CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-688

MEDICAL REVIEW

CLINICAL REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #:	21-688	**Application Type:**	NDA
Sponsor:	Amgen	**Proprietary Name:**	Sensipar
Pharmaceutical Category:	Calcimimetic	**Route of Administration:**	Oral
Indications:	Treatment of Secondary Hyperparathyroidism and Parathyroid Carcinoma	**Dosage:**	30 – 180 mg
Reviewers:	Theresa Kehoe, MD Patricia Beaston, MD, PhD Eric Colman, MD	**Date Review Completed:**	2/20/04

Chemistry Reviewer: Sheldon Markofsky, Ph.D.
Pharmacology Reviewer: Gemma Kuijpers, Ph.D.
Biopharmaceutics Reviewer: Johnny Lau, Ph.D.
Statistical Reviewer: Joy Mele, M.S.

REVIEW SUMMARY: See Executive Summary

OUTSTANDING ISSUE: See Executive Summary

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies	_____ **Clinical Hold**	_____ **Study May Proceed**
NDA, Efficacy/Label supplement:	_____ **Approvable**	_____ **Not Approvable**
	_____ **Approve**	

SIGNATURES:

Medical Reviewers: Theresa Kehoe, M.D. **Date:** _____
Patricia Beaston, M.D. Ph.D.

Medical Team Leader: Eric Colman **Date:** _____

Table of Contents

Clinical Review for NDA 21-688

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Approve for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease receiving.

Approve for the treatment of hypercalcemia associated with parathyroid carcinoma.

Approvable for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease not receiving dialysis

Approvable for the treatment of primary hyperparathyroidism when parathyroidectomy is not a treatment option.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Seizure: (1) Product labeling should clearly state that a small percentage of patients treated with cinacalcet suffered seizures during participation in pre-approval trials. The mechanism responsible for this finding, if not a chance occurrence, is probably inappropriately low serum calcium levels. (2) *In vitro* enzyme induction studies should be done to examine the potential for cinacalcet to increase the activity of enzymes known to metabolize common anti-seizure medications. (3) Amgen should provide the Division with biannual reports summarizing seizure data from ongoing trials and spontaneously-submitted MedWatch reports.

Cardiac Repolarization: Although the phase-3 data provide only a weak signal that cinacalcet may prolong the QT interval, a thorough QT study would provide a precise estimate of the drug's overall affect on cardiac repolarization, and if properly designed, would clarify whether cinacalcet's affect on the QT interval is due solely to its action to lower serum calcium levels.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Cinacalcet is the first oral calcimimetic drug submitted for market approval for the [redacted] treatment of secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD).

Amgen is requesting approval of cinacalcet for (1) the [redacted] treatment of secondary HPT in patients with CKD, receiving and not receiving dialysis; (2) the treatment of primary HPT when parathyroidectomy is not a treatment option; (3) the treatment of hypercalcemia in patients with parathyroid carcinoma.

The principal components of the cinacalcet clinical development program included three, 6-month, randomized, double-blind, placebo-controlled phase-3 studies of patients with CKD and secondary HPT receiving dialysis; a double-blind, placebo-controlled 6-month extension study of patients who completed two of the three CKD dialysis studies; two randomized, double-blind, placebo-controlled studies of patients with pre-dialysis CKD and secondary HPT; and an ongoing 3-year, open-label, single-arm study that enrolled 3 separate groups of patients: 2 with primary HPT who "failed" parathyroidectomy, 3 with primary HPT in whom parathyroidectomy was not an option, and 10 patients with parathyroid carcinoma.

B. Efficacy

Secondary Hyperparathyroidism in Patients with CKD Receiving Dialysis: Studies 20000172, 20000183, and 20000188

To be eligible for these studies, patients had to be at least 18 years of age, have a serum iPTH > 300 pg/ml, and a serum calcium $\geq$ 8.4 mg/dL. The studies consisted of a 12-week, dose-titration phase and a 14-week efficacy-assessment phase. Patient were started on 30 mg once daily cinacalcet of placebo. The dose could be titrated up to 60 mg, 90 mg, 120 mg, and 180 mg at 4-week intervals. The dose was increased unless one of the following applied: iPTH $\leq$ 200 pg/ml, serum calcium < 7.8 mg/dL, or the subject was experiencing an adverse event that precluded a dose increase. If a patients experienced symptoms of hypocalcemia and/or a serum calcium < 8.4 mg/dL, calcium supplements and/or phosphate binders could be increased. If these measures were insufficient, the vitamin D dose could be increased.

All serum iPTH levels were measured using the Nichols IRMA assay. A total of 471 patients were randomized to placebo and 665 patients to cinacalcet. The mean age of the participants was 54 years, 62% were male, and 52% were Caucasian. The average duration of dialysis prior to study enrollment was 67 months and 96% of the patients were receiving hemodialysis; 4% were on peritoneal dialysis. The baseline iPTH level was 712 pg/ml, with 26% of subjects having baseline iPTH levels > 800 pg/ml, and the baseline Ca X P product was approximately 61$(mg/dL)^2$. Sixty-six percent of the subjects

were receiving vitamin D therapy at baseline, and 93% were on some type of phosphate binder. The mean dose of study drug during the efficacy-assessment phase for subjects who achieved a iPTH $\leq$ 250 was 85.0 mg. Seventy-eight percent of placebo patients and 71% of the Cinacalcet patients completed the 6-month studies.

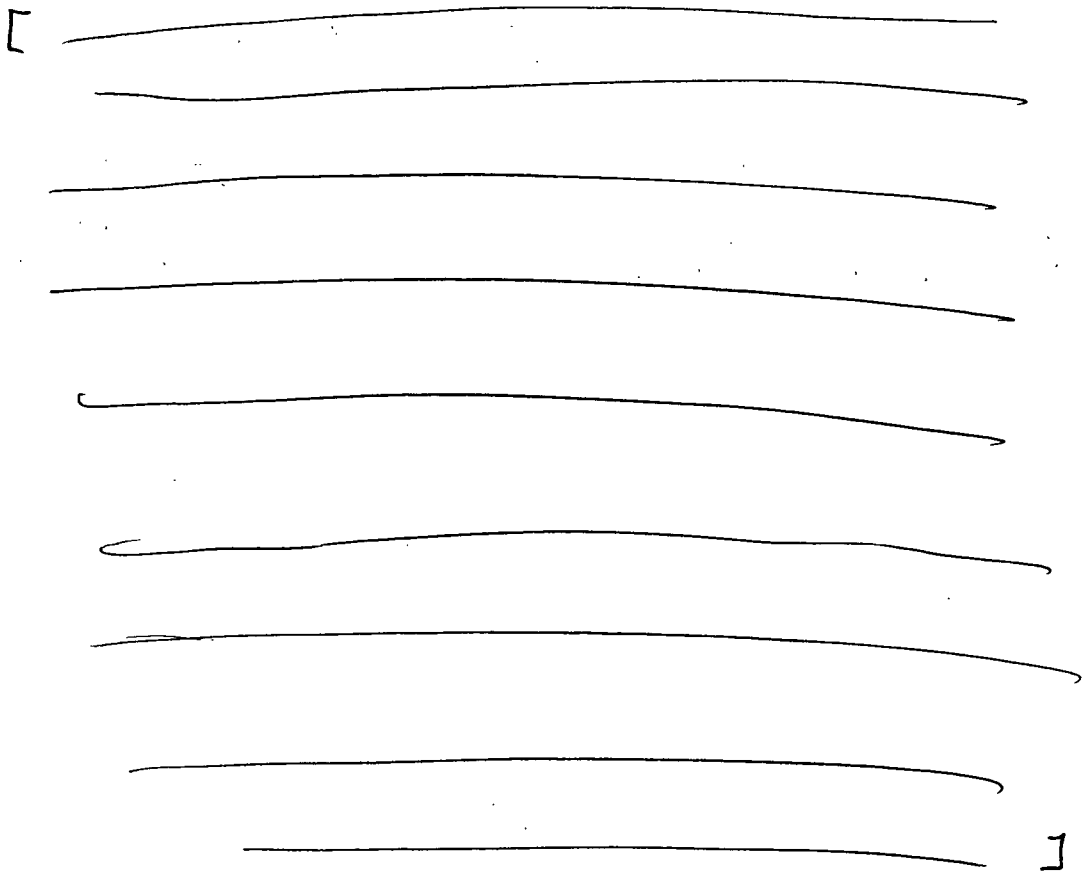
In the primary analysis of efficacy, 40% of cinacalcet patients compared with 5% of placebo subjects achieved a serum iPTH level $\leq$ 250 pg/ml during the efficacy-assessment phase of the trials ($p<0.001$).

Regarding secondary efficacy analyses, the following table provides the proportion of patients in each group who achieved the Kidney Disease Outcomes Quality Initiative (K/DOQI) treatment goals during the efficacy-assessment phase of the trials. A significantly larger percentage of patients treated with cinacalcet achieved the new treatment goals than did patients treated with placebo.

Proportion of Patients Achieving K/DOQI Treatment Goals

K/DOQI Treatment Target	Placebo	Cinacalcet
iPTH 150 – 300 pg/ml	9%	31%
Serum Ca 8.4 – 9.5 mg/dl	25%	47%
Serum Phos 3.5 – 5.5 mg/dl	33%	43%
Ca x P < 55 mg/dl^2	37%	63%
iPTH 150-300 & Ca x P < 55	5%	23%

Secondary Hyperparathyroidism in Patients with CKD Not Receiving Dialysis: Study 20000236



"Intractable" Primary Hyperparathyroidism and Parathyroid Carcinoma
Study 20000204

A total of 10 patients with parathyroid carcinoma were enrolled in this ongoing, open-label, single-arm, 3-year study. Five patients with primary hyperparathyroidism, 2 of whom reportedly had undergone unsuccessful parathyroidectomies and 3 whom Amgen claims parathyroidectomy was not a treatment option, were also enrolled into this trial. The company refers to these five patients as having "intractable" primary Hyperparathyroidism. At the end of a 16-week titration phase, 7/10 subjects with parathyroid carcinoma and 4/5 with intractable hyperparathyroidism had a reduction in serum calcium of at least 1.0 mg/dL. The doses of cinacalcet required to treat these patients populations, 30 mg BID to 90 mg QID, were much larger than those used to treat patients with secondary hyperparathyroidism.

C. Safety

The most common treatment-emergent adverse events in patients with CKD receiving dialysis were nausea and vomiting, which were reported by 31% and 27% of cinacalcet subjects compared with 19% and 15% of placebo-treated patients. There was a clear

dose-response relationship for vomiting, but not nausea. Nausea and vomiting were also commonly reported by patients with pre-dialysis CKD, although the incidence rates were lower in this population.

In CKD patients on dialysis, inappropriately low serum calcium levels (< 8.4 mg/dL) were noted in 66% of cinacalcet subjects vs. 25% of placebo patients. Approximately 5% of cinacalcet and 0.9% of placebo patients had 2 consecutive serum calcium values < 7.5 mg/dL. Of the patients who developed a serum calcium level < 8.4 mg/dL, 40% of cinacalcet patients vs. 34% of placebo subjects had their dose of calcium-based phosphate binder increased during the remainder of the trials.

In CKD patients not receiving dialysis, serum calcium levels < 8.4 mg/dL developed in 84% of cinacalcet patients and 9% of placebo patients. Of the patients who developed a serum calcium level < 8.4 mg/dL, 17% of cinacalcet patients vs. none of placebo subjects had their dose of calcium-based phosphate binder increased during the remainder of the trials; and 17% of active-drug treated patients compared with none of the placebo patients had their dose of vitamin D sterol increased during the remainder of the trials.

In the three, phase-3 studies of patients with CKD receiving dialysis, 1.4% (9/656) of cinacalcet-treated patients and 0.4% (2/470) of placebo-treated patients reported suffered a seizure – primarily grand mal. Some of the cinacalcet patients had a history of a seizure disorder and a few were taking anti-seizure medication at baseline. The doses of cinacalcet patients were taking at the time of the seizures ranged from 30 to 180 mg QD. Although it's unknown what the serum calcium levels were immediately before the seizures occurred, if cinacalcet does in fact increase the risk for seizures, it likely does so by way of hypocalcemia.

Regarding cardiac repolarization, limitations of the preclinical and clinical data do not allow for a comprehensive assessment of cinacalcet's potential to 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 uncertainty, a thorough QT study, if properly conducted, would provide valuable information regarding the safety profile of cinacalcet.

Confirming findings from a non-human primate study, treatment of male dialysis patients with cinacalcet for 6 months led to minor-to-modest reductions in mean serum total and free testosterone levels, without significant changes in FSH or LH concentrations. The mechanism responsible for and the clinical significance of these findings are unknown.

D. Dosing

One of the striking features of the phase-3 data was the wide range of cinacalcet doses patients were taking at the end of the studies. For example, at the completion of the three, 6-month CKD – dialysis studies, 40% of patients were receiving 180 mg once-daily of cinacalcet, while the remaining 60% of subjects were equally divided among the 30 mg, 60 mg, 90 mg, and 120 mg doses. This may reflect a host of factors, including baseline

iPTH and serum calcium levels, varying sensitivities to cinacalcet-induced nausea and vomiting, and varying rates of use of concomitant medications such as calcium supplements, phosphate binders, and vitamin D sterols. The dosing of cinacalcet is much more complicated than that for most other drugs because the dose is titrated not to a single endpoint, such as serum iPTH, but to changes in serum calcium and phosphate as well. The concomitant use of phosphate binders and vitamin D sterols also influence the dosing of cinacalcet.

E. Special Populations

Because cinacalcet is metabolized by the liver, patients with moderate-to-sever hepatic impairment must be closely monitored if treated with this drug. The pharmacokinetcs of cinacalcet is similar in patients less than and over the age of 65.

Clinical Review

I. Introduction and Background

I.A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Amgen, Inc. has submitted this new drug application for AMG 073, cinacalcet hydrochloride [N-[1-(R)-(-)-(1-naphthyl)ethyl]-3-[3 -(trifluoromethyl)phenyl]-1-aminopropane hydrochloride 364782-34-3 (αR)-(-)-α-methyl-N-[3- [3-(trifluoromethyl)phenyl]], proposed trade name Sensipar. Sensipar is a calcimimetic agent. Calcimimetic agents are organic small molecules that act as modulators of the calcium-sensing receptor (CaR) present on the surface of parathyroid and other cells. By targeting the CaR, calcimimetics regulate plasma PTH secretion by amplifying the receptor's sensitivity to extracellular calcium. Amgen proposes to market cinacalcet once daily for the [redacted] treatment of secondary HPT associated with chronic kidney disease, end stage renal disease (dialysis), secondary HPT associated with chronic renal insufficiency (pre-dialysis), intractable primary HPT, and e parathyroid carcinoma-induced hypercalcemia.

I.B. State of Armamentarium for Indication(s)

Current medications available for treatment of secondary HPT include phosphate binders (calcium and non-calcium based) and vitamin D sterols. Dietary phosphate restriction and phosphate binders are used to reduce serum phosphorus levels, while calcium supplements and vitamin D sterols are used to control PTH. Calcium-based phosphate binders and vitamin D sterols are limited by their propensity to increase serum calcium and phosphorus. These complications frequently require that treatment be withheld for safety considerations.

I.C. Important Milestones in Product Development

- In discussions with regulatory authorities in the US and Europe, it was agreed that a reduction in iPTH to less than 250 pg/mL was an appropriate primary endpoint for evaluating the efficacy of cinacalcet in CKD subjects receiving dialysis with secondary HPT.
- Additional recommendations included the collection of bone histomorphometry data (conducted - study 20010141).
- Based on a meeting with the Division on November 9, 2001, the clinical program was modified in accordance with this recommendation as follows:
- The phase 3 20000188 (randomized, double-blind, placebo-controlled, phase 3 study in CKD subjects receiving hemodialysis or peritoneal dialysis) study design was modified to be double-blind and placebo-controlled.
- Amgen initiated a 6-month, placebo-controlled, double-blind, extension study to the 6-month, phase 3 studies 20000172 and 20000183, providing 12-month exposure data in CKD subjects receiving dialysis (study 20010240).
- In May 12, 2003, cinacalcet received Orphan Designation from the US FDA for the treatment of hypercalcemia in patients with parathyroid carcinoma.

Cinacalcet Studies: Primary and Secondary Hyperparathyroidism, Safety and Efficacy						
Study	Treatment	Subjects enrolled (comp)	Age years	Population	Study Duration weeks	Primary Endpoint Complete Date
	Cinacalcet	166				
20000188 P3, R, DB, PC	Total Placebo Cinacalcet	395 101 294	52.2	ESRD, HD or PD PTH >300 pg/mL	26	PTH ≤ 250 pg/mL 3/28/2003
20000237 P2, R, DB, PC	Total Placebo Cinacalcet	82 41 41	53.3	ESRD, HD PTH >300 pg/mL	12	PTH ≤ 250 pg/mL 7/19/2001
20010240 DB, PC Extension	Total Placebo Cinacalcet	266 138 128	53.5	Studies 172, 183	26 52 total	Safety 6/23/2003
990126 Subset of 990101	Total Placebo Cinacalcet	15 6 9	50	Study 990101	26	Bone Histomorph 4/11/2000
20010141 P2, R, DB, PC	Total Placebo Cinacalcet	48 16 32	50.9	ESRD, HD PTH >300pg/mL	52	Bone Histomorph 5/14/2003
Controlled Studies, Secondary Hyperparathyroidism in Chronic Renal Insufficiency (pre-dialysis)						
20000236 P2, R, DB, PC						
20010239 P2, R, DB, PC						
Controlled Studies, Primary Hyperparathyroidism						
990120 P2, R, DB, PC						
990160 P2, R, DB, PC						
Uncontrolled Studies, ESRD						
20000130 OL extension	Cinacalcet	170	Studies 101,102,740,237		4 years	Safety ongoing
Uncontrolled Studies, Primary Hyperparathyroidism and Parathyroid Carcinoma						
20000159 OL extension						
20000204 P2, OL, single arm	Total 	15 10 5	 47.5 67.4	 Parathyroid Cancer Intractable PHPT Ca > 12.5	3 years	Serum calcium ongoing
Other						
20010142 OL extension	Cinacalcet	4 (plan: 140)	Study 20000236		18-29 d	Safety terminated
20020158 OL, extension	Cinacalcet	563 (open enroll, plan:850)	Studies 172, 183, 188, 141, 240		32-136	Safety ongoing

IV.C. Postmarketing Experience

Cinacalcet is not approved for marketing in any country.

IV.D. Literature Review

A MEDLINE review was conducted for cinacalcet and revealed 17 articles. The majority of the articles were included in the sponsor's references. The information included in the articles does not add materially to the information provided in the NDA.

V. Clinical Review Methods

V.A. How the Review was Conducted

This submission includes 47 clinical studies in normal volunteers and patients with primary or secondary HPT performed from December 1997 to June 2003. A total of 19 studies were conducted to evaluate safety and efficacy: 15 in subjects with secondary HPT, and 4 in subjects with primary HPT and parathyroid carcinoma. The remaining 28 studies provide biopharmaceutic and clinical pharmacology information as well as information on initial efficacy and tolerability of cinacalcet. Detailed review was conducted for 8 of the trials: studies 20000172, 20000183, 20000188, 20010141, 20000236 and 20010239 for the indication of secondary HPT and study 20000204 for the indication of parathyroid carcinoma and intractable primary HPT, and study 990120 for safety data in patients with primary HPT.

V.B. Overview of Materials Consulted in Review

This review was conducted utilizing data in the electronic submission of the NDA. All trials were conducted under IND 56,010.

V.C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigation (DSI) was consulted for this NDA and their audits did not identify any significant deviations from Standard Operating Procedures.

V.D. Were Trials Conducted in Accordance with Accepted Ethical Standards

All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

V.E. Evaluation of Financial Disclosure

Financial disclosure information was provided by the sponsor and reviewed. In the three Phase 3 trials evaluating safety and efficacy of cinacalcet in end stage renal disease, 18 of 183 sites had investigators who reported significant payments of other sorts and equity interest in the sponsoring company. These sites accounted for 12% of the enrolled subjects. In the two trials evaluating safety and efficacy of cinacalcet in stage 3 or 4 renal disease, 1 of 33 sites had investigators who reported significant payments of other sorts and equity interest in Amgen, while 3 sites had investigators who did not provide financial disclosure information, despite due diligence of the company. These sites accounted for 16% of the enrolled subjects. In the four trials evaluating safety and efficacy of cinacalcet in primary hyperparathyroidism and parathyroid carcinoma, 1 of 26 sites had investigators who reported significant payments of other sorts and equity interest in Amgen, while 1 site had investigators who did not provide financial disclosure information. These sites accounted for 2% of the enrolled subjects.

In order to adequately protect against and minimize potential bias, the sponsor conducted clinical site monitoring and clinical audits as well as an independent assessment of efficacy response data. The individual study designs were multicenter, randomized and blinded with objective endpoints measured in a blinded fashion by a central independent laboratory, which

will also play a role in minimizing potential bias. It is unlikely that the disclosed financial arrangements would impact the study outcome nor affect the conclusions drawn about the efficacy and safety of cinacalcet.

VI. Integrated Review of Efficacy

VI.A. Brief Statement of Conclusions

Secondary Hyperparathyroidism:

In subjects with secondary HPT associated with end stage renal disease, cinacalcet is effective in reducing plasma levels of iPTH. Therapy was more effective in those subjects with less severe HPT, with a 12% response rate (iPTH < 250 pg/ml) in subjects with baseline iPTH levels of greater than 800 pg/mL, compared with a 61% response rate in subjects with a baseline iPTH concentrations of 300-500 pg/ml. A higher proportion of subjects in both groups achieved a 30% reduction in baseline iPTH levels (62% in the cinacalcet-treated group vs. 11% in the placebo-treated group). The mean Ca x P ion product value was reduced by 14% in the cinacalcet group, compared with a 0.1% increase in the placebo group.

In subjects with secondary HPT associated with Stage 3 or 4 chronic kidney disease (pre-dialysis), [redacted]

Primary Hyperparathyroidism

In patients with parathyroid carcinoma and intractable primary hyperparathyroidism, cinacalcet [redacted]

VI.B. General Approach to Review of the Efficacy of the Drug

This review of the efficacy of cinacalcet was approached individually for each indication. Detailed reviews of each study are found in the appendix. Presentation and discussion of the efficacy data in the following section is based on integrated data for the indication.

VI.C. Detailed Review of Trials by Indication

VI.C.1. Secondary Hyperparathyroidism in Patients with End Stage Renal Disease

Amgen's clinical development program included three phase 3 trials (20000172, 20000183, 20000188) investigating the safety and efficacy of cinacalcet for the treatment of secondary HPT in patients on dialysis. These trials are the main focus of this integrated efficacy review. As well, study 20010141 evaluated the bone histomorphometric outcomes of cinacalcet use and study 20010240 was a 6-month extension of studies 20000172 and 20000183 for continued safety evaluation. Please see Appendix XI.B for the detailed reviews of these individual trials.

Objectives: The primary objective in all three studies was to investigate the efficacy of cinacalcet compared with placebo by determining the proportion of subjects with a mean plasma iPTH value ≤ 250 pg/mL during the efficacy-assessment phase.

Study Design: All studies were randomized, double-blind, placebo-controlled, parallel-group and 26 weeks in duration. Trials 2000172 and 20000183 had identical study designs, enrolling patients with secondary HPT on hemodialysis and stratifying patients based on iPTH and calcium-phosphate ion product level (Ca x P). Trial 20000188 enrolled dialysis (hemodialysis or peritoneal dialysis) patients with secondary HPT, although stratification criteria were slightly different (see below). In contrast to studies 20000172 and 20000183, no limit was placed on the number of subjects with a baseline iPTH > 800 pg/mL who could enroll in study 20000188. All studies consisted of 2 phases, a dose-titration phase and an efficacy-assessment phase. Studies 20000172 and 20000183 had a 12-week dose-titration phase followed by a 14-week efficacy-assessment phase. Study 20000188 had a 16-week dose-titration phase followed by a 10-week efficacy-assessment phase.

Stratification Criteria:
For studies 20000172 and 20000183, subjects were stratified as follows:

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

For study 20000188, subjects were stratified as follows:

- hemodialysis, and iPTH $\geq$ 300 pg/mL (31.8 pmol/L) to $\leq$ 500 pg/mL (53 pmol/L)
- hemodialysis, and iPTH $\geq$ 500 pg/mL to $\leq$ 800 pg/mL (84.8 pmol/L)
- hemodialysis, and iPTH > 800 pg/mL
- peritoneal dialysis, and iPTH $\geq$ 300 pg/mL

Study Methods: All measurements of iPTH were performed by [ ] Laboratory using the Nichols IRMA assay .

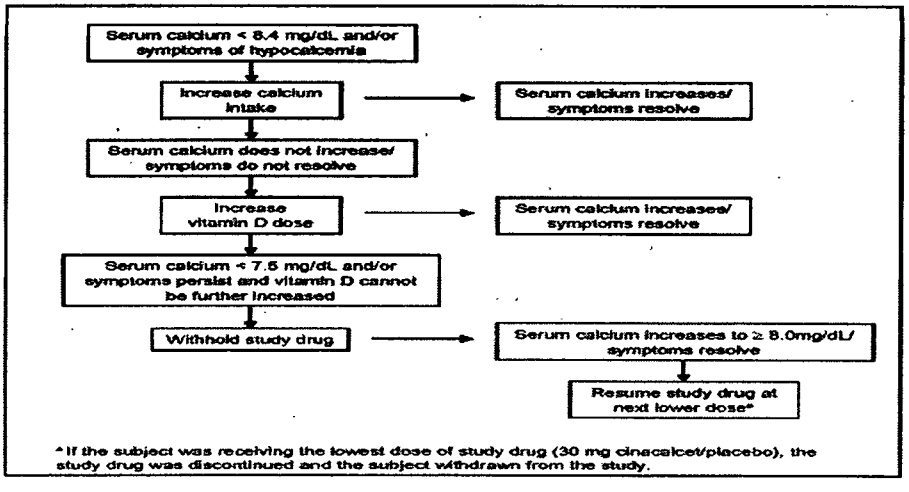
Study Medication and Dose Titration: All medications were administered orally with meals at a starting dose of 30 mg cinacalcet or placebo, once-daily. For all studies, possible sequential doses during the study were 30, 60, 90, 120, and 180 mg Cinacalcet or placebo, once-daily. In studies 20000172 and 20000183, dose titration occurred at Weeks 3, 6, 9, 12, 16, 20, and 24. For study 20000188, dose titration occurred at Weeks 4, 8, 12, 16, 20, and 24. Except during the screening phase, changes in phosphate binders/oral calcium supplements were permitted throughout the study. Changes in vitamin D therapy were only permitted based on protocol-specified guidelines.

Dose Titration: For all studies, a subject's dose was NOT increased if any of the following criteria applied:

- The central laboratory iPTH value from the preceding study visit was ≤ 200 pg/mL (21.2 pmol/L).
- 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 for 2 to 3 consecutive study visits, study medication was reduced to the next lower dose.

Treatment of Hypocalcemia: For all studies, 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 (Protocols 2000172 and 20000183 only). 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 any of these studies 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.

Primary Efficacy Endpoint – All Studies

The proportion of subjects with a mean iPTH value ≤ 250 pg/mL during the efficacy-assessment phase was the primary endpoint for all three phase 3 trials.

Secondary Efficacy Endpoints

- Proportion of subjects with a reduction from baseline in mean iPTH of ≥ 30%
- Percentage change from baseline in mean iPTH
- Percentage changes from baseline in Ca x P
- Percentage changes from baseline in serum calcium and phosphorus
- Change from baseline in self-reported cognitive functioning (studies 2000172 and 20000183) or patient reported outcomes (PRO) (study 20000188) scale scores

Tertiary Efficacy Endpoints (Studies 2000172 and 20000183)

- 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 (Study 20000172 only): 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
- Proportion of subjects who had ≥ 30% reduction from baseline in biPTH during the efficacy-assessment phase

Statistical Analyses: The sample size calculation for all three studies was based on a χ^2 test of equal proportions of subjects with a mean iPTH value $\leq$ 250 pg/mL during the efficacy-assessment phase, with a statistical significance level of 0.05 (2-sided). For studies 20000172 and 20000183, the placebo response was predicted on the basis of previous cinacalcet phase 2 studies to be $\leq$ 15% with a cinacalcet response rate of 35% assumed (the planned size yielded 98% power). For study 20000188, the placebo response was predicted on the basis of previous cinacalcet phase 2 studies to be $\leq$ 13% with a cinacalcet response rate of 30% assumed (the planned size yielded 91% power).

Results

Patient Disposition: As shown in the table below, 1136 subjects were enrolled and randomized into the three phase 3 studies. Approximately 78% of placebo and 71% of cinacalcet subjects completed the 26 week trials. Adverse events were the most common reason for early withdrawal, with the rate higher in the cinacalcet group.

Patient Disposition: Pooled Studies

	Placebo	Cinacalcet
Enrolled	471	665
No treatment	1	9
At least one dose	470	656
Withdrew - Total	103 (22)	189 (28)
Withdrew - AE	36 (8)	96 (14)
Deaths	12 (3)	12 (2)
Withdrew - Parathyroidectomy	7 (1)	0 (0)
Withdrew – Renal Transplant	20 (4)	25 (4)
Withdrew - Other	28 (6)	56 (8)
Completed Titration Phase	409 (87)	545 (82)
Completed Study	367 (78)	470 (71)

Protocol Violations: Protocol violations were numerous in all three studies. Of the 1136 subjects enrolled in the Phase 3 studies, 78% had at least one protocol deviation and 39% had at least one major protocol deviation. Protocol deviations were considered major in the phase 3 studies in CKD subjects receiving dialysis if they met the following criteria:

- Efficacy
  - Greater than 2 missing iPTH, serum calcium, or serum phosphorus values during the efficacy assessment phase
  - Two or more iPTH values at a visit used to titrate patients or during the efficacy assessment phase that were collected after study drug administration
  - Changes in vitamin D sterol dose that were not in compliance with the protocol which exceeded 2 consecutive dialysis visits
  - Missed doses of study drug (4 or more missed doses during a titration phase week or 7 or more missed doses during a 2-week efficacy assessment phase period for

studies 20000172 and 20000183 and 14 or more missed doses during a 4-week period for study 20000188)
    - Missed patient-reported outcome assessment at baseline or more than one missed patient-reported outcome assessment on study
    - Changed dialysate calcium concentration (20000172 and 10000183 only)
- Safety
    - Screening ECG obtained after day 1
    - Use of an excluded medication on study
- Pharmacokinetics
    - Missed week 24 pharmacokinetic profile (20000172 only)
- Other
    - Incorrect treatment assigned

When evaluated by treatment group and study, protocol deviations were slightly higher in those treated with cinacalcet (as shown in the table below).

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

	Placebo	Cinacalcet
	471	665
Study 20000172	205	205
Total	136 (33)	
Per group	59 (29)	77 (38)
Study 20000183	165	166
Total	178 (54)	
Per group	84 (51)	94 (57)
Study 20000188	101	294
Total	157 (40)	
Per group	37 (37)	120 (41)
Total - All	**180 (38)**	**291 (44)**

COMMENTS: Although there were numerous and varied protocol violations, the numbers and types of violations that could impact efficacy outcomes were relatively evenly distributed across the groups. It is unlikely that the protocol violations affected the principal efficacy or safety results.

Demographics: Baseline subject demographics were well balanced across the treatment groups (see table below). The disparity in the race of enrolled subjects is most likely due to the location of the trials (study 20000183 - Europe and Australia vs. studies 20000172 and study 20000188 – North America). Overall, 35% of enrolled subjects were black. In contrast to studies 20000172 and 20000183, no limit was placed on the number of subjects with a baseline iPTH > 800 pg/mL who could enroll in study 20000188, resulting in higher baseline iPTH levels. The mean (range) duration of dialysis was 65.1 (0.5 to 349) months for subjects receiving cinacalcet and 70.3 (2 to 359) months for subjects receiving placebo, with approximately 10% of subjects overall receiving dialysis for ≤ 1 year. In study 20000188, 12% of subjects were receiving PD.

Demographics: Phase 3 studies						
Study	**20000172**		**20000183**		**20000188**	
	Placebo	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**
N	20	205	165	166	101	294
Age (yrs.)	54.2 ± 14.6	53.3 ± 14.2	56.3 ± 15.0	55.2 ± 14.8	53.5 ± 13.9	51.8 ± 14.0
Sex						
Male	124 (60)	124 (60)	107 (65)	102 (61)	64 (63)	181 (62)
Female	81 (40)	81 (40)	58 (35)	64 (39)	37 (37)	113 (38)
Race						
Caucasian	69 (34)	62 (30)	157 (95)	147 (89)	39 (39)	115 (39)
Black	118 (58)	121 (59)	2 (1)	10 (6)	33 (35)	114 (39)
Other	18 (9)	22 (11)	6 (4)	9 (5)	27 (27)	65 (22)
Baseline Laboratories						
iPTH (pg/mL)	651 ± 398	636 ± 341	630 ± 316	652 ± 372	832 ± 486	848 ± 685
Serum Ca (mg/dL)	9.9 ± 0.8	9.8 ± 0.8	9.9 ± 0.7	10.0 ± 0.8	10.0 ± 0.9	9.8 ± 0.8
Ca x P (mg/dL)²	61.1 ± 16.1	62.0 ± 16.2	61.1 ± 14.9	61.0 ± 15.4	60.9 ± 14.0	59.6 ± 16.5
Serum Phos (mg/dL)	6.2 ± 1.6	6.3 ± 1.7	6.2 ± 1.5	6.1 ± 1.5	6.1 ± 1.4	6.1 ± 1.7
Baseline Vitamin D use						
Yes	139 (68)	144 (70)	109 (66)	102 (61)	70 (69)	191 (65)
No	66 (32)	61 (30)	56 (34)	64 (39)	31 (31)	103 (35)
Baseline Phosphate Binder use						
Yes	195 (95)	193 (94)	149 (90)	150 (90)	94 (93)	274 (93)
No	10 (5)	12 (6)	16 (10)	16 (10)	7 (7)	27 (7)

Primary Efficacy Outcomes

Proportion of subjects with a mean iPTH value ≤ 250 pg/mL during the efficacy-assessment phase: The mean baseline iPTH was 683 pg/mL in the placebo-treated group and 733 pg/mL in the cinacalcet-treated group (p=ns). As outlined in the table below, all three studies demonstrated that significantly more cinacalcet-treated than placebo-treated subjects achieved a mean iPTH level ≤ 250 pg/mL during the efficacy-assessment phase (40% vs. 5%; p <0.001). The proportion of cinacalcet-treated subjects who achieved this endpoint was somewhat higher in studies 20000172 and 20000183, as might be expected, because those studies enrolled fewer subjects with a baseline iPTH > 800 pg/mL, as discussed below. The effect of cinacalcet in reducing iPTH was independent of changes in concomitant vitamin D therapy. For subjects who achieved the primary endpoint, the mean dose of cinacalcet during the efficacy assessment phase was 85 mg daily.

Proportion of Subjects with mean iPTH ≤ 250 during Efficacy Assessment Phase						
Study	**20000172**		**20000183**		**20000188**	
	Placebo	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**
N	205	205	165	166	101	294
n (%)	8 (4)	84 (41)	11 (7)	76 (46)	6 (6)	104 (35)
CMH Statistic (χ^2)	83.41		71.62		38.01	
p-value	< 0.001		< 0.001		< 0.001	
Odds Ratio	15.70		11.11		7.90	
95% CI	7.64 , 32.27		5.42 , 22.78		3.29 , 18.99	
Pooled Data						
	Placebo (N=471)		**Cinacalcet (N=665)**			
n (%)	25 (5)		264 (40)			
CMH Statistic	Value = 174.22		p-value <0.001			

Proportion of Subjects with mean iPTH ≤ 250 during Efficacy Assessment Phase						
Study	**20000172**		**20000183**		**20000188**	
	Placebo	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**
Odds-ratio [b]	Value = 12.33			95% CI (7.96, 19.09)		
Response Difference	Value = 34			95% CI (30 , 39)		

When assessed by baseline disease severity, a higher proportion of the subjects with less severe disease achieved a mean iPTH level ≤ 250 pg/mL during the efficacy-assessment phase. Subjects with iPTH at baseline of greater than 800 pg/mL had a response rate of only 12%, compared with subjects with a baseline iPTH 300-500pg/ml, who had a response rate of 61%.

Proportion of Subjects Achieving a Mean iPTH ≤ 250 pg/mL During the Efficacy Assessment Phase by Disease Severity Subgroups (Pooled Phase 3 ESRD Studies - ITT Analysis Set)						
	Placebo		Cinacalcet		Odds Ratio*	95% Confidence Interval
	N	n (%)	N	n (%)		
iPTH						
> 300 and ≤ 500 pg/mL	193	22 (11)	244	147 (60)	10.85	(6.36, 18.49)
> 500 and ≤ 800 pg/mL	165	3 (2)	231	95 (41)	23.83	(8.28, 68.58)
> 800 pg/mL	113	0 (0)	188	22 (12)	10.85	(2.01, 58.50)
Ca x P						
≤ 70 $(mg/dL)^2$	343	24 (7)	486	210 (43)	10.41	(6.57, 16.49)
> 70 $(mg/dL)^2$	128	1 (1)	176	53 (30)	29.84	(7.09, 126)
Serum calcium						
< 11.0 mg/dL	424	25 (6)	611	252 (41)	11.86	(7.63, 18.44)
≥ 11.0 mg/dL	47	0 (0)	52	12 (23)	10.33	(1.81, 59.06)
Serum phosphorus						
< 6.5 mg/dL	273	22 (8)	399	176 (44)	8.93	(5.50, 14.52)
≥ 6.5 mg/dL	198	3 (2)	264	88 (33)	30.95	(10.32, 92.87)
Duration of Dialysis						
> 0 - 1 year	49	5 (10)	73	37 (51)	11.70	(3.94, 34.73)
> 1 - 5 years	238	10 (4)	312	138 (44)	19.98	(10.12, 39.47)
> 5 years	182	10 (5)	258	81 (31)	7.47	(3.71, 15.06)

Secondary Efficacy Outcomes

Proportion of subjects with a reduction from baseline in mean iPTH of ≥ 30% during the efficacy-assessment phase: As outlined in the table below, significantly more cinacalcet-treated subjects achieved a ≥ 30% reduction in iPTH during the efficacy-assessment phase than did placebo subjects (62% vs. 11%; nominal p<0.001). As seen with the primary endpoint, the proportion of cinacalcet-treated subjects who achieved a ≥ 30% reduction in iPTH was somewhat higher in studies 20000172 and 20000183.

Proportion of Subjects With ≥ 30% Reduction in iPTH						
Study	**20000172**		**20000183**		**20000188**	
	Placebo	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**
N	205	205	165	166	101	294
n (%)	23 (11)	126 (61)	19 (12)	113 (68)	10 (10)	174 (59)
CMH Statistic (χ^2)	111.1		109.0		73.58	
p-value	< 0.001		< 0.001		< 0.001	
Pooled Data						
	Placebo (N=471)			**Cinacalcet (N=665)**		

Proportion of Subjects With ≥ 30% Reduction in iPTH						
Study	**20000172**		**20000183**		**20000188**	
	Placebo	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**
n (%)	52 (11)			413 (62)		

The response rate for cinacalcet-treated subjects who achieved a ≥ 30% reduction in iPTH was similar among all baseline disease severity subgroups (see table below).

Proportion of Subjects With ≥ 30% Reduction in iPTH by Disease Severity Subgroups (Controlled Phase 3 ESRD Studies – ITT Analysis Set)						
	Placebo		Cinacalcet		Odds Ratio*	95% Confidence Interval
	N	n (%)	N	n (%)		
iPTH						
> 300 and ≤ 500 pg/mL	193	24 (12)	244	151 (62)	10.79	(6.46, 18.04)
> 500 and ≤ 800 pg/mL	165	21 (13)	231	157 (68)	14.75	(8.37, 25.98)
> 800 pg/mL	113	7 (6)	188	105 (56)	21.44	(9.25, 49.68)
Ca x P						
≤ 70 $(mg/dL)^2$	343	47 (14)	486	301 (62)	10.38	(7.19, 14.97)
> 70 $(mg/dL)^2$	128	5 (4)	176	111 (63)	46.59	(18.23,119)
Serum calcium						
< 11.0 mg/dL	424	50 (12)	611	381 (62)	13.14	(9.29, 18.59)
≥ 11.0 mg/dL	47	2 (4)	52	32 (62)	25.15	(6.37, 99.28)
Serum phosphorus						
< 6.5 mg/dL	273	36 (13)	399	250 (63)	11.31	(7.47, 17.12)
≥ 6.5 mg/dL	198	16 (8)	264	163 (62)	20.08	(11.17, 36.08)
Duration of Dialysis						
> 0 - 1 year	49	10 (20)	73	48 (66)	8.38	(3.41, 20.59)
> 1 - 5 years	238	23 (10)	312	191 (61)	16.70	(10.09, 27.64)
> 5 years	182	19 (10)	258	156 (60)	13.08	(7.57, 22.59)

Percent change from baseline in mean iPTH during the efficacy-assessment phase: As outlined in the table below, treatment with cinacalcet vs. placebo resulted in a significantly greater decrease from baseline in mean iPTH (-41.5 % vs. 8.1% ; nominal p <0.001)).

Percentage Change from Baseline in Mean iPTH Value						
Study	**20000172**		**20000183**		**20000188**	
	Placebo	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**
N	205	205	163	163	101	294
Baseline (SE)	646 (28)	636 (28)	630 (25)	653 (29)	832 (48)	848 (40)
Assessment Phase	698 (33)	384 (25)	687 (32)	361 (29)	852 (55)	526 (30)
Mean % Change	9.52	- 38.41	8.75	-47.50	4.07	- 40.30
CMH Statistic (χ^2)	99.81		106.6		83.36	
p-value	< 0.001		< 0.001		< 0.001	
Pooled Data						
	Placebo (N=471)		**Cinacalcet (N=665)**			
Baseline (SE)	683 (18)		733 (21)			
Assessment Phase	727 (22)		441 (17)			
Mean % Change	8.1 (1.7)		- 41.5 (1.4)			

Percentage changes from baseline in Ca x P, serum calcium, and phosphorus, during the efficacy-assessment phase:

Ca x P: In renal disease, the Ca x P product has been associated with a variety of adverse sequelae, including increased risk of cardiac, visceral, and vascular calcifications. The mean Ca x P value at baseline was 61 $(mg/dL)^2$ for subjects in both treatment groups The mean Ca x P value during the efficacy-assessment phase was 51 $(mg/dL)^2$ for the cinacalcet group and 59 $(mg/dL)^2$ for the placebo group. The mean Ca x P value was reduced by 14% in the cinacalcet group, compared with essentially no change in the placebo group ($p < 0.001$).

Percentage Change from Baseline in Mean Ca x P Value						
Study	**172**		**183**		**188**	
	Placebo	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**
N	202	200	163	163	101	294
Baseline	62.1 (1.2)	61.2 (1.1)	61.2 (1.2)	61.2 (1.2)	60.9 (1.4)	59.6 (1.0)
Assessment Phase	59.8 (1.0)	52.3 (1.0)	59.4 (1.2)	49.9 (1.3)	58.1 (1.3)	50.9 (0.9)
Mean % Change	1.45	- 12.96	- 0.68	- 16.69	- 1.43	- 12.85
CMH Statistic (χ^2)	37.55		33.72		20.27	
p-value	< 0.001		< 0.001		< 0.001	
Pooled Data						
	Placebo (N=471)		**Cinacalcet (N=665)**			
Baseline	61 (0.7)		61 (0.6)			
Assessment Phase	59 (0.7)		51 (0.6)			
Mean % Change	0.1 (1.2)		- 13.8 (1.0)			

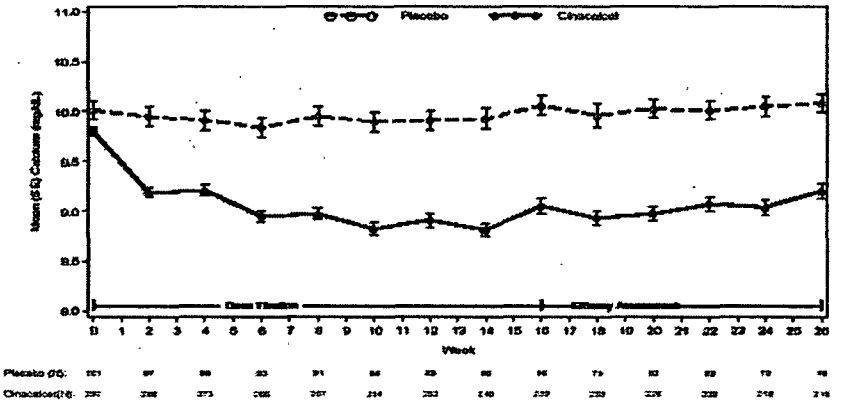
Calcium: Hypocalcemia is a recognized pharmacodynamic effect of cinacalcet treatment. The baseline serum calcium concentrations were 9.9 mg/dL for both treatment groups. The mean serum calcium concentration during the efficacy-assessment phase was 9.2 mg/dL for the cinacalcet group and 10.0 mg/dL for the placebo group. The mean serum calcium concentration was reduced by 7 % in the cinacalcet group, compared with a < 1% increase in the placebo group (nominal $p < 0.001$). For each treatment group, changes in serum calcium were similar across all pre-defined baseline strata.

Percentage Change from Baseline in Mean Calcium Levels						
Study	**172**		**183**		**188**	
	Placebo	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**
N	205	205	163	163	100	288
Baseline	9.9 (0.1)	9.8 (0.1)	9.9 (0.1)	10.0 (0.1)	10.0 (0.1)	9.8 (0.1)
Assessment Phase	9.9 (0.1)	9.2 (0.1)	9.2 (0.1)	9.9 (0.1)	10.1 (0.1)	9.1 (0.1)
Mean % Change	0.53	- 6.25	0.35	-7.55	0.90	- 6.46
CMH Statistic (χ^2)	68.13		72.86		51.78	
p-value	< 0.001		< 0.001		< 0.001	
Pooled Data						
	Placebo (N=471)		**Cinacalcet (N=665)**			
Baseline	9.9 (0.04)		9.9 (0.03)			
Assessment Phase	10.0 (0.04)		9.2 (0.03)			
Mean % Change	0.5 (0.2)		- 6.7 (0.4)			

As depicted in the figure below (from study 20000188), the mean serum calcium concentration in the cinacalcet group decreased until Weeks 7 to 10 of the titration phase, then increased

slightly and remained reduced relative to placebo throughout the remainder of the study. Similar responses were seen in studies 20000172 and 20000183.

Study 20000188: Mean (± SE) Serum Calcium Values by Scheduled Visit (mg/dL)



Approximately 66% of cinacalcet-treated subjects and 25% of placebo-treated subjects had at least one serum calcium level < 8.4 mg/dL (see table below).

Proportion of Subjects with at Least One Serum Calcium < 8.4 mg/dL During Study Weeks 0-26 by Baseline Stratum

		Placebo	Cinacalcet
iPTH Stratum	**Ca x P Stratum**	**(N = 470)**	**(N = 656)**
[pg/mL]	$[mg/dL]^2$	n/N1(%)	n/N1(%)
≥ 300 and ≤ 500	≤ 70	46/146 (32)	119/187 (64)
	> 70	8/41 (20)	25/44 (57)
	All	54/187 (29)	144/232 (62)
> 500 and ≤ 800	≤ 70	31/119 (26)	115/163 (71)
	> 70	9/45 (20)	39/55 (71)
	All	40/164 (24)	154/218 (71)
> 800	≤ 70	14/73 (19)	69/103 (67)
	> 70	8/34 (24)	52/69 (75)
	All	22/107 (21)	121/172 (70)
All PTH	≤ 70	91/338 (27)	303/453 (67)
All PTH	> 70	25/120 (21)	116/168 (69)
Peritoneal Dialysis		0/12 (0)	14/34 (41)

Phosphorus: The mean serum phosphorus concentrations at baseline were 6.2 mg/dL for both treatment groups. The mean serum phosphorus concentration during the efficacy-assessment phase was 5.5 mg/dL for the cinacalcet group and 6.0 mg/dL for the placebo group. The mean serum phosphorus concentration was reduced by 8% in the cinacalcet group, compared with a 0.3% reduction in the placebo group.

Percentage Change from Baseline in Mean Phosphorus Levels						
Study	**172**		**183**		**188**	
	Placebo	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**
N	205	205	163	163	101	294
Baseline	6.2 (0.1)	6.3 (0.1)	6.2 (0.1)	6.1 (0.1)	6.1 (0.1)	6.1 (0.1)
Assessment Phase	6.0 (0.1)	5.7 (0.1)	6.0 (0.1)	5.4 (0.1)	5.8 (0.1)	5.5 (0.1)
Mean % Change	1.05	- 7.13	- 0.90	- 9.86	-2.17	- 7.20
CMH Statistic (χ^2)	15.28		10.59		4.26	
p-value	< 0.001		0.001		0.039	
Pooled Data						
	Placebo (N=471)		**Cinacalcet (N=665)**			
Baseline	6.2 (0.1)		6.2 (0.1)			
Assessment Phase	6.0 (0.1)		5.5 (0.1)			
Mean % Change	- 0.3 (1.1)		- 7.8 (1.0)			

Changes in PRO scale scores: The KDQOL Cognitive Functioning scale was used in these studies as well as several other scales. The KDQOL scales, including the Cognitive Functioning scale have been reported to be valid and reliable in the ESRD population. It is scored from 0-100, with higher scores indicating better function. As outlined in the table below, there was no significant difference in KDQOL Cognitive Functioning Scale Score observed between treatment groups. Changes from baseline were not statistically significantly correlated with percentage change in serum iPTH or calcium for any scale.

Change from Baseline in KDQOL Cognitive Functioning Scale Score						
Study	**20000172**		**20000183**		**20000188**	
	Placebo	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**
N						
Baseline (SD)	79.0 (18.2)	80.9 (18.2)	79.0 (20.0)	76.4 (18.7)	80.9 (16.7)	80.7 (17.7)
Change (SE)	1.2 (1.15)	0.5 (1.08)	- 1.6 (1.16)	0.6 (1.32)	- 3.0 (1.45)	-1.8 (0.99)
Difference	- 0.6		2.1		1.23	
95% CI	-3.69 , 2.51		-1.33 , 5.53		- 2.5 , 5.0	
p-value	0.663		0.317		0.258	

Exploratory Bio-intact PTH Analyses: Discussed in following section VI.C.4.

Medical Officer Conclusions: Secondary HPT is a common and serious sequelae of chronic renal disease. Current therapies to control HPT associated with renal disease include phosphate binders (calcium and non-calcium based) and vitamin D. Calcium-based phosphate binder and vitamin D use is limited by their propensity to increase serum calcium and phosphorus. In recognition of the need for improved disease management, the NKF K/DOQI has issued guidelines[1] recommending target ranges for iPTH and Ca x P (see table below).

Target Range of Relevant Laboratories in CKD					
CKD Stage	GFR Range ($mL/min/1.73m^2$)	Target iPTH (pg/mL)	Target Ca x P mg/dl^2	Serum Ca mg/dl	Serum Phos mg/dl
3	30 – 59	35 - 70	< 55	8.4 - 9.5	3.5 - 5.5
4	15 – 29	70 - 110	< 55	8.4 - 9.5	3.5 - 5.5
5	< 15 or dialysis	150 - 300	< 55	8.4 - 9.5	3.5 - 5.5

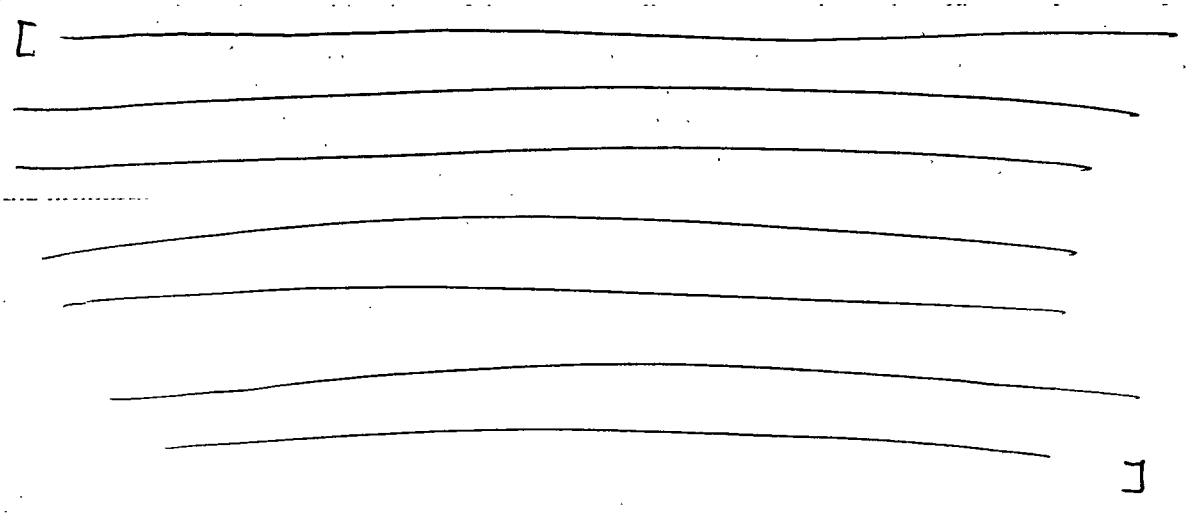
[1] K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003, Oct. 42 (4) Supplement 3.

These phase 3 studies demonstrate that cinacalcet is effective in reducing plasma levels of iPTH in subjects with secondary HPT due to end stage renal disease. While 40% of cinacalcet-treated subjects achieved a mean iPTH level of < 250 pg/ml during the efficacy-assessment phases of the studies, only 5% of placebo-treated patients achieved this treatment goal ($p<0.001$). For subjects who achieved the primary endpoint, the mean dose of cinacalcet during the efficacy-assessment phase was 85 mg daily. As expected, a higher proportion of the subjects with less severe disease achieved a mean iPTH level $\leq$ 250 pg/mL, as evidenced by a 12% response rate in subjects with iPTH at baseline of greater than 800 pg/mL, compared with a 61% response rate in subjects with a baseline iPTH 300-500pg/ml. A higher proportion of subjects in both groups achieved a 30% reduction in baseline iPTH levels (62% in the cinacalcet-treated groups vs. 11% in the placebo-treated groups).

In renal disease, the Ca x P product has been associated with a variety of adverse sequelae, including increased risk of cardiac, visceral, and vascular calcifications. The mean Ca x P value at baseline was 61 $(mg/dL)^2$ for subjects in both treatment groups. Over the course of the studies, the mean Ca x P value was reduced by 14% in the cinacalcet group, compared with a 0.1% increase in the placebo group (nominal $p < 0.001$). The proposed NKF K/DOQI target for Ca x P is ≤ 55 $(mg/dL)^2$. This goal was achieved with cinacalcet therapy (the mean Ca x P value during the efficacy-assessment phase was 51 $(mg/dL)^2$ for the cinacalcet group vs. 59 $(mg/dL)^2$ for the placebo group). The mean serum calcium concentration was reduced by 7 % in the cinacalcet group, compared with a < 1% increase in the placebo group (nominal $p < 0.001$). Approximately 66% of cinacalcet-treated subjects and 25% of placebo-treated subjects had at least one serum calcium level < 8.4 mg/dL.

VI.C.2. Secondary Hyperparathyroidism in Patients with Chronic Renal Insufficiency

Amgen's clinical development program included two phase 2 trials (20000236 and 20010239) investigating the safety and efficacy of cinacalcet for the treatment of secondary HPT in pre-dialysis patients with Stage 3 or 4 chronic kidney disease. Please see Appendix for the complete reviews on the individual trials.



4 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

(b4)

[redacted]

VI.C.3. Primary Hyperparathyroidism

Background: Amgen seeks indications for the treatment of hypercalcemia in patients with parathyroid carcinoma and intractable primary hyperparathyroidism.

[redacted]

Hypercalcemia is associated with urolithiasis/nephrocalcinosis, gastrointestinal distress (ulcers, pancreatitis, and vomiting), muscle weakness, and neurobehavioral disorders (anxiety and

depression). Hyperparathyroidism is associated with bone disease, pain, fractures, or mineral loss in addition to the hypercalcemia.

There are no medical treatments approved for primary HPT and surgery is the only curative therapy available. Patients with parathyroid carcinoma can have recurrence of the hyperparathyroidism and hypercalcemia after surgery from incomplete resection or metastasis. Patients with intractable hyperparathyroidism are typically defined as patients who have failed parathyroid surgery or patients for whom surgery in contraindicated. Medical management for the hypercalcemia associated with primary HPT include bisphosphonates, hydration, and loop diuretics. These interventions offer acute but not chronic management of the hypercalcemia.

According to Amgen's report, parathyroid cancer is extremely rare and accounts for 0.5% of all primary hyperparathyroidism with an estimated prevalence of 500 cases in the United States. Approximately 20,000 people in the United States have intractable primary HPT.

Clinical Program: Amgen's clinical development program included 5 phase 2 trials investigating the safety and efficacy of cinacalcet for the treatment of primary hyperparathyroidism. The trials consist of an open-label treatment trial for patients with parathyroid carcinoma or intractable hyperparathyroidism (20000204); a randomized, placebo-controlled, tolerability trial (990160); a randomized, double-blind, placebo-controlled pharmacokinetic study (980125); a randomized, placebo-controlled, dose-titration trial (990120), and its open-label continuation trial (20000159). Please see the Appendix for the complete reviews of trials 20000204 and 990120.

COMMENT: Trial 20000204 is the only trial performed in the population in which the indication is sought. The remaining trials were phase 2 trials in patients with mild-to-moderate primary hyperparathyroidism. Study 990120 was reviewed in detail for general safety information.

Objectives: The primary objective of the studies in patients with primary hyperparathyroidism was to lower serum calcium. In study of patients with parathyroid carcinoma and intractable primary hyperparathyroidism (20000204), the goal was to lower serum calcium by 1 mg/dL. In the study of patients with primary hyperparathyroidism, the goal was to lower serum calcium into the normal range

COMMENT: All studies were phase 2. To the best of this reviewer's knowledge, there were no substantive discussion between DMEDP and Amgen regarding appropriate designs for studies to support an indication for parathyroid carcinoma or intractable primary hyperparathyroidism. The End-of-Phase 2 meeting held for cinacalcet focused on the secondary hyperparathyroidism indication.