receive the next bottle number(s). The site personnel were asked for subject information that included central laboratory iPTH and serum calcium values and safety information.

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

For weeks 3, 6, 9 and 12:
- The mean of the 2 central laboratory iPTH values from the preceding 2 weeks was ≤ 200 pg/mL (21.2 pmol/L), with any missing values excluded from calculation.
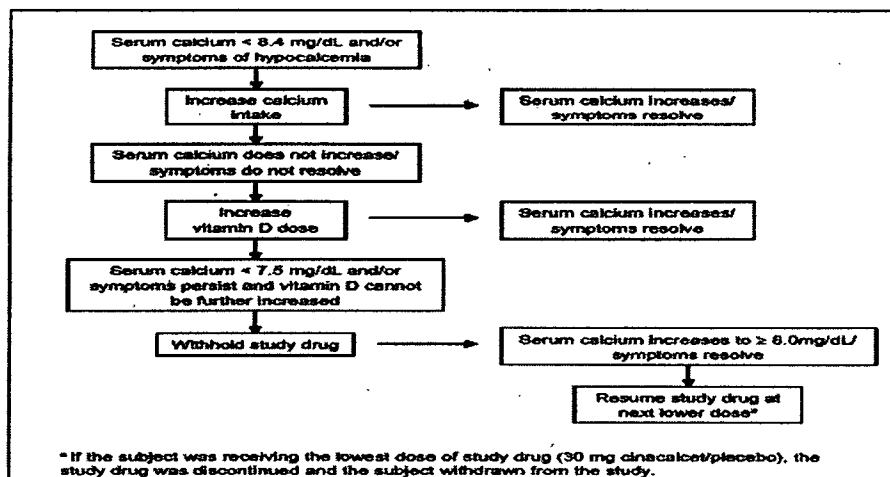
For weeks 16, 20, and 24:
- The central laboratory iPTH value from the preceding study visit was ≤ 200 pg/mL (21.2 pmol/L) with any missing value replaced by the most recent past value.

For weeks 3, 6, 9, 12, 16, 20, and 24:
- The highest dose of study medication was reached.
- The serum calcium was < 7.8 mg/dL (1.95 mmol/L) or the subject was experiencing symptoms of hypocalcemia.
- The subject was experiencing an adverse event that precluded a dose increase.

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

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

* If the subject was receiving the lowest dose of study drug (30 mg cinacalcet/placebo), the study drug was discontinued and the subject withdrawn from the study.

Protocol Specified Guidelines for Changes in Vitamin D therapy: If a subject's iPTH concentration increased ≥ 50% from baseline for 3 consecutive study visits, vitamin D therapy

was increased. If a subject's serum calcium concentration was ≥ 11 mg/dL (2.75 mmol/L), or serum phosphorus concentration was ≥ 6.5 mg/dL (2.1 mmol/L), and/or Ca x P was ≥ 70 $(mg/dL)^2$ (5.65 $[mmol/L])^2$, the investigator could modify diet and/or change dose or brand of phosphate binders. If these measures were not sufficient, vitamin D could be withheld or the dose reduced until the serum calcium, phosphorus, and Ca x P were below these levels. If vitamin D sterol was withheld, it was restarted at the investigator's discretion.

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

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

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

The sample size calculation was based on a χ^2 test of equal proportions of subjects with a mean iPTH value ≤ 250 pg/mL during the efficacy-assessment phase, with a statistical significance level of 0.05 (2-sided). The placebo response was predicted on the basis of previous cinacalcet phase 2 studies to be $\leq 15\%$. With a cinacalcet response rate of 35% assumed for the purpose of sample size considerations, the planned 320 subjects (160 cinacalcet, 160 placebo) yielded 95% power.

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

Descriptive statistics were used to summarize each efficacy endpoint at each measurement time point during the dose-titration and efficacy-assessment phases. Descriptive statistics included mean, median, SE, 25th and 75th percentiles, minimum, and maximum for continuous variables and number and percent for categorical variables. For continuous efficacy variables, 95% 2-sided confidence intervals (CIs) were provided for the means. For categorical efficacy variables,

the odds ratio of achieving the endpoint under consideration and the difference between the treatment groups were presented with the associated 95% CIs.

The statistical analysis plan was amended once (22 April 2003). The amendment included the following changes:

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

Protocol Amendments: The protocol was amended once changes noted below:
- Changed the tertiary endpoint, proportion of subjects with a reduction from baseline in mean iPTH of ≥ 30%, to a secondary endpoint
- The eligibility criteria were clarified to allow women with a definite history of amenorrhea to enroll in the study if the pregnancy test falsely reported as positive

Results

Patient Disposition: As shown in the table below, 498 subjects were screened and 331 subjects were enrolled and randomized this study. Approximately 80% of placebo and 64% of cinacalcet subjects completed the 26 week trial. Adverse events were the most common reason for early withdrawal, with the rate higher in the cinacalcet-treated group (23%) compared with the placebo-treated group (5%).

20000183: Patient Disposition	Placebo	Cinacalcet
Enrolled	165	166
No treatment	0	1
At least one dose	165	165
Withdrew – Total	33 (20)	58 (35)
Withdrew – AE	9 (5)	38 (23)
Deaths	5 (3)	3 (2)
Withdrew – Parathyroidectomy	3 (2)	0 (0)
Withdrew – Renal Transplant	9 (5)	8 (5)
Withdrew – Other	7 (4)	9 (5)
Completed Titration Phase (Weeks 1-16)	151 (92)	136 (82)
Completed Study	132 (80)	107 (64)

Protocol Violations: Twenty one (6%) subjects had eligibility deviations in this study, which were discovered after subjects were enrolled. The most common eligibility deviation was a change in vitamin D sterol dose during the 30 days before day 1. Major protocol deviations occurred in 51% of the placebo-treated subjects and 57% of the cinacalcet-treated subjects (see table below). Compliance with study drug was 91% in the cinacalcet treated group and 94% in the placebo treated group.

Study 20000183: Subject Incidence of Major Protocol Deviations by Treatment Group and Baseline Randomization Strata	Placebo	Cinacalcet
	n/N (%)	n/N (%)
Study 20000183		
iPTH 300 to 500 and Ca x P 70	27/55 (49%)	31/55 (56%)
iPTH 300 to 500 and Ca x P > 70	5/14 (36%)	8/14 (57%)
iPTH 501 to 800 and Ca x P 70	24/46 (52%)	26/47 (55%)
iPTH 501 to 800 and Ca x P > 70	9/18 (50%)	8/17 (47%)
iPTH > 800 and Ca x P 70	13/22 (59%)	14/23 (61%)
iPTH > 800 and Ca x P > 70	6/10 (60%)	7/10 (70%)

COMMENTS: Although there were numerous and varied protocol violations, the numbers and types of violations were fairly 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). Ninety-two percent of enrolled subjects were white and 63% were male. Approximately 33% of enrolled subjects were $\geq$ 65 years of age. The duration of dialysis ranged from 3 to 358 months, with a mean of 81 months. Randomization within each baseline stratum was balanced between treatment groups. At baseline, mean iPTH, Ca x P, serum calcium, and serum phosphorus were similar in the cinacalcet and placebo groups. At study entry, vitamin D and phosphate binder use were similar in the 2 treatment groups.

Study 20000183: Demographics	Placebo	Cinacalcet
N	165 (%)	166 (%)
Age (yrs.)	56.3 ± 15.0	55.2 ± 14.8
$\geq$ 65 years	56 (34)	51 (31)
$\geq$ 75 years	19 (12)	16 (10)
Sex		
Male	107 (65)	102 (61)
Female	58 (35)	64 (39)
Race		
Caucasian	157 (95)	147 (89)
Black	2 (1)	10 (6)
Other	6 (4)	9 (5)
Randomization Strata		
PTH 300 – 500, Ca x P $\leq$ 70	55 (33)	55 (33)
PTH 300 – 500, Ca x P > 70	14 (8)	14 (8)
PTH 500 – 800, Ca x P $\leq$ 70	46 (28)	47 (28)
PTH 500 – 800, Ca x P > 70	18 (11)	17 (10)
PTH > 800, Ca x P $\leq$ 70	22 (13)	23 (14)
PTH > 800, Ca x P > 70	10 (6)	10 (6)
Baseline Labs		
iPTH (pg/mL)	630.0 ± 316.9	651.8 ± 372.0
Serum Ca (mg/dL)	9.90 ± 0.74	10.03 ± 0.76
Ca x P (mg/dL)^2	61.10 ± 14.88	61.01 ± 15.40
Serum Phos (mg/dL)	6.19 ± 1.51	6.08 ± 1.54
Baseline Vitamin D use		
Yes	109 (66)	102 (61)
No	56 (34)	64 (39)

Study 20000183: Demographics		
	Placebo	Cinacalcet
Baseline Phosphate Binder use		
Yes	149 (90)	150 (90)
No	16 (10)	16 (10)

Primary Efficacy Outcomes

iPTH Proportion of subjects with a mean iPTH value ≤ 250 pg/mL during the efficacy-assessment phase: The mean (SD) baseline iPTH concentration was 652 (372) pg/mL in the cinacalcet group and 630 (317) pg/mL in the placebo group. Significantly more subjects in the cinacalcet group (46%) compared with the placebo group (7%) achieved a mean iPTH concentration ≤ 250 pg/mL during the efficacy-assessment phase (p < 0.001). More cinacalcet-treated subjects in the lowest baseline iPTH strata achieved an iPTH concentration ≤ 250 pg/mL than subjects in the higher baseline iPTH strata: 65% in the ≥ 300 and ≤ 500 pg/mL stratum, 44% in the > 500 and ≤ 800 pg/mL stratum, and 9% in the > 800 pg/mL stratum (see table below). In the baseline Ca x P ≤ 70 [mg/dL]2 strata, 49% of cinacalcet-treated subjects achieved an iPTH ≤ 250 pg/mL, compared with 37% in the > 70[mg/dL]2 strata. In the placebo group, the proportions of subjects within each baseline iPTH and Ca x P stratum who achieved the target iPTH concentration ranged from 0% to 18%. The primary endpoint was also analyzed separately by age (< 65 , ≥ 65 years), sex, and race (black, white, other). Results were similar for all subgroups and were comparable to the primary analysis.

Study 20000183: Proportion of Subjects With a Mean iPTH Concentration ≥ 250 pg/mL			
		Placebo	Cinacalcet
iPTH Stratum	**Ca x P Stratum**	(N = 165)	(N = 165)
[pg/mL]	[mg/dL]^2	n/N1(%)	n/N1(%)
≥ 300 and ≤ 500	≤ 70	10/55 (18)	36/55 (65)
	> 70	0/14 (0)	9/14 (64)
	All	10/69 (14)	45/69 (65)
> 500 and ≤ 800	≤ 70	1/46 (2)	23/47 (49)
	> 70	0/18 (0)	5/17 (29)
	All	1/64 (2)	28/64 (44)
> 800	≤ 70	0/22 (0)	2/23 (9)
	> 70	0/10 (0)	1/10 (10)
	All	0/32 (0)	3/33 (9)
All	≤ 70	11/123 (9)	61/125 (49)
All	> 70	0/42 (0)	15/41 (37)
Overall		11/165 (7)	76/166 (46)

Test Statistics:					
CMH Statistic (χ^2)		Odds Ratio (Cinacal/Plac)		Difference (Cinacal-Plac)	
Value	P-value	Value	95% CI	Value	95% CI
71.62	< 0.001	11.11	(5.42, 22.78)	39%	(31%, 48%)

Analysis by Dose Level: Cinacalcet treatment was titrated based on an individual subject's iPTH response and tolerability. At the end of the study (Week 26), subjects were distributed across all dose levels of cinacalcet, with 36% of subjects receiving 180 mg (see table below). In the placebo group, 93% of subjects were at the 180-mg placebo dose level.

Study 20000183: Summary of Study Drug Dose Level	Placebo (N = 165)	Cinacalcet (N = 165)
Daily dose (mg) after titration (week 14) - n/N1 (%)		
30	1/150 (1)	20/135 (15)
60	2/150 (1)	19/135 (14)
90	8/150 (5)	29/135 (21)
120	21/150 (14)	28/135 (21)
180	118/150 (79)	39/135 (29)
Daily dose (mg) at end of study (week 26) - n/N1 (%)		
30	0/131 (0)	22/108 (20)
60	0/131 (0)	14/108 (13)
90	5/131 (4)	14/108 (13)
120	4/131 (3)	19/108 (18)
180	122/131 (93)	39/108 (36)
Dose taken most frequently (over whole study) - n (%)		
30	14 (8)	48 (29)
60	6 (4)	30 (18)
90	10 (6)	29 (18)
120	6 (4)	21 (13)
180	129 (78)	37 (22)

Secondary Efficacy Outcomes

Proportion of subjects with a reduction from baseline in mean iPTH of $\geq$ 30%: A significantly greater proportion of subjects in the cinacalcet group (68%) compared with the placebo group (12%) had a 30% decrease from baseline in mean iPTH concentration during the efficacy-assessment phase (p < 0.001). The proportion of subjects in the cinacalcet group who achieved a $\geq$ 30% reduction in iPTH concentration was similar for all baseline iPTH strata: 67% in the $\geq$ 300 and $\leq$ 500 pg/mL stratum, 73% in the > 500 and $\leq$ 800 pg/mL stratum, and 61% in the > 800 pg/mL stratum (see table below). The proportion of cinacalcet-treated subjects who reached this endpoint was also similar for both baseline Ca x P $\leq$ 70 [mg/dL]2 strata, 66% of cinacalcet-treated subjects achieved an iPTH $\leq$ 250 pg/mL, compared with 76% in the > 70[mg/dL]2 strata. In the placebo group, the proportions of subjects within each baseline iPTH and Ca x P stratum who achieved the target iPTH concentration ranged from 0% to 16%.

Study 20000183: Proportion of Subjects a $\geq$ 30% Reduction From Baseline in Mean iPTH Concentration			
		Placebo (N = 165)	Cinacalcet (N = 165)
iPTH Stratum [pg/mL]	**Ca x P Stratum** $[mg/dL]^2$	n/N1(%)	n/N1(%)
$\geq$ 300 and $\leq$ 500	$\leq$ 70	9/51 (18)	36/45 (80)
	> 70	1/12 (8)	10/11 (91)
	All	10/63 (16)	46/56 (82)
> 500 and $\leq$ 800	$\leq$ 70	6/45 (13)	33/37 (89)
	> 70	1/16 (6)	14/16 (88)
	All	7/61 (11)	47/53 (89)
> 800	$\leq$ 70	2/16 (13)	13/20 (65)
	> 70	0/10 (0)	7/10 (70)
	All	2/26 (8)	20/30 (67)

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Study 20000183: Proportion of Subjects a ≥ 30% Reduction From Baseline in Mean iPTH Concentration			
		Placebo	Cinacalcet
iPTH Stratum	Ca x P Stratum	(N = 165)	(N = 165)
All	≤ 70	17/112 (15)	82/102 (80)
All	> 70	2/38 (5)	31/37 (84)
Overall		19/150 (13)	113/139 (81)

Test Statistics:

CMH Statistic (χ^2)		Odds Ratio (Cinacal/Plac)		Difference (Cinacal-Plac)	
Value	P-value	Value	95% CI	Value	95% CI
136.4	< 0.001	29.85	(15.24, 58.48)	69%	(60%, 77%)

Percentage change from baseline in mean Ca x P: The mean (SE) Ca x P value at baseline was 61.2 (1.2) (mg/dL)2 for subjects in both treatment groups. The mean Ca x P value during the efficacy-assessment phase was 49.9 (1.3) (mg/dL)2 for the cinacalcet group and 59.4 (1.2) (mg/dL)2 for the placebo group. The mean Ca x P value was reduced by 17% in the cinacalcet group, compared with a 1% reduction in the placebo group (p < 0.001). Within each treatment group, percentage changes in mean Ca x P were consistent across all baseline iPTH stratum, with reductions ranging from 13% to 20% in the cinacalcet group and changes ranging from a decrease of 2% to an increase of 1% in the placebo group. In contrast, differences were observed across the baseline Ca x P strata. In the ≤ 70 (mg/dL)2 strata, the mean Ca x P value decreased from baseline by 13% for subjects in the cinacalcet group, compared with an increase of 3% for subjects in the placebo group. In the > 70 (mg/dL)2 strata, the Ca x P value decreased by 27% for subjects in the cinacalcet group, compared with 10% for subjects in the placebo group.

Study 20000183: Percentage Change from Baseline in Mean Ca X P					
		Placebo		Cinacalcet	
iPTH Stratum	Ca x P Stratum	(N = 165)		(N = 165)	
[pg/mL]	[mg/dL]^2	n	Mean (SE)	n	Mean (SE)
≥ 300 and ≤ 500	≤ 70	55	2.22 (4.05)	55	-9.65 (4.66)
	> 70	14	-12.65 (4.97)	14	-23.71 (3.54)
	All	69	-0.80 (3.45)	69	-12.50 (3.84)
> 500 and ≤ 800	≤ 70	45	1.46 (2.53)	44	-15.90 (3.56)
	> 70	17	-9.65 (3.99)	17	-30.93 (3.75)
	All	62	-1.59 (2.21)	61	-20.09 (2.89)
> 800	≤ 70	22	5.69 (5.19)	23	-16.65 (4.33)
	> 70	10	-8.30 (6.15)	10	-24.93 (5.89)
	All	32	1.32 (4.17)	33	-19.16 (3.52)
All	≤ 70	122	2.57 (2.24)	122	-13.22 (2.59)
All	> 70	41	-10.34 (2.74)	41	-27.00 (2.43)
Overall		163	-0.68 (1.86)	163	-16.69 (2.09)

Test Statistics:

	Value	P-value
CMH Statistic (χ^2)	33.72	< 0.001

Change from baseline in self-reported cognitive functioning scale score: Changes in Self-reported Cognitive Functioning Scale Score From Baseline to the End of the Efficacy-assessment phase was conditional on achieving statistical significance for the key secondary endpoint. Statistical significance was achieved for the key secondary endpoint (p < 0.001), therefore this

endpoint was tested. The mean (SD) baseline KDQOL Cognitive Functioning scale score for subjects in this study was 77.7 (19.3), which is similar to the baseline score of 82.4 for the Medical Outcomes Study population (n = 3,053) in which the scale was developed. During the efficacy-assessment phase, the mean (SE) change from baseline in the KDQOL Cognitive Functioning scale score was 0.6 (1.32) for the cinacalcet group and -1.6 (1.16) for the placebo group (p = 0.317).

Tertiary Efficacy Outcomes

Percentage changes from baseline in mean iPTH, serum calcium, and serum phosphorus

iPTH: Mean (SE) baseline iPTH concentrations were similar between treatment groups: 653 (29) and 630 (25) pg/mL for subjects who received cinacalcet and placebo, respectively. The mean iPTH concentration during the efficacy-assessment phase was 361 (29) pg/mL for the cinacalcet group and 687 (32) pg/mL for the placebo group. The mean plasma iPTH concentration was reduced by 48% in the cinacalcet group, compared with an increase of 9% in the placebo group (p < 0.001) (see table below). For the cinacalcet group, the mean percentage reduction in iPTH concentration in all baseline iPTH strata was 46% in the ≥ 300 and ≤ 500 pg/mL stratum; 55% in the 500 and ≤ 800 pg/mL stratum; and 36% in the > 800 pg/mL stratum (see table below). The percentage reduction in iPTH concentration was similar across the baseline Ca x P strata (47% and 50% in the ≤ 70 [mg/dL]2 and > 70 [mg/dL]2 strata, respectively). For the placebo group, increases in iPTH concentrations within each baseline iPTH and Ca x P stratum ranged from 1% to 25%.

Study 20000183: Percentage Change from Baseline in Mean iPTH					
		Placebo		Cinacalcet	
iPTH Stratum	Ca x P Stratum	(N = 165)		(N = 166)	
[pg/mL]	[mg/dL]^2	n	Mean (SE)	n	Mean (SE)
≥ 300 and ≤ 500	≤ 70	55	1.36 (5.13)	55	-44.56 (5.60)
	> 70	14	24.93 (9.78)	14	-54.00 (8.11)
	All	69	6.14 (4.65)	69	-46.47 (4.76)
> 500 and ≤ 800	≤ 70	45	12.60 (5.52)	44	-55.22 (4.41)
	> 70	17	3.70 (7.09)	17	-53.55 (5.90)
	All	62	10.16 (4.45)	61	-54.75 (3.56)
> 800	≤ 70	22	7.70 (6.94)	23	-35.71 (7.85)
	> 70	10	20.27 (6.41)	10	-37.41 (10.24)
	All	32	11.63 (5.22)	33	-36.23 (6.20)
All	≤ 70	122	6.65 (3.33)	122	-46.74 (3.37)
All	> 70	41	14.99 (4.85)	41	-49.76 (4.48)
Overall		163	8.75 (2.78)	163	-47.50 (2.76)
Test Statistics:					
		Value		P-value	
CMH Statistic (χ^2)		106.6		< 0.001	

Calcium: Mean (SE) baseline serum calcium concentrations were similar between treatment groups: 10.0 (0.1) and 9.9 (0.1) mg/dL for subjects who received cinacalcet and placebo, respectively. The mean serum calcium concentration during the efficacy-assessment phase was 9.2 (0.1) mg/dL for the cinacalcet group and 9.9 (0.1) mg/dL for the placebo group. The mean serum calcium concentration was reduced by 8% in the cinacalcet group, compared with a < 1%

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increase in the placebo group (p < 0.001) (see table below). For each treatment group, changes in serum calcium were similar across all strata.

Study 20000183: Percentage Change from Baseline in Mean Serum Calcium					
		Placebo		Cinacalcet	
iPTH Stratum	Ca x P Stratum	(N = 165)		(N = 166)	
[pg/mL]	[mg/dL]^2	n	Mean (SE)	n	Mean (SE)
≥ 300 and ≤ 500	≤ 70	55	0.34 (0.64)	55	-5.52 (1.02)
	> 70	14	-0.40 (1.19)	14	-8.51 (1.39)
	All	69	0.19 (0.56)	69	-6.13 (0.87)
> 500 and ≤ 800	≤ 70	45	-0.11 (0.65)	44	-7.61 (1.32)
	> 70	17	0.62 (1.10)	17	-7.05 (1.99)
	All	62	0.09 (0.56)	61	-7.46 (1.10)
> 800	≤ 70	22	0.90 (1.02)	23	-10.43 (1.90)
	> 70	10	1.80 (1.95)	10	-11.31 (2.64)
	All	32	1.18 (0.91)	33	-10.70 (1.52)
All	≤ 70	122	0.27 (0.41)	122	-7.20 (0.76)
All	> 70	41	0.56 (0.76)	41	-8.59 (1.15)
Overall		163	0.35 (0.36)	163	-7.55 (0.64)
Test Statistics:					
		Value		P-value	
CMH Statistic (χ^2)		72.66		< 0.001	

Phosphorus: Mean (SE) serum phosphorus concentrations at baseline were similar between treatment groups: 6.1 (0.1) and 6.2 (0.1) mg/dL for subjects who received cinacalcet and placebo, respectively. The mean serum phosphorus concentration during the efficacy-assessment phase was 5.4 (0.1) mg/dL for the cinacalcet group and 6.0 (0.1) mg/dL for the placebo group. The mean serum phosphorus concentration was reduced by 10% in the cinacalcet group, compared with a 1% reduction in the placebo group (p < 0.001). Within each treatment group, percent changes from baseline in phosphorus were generally similar between baseline iPTH strata, with reductions ranging from 7% to 13% in the cinacalcet group and from 1% to 0% in the placebo group(see table below). In contrast, differences were observed between the baseline Ca x P strata. In the ≤ 70 (mg/dL)^2 strata, the mean phosphorus concentration decreased by 6% for subjects in the cinacalcet group, compared with a 2% increase in the placebo group. In the > 70 (mg/dL)^2 strata, the mean phosphorus concentration decreased by 20% and 11% for subjects in the cinacalcet and placebo groups, respectively.

Study 20000183: Percentage Change from Baseline in Mean Serum Phosphorus					
		Placebo		Cinacalcet	
iPTH Stratum	Ca x P Stratum	(N = 165)		(N = 166)	
[pg/mL]	[mg/dL]^2	n	Mean (SE)	n	Mean (SE)
≥ 300 and ≤ 500	≤ 70	55	2.03 (4.08)	55	-4.81 (4.21)
	> 70	14	-12.35 (4.80)	14	-16.66 (3.56)
	All	69	-0.89 (3.46)	69	-7.22 (3.47)
> 500 and ≤ 800	≤ 70	45	1.75 (2.46)	44	-8.27 (3.68)
	> 70	17	-10.04 (4.20)	17	-25.52 (3.87)
	All	62	-1.48 (2.21)	61	-13.08 (3.02)
> 800	≤ 70	22	4.96 (5.07)	23	-6.77 (4.88)
	> 70	10	-10.27 (5.42)	10	-15.64 (5.54)
	All	32	0.20 (4.03)	33	-9.46 (3.81)

Study 20000183: Percentage Change from Baseline in Mean Serum Phosphorus		Placebo		Cinacalcet	
iPTH Stratum	Ca x P Stratum	(N = 165)		(N = 166)	
All	≤ 70	122	2.45 (2.23)	122	-6.43 (2.48)
All	> 70	41	-10.88 (2.67)	41	-20.08 (2.47)
Overall		163	-0.90 (1.85)	163	-9.86 (2.01)

Test Statistics:			
		Value	P-value
CMH Statistic (χ^2)		10.59	0.001

Proportion of subjects with both a mean iPTH ≤ 250 pg/mL and a reduction from baseline in mean Ca x P: Forty-two percent of subjects in the cinacalcet group compared with 5% in the placebo group had both a mean iPTH ≤ 250 pg/mL and a reduction from baseline in mean Ca x P during the efficacy-assessment phase, (p < 0.001). Since 46% percent of subjects had a mean iPTH ≤ 250 pg/mL, approximately 91% of subjects who achieved an iPTH ≤ 250 pg/mL also had reductions in Ca x P.

Efficacy Conclusions: The proportion of subjects who achieved a target iPTH concentration < 250 pg/mL (primary endpoint) was significantly greater in the cinacalcet group than in the placebo group (46% versus 7%; p < 0.001). A significantly greater proportion of subjects in the cinacalcet group (68%) compared with the placebo group (12%) had a 30% reduction in iPTH concentration (nominal p < 0.001). The mean iPTH concentration was reduced by 48% in the cinacalcet group, compared with a 9% increase in the placebo group (nominal p < 0.001). Consistent reductions in iPTH concentrations occurred in all strata of baseline iPTH and Ca x P levels. The effects of cinacalcet on iPTH were independent of vitamin D sterol use or dose changes.

In the cinacalcet group, reductions in iPTH concentrations were accompanied by significant reductions in Ca x P levels. The mean Ca x P value in the cinacalcet group was reduced by 17% during the efficacy-assessment phase, compared with a 1% reduction in the placebo group (nominal p < 0.001). Reductions in Ca x P in the cinacalcet group resulted from reductions in both serum calcium (-8%) and phosphorus (-10%) concentrations (nominal p < 0.001, compared with placebo). In the placebo group, mean serum calcium, phosphorus, and Ca x P remained at baseline levels throughout the study.

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

Safety

Disposition: As shown in the table below, 93% of placebo-treated subjects and 93% of cinacalcet-treated subjects experienced adverse events during the study. Serious adverse events were equally distributed between the two groups. Adverse events leading to withdrawal from the study were higher in the cinacalcet-treated group (22%) compared with the placebo-treated group (5%).

Clinical Review Section

Study 20000183 Disposition	Placebo n (%)	Cinacalcet n (%)
Subjects evaluable for safety	165	165
Deaths on study [a]	7 (4)	6 (4)
Serious adverse events	51 (31)	47 (28)
Withdrawal due to adverse events	9 (5)	37 (22)
All adverse events	153 (93)	153 (93)

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

Exposure: A total of 330 (165 cinacalcet, 165 placebo) subjects received study medication (see table below). The mean (range) number of days of exposure to study drug was 148 (1 to 199) days for the cinacalcet group and 163 (1, 203) days for the placebo group. The mean (range) cumulative dose of cinacalcet was 11, 706 (————— mg.

Study 20000183: Summary of Exposure to Study Drug	Placebo (N=165)	Cinacalcet (N=165)
Number of days of exposure		
Mean	162.8	147.7
SD	45.2	55.9
Min, Max	1, 203	1, 199
Cumulative dose of cinacalcet (mg)		
Mean	0.0	11706.4
SD	0.0	7406.3
Min, Max		
Dose compliance (%)		
Mean	93.5	91.0
SD	8.4	9.6
Min, Max		

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

Deaths: A total of 13 (7 in the placebo group and 6 in the cinacalcet group) deaths occurred during the study. Of the deaths occurring during the study, 6 (1 event in the placebo group and 5 events in the cinacalcet group) were due to cardiac arrest. Other events occurring in the cinacalcet treated group include one event of cardiac failure. Events occurring in the placebo treated group included one each due to access hemorrhage, pulmonary edema, cerebral hemorrhage, myocardial infarction and renal failure. One death (in the placebo group) was due to unknown causes. Causes of death were consistent with this population's baseline comorbid conditions and similar to causes of death in the general population of patients with ESRD.

Serious Adverse Events: Serious adverse events were reported by 51 (31%) placebo-treated subjects and 47 (28%) cinacalcet-treated subjects (see table below). The most common serious adverse events were pneumonia (1 % of the placebo treated group and 5% of the cinacalcet treated group), non-cardiac chest pain (1 % of the placebo treated group and 3% of the cinacalcet treated group), sepsis (0 % of the placebo treated group and 3% of the cinacalcet treated group) and cardiac failure (1 % of the placebo treated group and 3% of the cinacalcet treated group).

20000183: Serious Adverse Events, by Body System		
	Placebo	Cinacalcet
Subjects Receiving Dose	165	165
Subjects Reporting SAEs	51 (31)	47 (28)
Events:		
Gastrointestinal	9 (5)	11 (7)
Liver / Biliary	0 (0)	1 (1)
Nervous	5 (3)	8 (5)
Cardiovascular	3 (2)	5 (3)
Heart Rate / Rhythm	3 (2)	8 (5)
Myo/Endo/Pericardial	5 (3)	4 (2)
Respiratory	8 (5)	6
Body as a whole	12 (7)	9 (5)
Endocrine/Metabolic	2 (1)	1 (1)
Musculoskeletal	8 (5)	4 (2)
Infectious	9 (5)	3 (2)
Blood and Lymphatic		
Skin and Appendages	0 (0)	2 (1)
Urinary Disorders	1 (1)	0 (0)
Vascular Disorders	8 (5)	8 (5)
Vision Disorders	0 (0)	2 (1)
Psychiatric	0 (0)	1 (1)

Adverse Events Leading to Withdrawal: A total of 46 subjects had adverse events leading to withdrawal from the study [37 (22%) from the cinacalcet group and 9 (5%) from the placebo group]. The most common adverse events leading to withdrawal were: vomiting (7%,0%), nausea (6% ,0%), diarrhea (2%,1%), dyspepsia (2%,0%), fatigue (2%,0%) and abdominal pain (2%,0%). One subject from the cinacalcet group withdrew from the study because of hypocalcemia.

Adverse Events Leading to Dose Alteration: A total of 74 subjects had adverse events leading to dose alteration [54 (33%) from the cinacalcet group and 20 (12%) from the placebo group]. The most common adverse events were gastrointestinal [40 (24%) from the cinacalcet group and 9 (5%) from the placebo group], predominantly nausea and vomiting. One subject in the cinacalcet group and no subjects in the placebo group required dose alteration because of hypocalcemia.

Adverse Events: A total of 93 % of subjects in the both groups reported at least 1 adverse event during the study (see table below). The most common adverse events were vomiting (39% cinacalcet, 13% placebo), nausea (31% cinacalcet, 19% placebo), diarrhea (16% cinacalcet, 18% placebo), myalgia (16% cinacalcet, 16% placebo), and headache (15% cinacalcet, 22% placebo). Adverse events with a ≥ 5% difference between treatment groups included vomiting (39% cinacalcet, 13% placebo), nausea (31% cinacalcet, 19% placebo), headache (15% cinacalcet, 22% placebo), hypotension (8% cinacalcet, 13% placebo), and upper respiratory infection (3% cinacalcet ,11% placebo).

Clinical Review Section

20000183: Adverse Events by Body System	Placebo	Cinacalcet
Subjects Receiving Dose	165	165
Subjects Reporting AEs	153 (93)	153 (93)
Events:		
Body as a whole	68 (41)	62 (38)
Gastrointestinal	87 (53)	117 (71)
Liver / Biliary	0 (0)	3 (2)
Nervous	62 (38)	58 (35)
Cardiovascular	28 (17)	27 (16)
Heart Rate / Rhythm	16 (10)	23 (14)
Myo/Endo/Pericardial	12 (7)	8 (5)
Respiratory	50 (30)	42 (25)
Endocrine/Metabolic	5 (3)	8 (5)
Musculoskeletal	63 (38)	56 (34)
Infectious	15 (9)	14 (8)
Blood and Lymphatic	7 (4)	8 (5)
Skin and Appendages	34 (21)	28 (17)
Urinary Disorders	6 (4)	9 (5)
Reproductive	5 (3)	3 (2)
Vascular Disorders	17 (10)	13 (8)
Vision Disorders	12 (7)	8
Hearing / Vestibular	8 (5)	2 (1)
Psychiatric	10 (6)	7 (4)

Adverse Events of Special Interest:

Convulsions: Three serious adverse events of convulsions and 1 serious adverse event of status epilepticus were reported in the cinacalcet group. No reports of seizure activity occurred in the placebo group.

GI Adverse Events: Gastrointestinal adverse events are common with cinacalcet treatment. Serious adverse events related to the gastrointestinal system were reported for 7% of subjects in the cinacalcet group and 5% of subjects in the placebo group. Nausea was reported in 31% of cinacalcet-treated patients and 19% of placebo treated patients. Vomiting was reported in 39% of cinacalcet-treated patients and 13% of placebo-treated patients. Diarrhea was reported in 16% of cinacalcet-treated patients and 18% of placebo treated patients. Nausea was considered severe in 4% of subjects in the cinacalcet group and 0% of subjects in the placebo group. Vomiting was considered severe in 1% of subjects in the cinacalcet group and 0% of subjects in the placebo group. GI hemorrhage was reported in 1 (1%) cinacalcet-treated patient and 8 (5%) placebo-treated patients. Dyspepsia was reported in 12 (7%) of cinacalcet-treated subjects and 6 (5%) of placebo-treated subjects. Gastric ulcer was reported in 2 (1%) cinacalcet-treated subjects and 1 (1%) placebo-treated subject. There were 3 (2) reports of gastritis in the cinacalcet group and 1 (1%) report in the placebo group. Esophagitis was reported in one subject in the cinacalcet-treated group.

Cataracts: One subject in the placebo group developed cataracts during the study.

Laboratory: Safety laboratory assessments were performed at screening and follow-up.

Clinical Review Section

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

Other Safety Tests:

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

ECGs: ECGs were collected predialysis, at approximately nadir drug concentrations. Investigator interpretation of ECGs was categorized on the case report form as normal; abnormal, but not clinically significant; or abnormal, clinically significant. Approximately one-half of the subjects (58% cinacalcet, 53% placebo) had an abnormal ECG at baseline. Of those subjects without clinically significant ECG abnormalities at baseline, 2 subjects (1%) in the cinacalcet group and 8 subjects (5%) in the placebo group had findings that were considered clinically significant at the end of the study. One of the subjects who received cinacalcet had first-degree atrioventricular block, and the other had a partial right bundle branch block and a prominent T wave. Of the 8 subjects in the placebo group, 3 subjects had no discernable changes from the baseline ECG report, and 1 subject each had atrial fibrillation, a prolonged QT interval, left ventricular hypertrophy, tachycardia, or peaked T waves).

QT intervals corrected for heart rate using Bazett's (QTcB) and Fridericia's (QTcF) correction formulae were measured at baseline and Weeks 14 and 26. At Weeks 14 and 26, the cinacalcet group had a mean change in QTcB that was 6.4 and 1.8 msec greater than the placebo group, respectively. When the QT interval was corrected using the Fridericia's formula, similar differences in mean change were observed. When subjects were categorized with regard to change in QTc from baseline (<30, 30 to 60, > 60 msec), similar proportions of subjects had an increase of > 60 msec at all time points, regardless of the correction formula used. Increases in QTc of 30 to 60 msec were observed at Week 14 in 16% and 6% of subjects in the cinacalcet and placebo group, respectively. At Week 26, increases in QTcB of 30 to 60 msec were observed in 14% and 21% of the cinacalcet and placebo group, respectively. No notable differences between treatment groups were observed in the occurrence of an absolute QTc > 500 msec at any time point during the study.

QTc (Bazett's Correction) – Baseline and Each Visit		
	Placebo	Cinacalcet
QTc (msec)	165	165
Baseline	163	163
Mean	421.1	415.2
SE	2.6	2.2
Median	422.0	413.0

Clinical Review Section

QTc (Bazett's Correction) - Baseline and Each Visit		
	Placebo	Cinacalcet
Week 14	143	130
Mean	418.2	418.2
SE	2.6	2.8
Median	415.0	419.0
Week 26	127	102
Mean	421.4	416.1
SE	3.1	3.4
Median	416.0	415.0
End of Study	156	150
Mean	422.9	417.0
SE	2.7	2.8
Median	417.5	416.0

The proportion of subjects with at least 1 absolute increase in QTcB beyond the upper limit of normal (450 msec [men] and 470 msec [women]) was slightly higher in the cinacalcet group compared with the placebo group at Week 14 (12% versus 8%, respectively), but was higher in the placebo group compared with the cinacalcet group at Week 26 and end of study (13% versus 7% and 14% versus 8%, respectively). For the subjects with an increase beyond the upper limit of normal, the mean increase in QTcB was 43 msec for the cinacalcet group and 33 msec for the placebo group at Week 14, and 45 msec for both groups at Week 26.

Proportion of Subjects with Each Category of QTcB Change from Baseline (Safety Subjects)		
	Placebo	Cinacalcet
	(N = 101)	(N = 291)
	n/N1 (%)	n/N1 (%)
Week 14		
Decrease	69/141 (49)	53/129 (41)
Increase < 30 msec	58/141 (41)	49/129 (38)
Increase 30-60 msec	8/141 (6)	21/129 (16)
Increase > 60 msec	1/141 (1)	3/129 (2)
Week 26		
Decrease	58/125 (46)	44/102 (43)
Increase < 30 msec	38/125 (30)	41/102 (40)
Increase 30-60 msec	26/125 (21)	14/102 (14)
Increase > 60 msec	2/125 (2)	1/102 (1)
End of Study		
Decrease	70/154 (45)	66/149 (44)
Increase < 30 msec	50/154 (32)	60/149 (40)
Increase 30-60 msec	30/154 (19)	18/149 (12)
Increase > 60 msec	3/154 (2)	3/149 (2)
Maximum During Study		
Decrease	52/154 (34)	42/149 (28)
Increase < 30 msec	64/154 (42)	68/149 (46)
Increase 30-60 msec	34/154 (22)	31/149 (21)
Increase > 60 msec	4/154 (3)	6/149 (4)

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

Safety Conclusions: In this 6-month study, 330 (165 cinacalcet, 165 placebo) received study drug and were evaluable for safety. The incidence of serious adverse events and deaths was similar across treatment groups. Nausea and vomiting occurred more often in cinacalcet-treated subjects. The proportion of subjects who withdrew due to adverse events was higher in the cinacalcet group than in the placebo group, primarily because of withdrawals due to vomiting or nausea. Four subjects in the cinacalcet group and no subjects in the placebo group discontinued the study because of convulsions. It is not clear if the seizures are solely due to change in calcium concentration. Similar to study 20000172, the incidence of esophagitis, gastritis and gastric ulcer occurred more frequently in the cinacalcet-treated subjects, possibly signaling a cinacalcet effect on gastric acid secretion. No trends indicative of a treatment effect were noted in clinical laboratory measurements, other than expected differences in plasma iPTH, serum calcium, and phosphorus concentrations. Evaluation of ECGs, including the QTc interval, indicated a change in QTc that was greater in the cinacalcet group than in the placebo group at week 14. No notable difference between treatment groups was observed at week 26 or end of study. The proportion of subjects with a > 60 msec prolongation in the QTc interval or an absolute QTc > 500 msec was similar between treatment groups.

Discussion and Conclusions: Secondary HPT develops early in chronic kidney disease before the initiation of dialysis and progresses after patients reach ESRD. In recognition of the need for improved disease management, the NKF-K/DOQI has recommended target ranges for iPTH and Ca x P (see table below).

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

In this phase 3 study, the severity of secondary HPT in enrolled subjects ranged from mild to severe, with mean baseline iPTH concentrations of 653 and 630 pg/mL for the cinacalcet and placebo groups, respectively. Twenty percent of subjects had a baseline iPTH concentration > 800 pg/mL. Twenty-five percent of subjects had baseline Ca x P values > 70 (mg/dL)^2, a level above which vitamin D therapy is generally contraindicated. The proportion of subjects with a mean iPTH $\leq$ 250 pg/mL during the efficacy-assessment phase (primary endpoint) was 46% in the cinacalcet group and 7% in the placebo group (p < 0.001). A significantly greater proportion of subjects in the cinacalcet group (68%) compared with the placebo group (12%) had a $\geq$ 30% reduction in mean iPTH during the efficacy-assessment phase (nominal p < 0.001). Reductions in iPTH were observed across all baseline iPTH and Ca x P strata.

Reductions in iPTH in subjects treated with cinacalcet were accompanied by significant reductions in Ca x P, serum calcium, and phosphorus compared with the placebo group. Ca x P decreased by 17% in the cinacalcet group, compared with a decrease of 1% in the placebo group (nominal $p < 0.001$).

The occurrence of serious adverse events and deaths was similar between treatment groups. Nausea and vomiting occurred more frequently in subjects who received cinacalcet. The proportion of subjects who withdrew due to adverse events was higher in the cinacalcet group than in the placebo group, primarily because of withdrawals due to vomiting or nausea. Of concern, convulsions occurred in 4 subjects dosed with cinacalcet, compared with no reports in the placebo group. It is not clear if the seizures are solely due to change in calcium concentration. Esophagitis, gastritis and gastric ulceration occurred more frequently in the cinacalcet-treated subjects, possibly signaling a cinacalcet effect on gastric acid secretion.

Evaluation of ECGs, including the QTc interval, indicated a change in QTc that was slightly greater in the cinacalcet group than in the placebo group at week 14. No notable difference between treatment groups was observed at week 26 or end of study. The proportion of subjects with a > 60 msec prolongation in the QTc interval or an absolute QTc > 500 msec was similar between treatment groups.

Study 20000188: A Placebo-controlled, Double-blind, Multicenter Study to Assess the Efficacy and Safety of an Oral Calcimimetic Agent (AMG 073) in Secondary Hyperparathyroidism of Chronic Kidney Disease (Hemodialysis and Peritoneal Dialysis)

This was a randomized, double-blind, placebo-controlled, multicenter study of the efficacy and safety of cinacalcet in patients with secondary hyperparathyroidism and chronic kidney disease (hemodialysis and peritoneal dialysis).

Objectives: The primary objective of this study was to investigate the efficacy of cinacalcet hydrochloride, AMG 073) compared with placebo by determining the proportion of subjects with a mean plasma intact parathyroid hormone (iPTH) value ≤ 250 pg/mL (26.5 pmol/L) during the efficacy - assessment phase.

Study Design: This was a randomized, double-blind, placebo-controlled, parallel-group, 26-week study. Sixty centers in North America and Australia participated in the study. After a 30-day screening period, subjects who qualified for the study were randomized in a 3:1 ratio to cinacalcet or placebo within 1 of 4 strata defined by baseline mean iPTH and dialysis modality. In contrast to phase 3 studies 20000172 and 20000183, no limit was placed on the number of subjects with a baseline iPTH > 800 pg/mL who could enroll. Throughout the study, investigators could prescribe concomitant therapy considered necessary

The study consisted of 2 phases: a 16-week dose-titration phase followed by a 10-week efficacy-assessment phase. Possible sequential daily doses during the treatment period were 30, 60, 90, 120, and 180 mg cinacalcet or placebo. Biweekly visits occurred during the titration and

efficacy-assessment phases. At the week 4, 8, 12, 16, 20, and 24 study visits, subjects were titrated up to the next sequential dose level of cinacalcet/placebo based on iPTH response and safety monitoring (see figure below)
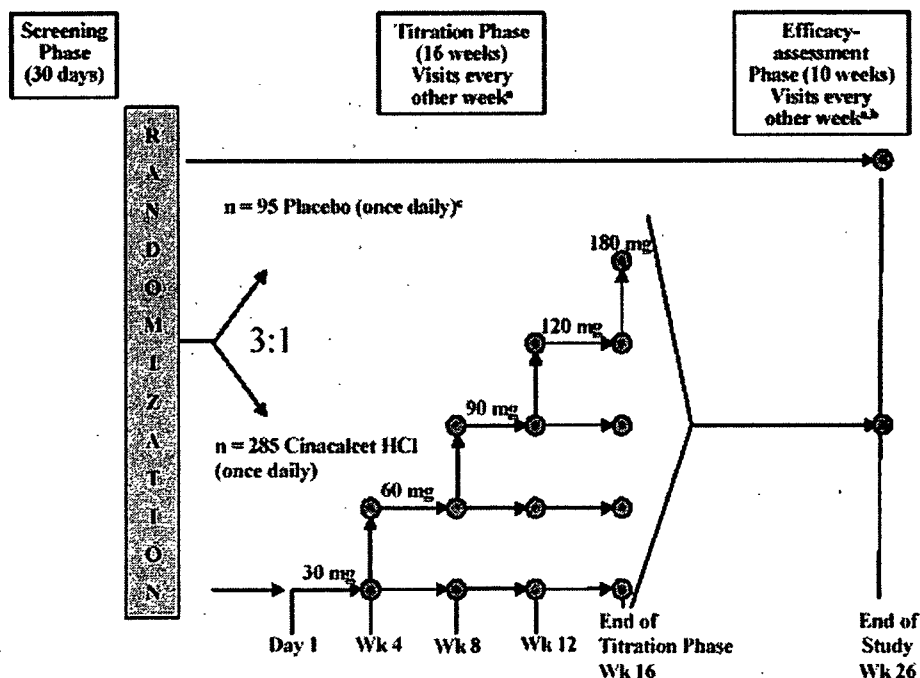
Population: The study population consisted of subjects with end stage renal disease who were maintained on dialysis. Subjects were stratified as follows:

- hemodialysis, and iPTH ≥ 300 pg/mL (31.8 pmol/L) to ≤ 500 pg/mL (53 pmol/L)
- hemodialysis, and iPTH ≥ 500 pg/mL to ≤ 800 pg/mL (84.8 pmol/L)
- hemodialysis, and iPTH > 800 pg/mL
- peritoneal dialysis, and iPTH ≥ 300 pg/mL

Inclusion Criteria

- ≥ 18 years of age at the start of screening
- agreed to use, in the opinion of the principal investigator, highly effective contraceptive measures throughout the study
- mean of 2 central laboratory iPTH values ≥ 300 pg/mL obtained within 30 days before Day 1
- mean of 2 central laboratory serum calcium values ≥ 8.4 mg/dL (2.1 mmol/L) obtained within 30 days before Day 1
- prescribed hemodialysis or peritoneal dialysis (continuous ambulatory peritoneal dialysis or automated peritoneal dialysis) for ≥ 1 month before Day 1

- signed the IRB-approved informed consent document before any study-specific procedures were initiated

Exclusion Criteria

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

COMMENT: The inclusion and exclusion criteria appear appropriate.

Study Medication: All medications were administered orally with a starting dose of 30mg cinacalcet or placebo. Tablets were taken with food or shortly after a meal if feasible and were swallowed whole without biting or chewing. The study drug was provided as light green film-coated tablets of 30-, 60-, and 90-mg free-base equivalents or placebo, which were graduated in size, smallest to largest. Possible sequential doses during the study were 30, 60, 90, 120, and 180 mg cinacalcet or placebo. Combinations of the tablets were used for the 120- and 180-mg doses (two 60-mg and two 90-mg tablets, respectively). Except during the screening phase, changes in phosphate binders/oral calcium supplements were permitted throughout the study. Changes in vitamin D therapy were only permitted based on protocol-specified guidelines.

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

Efficacy Measures: A reduction in iPTH to ≤ 250 pg/mL was chosen as the primary endpoint for the phase 3 program. In patients with ESRD, relatively normal bone histology has been observed with PTH concentrations of approximately 2 to 4 times the upper limit of normal, corresponding to approximately 100 to 250 pg/mL. A reduction in iPTH $\geq 30\%$ is also

considered clinically meaningful by many nephrologists and has been used as the primary endpoint in trials for vitamin D sterols in treatment of secondary HPT.

Primary Efficacy Endpoint

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

Secondary Efficacy Endpoints

- Proportion of subjects with a reduction from baseline in mean iPTH of ≥ 30% during the efficacy-assessment phase
- Percentage change from baseline in mean iPTH during the efficacy-assessment phase
- Percentage changes from baseline in Ca x P, serum calcium, and phosphorus, during the efficacy-assessment phase

Exploratory Efficacy Endpoints

- Changes in PRO scale scores

COMMENT: The primary endpoint target range of iPTH is appropriate. K/DOQI guidelines[7] list the target range of iPTH in dialysis patients as 150 – 300 pg/mL.

Safety Measures: Safety was assessed by adverse events, laboratory measurements, electrocardiograms (ECGs), vital signs, and physical exams. Reductions in testosterone levels, and increases in tri-iodothyronine (T3) and decreases in free thyroxine (T4) with no overall change in thyroid-stimulating hormone (TSH) were observed in a 1-year monkey toxicology study. Therefore, TSH and T4 hormone levels were assessed for all subjects, and total and free testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels were assessed in all men.

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

Dose Titration: Subjects could be titrated up to the next sequential dose level of study drug at the week 4, 8, 12, 16, 20, and 24 study visits. For each of these visits, a site representative called the IVRS within 5 days before and 3 days after the scheduled visit in order for a subject to receive the next bottle number(s). The site personnel were asked for subject information that included central laboratory iPTH and serum calcium values and safety information.

If any of the following criteria applied, a subject's dose was NOT increased:
For weeks 4, 8, 12, 16, 20, and 24:

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[7] K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003, Oct. 42 (4) Supplement 3.
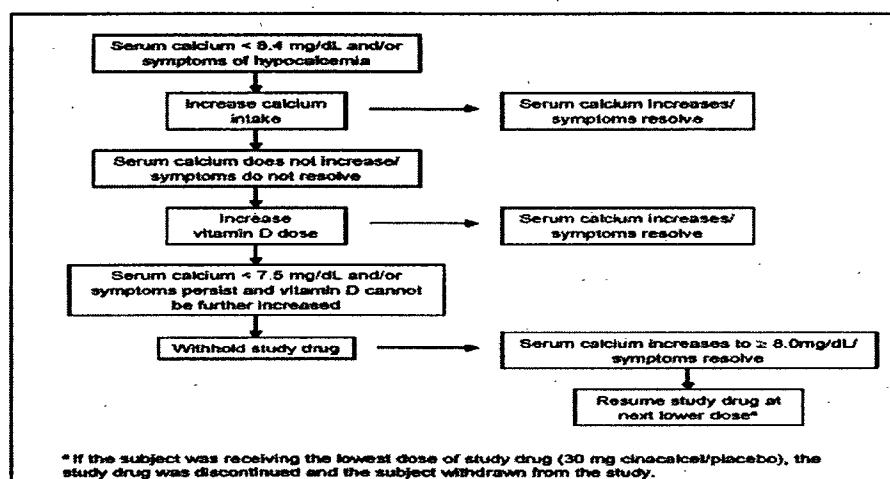
- The central laboratory iPTH value from the preceding study visit was ≤ 200 pg/mL (21.2 pmol/L).
- The highest dose of study medication was reached.
- The serum calcium was < 7.8 mg/dL (1.95 mmol/L) or the subject was experiencing symptoms of hypocalcemia.
- The subject was experiencing an adverse event that precluded a dose increase

If iPTH values were < 100 pg/mL (10.6 pmol/L) for 2 consecutive study visits, study medication was reduced to the next lower dose.

Treatment of Hypocalcemia: Guidelines used for management of hypocalcemia are outlined in the figure below:

* If the subject was receiving the lowest dose of study drug (30 mg cinacalcet/placebo), the study drug was discontinued and the subject withdrawn from the study.

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

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

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

- Cinacalcet decreases mean iPTH concentrations to ≤ 250 pg/mL in a significantly greater proportion of subjects with ESRD and secondary HPT compared with placebo.

- Cinacalcet reduces mean iPTH concentrations by ≥ 30% in a significantly greater proportion of subjects compared with placebo.
- Cinacalcet significantly reduces iPTH compared with placebo.

The sample size calculation was based on a χ^2 test of equal proportions of subjects with a mean iPTH value ≤ 250 pg/mL during the efficacy-assessment phase, with a statistical significance level of 0.05 (2-sided). The placebo response was predicted on the basis of previous cinacalcet phase 2 studies to be ≤ 13%. With a cinacalcet response rate of 30% assumed for the purpose of sample size considerations, the planned 380 subjects (285 cinacalcet, 95 placebo) yielded 91% power.

A 3-stage hypothesis testing procedure was performed for the primary and secondary endpoints. The primary endpoint was tested at a significance level of 0.05. The statistical inference for the secondary endpoint of the proportion of subjects with a reduction from baseline in mean iPTH of 30% during the efficacy-assessment phase was made only if statistical significance was achieved for the primary endpoint. The statistical inference for the percentage change from baseline in mean iPTH during the efficacy-assessment phase was made only if statistical significance was achieved for both the primary endpoint and the first secondary endpoint at a significance level of 0.05.

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

The statistical analysis plan (SAP) was revised twice. The second version, dated 16 August 2002, applied to the protocol amendment as described below, and provided a detailed description of the new principal features of the statistical considerations described in the protocol and provided guidelines from which the analyses would proceed. The final version of the SAP, dated 23 April 2003, included the following changes:

- redefinition of the primary iPTH dataset and addition of sensitivity analyses for iPTH-related endpoints after identification of inconsistencies in global procedures to measure iPTH and affected iPTH values during a global audit of —————————— ——— and affiliates
- inclusion of analyses of ECG interval data
- redefinition of the conversion factor for paricalcitol equivalents

Protocol Amendments: The protocol was amended once, on 21 March 2002. The changes were implemented before enrollment of the first subject and included:

- A placebo group was added to allow for comparison of the effects of cinacalcet on safety and efficacy in subjects with secondary HPT of ESRD.
- The study was changed from open-label to double-blind.
- The study was designated as an additional phase 3 study, and the primary endpoint was changed to match the primary endpoint in the other phase 3 studies.
- Randomization (3:1, cinacalcet:placebo) and stratification by dialysis modality and baseline iPTH were added.
- The sample size was increased to 380.
- The number of centers was increased to approximately 60.
- The study duration was changed to 46 weeks.
- Hormone levels (i.e., TSH and free T4 hormone for all subjects; total and free testosterone, LH, and FSH for men only) were added as laboratory assessments.
- PRO assessments were added.
- Eligibility requirements for iPTH and serum calcium were changed: the mean of 2 central laboratory iPTH values obtained within 30 days before day 1 was to be ≥ 300 pg/mL, and the mean of 2 central laboratory serum calcium values obtained within 30 days before day 1 was to be ≥ 8.4 mg/dL. Previously, only single values (not means) were required.
- Instructions were provided for adjusting phosphate binders/calcium supplements and vitamin D sterols based on specific serum calcium, phosphorus, and Ca x P values.
- ECG assessments at weeks 18 and 26 were added.

Results

Patient Disposition: As shown in the table below, 662 subjects were screened and 395 subjects were enrolled and randomized into this study. Approximately 76% of placebo and 74% of cinacalcet subjects completed the 16 week trial. A slightly higher proportion overall of hemodialysis subjects (76%) completed the efficacy assessment phase than peritoneal dialysis subjects (65%). Adverse events were the most common reason for early withdrawal, with the rate higher in the cinacalcet group.

20000188: Patient Disposition		
	Placebo	**Cinacalcet**
Enrolled	101	294
No treatment	0	3
At least one dose	101	291
Withdrew - Total	24 (24)	77 (26)
Withdrew - AE	8 (8)	39 (13)
Deaths	2 (2)	3 (1)
Withdrew - Parathyroidectomy	2 (2)	0 (0)
Withdrew – Renal Transplant	6 (6)	10 (3)
Withdrew - Other	6 (6)	25 (8)
Completed Titration Phase (Weeks 1-16)	84 (83)	239 (81)
Completed Study	77 (76)	217 (74)

Protocol Violations: Eighteen (5%) subjects had eligibility deviations in this study, which were discovered after subjects were enrolled. The most common eligibility deviation was a change in vitamin D sterol dose during the 30 days before day 1. Major protocol deviations occurred in

40% of subjects overall. Deviations were equally distributed between the two groups. Compliance with study drug was 87% in each treatment group.

Study 20000188: Incidence of Major Protocol Deviations by Treatment Group and Baseline Randomization Strata		
	Placebo	Cinacalcet
	n/N (%)	n/N (%)
Total	37/101 (37%)	120/294 (41%)
Hemodialysis and iPTH 300 to 500	8/25 (32%)	28/74 (38%)
Hemodialysis and iPTH 501 to 800	10/29 (34%)	32/84 (38%)
Hemodialysis and iPTH > 800	15/35 (43%)	44/102 (43%)
Peritoneal Dialysis and iPTH 300	4/12 (33%)	16/34 (47%)

COMMENTS: There were numerous and varied protocol violations. The predominant major violation, missed doses, was evenly distributed between the two groups (17%). It is unlikely that the protocol violations affected the principal efficacy results.

Demographics: Baseline subject demographics were well balanced across the treatment groups (see table below). Thirty-eight percent of enrolled subjects were Black and approximately 20% of subjects were $\geq$ 65 years of age. The duration of dialysis ranged from 1 to 359 months, with a mean of 58 months. Randomization within each baseline stratum was balanced between treatment groups. At baseline, mean iPTH, Ca x P, serum calcium, and serum phosphorus were similar in the cinacalcet and placebo groups. Baseline mean iPTH values were higher in this study than in studies 20000172 and 20000183 due to a higher percentage of subjects (35% versus a maximum of 20% in phase 3 studies 20000172 and 20000183) who enrolled in this study with a baseline iPTH > 800 pg/mL. At study entry, vitamin D and phosphate binder use were similar in the 2 treatment groups.

Study 20000188: Demographics		
	Placebo	Cinacalcet
N	101 (%)	294 (%)
Age (yrs.)	53.5 ± 13.9	51.8 ± 14.0
$\geq$ 65 years	23 (23)	52 (18)
$\geq$ 75 years	8 (8)	18 (6)
Sex		
Male	64 (63)	181 (62)
Female	37 (37)	113 (38)
Race		
Caucasian	39 (39)	115 (39)
Black	33 (35)	114 (39)
Other	27 (27)	65 (22)
Randomization Strata		
HD, PTH 300 - 500	25 (25)	74 (25)
HD, PTH 500 - 800	29 (29)	84 (29)
HD, PTH > 800	35 (35)	102 (35)
PD, PTH >300	12 (12)	34 (12)
Baseline Labs		
iPTH (pg/mL)	832 ± 486	848 ± 685
Serum Ca (mg/dL)	10.01 ± 0.86	9.79 ± 0.81
Ca x P (mg/dL)^2	60.87 ± 14.04	59.56 ± 16.49
Serum Phos (mg/dL)	6.10 ± 1.44	6.10 ± 1.69

Clinical Review Section

Study 20000188: Demographics	Placebo	Cinacalcet
Baseline Vitamin D Use		
Yes	76 (69)	191 (65)
No	31 (31)	103 (35)
Baseline Phosphate Binder Use		
Yes	94 (93)	274 (93)
No	7 (7)	20 (7)

Baseline blood pressure, height, weight, and selected medical history were similar between treatment groups.

Primary Efficacy Outcomes

Proportion of subjects with a mean iPTH value ≤ 250 pg/mL during the efficacy-assessment phase: The primary analyses of the efficacy endpoints were based on the ITT analysis set. The mean baseline iPTH was 832 pg/mL in the placebo-treated group and 848 pg/mL in the cinacalcet-treated group. Significantly more subjects in the cinacalcet group (35%) compared with the placebo group (6%) achieved a mean iPTH concentration ≤ 250 pg/mL during the efficacy-assessment phase (p < 0.001). More cinacalcet-treated subjects in the lowest baseline iPTH stratum achieved an iPTH concentration ≤ 250 pg/mL than did subjects in the higher baseline iPTH strata: (65% in the iPTH ≥ 300 pg/mL and ≤ 500 pg/mL stratum, 39% in the iPTH > 500 pg/mL and ≤ 800 pg/mL stratum, and 10%in the iPTH > 800 pg/mL stratum). Intact PTH response in the cinacalcet group was similar regardless of dialysis modality (35% in hemodialysis subjects and 38% in the peritoneal dialysis subjects. In the placebo group, the proportions of subjects within each stratum who achieved an iPTH concentration ≤ 250 pg/mL ranged from 0% to 24%.

Study 20000188: Proportion of Subjects With a Mean iPTH Value ≤ 250 pg/mL During the Efficacy-assessment Phase	Placebo	Cinacalcet
	(N = 101)	(N = 294)
	n/N1 (%)	n/N1 (%)
All	6/101 (6)	104/294 (35)
Randomization Stratum		
Hemodialysis and iPTH ≥ 300 & ≤ 500 pg/mL	6/ 25 (24)	48/ 74 (65)
Hemodialysis and iPTH > 500 & ≤ 800 pg/mL	0/ 29 (0)	33/ 84 (39)
Hemodialysis and iPTH > 800 pg/mL	0/ 35 (0)	10/102 (10)
Peritoneal Dialysis and iPTH 300 pg/mL	0/ 12 (0)	13/ 34 (38)

Subgroup Analyses: The primary endpoint was also analyzed separately by age (< 65, 65 years), sex, and race (black, white, other). Results were similar across all subgroups and were comparable to those of the primary analysis, with the exception that 40% of cinacalcet-treated men achieved the primary endpoint versus 27% of cinacalcet-treated women. A slightly higher percentage of women (45%) than men (37%) had a baseline iPTH > 800 pg/mL which may contribute to the difference seen.

Analysis by Dose Level: Cinacalcet treatment was titrated based on an individual subject's iPTH response and tolerability. Study drug dose level distribution is presented in the table

below. At the end of study (week 26), subjects were distributed across all dose levels of cinacalcet, with 41% of subjects receiving 180 mg. In the placebo group, 90% of subjects were receiving the 180-mg matching dose level.

Study 20000188: Summary of Study Drug Dose Level	Placebo (N=101)	Cinacalcet (N=291)
Daily dose (mg) at end of titration (week 16) - n(%)		
30	1 (1)	34 (14)
60	3 (4)	40 (17)
90	7 (9)	42 (18)
120	8 (10)	42 (18)
180	63 (77)	76 (32)
Daily dose (mg) at end of study (week 26) - n(%)		
30	1 (1)	29 (13)
60	2 (3)	36 (17)
90	3 (4)	31 (14)
120	2 (3)	31 (14)
180	70 (90)	88 (41)
Most frequent dose taken during the study - n(%)		
30	15 (15)	89 (31)
60	10 (10)	43 (15)
90	8 (8)	61 (21)
120	5 (5)	32 (11)
180	63 (62)	66 (23)

Secondary Efficacy Outcomes

Proportion of subjects with a reduction from baseline in mean iPTH of $\geq$ 30% during the efficacy-assessment phase: A significantly greater proportion of subjects in the cinacalcet group (59%) compared with the placebo group (10%) achieved a $\geq$ 30% decrease in mean iPTH concentration from baseline to the efficacy-assessment phase (p < 0.001). The proportion of subjects in the cinacalcet group who achieved a $\geq$ 30% reduction in iPTH concentration was similar for each baseline iPTH stratum: 65% in the iPTH $\geq$ 300 pg/mL and $\leq$ 500 pg/mL, 63% in the iPTH > 500 pg/mL and $\leq$ 800 pg/mL, and 51% in the iPTH > 800 pg/mL). In addition, iPTH response in the cinacalcet group was similar in hemodialysis (59%) and peritoneal dialysis (62%). For subjects in the placebo group, the proportion of subjects within each stratum who achieved this endpoint ranged from 0% to 24%. Analysis by age (< 65, > 65 years), sex, and race was also performed. Results were similar for all subgroups and were comparable to those of the primary analysis.

Study 20000188: Proportion of Subjects with 30% Reduction From Baseline in Mean iPTH during the Efficacy Assessment Phase		
	Placebo	Cinacalcet
	(N = 101)	(N = 294)
	n/N1(%)	n/N1(%)
All	10/101 (10)	174/294 (59)
Randomization Stratum		
Hemodialysis and iPTH 300 & 500 pg/mL	6/ 25 (24)	48/ 74 (65)
Hemodialysis and iPTH > 500 & 800 pg/mL	2/ 29 (7)	53/ 84 (63)
Hemodialysis and iPTH > 800 pg/mL	2/ 35 (6)	52/102 (51)
Peritoneal Dialysis and iPTH 300 pg/mL	0/ 12 (0)	21/ 34 (62)

Percentage change from baseline in mean iPTH during the efficacy-assessment phase:
Mean (SE) baseline iPTH concentrations were 848 (40) and 832 (48) pg/mL for subjects in the cinacalcet and placebo groups, respectively. The mean iPTH concentration during the efficacy-assessment phase was 526 (30) pg/mL for the cinacalcet group and 852 (55) pg/mL for the placebo group. Mean plasma iPTH concentrations were reduced by 40% in the cinacalcet group, compared with an increase of 4% in the placebo group (p < 0.001) (see table below). For the cinacalcet group, the percentage decreases in iPTH were similar across all baseline strata. The mean change in iPTH was also analyzed separately by age (< 65 , 65 years), sex, and race. Results were similar across all subgroups and were comparable to those of the primary analysis.

Study 20000188: Percentage Change From Baseline in Mean iPTH				
	Placebo		Cinacalcet	
	(N = 101)		(N = 294)	
	n	Mean (SE)	n	Mean (SE)
All	100	4.07 (3.41)	288	-40.30 (2.05)
Baseline Stratum				
HD and iPTH 300 and 500 pg/mL	25	2.02 (8.37)	70	-46.69 (3.88)
HD and iPTH > 500 and 800 pg/mL	29	6.29 (5.62)	83	-43.98 (3.82)
HD and iPTH > 800 pg/mL	34	1.26 (4.82)	101	-33.35 (3.59)
PD and iPTH 300 pg/mL	12	10.93 (12.50)	34	-38.82 (5.71)
Test Statistics:				
CMH Statistic for Mean Scores Difference (χ^2)[a]		Value	P-value	
		83.36	< 0.001	

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

Ca x P Product: Mean (SE) Ca x P values at baseline were 59.6 (1.0) and 60.9 (1.4) (mg/dL)^2 for the cinacalcet and placebo groups, respectively. The mean (SE) Ca x P value during the efficacy-assessment phase was 50.0 (0.9) (mg/dL)^2 for the cinacalcet group and 58.1 (1.3) (mg/dL)^2 for the placebo group, representing a mean decrease from baseline of 13% in the cinacalcet group, compared with a mean decrease of 1% in the placebo group (p < 0.001). Within each treatment group, percentage changes in mean Ca x P were consistent across each baseline hemodialysis iPTH stratum, ranging from -18% to -8% in the cinacalcet group and from -6% to 2% in the placebo group (see table below). In contrast, for peritoneal dialysis subjects, the percentage decrease was similar between the cinacalcet (8% decrease) and placebo (6%

decrease) groups. The 8% reduction with cinacalcet was consistent with the magnitude of reduction of Ca x P observed in other cinacalcet studies.

Study 20000188: Percent Change From Baseline in Mean Ca x P				
	Placebo		Cinacalcet	
		(N = 101)		(N = 294)
	n	Mean (SE)	n	Mean (SE)
All	100	-1.43 (2.42)	287	-12.85 (1.65)
Baseline Stratum				
HD and iPTH 300 and 500 pg/mL	25	2.26 (4.90)	69	-12.03 (3.38)
HD and iPTH > 500 and 800 pg/mL	29	1.15 (5.59)	83	-9.08 (3.54)
HD and iPTH > 800 pg/mL	34	-4.75 (3.40)	101	-17.98 (2.47)
PD and iPTH 300 pg/mL	12	-5.94 (5.48)	34	-8.45 (4.13)
Test Statistics:				
CMH Statistic for Mean Scores Difference $(\chi^2)^a$		Value		P-value
		20.27		< 0.001

Calcium: Mean (SE) serum calcium concentrations at baseline were 9.8 (0.1) and 10.0 (0.1) mg/dL for the cinacalcet and placebo groups, respectively. The mean (SE) serum calcium concentration during the efficacy-assessment phase was 9.1 (0.1) mg/dL for the cinacalcet group and 10.1 (0.1) mg/dL for the placebo group. As outlined in the table below, mean serum calcium concentration was reduced by 6% in the cinacalcet group, compared with a 1% increase in the placebo group (p < 0.001). For each treatment group, changes in serum calcium were similar across all iPTH and dialysis strata.

Study 20000188: Percentage Change From Baseline in Mean Calcium				
	Placebo		Cinacalcet	
		(N = 101)		(N = 294)
	n	Mean (SE)	n	Mean (SE)
All	100	0.90 (0.52)	288	-6.46 (0.57)
Baseline Stratum				
HD and iPTH 300 and 500 pg/mL	25	1.82 (1.14)	70	-5.55 (1.02)
HD and iPTH > 500 and 800 pg/mL	29	0.91 (0.90)	83	-5.75 (1.09)
HD and iPTH > 800 pg/mL	34	0.02 (0.95)	101	-7.35 (1.05)
PD and iPTH 300 pg/mL	12	1.48 (1.17)	34	-7.42 (1.37)
Test Statistics:				
CMH Statistic for Mean Scores Difference $(\chi^2)^a$		Value		P-value
		51.78		< 0.001

Phosphorus: Mean (SE) serum phosphorus concentrations at baseline were 6.1 (0.1) both for the cinacalcet group and placebo group. The mean serum phosphorus concentration during the efficacy-assessment phase was 5.5 (0.1) mg/dL for the cinacalcet group and 5.8 (0.1) mg/dL for the placebo group. As outlined in the table below, mean serum phosphorus concentrations in the cinacalcet group decreased by 7% in the cinacalcet group, compared with a 2% decrease in the placebo group (p = 0.039). For hemodialysis subjects, within each treatment group, percentage changes in mean phosphorus were greater in the cinacalcet group, with a range from -12% to -3%, than in the placebo group, with a range from -5% to 1%. For peritoneal dialysis subjects, the percentage decrease was lower in the cinacalcet group (2% decrease) compared with the placebo group (7% decrease). The 7% reduction observed in the placebo group was greater than expected compared with previous studies, but was not surprising given the higher baseline Ca x

P and serum phosphorus levels in these subjects. Subjects with higher baseline Ca x P and serum phosphorus are more aggressively managed during the study.

Study 20000188: Percentage Change From Baseline in Mean Serum Phosphorus				
	Placebo		Cinacalcet	
	(N = 101)		(N = 294)	
	n	Mean (SE)	n	Mean (SE)
All	100	-2.17 (2.46)	289	-7.20 (1.56)
Baseline Stratum				
HD and iPTH 300 and 500 pg/mL	25	0.62 (4.87)	71	-8.57 (2.69)
HD and iPTH > 500 and 800 pg/mL	29	0.62 (5.86)	83	-2.91 (3.62)
HD and iPTH > 800 pg/mL	34	-4.75 (3.44)	101	-11.67 (2.34)
PD and iPTH 300 pg/mL	12	-7.40 (5.35)	34	-1.50 (3.97)
Test Statistics:				
CMH Statistic for Mean Scores Difference (χ^2)[a]		Value	P-value	
		4.26	3.039	

Vitamin D and Phosphate Binder Use: At baseline, 34% of subjects were not receiving vitamin D. At each individual time point, the incidence of vitamin D use remained similar to baseline and was comparable between treatment groups. The proportion of subjects who received vitamin D at any time during the study was comparable between treatment groups (80% cinacalcet, 76% placebo). Notably, the reduction in iPTH with cinacalcet treatment was independent of vitamin D use. At baseline, 93% of subjects were receiving phosphate binders in both the cinacalcet and placebo groups. Phosphate binder use remained similar to that at baseline and was comparable between treatment groups during the study.

Changes in PRO scale scores (exploratory): Exploratory analyses examined changes in PRO scale scores. No notable differences were observed between the treatment groups

Efficacy Conclusions: Current therapy for secondary HPT includes pharmacologic doses of vitamin D sterols and large oral doses of calcium-containing phosphate binders. Such therapy is often limited by elevations in Ca x P, which have been associated with a variety of adverse outcomes, including increased risk of cardiac, visceral, and vascular calcifications. The proportion of subjects who achieved a target iPTH $\leq$ 250 pg/mL was significantly greater in the cinacalcet group than in the placebo group (35% versus 6%; p < 0.001). In addition, a significantly greater proportion of subjects in the cinacalcet group (59%) compared with the placebo group (10%) had a $\geq$ 30% reduction in iPTH (nominal p < 0.001). Mean iPTH concentration was decreased by 40% in the cinacalcet group, compared with an increase of 4% in the placebo group (nominal p < 0.001). Consistent reductions in iPTH were observed regardless of baseline iPTH stratum or dialysis modality. The effects of cinacalcet on iPTH were independent of vitamin D sterol use or dose changes, indicating that cinacalcet can be used as a primary intervention or as part of combined therapy with vitamin D sterols to control secondary HPT.

Reductions in iPTH levels were accompanied by significant decreases in serum Ca x P, calcium, and phosphorus. Mean Ca x P in the cinacalcet group was reduced by 13% during the efficacy-assessment phase compared with a 1% decrease in the placebo group (nominal

p < 0.001). **Reductions in Ca x P in the cinacalcet group resulted from decreases in both serum calcium (-6%) and phosphorus (-7%). Among peritoneal dialysis subjects, the change in serum phosphorus was greater for the placebo group compared with the cinacalcet group, a finding that was likely driven by elevated baseline phosphorus levels, results from 2 outliers, and the small sample size in the placebo group (N = 12).**

Current K/DOQI guidelines[8] list the target range of iPTH in dialysis patients as 150 – 300 pg/mL and a mean Ca x P $\leq$ 55 (mg/dL)[2]. A post-hoc analysis was performed to analyze the proportion of subjects achieving these guideline targets. This analysis showed that 35% of cinacalcet subjects and 6% of placebo subjects met target goals. These results suggest that new therapeutic strategies using cinacalcet will assist in achieving the more stringent treatment goals that will be recommended for managing secondary HPT (NKF K/DOQI).

Safety

Disposition: As shown in the table below, 93% of placebo-treated subjects and 91% of cinacalcet-treated subjects experienced adverse events during the study. Serious adverse events were equally distributed between the two groups.

Study 20000188 Disposition		
	Placebo n (%)	Cinacalcet n (%)
Subjects evaluable for safety	101	291
Deaths on study [a]	2 (2)	2 (1)
Serious adverse events	26 (26)	80 (27)
Severe, life-threatening and fatal AE	26 (26)	76 (26)
Withdrawal due to adverse events	8 (8)	39 (13)
All adverse events	94 (93)	266 (91)

Exposure: A total of 392 (291 cinacalcet, 101 placebo) received study medication (see Table below). The mean (range) number of days of exposure to study drug was 156 (1 to 198) days for the cinacalcet group and 160 (9, 195) days for the placebo group. The mean (range) cumulative dose of cinacalcet was 10,926 ｢   ｣ mg.

Study 20000188: Summary of Exposure to Study Drug		
	Placebo (N=101)	Cinacalcet (N=291)
Number of days of exposure		
Mean	160.0	155.9
SD	50.4	55.4
Min, Max	9, 195	1, 198
Cumulative dose of cinacalcet (mg)		
Mean	0.0	10926.2
SD	0.0	6577.3
Min, Max		

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