) - n(%)		
30	0/160 (0)	19/146 (13)
60	0/160 (0)	19/146 (13)
90	2/160 (1)	21/146 (14)
120	5/160 (3)	22/146 (15)
180	153/160 (96)	65/146 (45)
Most frequent dose taken during the study - n(%)		
30	20 (10)	56 (28)
60	10 (5)	27 (14)
90	9 (4)	39 (20)
120	10 (5)	23 (12)
180	155 (76)	55 (28)

Secondary Efficacy Outcomes

Proportion of subjects with a reduction from baseline in mean iPTH of ≥ 30%: Statistical significance was achieved for the primary endpoint ($p < 0.001$), therefore the first secondary endpoint was tested. A significantly greater proportion of subjects in the cinacalcet group (61%) compared with the placebo group (11%) had a ≥ 30% decrease in mean iPTH concentration from baseline to the efficacy-assessment phase ($p < 0.001$).

The proportion of subjects in the cinacalcet group who achieved a ≥ 30% reduction in iPTH concentration was similar for all baseline iPTH strata: 58% in the ≥ 300 and ≤ 500 pg/mL stratum, 64% in the > 500 and ≤ 800 pg/mL stratum, and 65% in the > 800 pg/mL stratum. The proportion of cinacalcet-treated subjects who reached this endpoint was also similar for both baseline Ca x P strata. For subjects in the placebo group, the proportion of subjects within each iPTH and Ca x P stratum who reached this endpoint ranged from 0% to 22%.

Study 20000172: Proportion of Subjects a ≥ 30% Reduction From Baseline in Mean iPTH Concentration

iPTH Stratum [pg/mL]	Ca x P Stratum [mg/dL]^2	Placebo (N = 205) n/N1(%)	Cinacalcet (N = 205) n/N1(%)
≥ 300 and ≤ 500	≤ 70	7/70 (10)	42/70 (60)
	> 70	0/23 (0)	11/22 (50)
	All	7/93 (8)	53/92 (58)
> 500 and ≤ 800	≤ 70	11/51 (22)	31/52 (60)
	> 70	2/21 (10)	16/21 (76)
	All	13/72 (18)	47/73 (64)
> 800	≤ 70	2/26 (8)	16/26 (62)
	> 70	1/14 (7)	10/14 (71)
	All	3/40 (8)	26/40 (65)
All	≤ 70	20/147 (14)	89/148 (60)
All	> 70	3/58 (5)	37/57 (65)
Overall		23/205 (11)	126/205 (61)

Test Statistics:

CMH Statistic (χ^2)		Odds Ratio (Cinacal/Plac)		Difference (Cinacal-Plac)	
Value	P-value	Value	95% CI	Value	95% CI
111.1	< 0.001	11.61	(6.81, 19.79)	50%	(42%, 58%)

Percentage change from baseline in mean Ca x P: Mean (SE) baseline Ca x P values were similar between treatment groups: 62.1 (1.2) and 61.2 (1.1) $(mg/dL)^2$ for subjects who received cinacalcet and placebo, respectively. The mean Ca x P value during the efficacy-assessment phase was 52.3 (1.0) $(mg/dL)^2$ for the cinacalcet group and 59.8 (1.0) $(mg/dL)^2$ for the placebo group, representing a mean decrease from baseline of 13% in the cinacalcet group, compared with an increase of 1% in the placebo group ($p < 0.001$).

Within each treatment group, percentage changes in mean Ca x P were consistent across each baseline iPTH stratum. Differences were observed across the baseline Ca x P strata. In the ≤ 70 $(mg/dL)^2$ stratum, mean Ca x P was reduced by a mean of 9% for subjects in the cinacalcet

group, compared with an increase of 9% for subjects in the placebo group. In the > 70 $(mg/dL)^2$ stratum, the Ca x P value decreased by 24% for subjects in the cinacalcet group, compared with a 16% reduction for subjects in the placebo group.

Study 20000172: Percentage Change from Baseline in Mean Ca x P

		Placebo		Cinacalcet	
iPTH Stratum	**Ca x P Stratum**	**(N = 205)**		**(N = 205)**	
[pg/mL]	$[mg/dL]^2$	n	Mean (SE)	n	Mean (SE)
≥ 300 and ≤ 500	≤ 70	69	10.5 (3.3)	69	-7.0 (3.0)
	> 70	23	-19.8 (2.7)	22	-19.2 (3.9)
	All	92	2.9 (2.9)	91	-10.0 (2.5)
> 500 and ≤ 800	≤ 70	50	8.0 (3.8)	50	-11.6 (3.5)
	> 70	21	-12.0 (3.3)	21	-26.5 (4.5)
	All	71	2.1 (3.1)	71	-16.0 (2.9)
> 800	≤ 70	25	4.6 (4.2)	24	-7.3 (4.5)
	> 70	14	-17.0 (3.9)	14	-26.6 (4.0)
	All	39	-3.1 (3.4)	38	-14.4 (3.5)
All	≤ 70	144	8.6 (2.2)	143	-8.7 (2.0)
All	> 70	58	-16.3 (1.9)	57	-23.7 (2.4)
Overall		202	1.4 (1.8)	200	-13.0 (1.7)

Test Statistics:

	Value	P-value
CMH Statistic (χ^2)	37.55	< 0.001

Change from baseline in self-reported cognitive functioning scale score: Testing of this endpoint was conditional on achieving statistical significance for the key secondary endpoint. Statistical significance was achieved for the key secondary endpoint ($p < 0.001$), therefore this endpoint was tested. The mean (SD) baseline KDQOL Cognitive Functioning scale score for subjects in this study was 79.9 (17.9), which is similar to the baseline score of 82.4 for the Medical Outcomes Study population (n = 3,053) in which the scale was developed. During the efficacy-assessment phase, the mean (SE) change from baseline in the KDQOL Cognitive Functioning scale score was 0.5 (1.08) for the cinacalcet group and 1.2 (1.15) for the placebo group ($p = 0.663$). Sensitivity analyses assessing the effects of missing data provided similar results.

Tertiary Efficacy Outcomes

Percentage changes from baseline in mean iPTH, serum calcium, and serum phosphorus
iPTH: Mean (SE) baseline iPTH concentrations were similar between treatment groups: 636 (24) and 646 (28) pg/mL for subjects who received cinacalcet and placebo, respectively. The mean iPTH concentration during the efficacy-assessment phase was 384 (25) pg/mL for the cinacalcet group and 698 (33) pg/mL for the placebo group. Mean plasma iPTH concentrations were reduced by 38% in the cinacalcet group, compared with an increase of 10% in the placebo group ($p < 0.001$). For the cinacalcet group, the percentage change in iPTH was similar across all baseline strata. In contrast, for the placebo group, subjects in the ≤ 70 $(mg/dL)^2$ strata had a 5% increase from baseline in iPTH, compared with a 21% increase in the > 70 $(mg/dL)^2$ strata.

Study 20000172: Percentage Change from Baseline in Mean iPTH					
		Placebo		Cinacalcet	
iPTH Stratum	**Ca x P Stratum**	**(N = 205)**		**(N = 205)**	
[pg/mL]	[mg/dL]^2	n	Mean (SE)	n	Mean (SE)
≥ 300 and ≤ 500	≤ 70	70	6.7 (3.9)	69	-35.5 (4.6)
	> 70	23	41.0 (12.6)	22	-29.1 (10.4)
	All	93	15.2 (4.5)	91	-34.0 (4.3)
> 500 and ≤ 800	≤ 70	50	1.48 (5.3)	50	-43.3 (5.7)
	> 70	21	12.4 (9.8)	21	-50.1 (7.9)
	All	71	4.71 (4.7)	71	-45.3 (4.6)
> 800	≤ 70	25	7.3 (5.9)	24	-31.7 (9.3)
	> 70	14	0.1 (7.8)	14	-43.8 (9.5)
	All	39	4.7 (4.7)	38	-36.2 (6.8)
All	≤ 70	145	5.0 (2.8)	143	-37.6 (3.4)
All	> 70	58	20.8 (6.7)	57	-40.4 (5.5)
Overall		203	9.5 (2.8)	200	-38.4 (2.9)
Test Statistics:					
		Value		P-value	
CMH Statistic (χ^2)		99.81		< 0.001	

Calcium: Mean (SE) baseline serum calcium concentrations were similar between treatment groups: 9.8 (0.1) and 9.9 (0.1) mg/dL for subjects who received cinacalcet and placebo, respectively. The mean serum calcium concentration during the efficacy-assessment phase was 9.2 (0.1) mg/dL for the cinacalcet group and 9.9 (0.1) mg/dL for the placebo group. As outlined in the table below, the mean serum calcium concentration decreased by 6% in the cinacalcet group, compared with an increase of 1% in the placebo group (nominal $p < 0.001$). For each treatment group, changes in serum calcium were similar across all strata.

Study 20000172: Percentage Change from Baseline in Mean Calcium					
		Placebo		Cinacalcet	
iPTH Stratum	**Ca x P Stratum**	**(N = 205)**		**(N = 205)**	
[pg/mL]	[mg/dL]^2	n	Mean (SE)	n	Mean (SE)
≥ 300 and ≤ 500	≤ 70	69	0.6 (0.6)	69	-5.6 (1.0)
	> 70	23	-2.6 (1.2)	22	-5.9 (2.2)
	All	92	-0.2 (0.5)	91	-5.7 (0.9)
> 500 and ≤ 800	≤ 70	50	0.9 (0.7)	50	-6.5 (1.2)
	> 70	21	1.2 (1.0)	21	-7.2 (1.9)
	All	71	1.0 (0.6)	71	-6.7 (1.0)
> 800	≤ 70	25	1.0 (1.1)	24	-6.5 (1.6)
	> 70	14	2.0 (1.1)	14	-7.3 (2.6)
	All	39	1.4 (0.8)	38	-6.8 (1.4)
All	≤ 70	144	0.8 (0.4)	143	-6.1 (0.7)
All	> 70	58	-0.1 (0.7)	57	-6.7 (1.3)
Overall		202	0.5 (0.4)	200	-6.2 (0.6)
Test Statistics:					
		Value		P-value	
CMH Statistic (χ^2)		68.13		< 0.001	

Phosphorus: Mean (SE) baseline serum phosphorus concentrations were similar between treatment groups: 6.3 (0.1) and 6.2 (0.1) mg/dL for subjects who received cinacalcet and placebo, respectively. The mean serum phosphorus concentration during the efficacy-assessment

phase was 5.7 (0.1) mg/dL for the cinacalcet group and 6.0 (0.1) mg/dL for the placebo group. As outlined in the table below, the mean serum phosphorus concentration in the cinacalcet group decreased by 7% in the cinacalcet group, compared with a 1% increase in the placebo group (nominal $p < 0.001$). Within each treatment group, percentage changes from baseline in phosphorus were generally similar between baseline iPTH strata. Between the baseline Ca x P strata however, differences were observed. In the ≤ 70 $[mg/dL]^2$ strata, mean phosphorus decreased by 3% for subjects in the cinacalcet group, compared with an 8% increase in the placebo group. In the > 70 $[mg/dL]^2$ strata, the mean phosphorus decreased by 18% and 16% for subjects in the cinacalcet and placebo groups, respectively.

Study 20000172: Percentage Change from Baseline in Mean Phosphorus

		Placebo		Cinacalcet	
iPTH Stratum	**Ca x P Stratum**	**(N = 205)**		**(N = 205)**	
[pg/mL]	$[mg/dL]^2$	n	Mean (SE)	n	Mean (SE)
≥ 300 and ≤ 500	≤ 70	69	10.1 (3.2)	69	-1.5 (2.9)
	> 70	23	-17.4 (3.1)	22	-13.4 (4.2)
	All	92	3.2 (2.8)	91	-4.4 (2.5)
> 500 and ≤ 800	≤ 70	50	7.2 (3.9)	50	-5.4 (3.6)
	> 70	21	-12.9 (3.3)	21	-20.7 (4.5)
	All	71	1.2 (3.1)	71	-9.9 (3.0)
> 800	≤ 70	25	3.8 (4.1)	24	-1.1 (4.2)
	> 70	14	-18.7 (3.8)	14	-21.0 (3.5)
	All	39	-4.3 (3.4)	38	-8.5 (3.3)
All	≤ 70	144	8.0 (2.2)	143	-2.8 (2.0)
All	> 70	58	-16.1 (1.9)	57	-18.0 (2.5)
Overall		202	1.0 (1.8)	200	-7.1 (1.7)

Test Statistics:

	Value	P-value
CMH Statistic (χ^2)	15.28	< 0.001

Proportion of subjects with both a mean iPTH $\leq$ 250 pg/mL and a reduction from baseline in mean Ca x P: Thirty-six percent of subjects in the cinacalcet group had both a mean iPTH $\leq$ 250 pg/mL and a reduction from baseline in mean Ca x P, compared with 1% of subjects in the placebo group ($p < 0.001$). Since 41% of cinacalcet-treated subjects had a mean iPTH $\leq$ 250 pg/mL, approximately 90% of subjects who achieved an iPTH 250 pg/mL also had reductions in Ca x P. Forty-five percent of cinacalcet-treated subjects in the ≥ 300 and ≤ 500 pg/mL stratum achieved endpoint compared with 37% in the > 500 and ≤ 800 pg/mL stratum, and 15% in the > 800 pg/mL stratum. Similar proportions of cinacalcet-treated subjects in each baseline Ca x P stratum achieved this endpoint (35% in the ≤ 70 $[mg/dL]^2$ strata and 39% in the > 70 $[mg/dL]^2$ strata). For subjects who received placebo, the proportions who achieved the endpoint in each baseline stratum ranged from 0% to 5%.

In recognition of the proposed NKF-K/DOQI targets for iPTH and Ca x P, an additional post-hoc analysis was performed to analyze the proportion of subjects achieving both a mean iPTH concentration ≤ 300 pg/mL and a mean Ca x P value 55 $(mg/dL)^2$ during the efficacy-assessment phase. Using LVCF, 40% of cinacalcet subjects and 4% of placebo subjects achieved these target levels, demonstrating the effectiveness of cinacalcet in facilitating the achievement of NKF-K/DOQI targets.

Exploratory Bio-intact PTH Analyses: To enable correlation of the results of the new biPTH assay with the existing gold standard iPTH assay, duplicate plasma samples were collected for measurement of PTH concentrations using both assays. At baseline and during the efficacy-assessment phase, iPTH and biPTH values were highly correlated, with biPTH values comprising approximately 55% of iPTH values ($r = 0.89$ for cinacalcet and $r = 0.95$ for placebo at baseline, and $r = 0.96$ for cinacalcet and $r = 0.95$ for placebo during the efficacy-assessment phase). Treatment with cinacalcet did not change the relationship between iPTH and biPTH, as evidenced by similar regression equations for both treatment groups at baseline and during the efficacy-assessment phase. Reductions in mean PTH concentrations in the cinacalcet group compared with the placebo group were demonstrated using both the iPTH and biPTH assay.

Study 20000172: Comparison of biPTH and iPTH Assay Results

	Placebo (N=205)		Cinacalcet (N=205)	
	iPTH	**biPTH**	**iPTH**	**biPTH**
Mean (SE) baseline PTH (pg/mL)	651 (28)	337 (16)	636 (24)	326 (14)
Mean (SE) % change in PTH[a]	10% (2.8%)	23% (3.6%)	-38% (2.9%)	-38% (3.1%)
Subjects achieving target PTH[a,b] (n%)	4%	8%	41%	45%
> 30% reduction in mean PTH[a] (n%)	11%	10%	61%	56%

[a] During the efficacy-assessment phase, LVCF

[b] The target biPTH and iPTH concentrations were <=138 pg/ml and <=250 pg/ml, respectively

Efficacy Conclusions: The proportion of subjects who achieved a target iPTH ≤ 250 pg/mL (primary endpoint) was significantly greater in the cinacalcet group than in the placebo group (41% versus 4%; $p < 0.001$). In addition, a significantly greater proportion of subjects in the cinacalcet group (61%) compared with the placebo group (11%) had a $\geq$ 30% reduction in iPTH (nominal $p < 0.001$). Mean iPTH concentrations were decreased by 38% in the cinacalcet group, compared with a 10% increase in the placebo group ($p < 0.001$). Consistent reductions in iPTH concentrations occurred in all strata of baseline iPTH and Ca x P levels.

In the cinacalcet group, reductions in iPTH concentrations were accompanied by significant reductions in Ca x P, serum calcium, and phosphorus. Mean Ca x P levels in the cinacalcet group were reduced by 13% during the efficacy-assessment phase compared with a 1% increase in the placebo group (nominal $p < 0.001$). Reductions in Ca x P in the cinacalcet group resulted from reductions in both serum calcium (6% decrease) and phosphorus (7% decrease) (nominal $p < 0.001$). In the placebo group, mean serum calcium, phosphorus, and Ca x P remained at baseline levels throughout the study.

No difference between treatment groups was observed for the change from baseline to the efficacy-assessment phase in the KDQOL™ Cognitive Functioning scale.

Safety

Disposition: As shown in the table below, 95% of placebo-treated subjects and 90% of cinacalcet-treated subjects experienced adverse events during the study. Serious adverse events were equally distributed between the two groups.

Study 20000172 Disposition:	Placebo n (%)	Cinacalcet n (%)
Subjects evaluable for safety	204	200
Deaths on study [a]	6 (3)	6[a] (3)
Serious adverse events	71 (35)	61 (31)
Withdrawal due to adverse events	19 (10)	19 (10)
All adverse events	193 (95)	180 (90)

[a] includes one subject who died on Day 24 of the extension study, 20010240

Exposure: A total of 404 (200 cinacalcet, 204 placebo) received study medication (see table below). The mean (range) number of days of exposure to study drug was 154 (1 to 197) days for the cinacalcet group and 158 (3, 202) days for the placebo group. The mean (range) cumulative dose of cinacalcet was 12,610 (mg.

Study 20000172: Summary of Exposure to Study Drug	Placebo (N=101)	Cinacalcet (N=291)
Number of days of exposure		
Mean	158.2	153.8
SD	51.3	55.9
Min, Max	3, 202	1, 197
Cumulative dose of cinacalcet (mg)		
Mean	0.0	12610.4
SD	0.0	7318.2
Min, Max		
Dose compliance (%)		
Mean	92.8	90.3
SD	9.6	13.6
Min, Max		

Dosing Compliance (%) = 100 x (number of days dose taken / number of days prescribed).

Deaths: Among the 12 deaths that occurred in the study population, eleven occurred during the study and one was reported after the subject entered the extension study, 20010240. Of the deaths occurring during the study, 4 were due to sepsis (2 events each in the cinacalcet and placebo groups), 3 were due to cardiac arrest (2 in the cinacalcet group and 1 in the placebo group), 1 each were due to arrhythmia, pneumonia and pulmonary infarction in the cinacalcet group, and 1 each were due to aortic stenosis, coronary artery disorder and hypovolemic shock in the placebo group. One death was due to unknown causes (in the placebo group). Causes of death were consistent with this population's baseline comorbid conditions and similar to causes of death in the general population of patients with ESRD.

Serious Adverse Events: Serious adverse events were reported by 71 (35%) placebo-treated subjects and 61 (31%) cinacalcet-treated subjects (see Table below). The most common serious adverse events were pneumonia (1 % of the placebo treated group and 5% of the cinacalcet treated group), non-cardiac chest pain (1 % of the placebo treated group and 3% of the cinacalcet treated group), sepsis (0 % of the placebo treated group and 3% of the cinacalcet treated group) and cardiac failure (1 % of the placebo treated group and 3% of the cinacalcet treated group).

20000172: Serious Adverse Events, by Body System		
	Placebo	Cinacalcet
Subjects Receiving Dose	204	200
Subjects Reporting SAEs	71 (35)	61 (31)
Events:		
Gastrointestinal	7 (3)	15 (8)
Liver / Biliary	0 (0)	3 (2)
Nervous	3 (1)	7 (4)
Cardiovascular	7 (3)	6 (3)
Heart Rate / Rhythm	6 (3)	7 (4)
Myo/Endo/Pericardial	13 (6)	8 (4)
Respiratory	11 (5)	18 (9)
Body as a whole	24 (12)	17 (9)
Endocrine/Metabolic	12 (6)	7 (4)
Musculoskeletal	5 (2)	4 (2)
Infectious	10 (5)	8 (4)
Blood and Lymphatic	6 (3)	0 (0)
Skin and Appendages	5 (2)	2 (1)
Urinary Disorders	4 (2)	0 (0)
Vascular Disorders	14 (7)	6 (3)
Vision Disorders	0 (0)	1 (0)
Psychiatric	0 (0)	0 (0)

Adverse Events Leading to Withdrawal: Nineteen subjects (10%) in each treatment groups withdrew from the study due to adverse events. Adverse events that most commonly resulted in withdrawal involved the gastrointestinal system (cinacalcet, placebo) (7%, 2%), most predominantly vomiting (4%, 1%), abdominal pain (3%, 0%), and nausea (2%, 1%). Two subjects withdrew from the study because of low serum calcium values. One subject from the placebo group who had a calcium level of 8.7 mg/dL at baseline, 7.6 mg/dL at week one and an asymptomatic calcium of 5.6 mg/dL at week 2. One subject from the cinacalcet group had a baseline serum calcium of 9.2 mg/dL At week 16, while at the 180-mg dose level, the subject complained of perioral numbness and had a serum calcium concentration of 6.8 mg/dL. During week 18 (at the same dose level), the subject complained of perioral numbness, chest tightness, and dyspnea after playing basketball (local laboratory serum calcium = 6.2 mg/dL

Adverse Events Leading to Dose Alteration: A total of 84 subjects had adverse events leading to dose alteration [51 (26%) from the cinacalcet group and 33 (16%) from the placebo group]. The most common adverse events were gastrointestinal [30 (15%) from the cinacalcet group and 12 (6%) from the placebo group], predominantly nausea and vomiting. Six (3%) subjects in the cinacalcet group and one (< 1%) subject in the placebo group required dose alteration because of hypocalcemia

Adverse Events: Ninety percent of subjects in the cinacalcet group and 95% of subjects in the placebo group reported at least 1 adverse event during the study (see table below). The most common adverse events were (cinacalcet, placebo) nausea (33%, 19%), vomiting (24%, 17%), diarrhea (21%, 23%), and headache (16%, 17%). In addition to nausea and vomiting, adverse events with a $\geq$ 5% difference between treatment groups included (cinacalcet, placebo) dizziness (14%, 8%), hypocalcemia (8%, 1%), fever (7%, 12%), hypotension (5%, 11%), and back pain (1%, 9%).

20000172: Adverse Events, by Body System		
	Placebo	Cinacalcet
Subjects Receiving Dose	204	200
Subjects Reporting AEs	193 (95)	180 (90)
Events:		
Body as a whole	116 (57)	99 (50)
Gastrointestinal	110 (54)	118 (59)
Liver / Biliary	3 (1)	3 (2)
Nervous	71 (35)	72 (36)
Cardiovascular	39 (19)	24 (12)
Heart Rate / Rhythm	19 (9)	20 (10)
Myo/Endo/Pericardial	25 (12)	20 (10)
Respiratory	84 (41)	89 (45)
Endocrine/Metabolic	31 (15)	38 (19)
Musculoskeletal	77 (38)	62 (31)
Infectious	20 (10)	27 (14)
Blood and Lymphatic	19 (9)	8 (4)
Skin and Appendages	51 (25)	47 (24)
Urinary Disorders	15 (7)	15 (8)
Reproductive	5 (2)	6 (3)
Vascular Disorders	33 (16)	22 (11)
Vision Disorders	15 (7)	13 (7)
Hearing / Vestibular	7 (3)	5 (3)
Psychiatric	13 (6)	8 (4)

Adverse Events of Special Interest:

Convulsions: Two (1%) subjects in the cinacalcet group and 2 (1%) subjects in the placebo group suffered from an event of seizure activity during the study.

GI Adverse Events: Gastrointestinal adverse events are common with cinacalcet treatment. Nausea was reported in 33% of cinacalcet-treated patients and 19% of placebo treated patients. Vomiting was reported in 24% of cinacalcet-treated patients and 17% of placebo treated patients. Diarrhea was reported in 21% of cinacalcet-treated patients and 23% of placebo treated patients. Nausea was considered severe in 4% of subjects in the cinacalcet group and 0% of subjects in the placebo group. Vomiting was considered severe in 1% of subjects in the cinacalcet group and 0% of subjects in the placebo group. One episode of hepatic necrosis was reported in a cinacalcet-treated subject. GI hemorrhage was reported in 3 (4%) cinacalcet-treated patients and 5 (% placebo-treated patients. Dyspepsia was reported in 13 (7%) of cinacalcet-treated subjects and 17 (8%) of placebo-treated subjects. There were two reports of esophagitis in the cinacalcet-treated group and no reports in the placebo-treated group. Similarly, there were 3 reports of gastritis in the cinacalcet group and no reports in the placebo group.

Cataracts: Cataract formation associated with cinacalcet use was reported in animal studies. There were one report of cataract in a subject treated with cinacalcet in this trial.

COMMENT: Cinacalcet is a calcimimetic agent that acts as a modulator of the calcium-sensing receptor (CaR). Calcium-sensing receptor activity has been shown to exist on antral cells in the stomach, which secrete gastrin, which stimulates the production of

gastric acid[5]. The increases in esophagitis and gastritis noted in the cinacalcet-treated group compared to placebo in this study raise concern that cinacalcet may have the unintended side effect of increased gastric acid secretion.

Laboratory: Safety laboratory assessments were performed at screening and follow-up. Hypocalcemia was reported as an adverse event in 3% of subjects in each treatment group. A confirmed serum calcium < 7.5 mg/dL (2 consecutive measurements) during the study occurred in 5% and 2% of subjects in the cinacalcet and placebo groups, respectively. No trends indicative of other treatment-related effects in clinical chemistry, hematology, 1,25(OH)2D3, or Hb A1c were noted. Shift tables also demonstrated no evidence of a treatment.

Other Safety Tests:

Vital Signs: Mean blood pressure measurements were stable throughout the study and did not differ between treatment groups.

ECGs: ECGs were collected predialysis, at approximately nadir drug concentrations. Investigator interpretation of ECGs was categorized on the case report form as normal; abnormal, but not clinically significant; or abnormal, clinically significant. Most subjects (79% cinacalcet, 71% placebo) had an abnormal ECG at baseline. Of those subjects without clinically significant ECG abnormalities at baseline, 5 subjects (3%) in the cinacalcet group and 7 subjects (3%) in the placebo group had ECG abnormalities that were considered clinically significant at the end of the study. In the cinacalcet-treated group, one subject had left ventricular hypertrophy and one subject had a complete right bundle branch block reported. In the placebo-treated group, 2 subjects had first degree atrioventricular block, and 1 subject each had atrial fibrillation, flattened T waves, poor R-wave progression, and premature ventricular contractions with bigeminy.

QT intervals corrected for heart rate using Bazett's and Fridericia's correction formulae were measured at baseline and weeks 14, 26, and end of study. No notable differences were observed between treatment groups in the change in QTc interval from baseline to any time point, regardless of the correction formula used. When subjects were categorized with regard to change in QTc from baseline (<30, 30 to 60, > 60 msec), the proportion of subjects with an increase of > 60 msec during the study ranged from 2% to 9% and was similar between treatment groups at each time point using either correction formula. More subjects in the cinacalcet group compared with the placebo group had increases in QTc of 30 to 60 msec at week 14 (QTcB: 16% versus 8%, respectively; QTcF: 17% versus 9%, respectively). At week 26, the proportion of subjects with increases in QTc of 30 to 60 msec was similar between treatment groups (QTcB: 14% cinacalcet, 15% placebo; QTcF: 13% cinacalcet, 11% placebo). No notable differences between treatment groups were observed in the occurrence of an absolute QTcB or QTcF > 500 msec at any time point during the study.

[5] Buchan AM, Squires PE, Ring M, Meloche RM. Mechanism of action of the calcium-sensing receptor in human antral gastrin cells. Gastroenterology. 2001 Apr;120(5):1128-39.

The proportion of subjects who had a normal QTcB at baseline but subsequently had at least 1 absolute increase in QTcB beyond the upper limit of normal (450 msec [men] and 470 msec [women]) was slightly higher in the cinacalcet group (24% at week 14, 20% at week 26) compared with the placebo group (12% at week 14, 14% at week 26). For the subjects with an increase beyond the upper limit of normal, the mean increase in QTcB was 44 msec for the cinacalcet group and 38 msec for the placebo group at week 14, and 35 msec and 47 msec, respectively, at week 26. Similar results were obtained using Fridericia's correction formula.

COMMENT: It is well known that there is QT interval prolongation associated with decreases in serum calcium levels which may be the etiology of the increased QT intervals seen in this study. It is not clear if there is an additional direct effect from the drug itself.

Safety Conclusions: In this 6-month study, 404 (200 cinacalcet, 204 placebo) received study drug and were evaluable for safety. The incidence of serious adverse events, deaths, and withdrawals due to adverse events was similar across treatment groups. Nausea and vomiting occurred more often in cinacalcet-treated subjects. Esophagitis and gastritis occurred more frequently in the cinacalcet-treated subjects, possibly signaling a cinacalcet effect on gastric acid secretion. No trends indicative of a treatment effect were noted in clinical laboratory measurements, other than expected differences in plasma iPTH, serum calcium, and phosphorus concentrations. Evaluation of ECGs, including the QTc interval, indicated no notable changes in cinacalcet-treated subjects compared with placebo.

Discussion and Conclusions: Secondary HPT develops early in chronic kidney disease before the initiation of dialysis and progresses after patients reach ESRD. In recognition of the need for improved disease management, the NKF-K/DOQI has recommended target ranges for iPTH and Ca x P (see table below). Achieving these stringent targets will be challenging with currently available therapy, which have a propensity to increase serum calcium, phosphorus, and Ca x P. Awareness that derangements in bone mineral metabolism are associated with increased morbidity and mortality further emphasizes the need for new therapies to address elevated PTH without adversely affecting Ca x P.

Target Range of Intact PTH by Stage of CKD

CKD Stage	GFR Range ($mL/min/1.73m^2$)	Target iPTH (pg/mL)	Target Ca x P
3	30 – 59	35 - 70	< 55
4	15 – 29	70 - 110	< 55
5	< 15 or dialysis	150 - 300	< 55

In this study, the severity of secondary HPT in enrolled subjects ranged from mild to severe, with mean baseline iPTH concentrations of 636 and 651 pg/mL for the cinacalcet and placebo groups, respectively, and 20% of subjects had a baseline iPTH concentration > 800 pg/mL. Twenty-eight percent of subjects had Ca x P levels > 70 (mg/dL)2, a level above which vitamin D therapy is generally contraindicated. The proportion of subjects with a mean iPTH concentration ≤ 250 pg/mL during the efficacy-assessment phase (primary endpoint) was 41% in the cinacalcet group and 4% in the placebo group (p < 0.001). A significantly greater proportion of subjects in the cinacalcet group (61%)

compared with the placebo group (11%) had a 30% reduction in mean iPTH during the efficacy-assessment phase ($p < 0.001$). Reductions in iPTH were observed across all baseline iPTH and Ca x P strata, indicating the effectiveness of cinacalcet regardless of disease severity. Exploratory analyses comparing the iPTH (gold standard) and biPTH results demonstrated the efficacy of cinacalcet using either assay. Reductions in iPTH in subjects treated with cinacalcet were accompanied by significant reductions in Ca x P, serum calcium, and phosphorus compared with the placebo group. Ca x P decreased by 13% in the cinacalcet group, compared with a 1% increase in the placebo group (nominal $p < 0.001$).

The occurrence of deaths, serious adverse events, and withdrawals due to adverse events was similar between treatment groups. Although nausea and vomiting occurred more frequently in subjects who received cinacalcet. Esophagitis and gastritis occurred more frequently in the cinacalcet-treated subjects, possibly signaling a cinacalcet effect on gastric acid secretion. Evaluation of the QTc interval indicated no notable changes in subjects in the cinacalcet group compared with the placebo group.

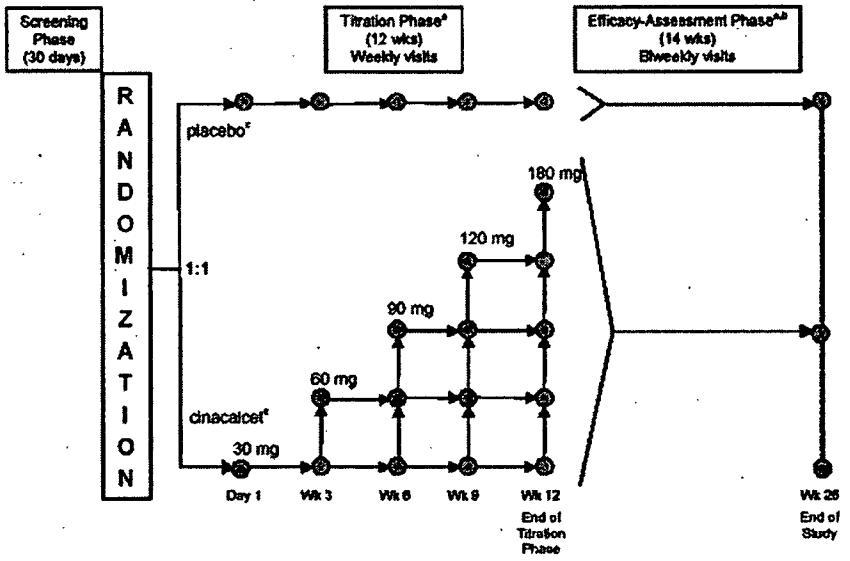
Study 20000183: A Phase 3 Study to Assess the Efficacy and Safety of an Oral Calcimimetic Agent (AMG 073) in Secondary Hyperparathyroidism of End Stage Renal Disease Treated with Haemodialysis

This was a randomized, double-blind, placebo-controlled, multicenter study of the efficacy and safety of cinacalcet in patients with secondary hyperparathyroidism of end stage renal disease treated with hemodialysis.

Objectives: The primary objective of this study was to investigate the efficacy of cinacalcet compared with placebo by determining the proportion of subjects with a mean plasma intact parathyroid hormone (iPTH) value ≤ 250 pg/mL (26.5 pmol/L) during the efficacy - assessment phase.

Study Design: This was a randomized, double-blind, placebo-controlled, parallel-group, 26-week study. Sixty two centers in Europe and Australia participated in the study. After a 30-day screening period, subjects who qualified for the study were randomized in a 1:1 ratio to cinacalcet or placebo within 1 of 6 strata defined by baseline mean iPTH and Ca x P concentrations. Throughout the study, investigators could prescribe concomitant therapy considered necessary

The study consisted of 2 phases: a 12-week dose-titration phase followed by a 14-week efficacy-assessment phase. Possible sequential daily doses during the treatment period were 30, 60, 90, 120, and 180 mg cinacalcet or placebo. Visits occurred weekly during the titration phase and biweekly during the efficacy-assessment phase. At the week 3, 6, 9, 12, 16, 20, and 24 study visits, subjects could be titrated up to the next sequential dose level of cinacalcet/placebo based on iPTH response and safety monitoring (see figure below)



Population: The study population consisted of subjects with end stage renal disease who were maintained on hemodialysis. Subjects were stratified as follows:

- iPTH ≥ 300 pg/mL (31.8 pmol/L) to ≤ 500 pg/mL (53 pmol/L) and Ca x P ≤ 70 $(mg/dL)^2$ $(5.65\ [mmol/L]^2)$
- iPTH ≥ 300 to ≤ 500 pg/mL and Ca x P > 70 $(mg/dL)^2$
- iPTH > 500 to ≤ 800 pg/mL (84.8 pmol/L) and Ca x P ≤ 70 $(mg/dL)^2$
- iPTH > 500 to ≤800 pg/mL and Ca x P > 70 $(mg/dL)^2$
- iPTH > 800 pg/mL and Ca x P ≤ 70 $(mg/dL)^2$
- iPTH > 800 pg/mL and Ca x P > 70 $(mg/dL)^2$

A maximum of 20% of subjects with baseline iPTH > 800 pg/mL were allowed in the study.

Inclusion Criteria

- ≥ 18 years of age at the start of screening
- Agreed to use, in the opinion of the principal investigator, highly effective contraceptive measures throughout the study
- Mean of 3 central laboratory iPTH values ≥ 300 pg/mL obtained within 30 days before Day 1
- Mean of 3 central laboratory serum calcium values ≥ 8.4 mg/dL (2.1 mmol/L) obtained within 30 days before Day 1
- Prescribed hemodialysis 3 times weekly for ≥ 3 months before Day 1
- Signed the IEC-approved informed consent document before any study-specific procedures were initiated

Exclusion Criteria

- Had an unstable medical condition, defined as having been hospitalized, other than for dialysis vascular access revision, within 30 days before day 1, or were otherwise unstable in the judgment of the investigator
- Pregnant or nursing
- Parathyroidectomy in the 3 months before day 1
- Received vitamin D sterol therapy for < 30 days before day 1 or required a change in vitamin D sterol brand or dose within 30 days before day 1 (for subjects prescribed vitamin D)
- Changed the brand or dose of phosphate binder or oral calcium supplement in the 30 days before Day 1
- Changed dialysate calcium concentration in the 30 days before day 1
- Received, within 21 days before day 1, therapy with flecainide, lithium, thioridazine, haloperidol, or tricyclic antidepressants (e.g., imipramine or desipramine) (except the tricyclic antidepressant amitriptyline was permitted)
- Experienced a myocardial infarction within 3 months before day 1
- Enrolled in, or not yet completed < 30 days before day 1, other invasive investigational device or drug trials, or were receiving other investigational agents (experimental dialysis machines were acceptable)
- GI disorder that may have been associated with impaired absorption of orally administered drugs or an inability to swallow tablets
- Disorder that would have interfered with understanding and giving informed consent or compliance with protocol requirements
- Participated in other studies with cinacalcet

Applicable to subjects enrolled in Denmark:

- Known hypersensitivity to any of the cinacalcet excipients
- Severe hepatic impairment (class C liver disease as defined by Pugh's modification of Child's Classification of Severity of Liver Disease).

COMMENT: The inclusion and exclusion criteria appear appropriate.

Study Medication: All medications were administered orally with a starting dose of 30mg cinacalcet or placebo. Tablets were taken with food or shortly after a meal if feasible and were swallowed whole without biting or chewing. The study drug was provided as light green film-coated tablets of 30-, 60-, and 90-mg free-base equivalents or placebo, which were graduated in size, smallest to largest. Possible sequential doses during the study were 30, 60, 90, 120, and 180 mg cinacalcet or placebo. Combinations of the tablets were used for the 120- and 180-mg doses (two 60-mg and two 90-mg tablets, respectively). Except during the screening phase, changes in phosphate binders/oral calcium supplements were permitted throughout the study. The prescribed dialysate calcium concentration was not to change in the 30 days before day 1 or during the study. Changes in vitamin D therapy were only permitted based on protocol-specified guidelines.

COMMENT: Dosing instructions appear appropriate, as drug absorption is improved with food.

Efficacy Measures A reduction in iPTH to ≤ 250 pg/mL was chosen as the primary endpoint for the phase 3 program. In patients with ESRD, relatively normal bone histology has been observed with PTH concentrations of approximately 2 to 4 times the upper limit of normal, corresponding to approximately 100 to 250 pg/mL. A reduction in iPTH ≥ 30% is also considered clinically meaningful by many nephrologists and has been used as the primary endpoint in trials for vitamin D sterols in treatment of secondary HPT.

The Nichols iPTH IRMA assay was used to measure all iPTH levels in this study.

Primary Efficacy Endpoint

- Proportion of subjects with a mean iPTH value ≤ 250 pg/mL during the efficacy-assessment phase.

Secondary Efficacy Endpoints

- Proportion of subjects with a reduction from baseline in mean iPTH of ≥ 30%
- Percentage change from baseline in mean Ca x P
- Change from baseline in self-reported cognitive functioning scale score

Tertiary Efficacy Endpoints

- Percentage changes from baseline in mean iPTH, serum calcium, and serum phosphorus
- Proportion of subjects with both a mean iPTH ≤ 250 pg/mL and a reduction from baseline in mean Ca x P

COMMENT: The primary endpoint target range of iPTH is appropriate. K/DOQI guidelines[6] list the target range of iPTH in dialysis patients as 150 – 300 pg/mL.

Safety Measures: Safety was assessed by adverse events, laboratory measurements, electrocardiograms (ECGs), vital signs, and physical exams.

Study Methods: [redacted] was used to analyze the samples for the primary, secondary and safety endpoints. All iPTH levels were obtained utilizing the manual IRMA methodology.

Dose Titration: Subjects could be titrated up to the next sequential dose level of study drug at the Week 3, 6, 9, 12, 16, 20, and 24 study visits. For each of these visits, a site representative called the IVRS within 5 days before and 3 days after the scheduled visit in order for a subject to

[6] K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003, Oct. 42 (4) Supplement 3.