CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-688

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-688

Drug Name: SENSIPAR (cinacalcet HCl)

Indication(s): ———— treatment of secondary hyperparathyroidism in patients with Chronic Kidney Disease, receiving or not receiving dialysis.

Treatment of hypercalcemia in patients with parathyroid carcinoma, or in patients with primary hyperparathyroidism for whom parathyroidectomy is not a treatment option.

Applicant: Amgen

Date(s): Submitted 9/5/03. PDUFA due date 3/8/04

Review Priority: Priority

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Keywords: NDA review, Clinical studies, Safety analyses

1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

The applicant's proposed indications for cinacalcet (sensipar) are the following:

- Treatment of hypercalcemia in patients with primary hyperparathyroidism or with parathyroid carcinoma
- Treatment of secondary hyperparathyroidism
- Control of parathyroid hormone (PTH), serum calcium x phosphorus, phosphorus and calcium levels in patients with chronic kidney disease receiving or not receiving dialysis

With regard to primary hyperparathyroidism, this reviewer has the following comments and conclusions based on this statistical review:

- [redacted]
- [redacted]
- [redacted]

  [redacted]. No assessment of safety can be made just based on 990120 since clearly patients with serious ADE's in 980125 would not continue into 990120.
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

With regard to secondary hyperparathyroidism in patients with ESRD and receiving dialysis, this reviewer has the following comments and conclusions based on this statistical review:

- Three Phase 2 studies showed that doses above 50 mg per day are usually needed to significantly impact PTH particularly in patients with baseline PTH above about 525.
- In the three large Phase 3 studies (172, 183 and 188), about 39% had mild HPT

(300≤iPTH≤500), about 35% had moderate HPT (500<iPTH≤800) and about 27% had severe HPT (iPTH>800).

- Two to three times more cinacalcet patients dropped out of the Phase 3 studies due to gastrointestinal ADE's than placebo patients (see Table 17). The dropout rate in the European study (183) was considerably higher (14% cinacalcet vs. 2% placebo). Gastrointestinal ADE was also the major reason for cinacalcet dropouts in the extension study.
- The median cinacalcet dose was 90 mg. A little more than 1/3 of the randomized cinacalcet patients were on the highest dose at the end of their treatment. Titration to the highest dose of180 mg was related to baseline iPTH; about 60% of patients in the highest baseline iPTH tertile were titrated to the 180 mg dose.
- Cinacalcet significantly decreased iPTH by about 50% over placebo. About half the patients had a decrease of 30% or more.
- About 40% of patients treated with cinacalcet had mean iPTH during maintenance lower than 250 pg/ml (the primary endpoint) compared to about 5% for placebo; about half of the cinacalcet patients were below the normal range (<150 pg/ml, Table 20).
- Cinacalcet significantly lowered calcium, phosphorus and Ca x P compared to placebo (Table 21). Changes in these endpoints were not correlated with changes in the primary endpoint, iPTH.
- A double-blind extension study (240) of a total of 266 patients from Study 172 (about 52% of the randomized patients) and from Study 183 (about 15% of the randomized patients) followed patients for an additional 26 weeks (total of one year). Less than one-third of the randomized patients from those studies completed the extension.
- Nearly half of the patients in the extension study required the highest dose of 180 mg per day to adequately lower iPTH.
- In the 3 phase three trials, about 1/5 of the patients had a mean iPTH below 150 pg/mL (the target range was 150 to 250); about half of those patients (~10% of the total) had levels below 100 pg/mL. In the applicant's bone study, two patients who developed adynamic bone disease had iPTH levels below 100; a preliminary review indicates that only two patients in that study had an iPTH below 100 (this reviewer will confirm this after completion of this document).
- Patients with high levels of iPTH (>800 for secondary HPT, ESRD patients) are not able to achieve levels of 250 or less even on the highest dose; the median iPTH for this subgroup during the efficacy phase was 703 pg/mL for cinacalcet and 1160 for placebo.

With regard to <u>secondary hyperparathyroidism in patients with CRI and not receiving dialysis</u>, this reviewer has the following comments and conclusions based on this statistical review:

- [redacted]
- [redacted]

Given that HPT is a chronic disease requiring chronic treatment, it is important to look at the number of patients maintained on treatment in the extension studies. In Study 20010240 (an extension of Studies 172 and 183 in secondary HPT patients), only 28% (n=210, 97 on cinacalcet) of the originally randomized patients completed the 26-week extension study. Two additional extension studies were conducted, Studies 20000130 and 20020158. Study 20020158 is ongoing and data from this study were not provided in the NDA. Study 2000130 enrolled 170 patients from the Phase 2 studies and Study 237. After 1 year of treatment, 117 patients were on study; about 40% had an iPTH value less than 250 pg/dL. So the data for secondary HPT patients one year and beyond is limited in the application, although the applicant continues to treat patients in 20020158 which should provide a much larger database of patients treated long-term. [redacted]

The clinical trials provide statistical evidence of the efficacy of cinacalcet for the treatment of [redacted] secondary HPT. Two problems with the efficacy are evident: 1) most secondary HPT patients with high levels of iPTH and parathyroid carcinoma patients with high levels of calcium are not able to achieve normal levels so dosing does not appear to be sufficient for patients with severe disease and 2) about half the responders reach levels below the target range of iPTH. Oversuppression of iPTH can lead to detrimental effects on bone. In addition, the benefits need to be weighed against risks which may include hypocalcemia, QT interval prolongation, changes in testosterone levels and seizure.

1.2 Brief Overview of Clinical Studies

The applicant has submitted the results of 25 Phase 2 and Phase 3 clinical trials designed to demonstrate the efficacy and safety of cinacalcet for the treatment of primary and secondary hyperparathyroidism (HPT); these trials are briefly described in the following two sections of this review.

1.2.1 Primary Hyperparathyroidism

For patients with primary HPT, the applicant is seeking an indication for the treatment of hypercalcemia.

Three studies (980125, 990120 and 990160), designed to study primary HPT in patients with above normal iPTH and above normal serum calcium (Table 1), were placebo-controlled studies. Study 980125 was primarily a PK study but also provided some efficacy data. In Studies 980125 and 990120, titration studies, the highest dose administered was 50 mg BID. In Study 990160, a higher dose of 65 mg BID was studied.

1.2.2 Secondary Hyperparathyroidism

The applicant studied the effects of cinacalcet in two populations of patients with secondary HPT; end-stage renal disease (ESRD) patients on dialysis and chronic renal insufficiency (CRI) patients not on dialysis.

The results of 8 placebo-controlled clinical trials were submitted to support a secondary HPT indication in patients with ESRD (Table 2); all patients were receiving dialysis. In all trials the entry criterion for iPTH at baseline was 300 pg/mL or greater. In three Phase 2 trials, 990101, 990102 and 990740, it was determined that doses up to 100 mg daily were not sufficient and so subsequent trials (20000172, 20000183 and 2000188) used doses up to 180 mg daily; these latter three trials are considered the pivotal trials in ESRD patients and therefore receive the most attention in this review. Study 20000237 was similar in design to the 3 large trials and is not reviewed here due to its small size (82 patients) and short treatment period (12 weeks). Two studies (990126 and 20010141) were designed to examine effects on bone and are not reviewed here (see the review of medical reviewer, Dr. Theresa Kehoe, for further details).

Table 2. Randomized, double-blind, placebo-controlled studies in patients with secondary HPT as a consequence of end-stage renal disease (ESRD)

Study	Entry Criteria	Treatment groups (N)	Cinacalcet Dosing Once Daily	Treatment Periods	Primary Endpoint
990101	iPTH≥300 pg/mL Hemodialysis ≥3 mos.	Cinacalcet (39) Placebo (39)	Start 20 mg Titrate to 10, 30, 40 and 50 mg	Titration: 12 wks Maintenance:6 wks Follow-up: 36 wks	% of pts. with iPTH % ch≥30%
Substudy 990126	990101 pts with iPTH≥500 pg/mL	Cinacalcet (9) Placebo (6)	Start 20 mg Titrate to 10, 30, 40 and 50 mg	Titration: 12 wks Maintenance:6 wks Follow-up: 36 wks	BONE
990102	iPTH≥300 pg/mL Hemodialysis	Cinacalcet (31) Placebo (31)	Start 20 mg Titrate to 10, 30, 40 and 50 mg	Titration: 12 wks (open label; rand. after titration) Maintenance:9 wks Follow-up: 32 wks	% of pts. with iPTH % ch≥30%
990740	iPTH≥300 pg/mL Hemodialysis ≥3 mos.	Cinacalcet (36) Placebo (35) w/Vit. D	Start 25 mg Titrate to 50, 75 and 100 mg	Titration: 12 wks Maintenance:6 wks Follow-up: 36 wks	% of pts. with iPTH % ch≥30%
20000172	iPTH≥300 pg/mL Hemodialysis ≥3 mos. Corrected ser. Ca≥8.4 mg/dL	Cinacalcet (205) Placebo (205)	Start 30 mg Titrate to 60, 90, 120 and 180 mg	Titration: 12 wks Maintenance:14 wks	% pts. with iPTH≤250 pg/mL
20000183	iPTH≥300 pg/mL Hemodialysis ≥3 mos. Corrected ser. Ca≥8.4 mg/dL	Cinacalcet (166) Placebo (165)	Start 30 mg Titrate to 60, 90, 120 and 180 mg	Titration: 12 wks Maintenance:14 wks	% pts. with iPTH≤250 pg/mL
20000188	Mean iPTH≥300 pg/mL Hemodialysis or peritoneal dialysis ≥1 mo.	Cinacalcet (294) Placebo (101)	Start 30 mg Titrate to 60, 90, 120 and 180 mg	Titration: 16 wks Maintenance:10 wks	% pts. with iPTH≤250 pg/mL
20000237	Mean iPTH≥300 pg/mL Hemodialysis ≥3 mos.	Cinacalcet (41) Placebo (41)	Start 50 mg Titrate to 70, 90, 120 and 180 mg	Titration: 8 wks Maintenance:4 wks	% pts. with iPTH≤250 pg/mL
20010141	iPTH≥300 pg/mL Hemodialysis ≥1mo.	Cinacalcet (32) Placebo (16)	Start 30 mg Titrate to 50, 70, 90, 120 and 180 mg	Titration: 24 wks Maintenance:28 wks	BONE

Two studies were conducted in patients with secondary HPT as a consequence of CRI (Table 3); these patients were not receiving dialysis. These two trials (2000236 and 20010239) differed on entry criteria, titration schemes and primary endpoints. The results from 236 were used to design 239. Both trials are reviewed here.

Table 3. [redacted] studies in patients with secondary HPT as a consequence of chronic renal insufficiency (CRI)

Study (location and # of centers)	Entry Criteria	Treatment groups (N)	Cinacalcet Dosing	Treatment Periods	Primary Endpoint
20000236	[redacted]				
20010239	[redacted]				

Patients completing double-blind treatment in one of the aforementioned studies could continue treatment in one of the extension studies listed in Table 4. Only Study 20010240 is reviewed in any detail here. This study was an extension of Studies 172 and 183; patients remained on randomized treatment in this study and the study retained the double-blind for 26 weeks.

Table 4. Extension studies in patients with secondary HPT

Extension Study	Source Studies	Cinacalcet Doses + Sample Size	Treatment periods
20010240 double-blind placebo-controlled	20000172 + 20000183	Start 30 mg Titrate to 60, 90, 120 and 180 mg N=128 cinacalcet N=138 placebo	Maintenance: 26 wks
20000130 open-label	990101, 990102, 990740 +20000237	Start 30 mg Titrate to 50, 70/75, 90/100, 120 and 180 mg N=170	Titration: 12 wks Maintenance:up to 4 years
20010142 open-label	20000236	Start 30 mg Titrate to 60, 90, and 120 N=4	Titration: 10 wks Maintenance:100 wks planned but study stopped
20020158 open-label	20000172, 20000183, 20000188, 20010141 +20010240	Start 30 mg Titrate to 60, 90, 120 and 180 mg N=563, still enrolling	[redacted]

1.3 Statistical Issues

There were no issues regarding the statistical methods used that impacted the interpretation of the efficacy results.

Some of the issues examined by the reviewer but not discussed in detail in the body of the review were:

- The sensitivity analyses performed by the applicant.
    - There were several instances where problems with the PTH assay resulted in rerunning the assays. This reviewer found no impact on the efficacy results.
    - Analyses of LOCF data were consistent with completer analyses
- Averaging of the maintenance values
    - For each study, this reviewer looked at the by-week results to be sure that these results were consistent with the results of the primary analysis of the averaged values.
- Normality of the data
    - When the data was found to depart from normality, nonparametric analyses were performed by the reviewer (e.g. testosterone)
- Impact of dropouts
    - Dropouts were not a major issue with, usually, more than 80% of the patients providing data for the efficacy analyses.
    - A difference between reasons for dropout for European and US studies was examined carefully by this reviewer.

Due to the complexity of this review and the shortened review time , there were a number of issues that arose at the end of the review process that could not be addressed in this review. If this reviewer finds with further review that these issues should be documented, an addendum to this review will be created.

2. Introduction

2.1 Overview

Cinacalcet, a calcimimetic, regulates "plasma PTH secretion by amplifying the receptor's sensitivity to extracellular calcium and thereby reducing PTH concentrations" (page 36 of the applicant's clinical report of Study 172). In addition to controlling iPTH levels, cinacalcet is intended to control phosphorus and calcium levels. Levels of phosphorus greater than 6.5 mg/dL and/or of Ca x P greater than 72 $(mg/dL)^2$ elevate the risk of death in dialysis patients.

The applicant is seeking indications for both primary and secondary HPT. For primary HPT, the database presented here is small. Most of the application consists of data from patients with secondary HPT so most of this review is focussed on secondary HPT. See Tables 1 through 4 in the previous section of this review for a summary of the clinical trials provided in the NDA for cinacalcet.

The primary goal of cinacalcet therapy in patients with secondary HPT is to control levels of iPTH, Ca x P, Ca and P reaching the target values shown in Table 5 (from the NDA). In most of the secondary HPT trials in this submission, the primary endpoint was percentage of patients reaching an iPTH level of 250 pg/mL. Measures of effect on Ca, P and Ca x P were included as secondary endpoints.

Table 5. Target values for secondary HPT Metabolic parameters in ESRD

Parameter	Target Serum Concentration
IPTH	150-300 pg/mL
Ca x P	≤ 55 $(mg/dL)^2$
Calcium	8.4-9.5 mg/dL
Phosphorus	3.5-5.5 mg/dL

2.2 Data Sources

Datesets and study reports were accessible from the CDER Electronic Document Room at \\CDSESUB1\N21688\N 000\2003-09-05. Hardcopies of study reports for studies selected by this reviewer were reviewed also.

All graphs and tables were created by the reviewer unless otherwise noted. Also results presented in tables were calculated by the reviewer unless otherwise noted.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Primary Hyperphosphotemia

[redacted]

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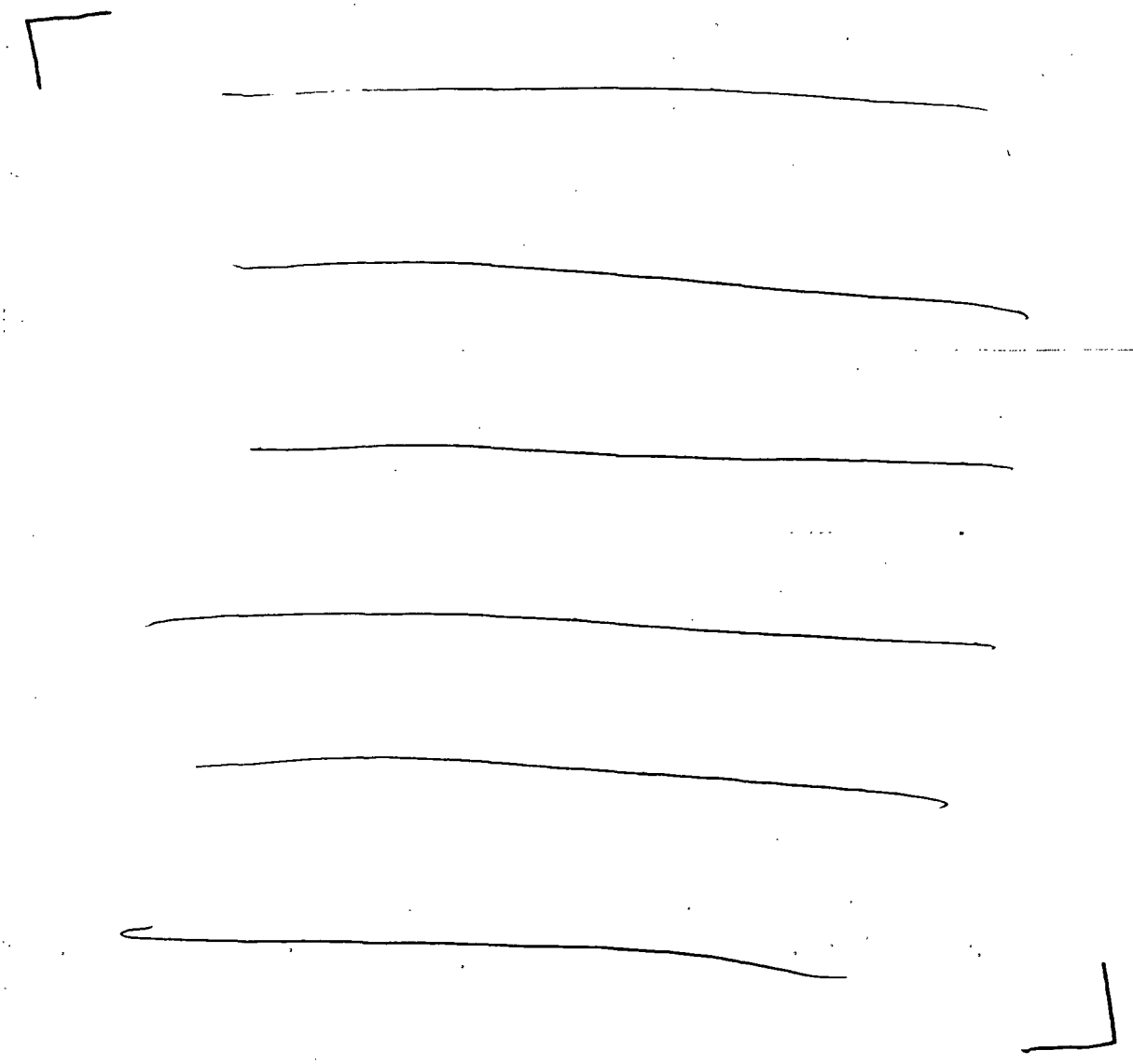

3.1.2 Secondary Hyperphosphotemia in Patients with End Stage Renal Disease

3.1.2.1 Phase 2 Studies 990101, 990102 and 990740

The applicant conducted three Phase 2 studies (990101, 990102 and 990740) in patients with secondary HPT as a consequence of ESRD (Table 10). The to-be-marketed formulation for sensipar was not used in these studies. The inclusion criteria (Table 11) were essentially the same for the three studies. Patients were excluded if they had a parathyroidectomy within six months, had received an investagational drug within 28 days, had a seizure within 12 months or had a gastrointestinal disorder with impaired absorption.

In the first studies conducted (101 and 102), patients were titrated to a maximum dose of 50 mg; in the third Phase 2 study (740), patients could be titrated to a maximum of 100 mg per day. In all studies the primary outcome variable was proportion of patients with a percent change from

baseline of 30% or more during a maintenance phase.

Table 11. Secondary HPT in patients with end-stage renal disease (ESRD): Phase 2 studies

Study	Entry Criteria	Treatment groups (N)	Cinacalcet Dosing Once Daily	Treatment Periods	Primary Endpoint
990101 (US and Canada)	iPTH≥300 pg/mL Hemodialysis ≥3 mos.	Cinacalcet (39) Placebo (39)	Start 20 mg Titrate to 10, 30, 40 and **50 mg**	Titration: 12 wks Maintenance:6 wks Follow-up: 36 wks	% of pts. with iPTH % ch≥30%
Substudy 990126	990101 pts with iPTH≥500 pg/mL	Cinacalcet (9) Placebo (6)	Start 20 mg Titrate to 10, 30, 40 and 50 mg	Titration: 12 wks Maintenance:6 wks Follow-up: 36 wks	BONE
990102 (Europe)	iPTH≥300 pg/mL Hemodialysis	Cinacalcet (31) Placebo (31)	Start 20 mg Titrate to 10, 30, 40 and **50 mg**	Titration: 12 wks (open label cinacalcet; randomized after titration) Maintenance:9 wks Follow-up: 32 wks	% of pts. with iPTH % ch≥30%
990740 (US)	iPTH≥300 pg/mL Hemodialysis ≥3 mos.	Cinacalcet (36) Placebo (35) w/Vit. D	Start 25 mg Titrate to 50, 75 and **100 mg**	Titration: 12 wks Maintenance:6 wks Follow-up: 36 wks	% of pts. with iPTH % ch≥30%

In Studies 101 and 102 about 85% of the patients completed the maintenance phase while retention was a little higher in Study 740 at 92 %.

About 60% of the patients in Studies 101 and 102 were titrated to 50 mg per day; about 47% were titrated to 100 mg in Study 740 with another 22% titrated to 75 mg.

The iPTH results for the Phase 2 studies are summarized in Table 12 below. Within each study, treatment groups are comparable for iPTH at baseline though considerable variability is evident in each group. The treatment effects on iPTH are summarized by this reviewer using three different endpoints; proportion of patients with iPTH of 250 or less (a primary endpoint in the Phase 3 studies), proportion of patients with decrease in iPTH % change from baseline of 30% or more (the primary endpoint in these studies) and the mean % change from baseline. The results for Study 990740 show statistically significant treatment effects for all three endpoints and generally larger effects than those observed in Studies 990101 and 990102[1]. The results from these studies demonstrate that doses higher than 50 mg are needed to obtain significant lowering; this reviewer found this to be particularly true for patients with baseline values of iPTH above about 525 pg/ml.

Table 12. Secondary HPT in patients with ESRD: Phase 2 Studies
Applicant's iPTH results during the maintenance phase

	Study 990101			Study 990102			Study 990740		
	Placebo (n=39)	Cinacal (n=39)	p-value	Cin/Pla (n=31)	Cin/Cin (n=31)	p-value	Placebo (n=35)	Cinacal (n=36)	p-value
Baseline Mean (SD) Median	637 (456) 494	632 (280) 607	NS	600 (271) 496	680 (298) 598	0.21	583 (421) 461	626 (311) 579	NS
% of pts w/ iPTH≤250 pg/mL	10%	15%	0.5	13%	23%	0.32	20%	44%	0.03
% of pts w/ iPTH % ch ≥30% Dec	8%	38%	0.001	23%	35%	0.26	23%	53%	0.009
iPTH % ch Mean (SD) Median	+22% (38) +25%	-26% (29) -23%	<.0001	-2% (37) -2.4%	-13% (40) -17%	0.13	+3% (47) +2%	-32% (44) -49%	0.001

P-value results from stratified CMH to test proportions and from ANOVA to test continuous variables.

3.1.2.2 Phase 3 Studies 20000172, 20000183 and 20000188

Design

Studies 20000172 (referred henceforth as Study 172), 20000183 (183) and 20000188 (188) were multicenter, double-blind, randomized, controlled, Phase 3 clinical trials designed to assess the efficacy and safety of cinacalcet compared to placebo in patients with uncontrolled secondary hyperphosphotemia as a consequence of end-stage renal disease and on dialysis.

In all three studies, treatment (cinacalcet or placebo) was titrated from 30→60→90→120→180 mg, once daily, dependent on the patient's iPTH level (iPTH>200 pg/mL with serum Ca≥7.8) and safety endpoints. Cinacalcet was titrated to the next higher dose during the titration phase unless the iPTH was 200 or less, or the serum calcium was less than 7.8 or for an ADE.

In Studies 172 and 183, stratified randomization was 1:1 while for Study 188 the ratio was 3:1. For Studies 172 and 183, randomization to cinacalcet or placebo was stratified on baseline iPTH and Ca x P based on 3 levels of iPTH (300≤iPTH≤500, 500<iPTH≤800 and iPTH>800)

1 The results for Study 102 are clearly weak. Given the results, the unusual ADE rate and the design of switching from cinacalcet to randomized treatment, this reviewer questions whether there were more protocol violations than the few that were reported. Since this is a small Phase 2 trial, it does not deserve further reviewer scrutiny.

and 2 levels of Ca x P (≤70 and >70). For Study 188, randomization was stratified on baseline iPTH and dialysis modality using four strata (300≤iPTH≤500 and hemodialysis; 500<iPTH≤800 and hemodialysis; iPTH>800 and hemodialysis; and iPTH>300 and peritoneal dialysis).

Entry criteria included the following:

- Men and women aged 18 years or older
- Mean of 3 (2 for Study 188) iPTH measures taken within 30 days of Day 1 ≥300 pg/mL
- Mean of 3 (2 for Study 188) serum calcium measures taken within 30 days of Day 1 ≥8.4 mg/dL
- 3 times weekly in-center hemodialysis for ≥3 months before Day 1 for Studies 172 and 183; hemodialysis or peritoneal dialysis for ≥1 month before Day 1 for Study 188
- No change in vitamin D dose within 30 days prior to Day 1
- No change in phosphate binder dose, calcium supplement dose or dialysate calcium concentration within 30 days prior to Day 1 (Studies 172 and 183 only)

Patients with a history of seizures were allowed in these trials; in the applicant's Phase 2 trials of secondary HPT, patients with a history of seizures within the year previous to randomization were excluded.

In all three studies, concomitant therapy with phosphate binders and Vitamin D was allowed with changes to the dose levels permitted during the trial as described in the table below.

Table 13. Secondary HPT in patients with ESRD: Phase 3 Studies
Applicant's Table 2 describing concomitant therapy guidelines
(reformatted by reviewer)

	30 Days Before Study	Day 1 to End of Study	
Phosphate Binders	Fixed dose and brand	Complete flexibility of dose and brand	
Vitamin D Sterols	Fixed dose, brand, and route of administration	Decrease permitted if: Serum calcium ≥ 11 mg/dL OR Serum phosphorus ≥ 6.5 mg/dL OR Ca x P ≥ 70 (mg/dL)[2] iPTH <100 pg/mL on the lowest dose of study drug (30 mg cinacalcet/placebo)[a]	Increase permitted if: Serum calcium < 8.4 mg/dL OR Symptoms of hypocalcemia OR iPTH increases by ≥ 50% from baseline for 3 consecutive visits[a]

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All three trials consisted of three phases (Table 14), a screening phase, titration phase and efficacy assessment phase. Studies 172 and 183 had identical designs while Study 188 had a longer titration phase by 4 weeks. All three trials were 26 weeks long.

Table 14. Secondary HPT in patients with ESRD: Phase 3 Studies 172, 183 and 188
Trial phases

Phase	Study 172	Study 183	Study 188
Screening	30 days	30 days	30 days
Titration	**Weeks 1 to 12** Weekly Visits Titrate every 3 weeks from 30 mg to maximum of 180 mg based on iPTH response and safety	**Weeks 1 to 12** Weekly Visits Titrate every 3 weeks from 30 mg to maximum of 180 mg based on iPTH response and safety	**Weeks 1 to 16** Bi-weekly Visits Titrate every 4 weeks from 30 mg to maximum of 180 mg based on iPTH response and safety
Efficacy-assessment	**Weeks 13 to 26** 14 weeks Bi-weekly Visits Titration allowed at Weeks 16, 20 and 24	**Weeks 13 to 26** 14 weeks Bi-weekly Visits Titration allowed at Weeks 16, 20 and 24	**Weeks 17 to 26** 10 weeks Bi-weekly Visits Titration allowed at Weeks 20 and 24

The primary efficacy variable in all the trials was the proportion of subjects with a mean plasma iPTH value≤250 pg/mL during the efficacy assessment phase.

Secondary efficacy variables included the following:
- proportion of patients with mean iPTH % decrease from baseline ≥30% in the efficacy phase
- % ch from baseline in mean Ca x P during the efficacy phase
- change from baseline in cognitive function by the KDQOL at end of efficacy phase

Tertiary efficacy variables included the following:
- % change in mean iPTH, mean Ca and mean P during the efficacy phase
- proportion of pts with both a mean plasma iPTH value≤250 pg/mL and reduction from baseline in Ca x P during the efficacy phase

Patient Disposition

Studies 172 and 188 were primarily conducted in North America with the majority of the patients enrolled within the United States (Table 15). Most of the patients in Study 183 were enrolled in European centers.

Table 15. Secondary HPT in patients with ESRD: Phase 3 Studies 172, 183 and 188
Location of centers

	Study 172	Study 183	Study 188
# centers	63	62	60
Location	North America Canada N=38 US N=372	Europe and Australia Europe N=286 Australia N=45	North America and Australia Canada N=93 US N=288 Australia N=14

Roughly 400 patients were randomized in each of the three trials with 1:1 assignment in Studies 172 and 183 and 3:1 in Study 188 (Table 16). More than 80% of the patients in each treatment group completed the titration phase. About ¾ of the patients in Studies 172 and 188 (the US studies) completed the study. In the European study (183), the completion rates for the groups differ appreciably with only 64% of the Cinacalcet patients and 80% of the placebo patients completing.

Table 16. Secondary HPT in patients with ESRD: Phase 3 Studies 172, 183 and 188
Patient Disposition

	Study 172		Study 183		Study 188	
	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet
Randomized	205 (100%)	205 (100%)	165 (100%)	166 (100%)	101 (100%)	294 (100%)
Never treated	1	5	0	1	0	3
Titration Phase Week 1 Week 4 Week 8 Last Week[1]	204 (99+%) 174 (85%)	200 (98%) 170 (83%)	165 (100%) 151 (92%)	165 (>99%) 136 (82%)	101 (100%) 84 (83%)	291 (99%) 239 (81%)
Efficacy Phase Week 18 Week 22 Week 26	 158 (77%)	 146 (71%)	 132 (80%)	 107 (64%)	 77 (76%)	 294 (74%)
Completers	158 (77%)	146 (71%)	132 (80%)	107 (64%)	77 (76%)	294 (74%)
Pts with at least one value in efficacy phase	174 (85%)	169 (82%)	150 (91%)	139 (84%)	84 (83%)	238 (81%)

The major reason for patients discontinuing treatment in all treatment groups was the occurrence of an adverse event (Table 17). In Study 183 (the European study), nearly 5 times as many patients on cinacalcet (23%) dropped due to ADE than on placebo (5%). No significant treatment group difference in ADE incidence rates is seen in the two USA studies.

Table 17. Secondary HPT in patients with ESRD: Phase 3 Studies 172, 183 and 188
Reasons for discontinuation

	Study 172		Study 183		Study 188	
	Placebo (n=205)	Cinacalcet (n=205)	Placebo (n=165)	Cinacalcet (n=166)	Placebo (n=101)	Cinacalcet (n=294)
Ineligible	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
ADE	**19 (9%)**	**19 (9%)**	**9 (5%)**	**38 (23%)**	**8 (8%)**	**39 (13%)**
Consent Withdrawn	10 (5%)	12 (6%)	3 (2%)	4 (2%)	1 (1%)	13 (4%)
Inv. Decision	3 (1%)	6 (3%)	2 (1%)	0 (0%)	3 (3%)	6 (2%)
Lost-to-FU	1 (<1%)	4 (2%)	0 (0%)	2 (1%)	0 (0%)	3 (1%)
Death	5 (2%)	6 (3%)	5 (3%)	3 (2%)	2 (2%)	3 (1%)
Parathyroidectomy	2 (1%)	0 (0%)	3 (2%)	0 (0%)	2 (2%)	0 (0%)
Kidney transplant	5 (2%)	7 (3%)	9 (5%)	8 (5%)	6 (6%)	10 (3%)
Other	0 (0%)	0 (0%)	2 (1%)	3 (2%)	2 (2%)	1 (1%)

Within the cinacalcet group, the majority of the ADE's were gastrointestinal including diarrhea, nausea and vomiting. The incidence of these events is shown in Table 18 below. There is clearly

1 Week 12 in Studies 172 and 183 and Week 16 in Study 188.

a marked difference in gastrointestinal event rates between the placebo and cinacalcet groups with more than twice as many events in the cinacalcet group; the difference is particularly significant within Study 183, the European Study.

Table 18. Secondary HPT in patients with ESRD: Phase 3 Studies 172, 183 and 188 Gastrointestinal ADE's that resulted in treatment discontinuation summarized by treatment and country

	Study 172		Study 183		Study 188	
	Placebo (n=205)	Cinacalcet (n=205)	Placebo (n=165)	Cinacalcet (n=166)	Placebo (n=101)	Cinacalcet (n=294)
ADE	**19 (9%)**	**19 (9%)**	**9 (5%)**	**38 (23%)**	**8 (8%)**	**39 (13%)**
Gastrointestinal	**3 (1.5%)**	**12 (5.8%)**	**3 (1.8%)**	**23 (13.9%)**	**3 (3%)**	**24 (8.2%)**
Gastrointestinal ADE's by country						
US	3/185 (2%)	12/187 (6%)	NA	NA	3/69 (4%)	12/219 (5.5%)
Canada	0/20 (0%)	0/18 (0%)	NA	NA	0/28 (0%)	10/65 (15%)
Australia	NA	NA	1/23 (4%)	2/22 (9%)	0/4 (0%)	2/10 (20%)
Europe	NA	NA	2/142 (1%)	21/144 (15%)	NA	NA

The relatively low rates of gastrointestinal events within the US (about 6%) compared to the European rate of 15% could be related to the classification of reasons. This reviewer read the comments describing the reasons for patient withdrawals to determine if the reason for the country differences was related to misclassification of the reason for withdrawal (e.g. consent withdrawn because of an ADE) and found only one placebo patient in Study 172 complained of gastrointestinal problems but was recorded as withdrawing consent. There does not appear to be a systematic misclassification of withdrawal reasons that would explain the difference in ADE rates between the countries.

Baseline Demographics

Baseline demographics (Table 19 on the following page) show that about 3/5 of the patients were male and the average age was mid-fifties with about ¼ of the patients 65 or older. The European study (183) was predominantly Caucasian while the other two studies had a significant number of blacks (about 58% in Study 172 and about 37% in Study 188). About ½ of the patients presented with an iPTH of 500 or less and about ½ had a Ca x P of 70 or less at baseline; 1/3 had both. (For the distribution of baseline PTH, see Appendix 3.) In Studies 172 and 183, enrollment of patients with PTH greater than 800 pg/ml was limited to 20%; in Study 188 where no limitation on enrollment was made, the percentage is double. More than 90% of the patients were on phosphate binders at baseline and about 2/3 were taking Vitamin D. Most patients had hypertension and about 35-40% of USA patients had diabetes while only about 17% of European patients had diabetes.

Table 19. Secondary HPT in patients with ESRD: Phase 3 Studies 172, 183 and 188
Baseline demographics

	Study 172		Study 183		Study 188	
	Placebo (n=205)	Cinacalcet (n=205)	Placebo (n=165)	Cinacalcet (n=166)	Placebo (n=101)	Cinacalcet (n=294)
Gender						
Male	60%	60%	65%	61%	63%	62%
Female	40%	40%	35%	39%	37%	38%
Race						
White	34%	30%	95%	89%	39%	39%
Black	58%	59%	1%	6%	35%	39%
Other	9%	11%	4%	5%	27%	22%
Age						
Mean (SD)	54 (15)	53 (14)	56 (15)	55 (15)	54 (14)	52 (14)
Range	22-86	18-82	19-85	27-88	20-82	20-84
65 or older	28%	25%	34%	31%	23%	18%
75 or older	9%	9%	12%	10%	8%	6%
Rand. Strata						
300≤iPTH≤500	45%	45%	42%	42%	27%	29%
Ca x P≤70	34%	34%	33%	33%	23%	26%
Ca x P>70	11%	11%	8%	8%	4%	3%
500<iPTH≤800	35%	36%	39%	39%	32%	31%
Ca x P≤70	25%	26%	28%	28%	24%	25%
Ca x P>70	10%	10%	11%	10%	8%	6%
iPTH>800	20%	20%	19%	20%	42%	40%
Ca x P≤70	13%	13%	13%	14%	30%	24%
Ca x P>70	7%	7%	6%	6%	12%	16%
Vitamin D						
Yes (%)	68%	70%	66%	61%	69%	65%
Phosphate binder						
Yes (%)	95%	94%	90%	90%	93%	93%
Renagel						
Yes (%)	51%	55%	20%	22%	54%	50%
Zemplar						
Yes (%)	45%	45%	0%	1%	26%	23%
Dialysis (years)						
Mean (SD)	5.2 (4.6)	5.5 (4.7)	7.1 (6.7)	6.5 (5.8)	5.3 (5.4)	4.7 (4.4)
Median	3.5	4.3	4.4	4.7	4.1	3.5
Modality						
Hemodialysis	100%	100%	100%	100%	88%	88%
Peritoneal dialysis					12%	12%
Diabetes						
Yes (%)	41%	39%	15%	19%	38%	33%
Hypertension						
Yes (%)	99%	98%	90%	89%	96%	97%

Dosing

Patients were titrated throughout the trial based on efficacy and safety. It is clear from Table 20 that patients on placebo were more often titrated to the highest dose in all studies, as would be expected in a blinded study. The median cinacalcet dose during maintenance was 90 mg. A little more than 1/3 of the randomized cinacalcet patients were on the highest dose at the end of their treatment. Among completers on cinacalcet, 45% in Study 172 , 37% in Study 183, and 41% in Study 188.were on the highest dose of 180 mg daily at the end of the study. Titration to the highest dose was related to baseline iPTH; about 60% of patients in the highest baseline iPTH tertile were titrated to the 180 mg dose.

Table 20. Secondary HPT in patients with ESRD: Phase 3 Studies 172, 183 and 188
Last dose taken by study and treatment group

	Study 172		Study 183		Study 188	
	Placebo (n=204)	Cinacalcet (n=200)	Placebo (n=165)	Cinacalcet (n=165)	Placebo (n=101)	Cinacalcet (n=291)
Dose at endpoint						
30	6%	19%	3%	22%	7%	21%
60	2%	14%	3%	19%	7%	17%
90	4%	15%	5%	14%	10%	15%
120	6%	13%	4%	16%	2%	13%
180	81%	40%	85%	28%	74%	33%

Statistical Methods

For the analysis of the primary endpoint (% of patients with mean PTH<250), patients without data during the efficacy-assessment phase were counted as non-responders. Two additional analyses of the primary endpoint were performed by the applicant: 1) excluding patients with no data in the efficacy phase and 2) carrying forward data from the titration phase. The results from these additional analyses yielded very similar results to the primary analysis and therefore are not presented here.

Secondary endpoints were only analyzed by the applicant if the primary endpoint results were significant; this was not an issue since primary endpoint results were significant.

Categorical endpoints were analyzed using a CMH test stratified on iPTH and Ca x P. Continuous variables were analyzed using analysis of covariance with baseline values as covariates.

Efficacy Results

The effects of cinacalcet on iPTH were examined using several variables defined in the protocols of Studies 172, 183 and 188. The primary efficacy variable was the proportion of subjects with a mean plasma iPTH value≤250 pg/mL during the efficacy assessment phase. A secondary efficacy variable was the proportion of patients with a mean iPTH percent decreases from baseline ≥30% during the efficacy assessment phase and a tertiary efficacy variable was the percent change in mean iPTH. For all three variables the mean iPTH for each patient is computed as the average of all iPTH values recorded during the efficacy assessment phase.

The results for all three variables are summarized for the three studies in the table below.

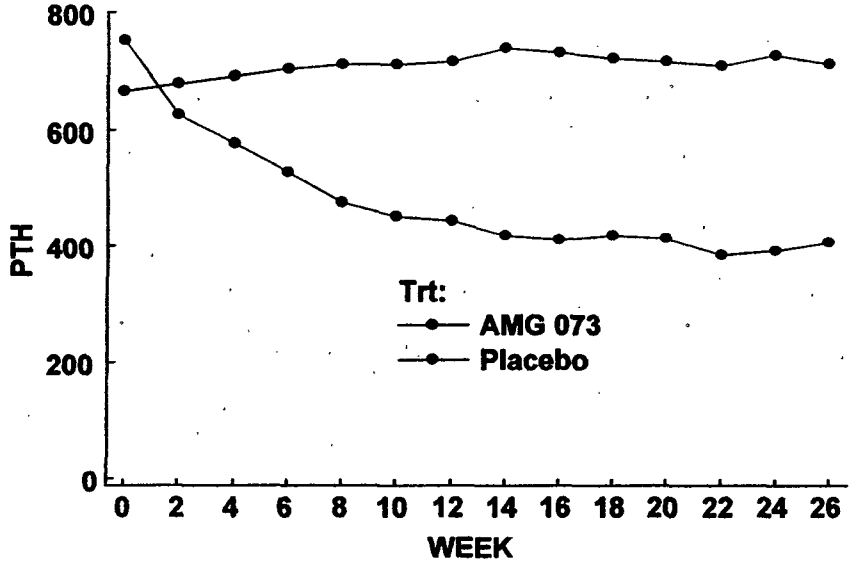
The treatment groups are seen to be comparable at baseline within each study; higher mean baselines are seen in Study 188 (about 830) than in the other two studies (about 640). All studies showed statistically significant treatment effects on all iPTH variables (p<.0001) with comparable treatment effects seen across the studies. A graph of iPTH overtime (Figure 4) for the three studies combined shows that on average the iPTH decreases steadily during the 12-week titration phase and then is maintained through the efficacy phase.

Table 21 Secondary HPT in patients with ESRD: Phase 3 Studies 172, 183 and 188 IPTH Efficacy Results

	Study 172			Study 183			Study 188		
	Placebo (n=205)	Cinacal (n=205)	p-value	Placebo (n=165)	Cinacal (n=166)	p-value	Placebo (n=101)	Cinacal (n=294)	p-value
Baseline Mean (SD) Median	651 (398) 535	636 (340) 537	0.41	630 (317) 556	652 (372) 547	0.36	832 (486) 669.5	847 (685) 703	0.77
% of pts w/ iPTH≤250 pg/mL	4% 8/205	41% 84/205	<.0001	7% 11/165	46% 76/166	<.0001	6% 101/294	35% 104/294	<.0001
% of pts w/ iPTH % ch ≥30%	11% 23/205	61% 126/205	<.0001	12% 19/165	68% 113/166	<.0001	10% 10/101	59% 174/294	<.0001
iPTH % ch Mean (SD) Median	+10% (41) +3.0%	-43% (40) -54%	<.0001	+7% (35) +6.6%	-52% (32) -59%	<.0001	+6% (35) +4%	-46% (31) -54%	<.0001
% of pts w/ iPTH<150 pg/ml	0.5% 1/205	18% 37/205	<.0001	1.8% 3/165	28% 47/166	<.0001	1% 1/101	16% 48/294	<.0001

P-value results from stratified CMH to test proportions and from ANCOVA to test continuous variables.

Figure 4. iPTH (pg/mL) by week on study for patients who completed Study 172, 183 or 188



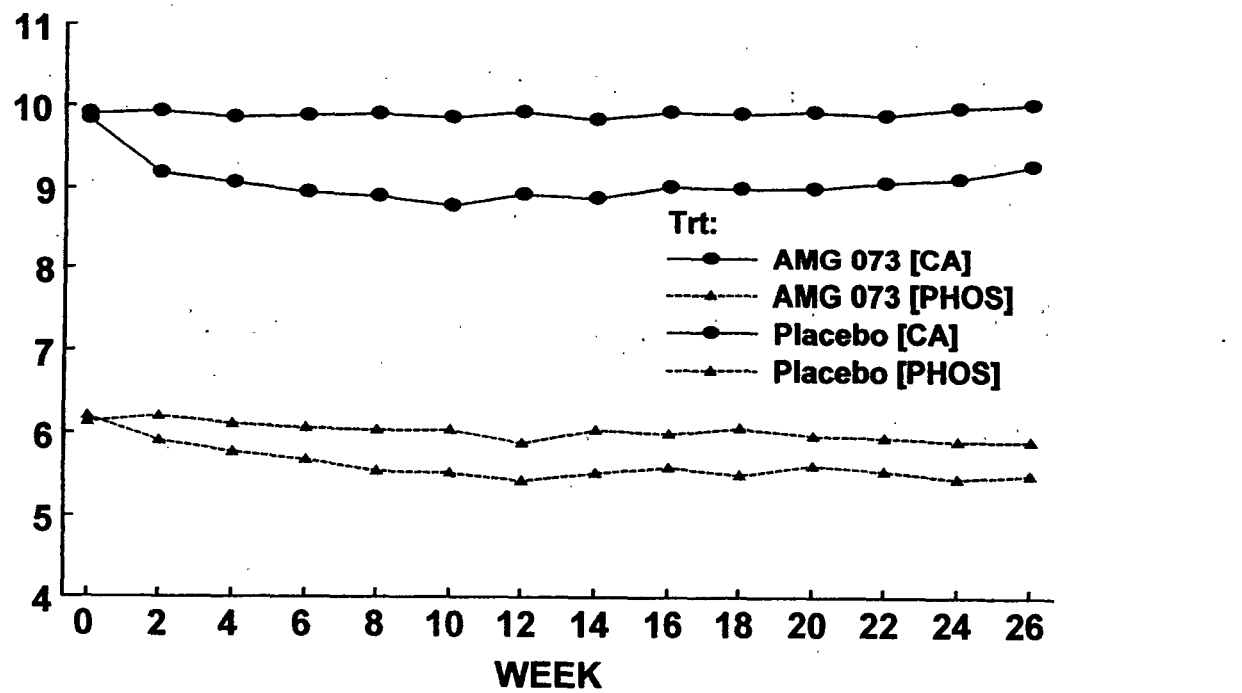
Results for secondary and tertiary endpoints show statistically significant treatment effects on all measures for all three studies (Table 22). Figure 3 illustrates the calcium and phosphorus levels over time.

Table 22. Secondary HPT in patients with ESRD: Phase 3 Studies 172, 183 and 188
Calcium, phosphorus and Ca x P results

	Study 172			Study 183			Study 188		
	Placebo (n=174)	Cinacal (n=169)	p-value	Placebo (n=165)	Cinacal (n=166)	p-value	Placebo (n=101)	Cinacal (n=294)	p-value
Calcium									
Baseline	9.9 (0.8)	9.8 (0.8)		9.9 (0.7)	10.0 (0.8)		10 (0.9)	9.8 (0.8)	
%change									
Mean	+0.6%	-6.9%		+0.4%	-7.3%		+0.8%	-7.1%	
(SD)	(5)	(8)	<.0001	(4.5)	(8)	<.0001	(5)	(9)	<.0001
Phos									
Baseline	6.2 (1.6)	6.3 (1.7)		6.2 (1.5)	6.1 (1.5)		6.1 (1.4)	6.1 (1.7)	
%change									
Mean	+0.9%	-7.4%		-1.1%	-10.4%		+0.4%	-9.1%	
(SD)	(25)	(24)	.0015	(21)	(23)	.0004	(24)	(25)	.004
Ca x P									
Baseline	61 (16)	62 (16)		61 (15)	61 (15)		61 (14)	60 (16)	
%change									
Mean	+1.3%	-14%		-0.9%	-17%		+1.1%	-15%	
(SD)	(25)	(23)	<.0001	(22)	(22)	<.0001	(24)	(27)	<.0001
% pts. w/ iPTH ≤250 + dec. Ca x P	1.5% (3/205)	34% (69/205)	<.0001	4.9% (8/165)	38% (63/166)	<.0001	0% (0/101)	28% (81/294)	<.0001

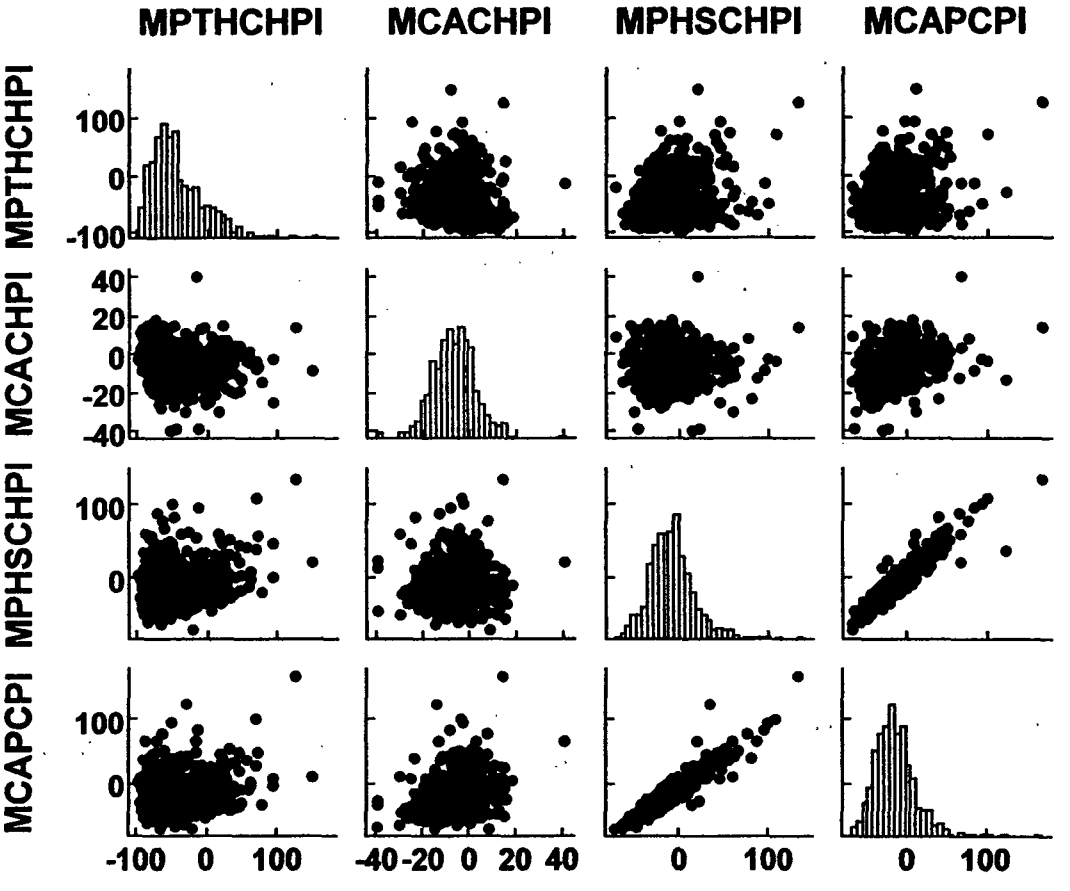
P-value results from stratified CMH to test proportions and from ANCOVA to test continuous variables.

Figure 5. Ca (mg/dL) and Phosphorus (mg/dL) by week on study for patients who completed Study 172, 183 or 188



The figure below shows, for the cinacalcet patients, that the secondary endpoints (% change of Ca, Phos and Ca x P) are not strongly correlated with the primary endpoint, % change iPTH; the first row of Figure 4 illustrates this point.

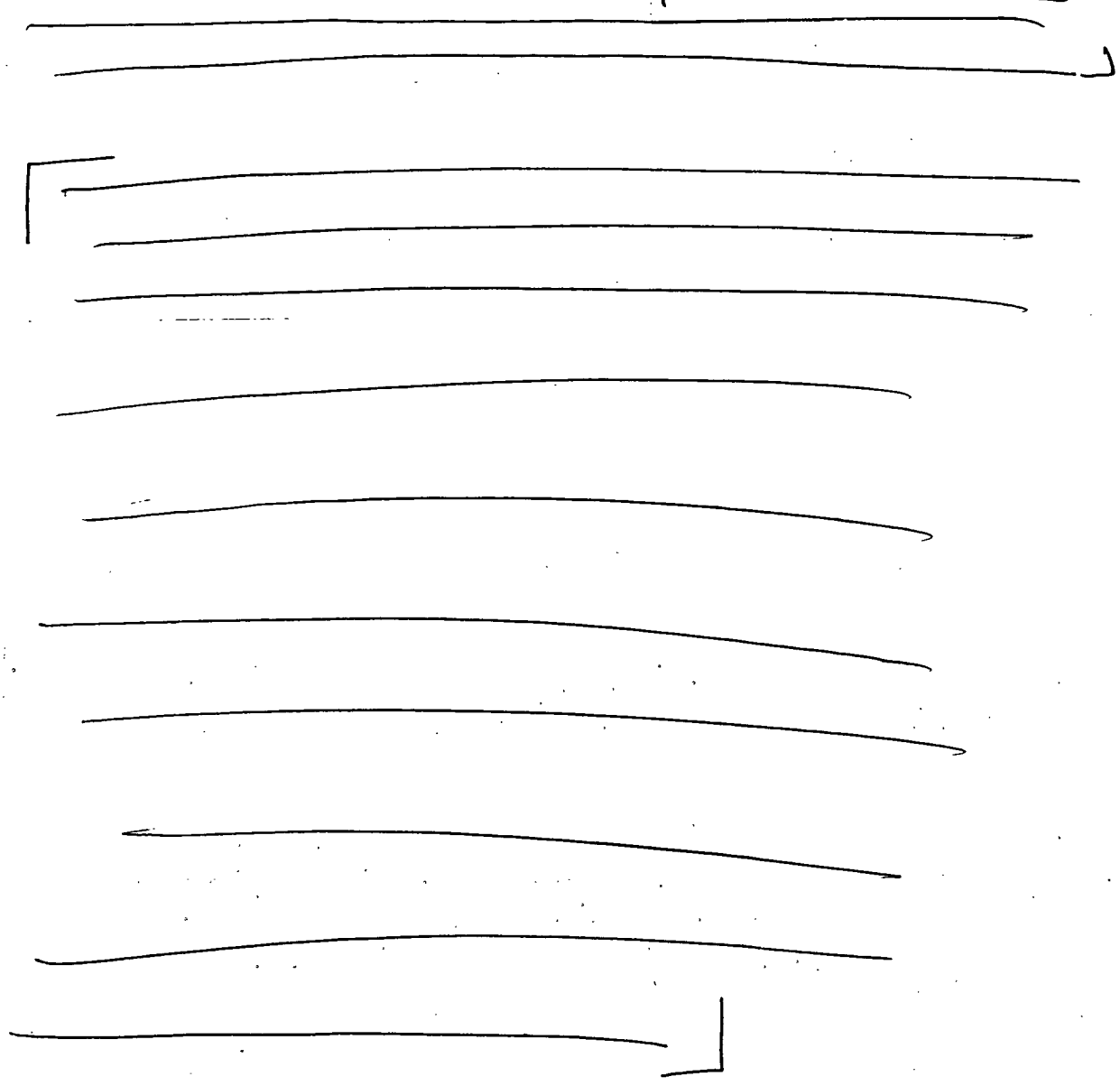
Figure 6 Scatter plot matrix of mean % change from baseline for iPTH, Ca, Phos and Ca x P for the cinacalcet (ITT) patients only in Studies 172, 183 and 188 (mean of all values during the maintenance phase)



Change from baseline in cognitive function (component of the KDQOL) at end of efficacy phase was named as a secondary endpoint. No significant treatment effect was seen for cognitive function (or for the mental component summary); also, the results were not correlated with changes in iPTH (the applicant reported that a significant correlation was observed in Phase 2 trials). This reviewer also looked at physical improvement scores (including the physical component summary, physical functioning score, role limitation physical score and the vitality score) on the KDQOL. [According to a reference submitted by the applicant, kidney disease patients are most concerned about "low energy level and lack of strength" , Hays, 1994.] For all patients, about 1/3 of the patients in both treatment groups showed some improvement on these scores. Among completers only (with the three studies combined), a greater improvement was seen for cinacalcet patients than placebo patients. Essentially no correlation between these measures of physical improvement and change in iPTH was seen.

3.1.3 Secondary Hyperphosphotemia in Patients with Chronic Renal Insufficiency

The applicant has submitted the results of two placebo-controlled, randomized clinical trials (2000236 and 2001039, Table 22) to support an indication for the treatments of secondary HPT in patients with chronic renal insufficiency (CRI). These patients unlike the ESRD patients were not undergoing dialysis. Both studies were considered



. In Study 236, about 85% of the patients completed the study (Table 24). Of the 4 cinacalcet patients discontinuing treatment, two discontinued due to ADE (one due to nausea and vomiting and the other due to hypocalcemia). In Study 239 , only about 70% completed the study. In the placebo group, the primary reason for withdrawal was consent withdrawn while in the cinacalcet group the primary reason was an ADE

(4; 1 due to nausea and 3 due to hypocalcemia).

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

3.1.4 Extension Study 20010240 in Patients with Secondary HPT

Patients who completed Studies 172 and 183 could continue randomized treatment at their final dose for an additional 26 weeks under Study 20010240. The double-blind was maintained during the extension study. Changes in vitamin D, phosphate binders and oral calcium supplements were allowed as specified by the protocol.

The main objective of this extension study was to monitor safety though efficacy endpoints were assessed and their outcomes mentioned in the proposed labeling. Analyses produced descriptive statistics; no formal hypothesis testing was planned. Baseline at the start of the study of origin was used as the baseline for this study. Endpoint data was computed as the mean of the last two measures; for the completer analysis, only extension weeks 24 and 26 were used and for an LOCF analysis, the last available two weeks (or one week for those patients with only one record) were used.

Before unblinding the data, the applicant discovered that 22 of the 1700 iPTH values collected were not assayed according to the protocol; the 22 values all came from 17 Australian patients. The samples were retested and the new values were used in the primary analyses. Sensitivity analyses were performed including the original values and also excluding those patients with errant values; there were essentially no differences in the outcomes.

About half the patients randomized in Study 172 continued into the extension study while less than 20% of the patients in Study 183 continued, so the majority of the patients in the extension study were enrolled at US sites. About 1/3 of the originally randomized patients completed the extension study.

Table 28 Patient disposition[1]

	Placebo			Cinacalcet		
	S172	S183	Total	S172	S183	Total
Study of origin # randomized # completing	205 158 (77%)	165 132 (80%)	370 290 (78%)	205 146 (71%)	166 107 (64%)	371 253 (68%)
# enrolled in extension	111 (54%)	27 (16%)	138 (37%)	105 (51%)	23 (14%)	128 (35%)
# on study by total weeks (extension week) Week 34 (8) Week 42 (16) Week 52 (26)	90 (44%)	23 (14%)	130 (35%) 117 (32%) 113 (31%)	81	16	116 (31%) 103 (28%) 97 (26%)
% of extension patients completing			113/138 82%			97/128 76%

[1] Percentages are computed as percentage of number originally randomized except for the last line.

About 20% of the patients enrolled in the extension study did not complete the 52 weeks (see table above). The most common reason for discontinuing was listed as "Other" in both groups; examination of these patients showed that consent withdrawn or administrative decision were the reason most often stated. In the cinacalcet group, the most common ADE was nausea or vomiting. One cinacalcet patient experienced convulsions during Study 172 and then again in about 8 weeks in to the extension study; this patient had a corrected serum calcium of 7.3 mg/dL at the time. Another cinacalcet patient experienced eyelid spasms that the investigator considered treatment related. Both of these patients were taking the 180 mg dose.

Table 29 Extension Study 20010240 Reasons for discontinuation

	Placebo			Cinacalcet		
	S172	S183	Total	S172	S183	Total
ADE	0	0	0	9	4	13
Death	6	1	7	3	0	3
Kidney transplant or parathyroidectomy	5	1	6	3	1	4
other	10	2	12	9	2	11

The baseline values and demographics for the extension sample were similar to those of the randomized population.

Forty-three cinacalcet patients who continued into the extension study were at the highest dose when they completed their original study. At the end of the extension study, 56 patients were taking the highest dose. So nearly half of the patients in the extension study required the highest dose of 180 mg per day to adequately lower iPTH (Table 30).

Table 30 Extension Study 20010240
Last dose taken at the end of long-term treatment
(Once a day dosing)

Last Dose mg/day	Placebo N=138	Cinacalcet N=128
30	1%	16%
60	1%	16%
90	1%	13%
120	2%	11%
180	95%	44%

The treatment difference of about 40% for the primary endpoint of proportion of patients with mean iPTH of 250 or less for the last two weeks of the study is consistent with the response seen in the qualifying studies where the treatment differences were about 38%. Results for other endpoints as well were consistent with those observed earlier (see Table 21 for comparison).

Table 31 Extension Study 20010240 Applicant's iPTH results

	Placebo (n=138)	Cinacalcet (n=128)
Baseline from Qualifying Study Mean (SD) Median	 640 (386) 525	 617 (310) 529
% of pts w/ iPTH≤250 pg/mL	18/136 (13%)	68/125 (54%)
% of pts w/ iPTH % ch ≥30%	30/136 (22%)	88/125 (70%)
iPTH % change from baseline Mean	+14%	-44%
% of pts w/ iPTH≤250 pg/mL by rand. Strata (LOCF) Mild 300-500 Ca x P <70 Ca x P ≥70 Mod >500 to 800 Ca x P <70 Ca x P ≥70 Sev >800 Ca x P <70 Ca x P ≥70	 10% 7% 8% 8% 0% 0%	 78% 69% 68% 36% 29% 14%

Though the results are consistent between the qualifying studies and the extension studies, the results as presented do not establish that the effects are maintained. To show the latter one should look at the change in iPTH during the extension study; no change would indicate that the patients maintained the effect seen in the qualifying study. In both groups a median increase in iPTH of 20 pg/mL was observed; the distribution of the changes was similar for both groups. An increase of 20 pg/mL is small and inconsequential given the large overall mean decreases seen for the cinacalcet patients. The extension study does demonstrate that the effect of cinacalcet can be maintained for up to one year in patients who can tolerate treatment beyond six months; it should be noted that less than 1/3 of randomized patients were able to complete this extension study.

3.1.5 Oversuppression of iPTH

During the review of the efficacy data, this reviewer noticed that many patients achieved levels of iPTH below the target range. The percentage of patients with low iPTH (<150, the low end of the target range based on guidelines for this population and <100, a definition of adynamic bone disease according to the applicant) are summarized for the cinacalcet patients in the table below (for most studies, no placebo patients achieve these low levels). Also presented in this table is the number of responders. About half the responders reach levels below the target range and about half of those reach levels below 100 (ranging from 6% to 18% in the clinical studies). The percentages below are computed from the mean iPTH during the efficacy assessment phase which was the primary endpoint; individual datapoints at each week for Study 183 are shown in Appendix 4; the boxplots in Appendix 4 clearly show that at several weeks during the trial about 25% of the patients have a value of under 100. Appendix 5 shows a plot of iPTH during the extension study 204; this graph clearly shows that even with long-term monitoring many patients have values of iPTH below 100. The number of times during the efficacy phase that a patient had a value below 100 or 150 is summarized in Appendix 6; it is clear that the patient means are based on repeated values below the cutoffs with about 17% of the cinacalcet patients having 3 or more values below 100 during the last 6 visits (last 10 weeks) on study versus 1.4% of the placebo patients.

Because of the time constraints on this review, this reviewer was not able to investigate the relationship between oversuppression of iPTH and the incidence of hypocalcemia and the effects on bone. Though changes in iPTH and changes in calcium were not correlated ($r<0.1$) across the full range of values observed, large changes in iPTH may be associated with hypocalcemia. Two patients in Study 141 (the bone study) developed adynamic bone disease as a result of oversuppression of PTH so clearly there is evidence for concern. This reviewer will examine this issue further and report findings in a subsequent document, if needed.

Table 32. % of cinacalcet patients with mean iPTH during the efficacy assessment phase below cutoffs of 250, 150 and 100 in Phase 2 and Phase 3 trials of secondary HPT patients

	Phase 2 ESRD[1]	Phase 3 ESRD					Phase 2 CRI	
	740	172	183	188	141	237	236	239
Median dose mg/day	75	120	90	90	120[2]	120	90	30
≤250 pg/mL	44%	41%	46%	35%	53%	59%		
<150 pg/mL	23%	18%	28%	16%	19%	33%		
<100 pg/mL	9%	9%	17%	6%	6%	18%		
≤65 pg/mL							63%	37%
<35 pg/mL							27%	11%

Another issue related to this reviewer's concern regarding oversuppression of iPTH with cinacalcet is the potential for overtreatment in this population by treating patients with inappropriate therapies because of overestimation of iPTH. This issue was brought to the attention of FDA via a communication from [redacted] a researcher with [redacted]

1 The other two Phase 2 studies (101 and 102) underdosed patients so the results for those studies are not reported here although it is worth mentioning that in Study 101 where the median dose was 50 and the responder rate was not significantly different from placebo, 3% of the cincalcet patients and 0% of the placebo patients achieved levels iPTH below 100.

2 At Week 41, 46% of the cinacalcet patients were on 180 mg and 9% on 120 mg.

[redacted] claims with supporting references that the Nichols Advantage Intact PTH Assay (used in clinical practice) reports PTH values 30-50% higher than the Nichols IRMA Intact PTH assay (the assay used throughout the Amgen clinical program) [from page 23 of a document titled "AmgenTrial Flawed1]. So oversuppression may be a critical issue for patients assessed in a clinic using the Nichols Advantage assay.

APPEARS THIS WAY
ON ORIGINAL

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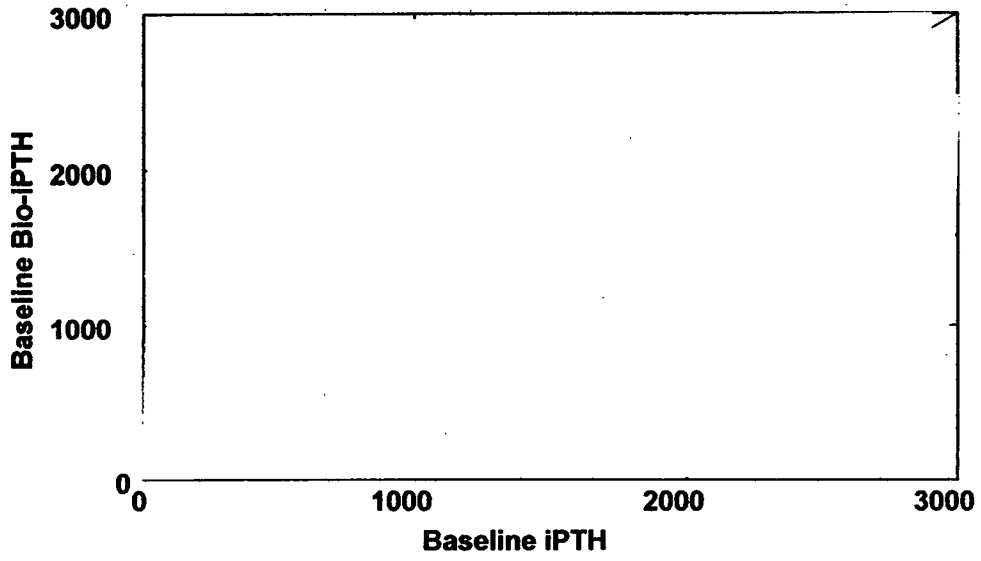
3.1.6 Bio intact PTH versus intact PTH

In response to a request from FDA, the applicant used two PTH assays on samples collected in Study 172. One assay measured intact PTH while the second assay measured intact PTH excluding the non-(1-84) PTH fragment. The second assay called the bio-intact assay in the submission provides a measure of the biologically active hormone. In patients with renal failure who are unable to excrete the PTH fragments, the intact PTH overestimates the amount of biologically active hormone as illustrated in the graph of the baseline data from Study 172 below.

Figure 9. Baseline bio-iPTH by baseline iPTH for patients in Study 172



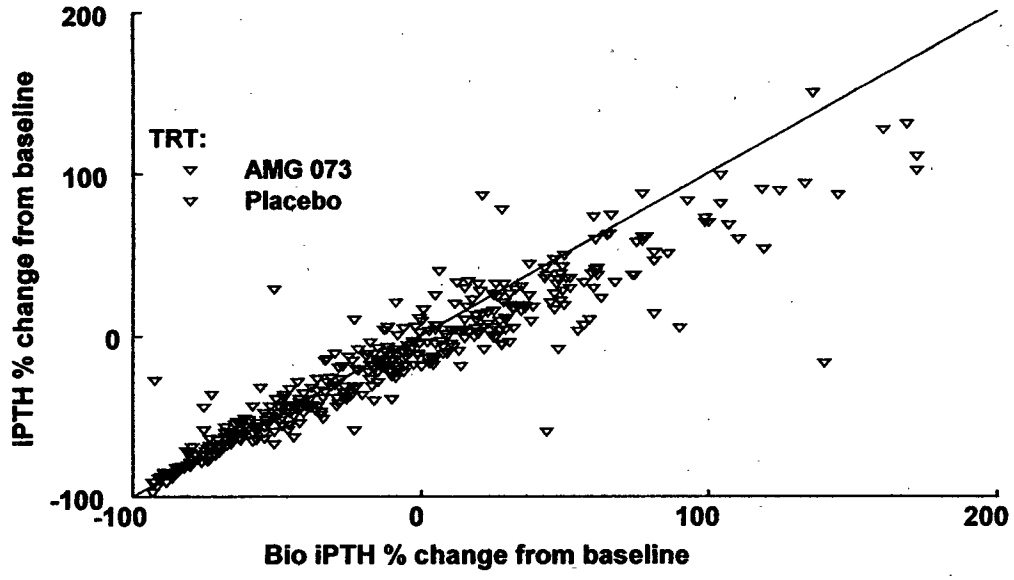
N = 410
Bio-iPTH = 0.53 iPTH -12.3
r = 0.92

Both the bio-intact and the whole iPTH show significant effects of cinacalcet though the magnitude of the treatment effects differ. The data in the last row of the table are illustrated in a graph on the following page.

Table 32. Study 172 Results for BiPTH and for iPTH

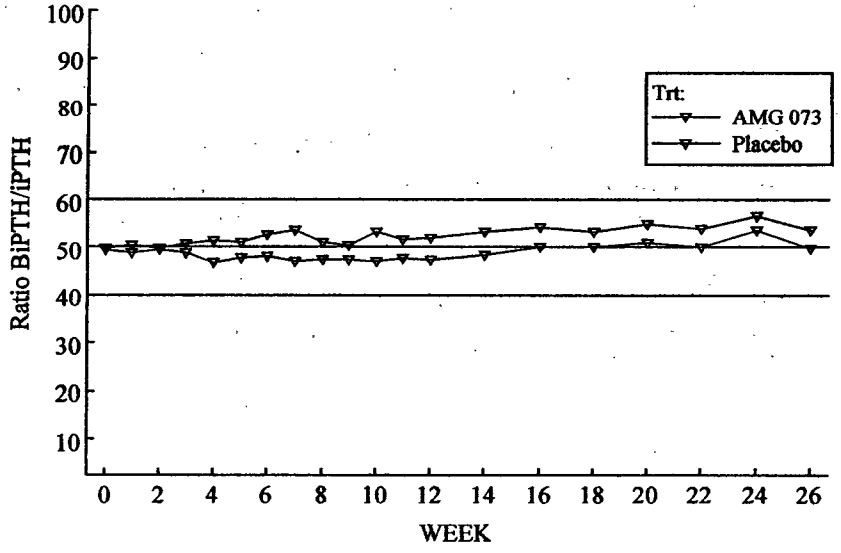
	Placebo (n=203) Mean (SD) Median	Cinacalcet (n=200) Mean (SD) Median
Baseline		
Bio iPTH	335 (225) 275	328 (204) 267
IPTH	646 (394) 534	636 (343) 537
Change		
Bio iPTH	+61 (147) +45	-128 (204) -114
iPTH	+51 (248) +15	-251 (327) -236
% change		
Bio iPTH	+23% (51) +16%	-38% (44) -49%
iPTH	+10% (40) +4%	-38% (41) -48%

Figure 10. Percent change in bio-iPTH by percent change in iPTH for patients in Study 172



The applicant's proposed label states that "[redacted]. The data in the previous table does suggest that the effect of sensipar is evident regardless of which PTH measure is used, however the relationship between the two does seem to be affected in small part by sensipar. A plot of the mean ratios of biPTH over iPTH overtime in Study 172 shows about a 5% higher ratio for placebo than sensipar indicating a higher percentage of bioactive PTH for placebo than sensipar. This data may indicate that sensipar relative to placebo is lowering the biPTH to a greater degree than the iPTH as a whole and therefore having a greater impact on bioactive iPTH.

Figure 10. Study 172 Ratio of BiPTH to iPTH by week on study for the ITT population



3.2 Evaluation of Safety

For a full review of safety, see the review of the medical officers.

With the time constraints imposed by the priority review, it was impossible to review safety issues by the initial deadline for CDER management review. In a subsequent document, this reviewer will investigate two safety issues. The first issue is the lack of an integrated safety review of the primary HPT population (excluding the carcinoma patients) by the applicant. This reviewer, working with Dr. Beaston, the medical reviewer, will create a database to look at the integrated data for the primary HPT population and summarize the serious adverse event data. The second issue is the impact of oversuppression of iPTH on some of the safety endpoints. Examination of this issue, primarily, will include reviewing the bone studies submitted by the applicant.

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4. Findings in Special/Subgroup Populations

Due to the small number of patients in the primary HPT population, subgroup results are only presented for the secondary HPT population in this section of the review. The results from the three placebo-controlled large Phase 3 trials (172, 183 and 188) in ESRD patients with secondary HPT are combined to assess efficacy in subgroups.

4.1 Gender, Race and Age

The results for the primary endpoint (% of patients with a mean iPTH of 250 or less) by subgroups defined by gender, race and age are shown in Table 33. The treatment effects are consistent for males and females and for blacks and whites. Younger patients appear to have a lower effect than older patients though the difference may be due to the slightly higher baseline values seen for the younger cinacalcet patients.

Table 33 % of patients with iPTH<250 during the efficacy assessment phase for Studies 172, 183 and 188 combined by gender race and age

	Placebo	Cinacalcet
Gender		
Male	21/295 7%	187/407 46%
Female	7/176 4%	97/258 38%
Age (years)		
<65	18/335 5%	212/510 42%
≥65	10/136 7%	72/155 46.5%
<55 (median)	13/224 6%	131/352 37%
≥55	15/247 6%	153/313 49%
Race		
Black	9/155 6%	97/245 40%
White	13/265 5%	146/324 45%
Other	8/53 12%	41/96 43%

4.2 Subgroup Populations Defined by Baseline Characteristics

The only notable subgroup result differences are the results by baseline iPTH (Table 34). It is clear that regardless of the how the cutpoints are defined, the treatment effects for patients with severe disease are appreciably lower than those for patients with mild and moderate disease. Another measure of disease severity may be the years of dialysis; here again the subgroup with the highest number of years (>6) showed the smallest effect. The correlation between years of dialysis and baseline iPTH is positive but weak with r^2 of only 0.01.

Table 34 % of patients with iPTH<250 during the efficacy assessment phase for Studies 172, 183 and 188 combined by various subgroups

	Placebo	Cinacalcet
Country		
United States	15/254 6%	154/406 38%
Europe	9/142 6%	73/144 51%
Australia	3/27 11%	15/32 47%
Canada	1/48 2%	42/83 51%
Baseline iPTH		
Tertiles		
<472	20 /164 12%	128/ 213 60%
472-724	5/162 3%	100/216 46%
>724	0/145 0%	36/234 15%
Disease severity		
Mild 300-500	22/193 11%	147/244 60%
Mod >500 to 800	3/165 2%	95/231 41%
Sev >800	0/133 0%	22/188 12%
Baseline Ca x P		
Tertiles		
<55	16/150 11%	119/233 51%
55-67	7/158 4%	76/210 36%
>67	2/163 1%	68/219 31%
Rand. Strata		
Mild 300-500		
Ca x P ≤70	17/125 14%	82/125 66%
Ca x P >70	0/37 0%	21/36 58%
Mod >500 to 800		
Ca x P ≤70	3/97 3%	46/99 47%
Ca x P >70	1/39 3%	15/38 40%
Sev >800		
Ca x P ≤70	0/48 0%	6/49 12%
Ca x P >70	0/24 0%	3/24 12%
Baseline Vit D Use		
No	4/153 3%	83/228 36%
Yes	24/318 8%	201/437 46%
Dialysis modality		
Peritoneal	0/12 0%	13/21 38%
Hemodialysis	28/459 6%	271/631 43%
Years of dialysis		
Tertiles (med iPTH)		
<2.5 (519)	9/157 6%	106/208 51%
2.5 to <6 (567)	11/151 7%	103/224 46%
6 or greater (657)	8/161 5%	67/211 32%
Diabetic		
Yes	13/147 9%	103/209 49%
No	15/334 5%	181/456 40%

Results for the primary efficacy variable clearly showed more responders among patients with mild or moderate disease than among patients with severe disease. It appears that titration even to the high dose of 180 mg per day was not adequate for most patients with high iPTH values at baseline. The results in the table below for change and % change of iPTH show significant decreases in iPTH for each cinacalcet subgroup but again insufficient lowering to attain normal levels for most patients in the group with severe disease.

Table 35. iPTH change and % change from baseline (Mean and SD) by subgroups defined by disease severity based on baseline iPTH

	Placebo	Cinacalcet
Mild 300-500	n=170	n=193
Mean Change	+42 (167)	-186 (145)
Mean % Change	+10% (43)	-46% (35)
Mod >500 to 800	n=148	n=190
Mean Change	+51 (223)	-336 (203)
Mean % Change	+8% (36)	-53% (31)
Sev >800	n=90	n=164
Mean Change	+53 (338)	-513 (573)
Mean % Change	+5% (28)	-39% (35)

5. Summary and Conclusions

5.1 Conclusions and Recommendations

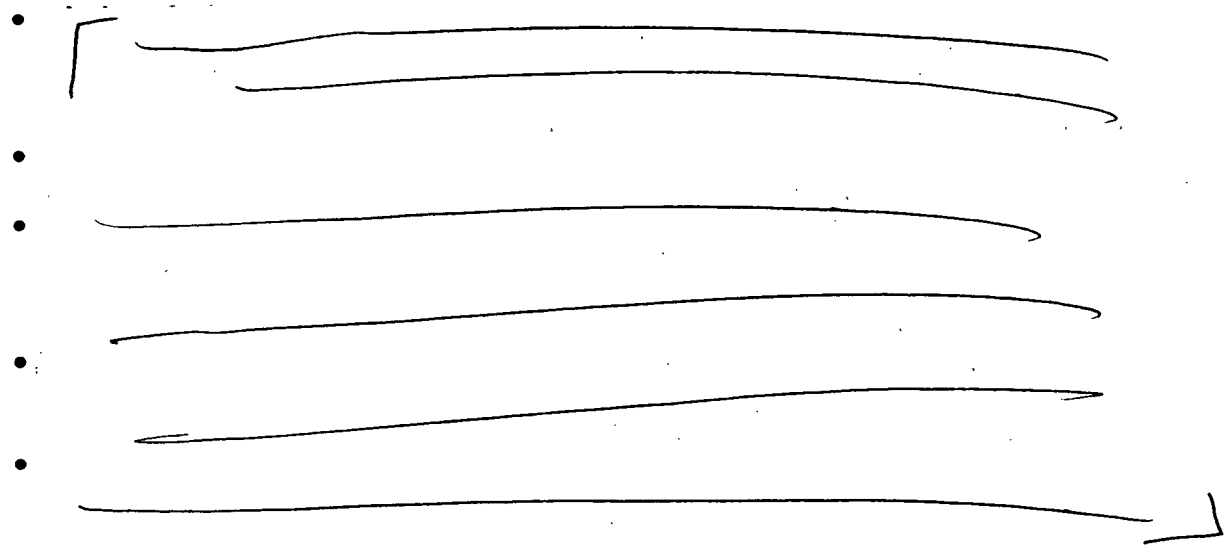
The applicant's proposed indications for cinacalcet (sensipar) are the following:

- Treatment of hypercalcemia in patients with primary hyperparathyroidism or with parathyroid carcinoma
- Treatment of secondary hyperparathyroidism
- Control of parathyroid hormone (PTH), serum calcium x phosphorus, phosphorus and calcium levels in patients with chronic kidney disease receiving or not receiving dialysis

With regard to primary hyperparathyroidism, this reviewer has the following comments and conclusions based on this statistical review:

- [redacted]
- [redacted]
- [redacted]

[redacted] No assessment of safety can be made just based on 990120 since clearly patients with serious ADE's in 980125 would not continue into 990120.



With regard to secondary hyperparathyroidism in patients with ESRD and receiving dialysis, this reviewer has the following comments and conclusions based on this statistical review:

- Three Phase 2 studies showed that doses above 50 mg per day are usually needed to significantly impact PTH particularly in patients with baseline PTH above about 525.
- In the three large Phase 3 studies (172, 183 and 188), about 39% had mild HPT 300≤iPTH≤500), about 35% had moderate HPT (500<iPTH≤800) and about 27% had severe HPT (iPTH>800).
- Two to three times more cinacalcet patients dropped out of the Phase 3 studies due to gastrointestinal ADE's than placebo patients (see Table 17). The dropout rate in the European study (183) was considerably higher (14% cinacalcet vs. 2% placebo). Gastrointestinal ADE was also the major reason for cinacalcet dropouts in the extension study.
- The median cinacalcet dose was 90 mg. A little more than 1/3 of the randomized cinacalcet patients were on the highest dose at the end of their treatment. Titration to the highest dose of180 mg was related to baseline iPTH; about 60% of patients in the highest baseline iPTH tertile were titrated to the 180 mg dose.
- Cinacalcet significantly decreased iPTH by about 50% over placebo. About half the patients had a decrease of 30% or more.
- About 40% of patients treated with cinacalcet had mean iPTH during maintenance lower than 250 pg/ml (the primary endpoint) compared to about 5% for placebo; about half of the cinacalcet patients were below the normal range (<150 pg/ml, Table 20).
- Cinacalcet significantly lowered calcium, phosphorus and Ca x P compared to placebo (Table 21). Changes in these endpoints were not correlated with changes in the primary endpoint, iPTH.
- A double-blind extension study (240) of a total of 266 patients from Study 172 (about 52% of the randomized patients) and from Study 183 (about 15% of the randomized patients) followed patients for an additional 26 weeks (total of one year). Less than one-third of the randomized patients from those studies completed the extension.
- Nearly half of the patients in the extension study required the highest dose of 180 mg per day to adequately lower iPTH.
- In the 3 phase three trials, about 1/5 of the patients had a mean iPTH below 150 pg/mL (the

target range was 150 to 250); about half of those patients (~10% of the total) had levels below 100 pg/mL. In the applicant's bone study, two patients who developed adynamic bone disease had iPTH levels below 100; a preliminary review indicates that only two patients in that study had an iPTH below 100 (this reviewer will confirm this after completion of this document).

- Patients with high levels of iPTH (>800 for secondary HPT, ESRD patients) are not able to achieve levels of 250 or less even on the highest dose (PUT HERE WHAT THEY DID ACH.)

With regard to secondary hyperparathyroidism in patients with CRI and not receiving dialysis, this reviewer has the following comments and conclusions based on this statistical review:

- [redacted]
- [redacted]

Given that HPT is a chronic disease requiring chronic treatment, it is important to look at the number of patients maintained on treatment in the extension studies. In Study 20010240 (an extension of Studies 172 and 183 in secondary HPT patients), only 28% (n=210, 97 on cinacalcet) of the originally randomized patients completed the 26-week extension study. Two [redacted]

The clinical trials provide statistical evidence of the efficacy of cinacalcet for the treatment of [redacted] secondary HPT. Two problems with the efficacy are evident: 1) most secondary HPT patients with high levels of iPTH and parathyroid carcinoma patients with high levels of calcium are not able to achieve normal levels so dosing does not appear to be sufficient for patients with severe disease and 2) about half the responders reach levels below the target range of iPTH. Oversuppression of iPTH can lead to detrimental effects on bone. In addition, the benefits need to be weighed against risks which may include hypocalcemia, QT interval prolongation, changes in testosterone levels and seizure.

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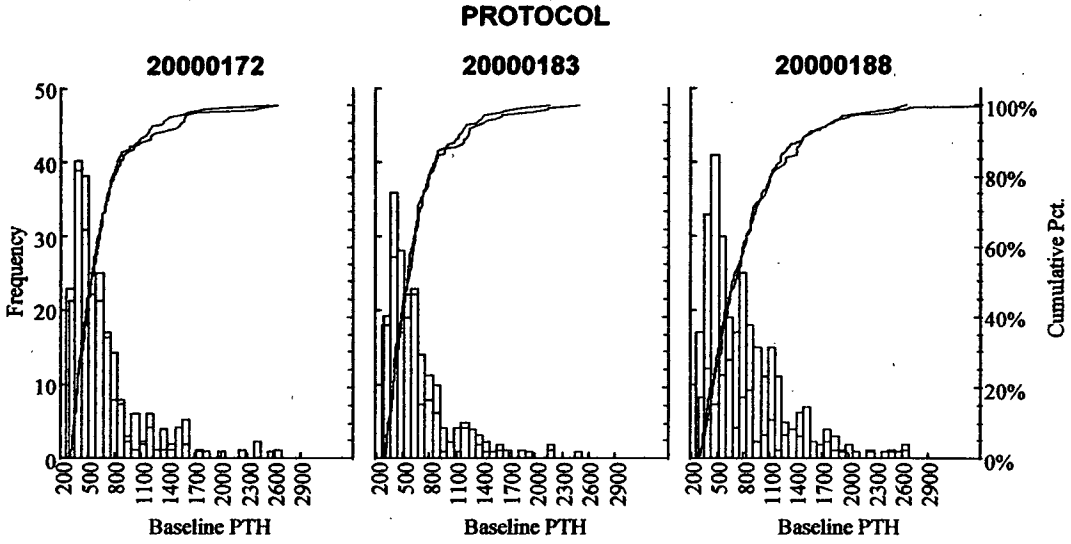
Appendix 3. Histogram and cumulative distribution plots of baseline iPTH (pg/mL) by protocol

(Note that 3:1 randomization was used in Study 188; red is cinacalcet and blue placebo)



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/s/

Joy Mele
2/20/04 09:26:08 AM
BIOMETRICS
This review is best viewed in color.

Todd Sahlroot
2/20/04 09:56:26 AM
BIOMETRICS

S. Edward Nevius
2/20/04 09:58:47 AM
BIOMETRICS
Concur with review.