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

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

For weeks 3, 6, 9 and 12:

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

For weeks 16, 20, and 24:

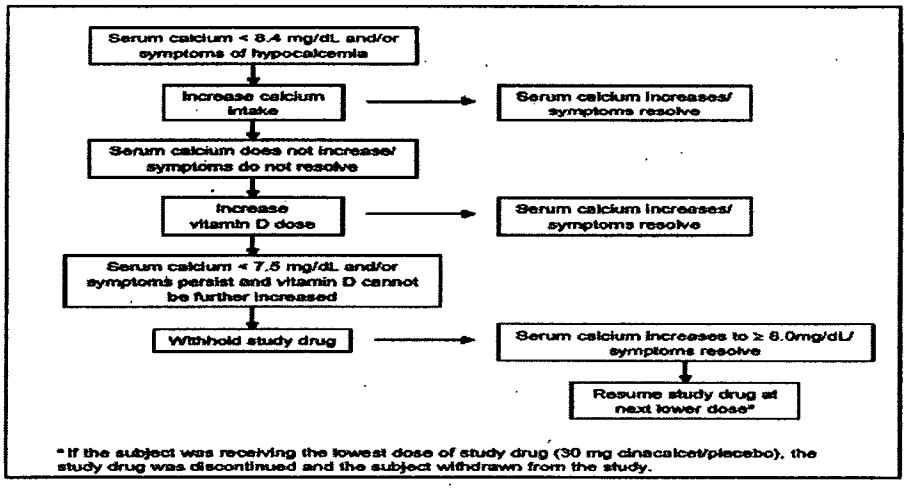
- The central laboratory iPTH value from the preceding study visit was ≤ 200 pg/mL (21.2 pmol/L) with any missing value replaced by the most recent past value.

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

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

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

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



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

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

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

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

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

The sample size calculation was based on a χ^2 test of equal proportions of subjects with a mean iPTH value ≤ 250 pg/mL during the efficacy-assessment phase, with a statistical significance level of 0.05 (2-sided). The placebo response was predicted on the basis of previous cinacalcet phase 2 studies to be ≤ 15%. With a cinacalcet response rate of 35% assumed for the purpose of sample size considerations, the planned 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 ≥ 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 [redacted] 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 ≥ 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
≥ 65 years	56 (34)	51 (31)
≥ 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 ≤ 70	55 (33)	55 (33)
PTH 300 – 500, Ca x P > 70	14 (8)	14 (8)
PTH 500 – 800, Ca x P ≤ 70	46 (28)	47 (28)
PTH 500 – 800, Ca x P > 70	18 (11)	17 (10)
PTH > 800, Ca x P ≤ 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.

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