Study 20000188: Summary of Exposure to Study Drug		
	Placebo	Cinacalcet
	(N=101)	(N=291)
Dose compliance (%)		
Mean	87.3	86.9
SD	19.0	17.4
Min, Max		

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

Deaths: Among the 5 deaths that occurred in the study population, four occurred during the study and one was reported after the database lock. Of the deaths occurring during the study, 2 were due to cardiac arrest (1 event each in the cinacalcet and placebo groups), 1 was due to cerebrovascular disorder (in the cinacalcet group), and 1 was due to unknown causes (in the placebo group). One death, due to hemorrhagic bowel ischemia and secondary lactic acidosis (in the placebo group) was reported after database lock. 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 26 (26%) placebo-treated subjects and 80 (27%) cinacalcet-treated subjects (see table below). The most common serious adverse events were dyspnea (0 % of the placebo treated group and 2% of the cinacalcet treated group), GI hemorrhage (0 % of the placebo treated group and 2% of the cinacalcet treated group), peripheral gangrene (0 % of the placebo treated group and 2% of the cinacalcet treated group), pulmonary edema (2 % of the placebo treated group and 1% of the cinacalcet treated group), and pneumonia (3 % of the placebo treated group and 1% of the cinacalcet treated group)

20000188: Serious Adverse Events, by Body System		
	Placebo	Cinacalcet
Subjects Receiving Dose	101	291
Subjects Reporting SAEs	26 (26)	80 (27)
Events:		
Gastrointestinal	3 (3)	23 (8)
Liver / Biliary	0 (0)	2 (1)
Nervous	3 (3)	9 (3)
Cardiovascular	1 (1)	9 (3)
Heart Rate / Rhythm	6 (6)	4 (1)
Myo/Endo/Pericardial	7 (7)	8 (3)
Respiratory	5 (5)	19 (7)
Body as a whole	7 (7)	18 (6)
Endocrine/Metabolic	3 (3)	4 (1)
Musculoskeletal	3 (3)	6 (2)
Infectious	1 (1)	12 (4)
Blood and Lymphatic	1 (1)	4 (1)
Skin and Appendages	1 (1)	4 (1)
Urinary Disorders	0 (0)	3 (1)
Vascular Disorders	0 (0)	9 (3)
Vision Disorders	1 (1)	1 (0)
Psychiatric	0 (0)	1 (0)

Adverse Events Leading to Withdrawal: A total of 47 subjects withdrew from the study due to adverse events [39 (13%) from the cinacalcet group and 8 (8%) from the placebo group]. The

most common adverse events were (cinacalcet, placebo) nausea (30%, 22%), diarrhea (24%, 19%), vomiting (23%, 12%), upper respiratory infection (18%, 13%), headache (17%, 12%), and myalgia (15%, 14%).The rate of withdrawal due to adverse events was similar between patients receiving hemodialysis and peritoneal dialysis. Adverse events that most commonly resulted in withdrawal involved the GI body system, predominantly nausea (7% cinacalcet, 3% placebo), vomiting (3% cinacalcet, 1% placebo), and diarrhea (2% cinacalcet, 0% placebo).

Adverse Events: Ninety-one percent of subjects in the cinacalcet group and 93% of subjects in the placebo group reported at least 1 adverse event during the study (see table below). The most common adverse events (≥ 15% in either treatment group) were (cinacalcet, placebo) nausea (30%, 22%), diarrhea (24%, 19%), vomiting (23%, 12%), upper respiratory infection (18%, 13%), headache (17%, 12%), myalgia (15%, 14%), and abdominal pain (12%, 18%). In addition, adverse events that occurred with a ≥ 5% difference between treatment groups included (cinacalcet, placebo) abdominal pain (12%, 18%), asthenia (8%, 2%), hypotension (7%, 12%), and wound (5%, 0%).

20000188: Adverse Events, by Body System

	Placebo	Cinacalcet
Subjects Receiving Dose	101	291
Subjects Reporting AEs	94 (93)	266 (91)
Events:		
Body as a whole	47 (47)	154 (53)
Gastrointestinal	53 (52)	187 (64)
Liver / Biliary	0 (0)	3 (1)
Nervous	28 (28)	114 (39)
Cardiovascular	18 (18)	46 (16)
Heart Rate / Rhythm	17 (17)	22 (8)
Myo/Endo/Pericardial	11 (11)	17 (6)
Respiratory	43 (43)	124 (43)
Endocrine/Metabolic	8 (8)	22 (7)
Musculoskeletal	39 (39)	100 (34)
Infectious	7 (7)	26 (9)
Blood and Lymphatic	10 (10)	29 (10)
Skin and Appendages	20 (20)	64 (22)
Urinary Disorders	8 (8)	24 (8)
Reproductive	4 (4)	8 (3)
Vascular Disorders	7 (7)	25 (9)
Vision Disorders	6 (6)	17 (6)
Hearing / Vestibular	0 (0)	9 (3)
Psychiatric	8 (8)	19 (7)

Adverse Events of Special Interest:

Convulsions: Three (1%) subjects in the cinacalcet group and no subjects in the placebo group discontinued the study because of convulsions. A 32-year-old female receiving peritoneal dialysis with past medical history significant only for hypertension suffered convulsions at Week 8 (60-mg cinacalcet dose level; serum calcium of 8.5 mg/dL) and Week 10 (90-mg cinacalcet dose level; serum calcium of 9.6 mg/dL). Baseline serum calcium was 10.0 mg/dL and baseline iPTH was 621 pg/mL. No on-study serum calcium values were below the normal range. A 62-year-old male receiving hemodialysis with past medical history significant for convulsions (not receiving anti-convulsant medication at baseline), hypertension, cerebrovascular accident, and

left ventricular hypertrophy experienced convulsions during week 16 (90-mg dose level; serum calcium of 9.3 mg/dL). Baseline serum calcium was 9.3 mg/dL and baseline iPTH was 455 pg/dL. A local laboratory reported an uncorrected serum calcium level of 7.4 mg/dL 1 day after the event. Corrected serum calcium ranged from 7.7 mg/dL to 9.3 mg/dL during the study. A 28-year-old female receiving hemodialysis with past medical history significant for intermittent convulsions (recently treated with Dilantin), hypertension, and asthma experienced convulsions during Week 5 (60-mg cinacalcet dose level; serum calcium 7.4 mg/dL) and Week 7 (60-mg cinacalcet dose level; serum calcium 8.8 mg/dL). Baseline serum calcium was 9.6 mg/dL and baseline iPTH was 1788 pg/dL. At the time of the first episode of convulsions, the Dilantin level was below normal (8 μmol/L; target therapeutic range = 40 to 80 μmol/L). At the time of the second episode of convulsions, study drug had been withheld for 19 days. Records indicate that Dilantin dosing was being adjusted and the investigator attributed the convulsions to noncompliance with Dilantin or a drug interaction between Dilantin and Coumadin .

GI Adverse Events: Gastrointestinal adverse events are common with cinacalcet treatment. Nausea was reported in 30% of cinacalcet-treated patients and 22% of placebo treated patients. Vomiting was reported in 23% of cinacalcet-treated patients and 12% of placebo treated patients. Diarrhea was reported in 24% of cinacalcet-treated patients and19% of placebo treated patients. GI hemorrhage was reported in 4% of cinacalcet-treated patients and 0% of placebo treated patients. Dyspepsia was reported in 9% of cinacalcet-treated patients and 11% of placebo treated patients. There was one report each of esophagitis and gastritis in the cinacalcet group and no reports in the placebo group.

Cataracts: Cataract formation associated with cinacalcet use was reported in animal studies. There were no reports of cataracts in this trial.

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

Laboratories of Special Interest: In response to the 1-year monkey toxicology findings, an evaluation of thyroid and gonadal function was included in this study. The primary objective of this analysis was to determine whether subjects receiving cinacalcet were at increased risk for developing thyroid or gonadal dysfunction. The following hormones were measured at study entry (baseline), week 16, and week 26 in subjects receiving cinacalcet or placebo: TSH, free T4, total and free testosterone, LH and FSH. TSH and free T4 hormone levels were assessed for all subjects. Total and free testosterone, LH, and FSH levels were assessed for men only.

The criteria used to define hyperthyroidism, hypothyroidism, and hypogonadism are provided in the table below. The definitions of hyperthyroidism and hypothyroidism were consistent with standard medical practice. Due to the lack of uniform clinical criteria, Amgen defined hypogonadism as a total testosterone < 200 mg/dL and a 25% reduction from baseline.

Study 20000188: Normal Ranges for Hormones*	
Hormone	**Normal Range**
TSH	0.32 to 5 μ IU/mL
T4	0.7 to 1.9 ng/dL
Total Testosterone	350 to 1030 ng/dL
Free Testosterone	52 to 280 pg/mL
LH	2 to 12 mIU/mL
FSH	1 to 15 mIU/mL

*Normal ranges for total and free testosterone, LH, and FSH are for males.

Laboratory Definitions of Hyperthyroidism, Hypothyroidism, and Hypogonadism*	
Condition	**Laboratory Definition**
Hyperthyroidism	Free T4 >1.9 ng/dL and TSH < 0.32 μIU/mL
Hypothyroidism	Free T4 <0.7 ng/dL and TSH > 5.0 μIU/mL
Hypogonadism	Total testosterone < 200 ng/mL and 25% reduction from baseline in total testosterone

*Diagnostic criteria had to be met at both weeks 16 and 26 (see Methods).

Assessment of Thyroid Function

TSH: As shown in the table below, baseline TSH levels were in the low end of the normal range in both treatment groups. TSH in female subjects receiving cinacalcet at baseline and week 16 was due to very high levels in 3 subjects. Two subjects completed the trial, one of whom was subsequently treated with thyroid hormone. The third subject was withdrawn because of an administrative decision.

Serum Thyroid Stimulating Hormone at Each Scheduled Visit				
Thyroid Stimulating Hormone (0.32 to 5 uU/mL)				
	Males		Females	
	Placebo (N=64)	Cinacalcet (N=180)	Placebo (N=37)	Cinacalcet (N=111)
Baseline				
Mean	1.59	1.61	1.92	6.75
SD	1.00	1.07	1.98	38.78
Median	1.29	1.40	1.63	1.87
Week 16				
Mean	1.80	1.78	2.47	6.58
SD	1.20	1.20	3.33	36.47
Median	1.65	1.48	1.67	2.10
Week 26				
Mean	1.67	1.70	2.20	2.36
SD	1.25	1.04	2.04	2.04
Median	1.36	1.45	1.62	2.07

The incidence of subjects with TSH levels outside the normal range at each time point is shown in the table below. In both treatment groups, 7 - 8% of subjects had TSH levels outside the normal range at baseline. The percentage of subjects with abnormal TSH levels remained stable throughout the study and was similar between treatment groups. Only a few subjects in either treatment group had normal baseline TSH levels that subsequently became abnormal.

Proportion of Subjects with Thyroid Stimulating Hormone Values Outside the Normal Range at Each Study Time Point			
	Baseline	Week 16	Week 26
Cinacalcet – N (%)	283	243	216
Within normal range	259 (92)	226 (93)	206 (95)
Above normal range	12 (4)	8 (3)	4 (2)
Below normal range	12 (4)	9 (4)	6 (3)
Normal at baseline / above normal range at week 16 or 26	NA	3 (1)	0 (0)
Normal at baseline / below normal range at week 16 or 26	NA	2 (1)	2 (1)
Placebo – N (%)	96	87	78
Within normal range	89 (93)	80 (92)	72 (92)
Above normal range	3 (3)	3 (3)	3 (4)
Below normal range	4 (4)	4 (5)	3 (4)
Normal at baseline / above normal range at week 16 or 26	NA	2 (2)	1 (1)
Normal at baseline / below normal range at week 16 or 26	NA	2 (2)	2 (2)

Free Thyroxine: A summary of free T4 levels at baseline, week 16, and week 26 in cinacalcet and placebo treated subjects is provided in the table below. Free T4 levels were in the low normal range at baseline and throughout the study in both treatment groups.

Serum Free Thyroxine Hormone at Each Scheduled Visit				
	Free Thyroxine (ng/dL)			
	Males		Females	
	Placebo	Cinacalcet	Placebo	Cinacalcet
	(N=64)	(N=180)	(N=37)	(N=111)
Baseline				
Mean	0.85	0.84	0.86	0.84
SD	0.18	0.16	0.19	0.16
Median	0.90	0.80	0.80	0.80
Week 16				
Mean	0.82	0.86	0.83	0.90
SD	0.16	0.17	0.21	0.19
Median	0.80	0.90	0.80	0.90
Week 26				
Mean	0.82	0.86	0.81	0.87
SD	0.17	0.17	0.18	0.16
Median	0.80	0.80	0.80	0.90

Eleven percent of subjects receiving cinacalcet and 15% of subjects receiving placebo had free T4 levels below the normal range at baseline (Table 6). The percentage of subjects with low free T4 levels remained stable throughout the study and was similar between treatment groups. Four to 6% of subjects in each treatment group had normal baseline levels that were subsequently below normal during the study.

Proportion of Subjects with Free Thyroxine Values Outside the Normal Range at Each Study Time Point			
	Baseline	Week 16	Week 26
Cinacalcet - N (%)	283	243	216
Within normal range	253 (89)	219 (90)	199 (92)
Below normal range	30 (11)	24 (10)	17 (8)
Normal at baseline / below normal range at week 16 or 26	NA	15 (6)	13 (5)

Proportion of Subjects with Free Thyroxine Values Outside the Normal Range at Each Study Time Point			
	Baseline	Week 16	Week 26
Placebo - N (%)	96	87	78
Within normal range	82 (85)	77 (89)	67 (86)
Below normal range	14 (15)	10 (11)	11 (14)
Normal at baseline / below normal range at week 16 or 26	NA	5 (6)	3 (4)

The proportion of subjects with both TSH and free T4 levels outside of the normal range at each time point is presented in Table 7. In the cinacalcet group, there were 4 (1%) subjects at baseline with elevated TSH and low free T4 levels; 2 of these subjects also had elevated TSH and low free T4 levels at week 16. No subject in either group met the definition of hyperthyroidism or hypothyroidism during the study (i.e., elevated TSH and low free T4 levels at both weeks 16 and 26).

Incidence of Thyroid Abnormalities at Each Scheduled Visit		
	Placebo	**Cinacalcet**
TSH > 5.0 μ IU/mL and free T4 < 0.7 ng/dL	N (n%)	N (n%)
Baseline	0/ 96 (0)	4/284 (1)
Week 16	0/ 87 (0)	2/243 (1)
Week 26	0/ 78 (0)	0/216 (0)
Week 16 and 26	0/ 77 (0)	0/215 (0)
TSH < 0.32 μ IU/mL and free T4 > 1.9 ng/dL	N (n%)	N (n%)
Baseline	0/ 96 (0)	0/284 (0)
Week 16	0/ 87 (0)	0/243 (0)
Week 26	0/ 78 (0)	0/216 (0)
Week 16 and 26	0/ 77 (0)	0/215 (0)

COMMENT: The majority of subjects in both treatment groups exhibited low to low-normal free T4 levels with normal TSH levels, which is consistent with the sick euthyroid profile characteristic of patients with ESRD. No subject in either group met the definition of hyperthyroidism or hypothyroidism during the study.

Assessment of Gonadal Function

Total Testosterone: Total testosterone levels were below the normal range (< 350 ng/dL) at baseline in both treatment groups (298 ng/dL in the placebo-treated group and 327 ng/dL in the cinacalcet-treated group). Total testosterone levels were significantly reduced in the Cinacalcet group when compared to placebo (see table below). At Week 16, the mean percent change from baseline in the cinacalcet group was -37.80 compared to11.73 in the placebo group (p=0.003). At Week 26, the mean percent change from baseline in the cinacalcet group was -50.97 compared to -1.58 in the placebo group (p=0.002).

Serum Total Testosterone - Baseline and Change at Each Visit		
	Placebo	Cinacalcet
Total Testosterone (ng/dL)	(N=57)	(N=165)
Baseline		
Mean	297.88	327.04
SD	190.44	171.22
Median	266.00	304.00

Serum Total Testosterone – Baseline and Change at Each Visit		
	Placebo	Cinacalcet
Percent Change from Baseline		
Week 16	n (51)	n (141)
Mean	11.73	- 37.80
SD	97.42	122.56
Median	23.00	-33.00
p-value	0.003	
Week 26	n (48)	n (125)
Mean	- 1.58	-50.97
SD	119.28	143.61
Median	-2.50	-46.00
p-value	0.002	

The incidence of subjects with baseline normal total testosterone levels who developed levels below normal range at each time point is shown in the table below. A significant number of subjects who were normal at baseline developed sub-normal testosterone levels when treated with cinacalcet.

Proportion of Subjects with Total Testosterone Levels Below Normal at Week 16 and 26 of Those Subjects with Normal Levels at Baseline		
	Week 16	**Week 26**
	n/N (%)	n/N (%)
Cinacalcet	26/61 (43)	24/61 (39)
Placebo	2/20 (10)	4/20 (20)
p-value (from Fisher's Exact test)	0.007	0.175

Free Testosterone: Free testosterone levels were below the normal range (< 52 pg/dL) at baseline in both treatment groups (64 pg/dL in the placebo-treated group and 68 pg/dL in the cinacalcet-treated group). Free testosterone levels were significantly reduced in the cinacalcet group when compared to placebo (see table below). At Week 16, the mean percent change from baseline in the cinacalcet group was -15.51 compared to -4.97 in the placebo group (p=0.005). At Week 26, the mean percent change from baseline in the cinacalcet group was -20.38 compared to -14.61 in the placebo group (p=0.061).

Serum Free Testosterone – Baseline and Change at Each Visit		
	Placebo	Cinacalcet
Total Testosterone (ng/dL)	(N=57)	(N=165)
Baseline		
Mean	64.10	67.51
SD	37.92	36.64
Median	56.00	62.50
Percent Change from Baseline		
Week 16	n (51)	n (140)
Mean	- 4.97	- 15.51
SD	31.32	41.85
Median	-1.00	-14.50
p-value	0.005	

Serum Free Testosterone – Baseline and Change at Each Visit		
	Placebo	Cinacalcet
Week 26	n (47)	n (123)
Mean	- 14.61	-20.38
SD	30.55	38.57
Median	-9.00	-19.00
p-value	0.061	

The incidence of subjects with baseline normal free testosterone levels who developed levels below normal range at each time point is shown in the table below. A significant number of subjects who were normal at baseline developed sub-normal free testosterone levels when treated with cinacalcet.

Proportion of Subjects with Free Testosterone Levels Below Normal at Week 16 and 26 of Those Subjects with Normal Levels at Baseline		
	Week 16	**Week 26**
	n/N (%)	n/N (%)
Cinacalcet	40/107 (37)	39/107 (36)
Placebo	3/34 (9)	10/34 (29)
p-value (from Fisher's Exact test)	0.001	0.538

Gonadotropin Levels: Baseline levels of LH were similar in the two groups: 11.5 mIU/ml in the placebo-treated group and 11.2 mIU/ml in the cinacalcet-treated group. The mean values at Week 26 were 12.3 mIU/ml and 9.9 mIU/ml in the placebo and cinacalcet groups, respectively. Of the cinacalcet-treated subjects with normal LH levels at baseline, 2% had elevated LH levels at Week 26. Among subjects receiving placebo with normal LH levels at baseline, 11% had elevated LH levels at Week 26. Baseline levels of FSH were similar in the two groups: 9.7 mIU/ml in the placebo-treated group and 9.5 mIU/ml in the cinacalcet-treated group. There were very small, insignificant changes in the levels of FSH from baseline to Week 26 in both groups. Very few subjects (1 to 2) in either treatment group had normal baseline FSH levels that subsequently were above the normal range at Week 26.

Proportion of Subjects with Gonadotropin Levels Outside the Normal Range at Each Study Time Point			
	Baseline	Week 16	Week 26
Luteinizing Hormone			
Cinacalcet - N (%)	**175**	**157**	**140**
Within normal range	124 (71)	114 (73)	106 (76)
Above normal range	46 (26)	37 (24)	28 (20)
Below normal range	5 (3)	6 (4)	6 (4)
Normal baseline / above normal range Week 16 or 26	NA	8 (6)	3 (2)
Normal baseline / below normal range Week 16 or 26	NA	3 (2)	2 (2)
Placebo - N (%)	**61**	**56**	**53**
Within normal range	45 (74)	40 (71)	40 (75)
Above normal range	15 (25)	16 (29)	13 (25)
Below normal range	1 (2)	0 (0)	0 (0)
Normal baseline / above normal range Week 16 or 26	NA	6 (13)	5 (11)
Normal baseline / below normal range Week 16 or 26	NA	0 (0)	0 (0)

Proportion of Subjects with Gonadotropin Levels Outside the Normal Range at Each Study Time Point			
	Baseline	Week 16	Week 26
Follicle Stimulating Hormone			
Cinacalcet - N (%)	**175**	**157**	**140**
Within normal range	149 (85)	135 (86)	124 (89)
Above normal range	26 (15)	22 (14)	16 (11)
Normal baseline / above normal range Week 16 or 26	NA	2 (1)	2 (1)
Placebo - N (%)	**61**	**56**	**53**
Within normal range	52 (85)	48 (86)	45 (85)
Above normal range	9 (15)	8 (14)	8 (15)
Normal baseline / above normal range Week 16 or 26	NA	1 (2)	1 (2)

The proportion of subjects in each treatment group who developed a total testosterone level of < 200 mg/dl and had a > 25% reduction from baseline, 4% of placebo subjects and 18% of cinacalcet subjects met these criteria at Week 26. Notably, most of the cinacalcet subjects with total testosterone < 200 mg/dL and a > 25% reduction from baseline at either week 16 or week 26 had low testosterone levels at baseline. The changes in FSH and LH for subjects meeting these criteria were also similar in both treatment groups. Cinacalcet treated subjects with a total testosterone < 200 mg/dL and a > 25% reduction from baseline had mean percent changes in LH of -18% and -10% and FSH of -4% and -2% at week 16 and week 26, respectively. Similarly, placebo treated subjects with a total testosterone < 200 mg/dL and a > 25% reduction from baseline had mean percent changes in LH of -13% and -13% and FSH of -3% and -20% at week 16 and week 26, respectively.

COMMENTS: Chronic renal failure is known to cause hypothalamic-pituitary dysfunction affecting the sex steroid axis. Gonadal dysfunction in uremia also occurs. As testosterone levels fall, gonadotropin levels generally increase. In addition to evidence of defects in pituitary and gonadal function, there are indicators suggesting the importance of alterations in hypothalamic regulation of pituitary-gonadal function in the pathogenesis of uremic hypogonadism. Cinacalcet is a calcimimetic agent that acts as a modulator of the calcium-sensing receptor (CaR). The calcium-sensing receptor has been shown to exist on anterior pituitary cells[9] as well as in the testes themselves[10]. The etiology of the decrease in serum testosterone levels with cinacalcet treatment is unclear. Long term sequelae of hypogonadism include infertility, osteopenia and impaired physical function.

Other Safety Tests:

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

ECGs: Of those subjects without clinically significant ECG abnormalities at baseline, 13 (5%) subjects in the cinacalcet group and no subjects in the placebo group had clinically significant

[9] Zivadinovic D, et.al. Cell-type specific messenger functions of extracellular calcium in the anterior pituitary. Endocrinology 2002. 143(2):445-455.

[10] Adebanjo OA, et.al.. The effect of extracellularly applied divalent cations on cytosolic Ca2+ in murine leydig cells: evidence for a Ca2+-sensing receptor. 1998. J Physiol 513 (Pt2):399-410.

abnormal ECG findings at the end of study. One subject was noted to have a prolonged QT interval, with a 33 and 31 msec increase in QT interval, corrected for heart rate by Bazett's formula (QTcB) at weeks 18 and 26, respectively. The subject completed the duration of the study and no adverse events potentially related to prolonged QT interval were reported.

QT Interval: QT intervals corrected for heart rate using Bazett's (QTcB) correction formula was measured at baseline and weeks 18, 26, and end of study. The mean QTcB interval was slightly higher in the cinacalcet group (426 msec) than the placebo group (423 msec) at baseline(see table below). The mean maximum increase during the study was 14.10 msec in the placebo-treated group compared to 20.05 msec in the cinacalcet-treated group. When the QT interval was corrected using Fridericia's formula, the results were similar to those observed using Bazett's correction formula.

QTc (Bazett's Correction) - Baseline and Each Visit		
	Placebo	Cinacalcet
QTc (msec)	(N=101)	(N=291)
Baseline	**n (101)**	**n (288)**
Mean	422.87	426.02
SE	3.47	1.87
Median	416.00	424.00
Week 18	**n (76)**	**n (229)**
Mean	425.39	438.16
SE	4.14	2.20
Median	422.00	434.00
Week 26	**n (73)**	**n (213)**
Mean	427.67	438.13
SE	4.48	2.31
Median	425.00	436.00
End of Study	**n (88)**	**n (261)**
Mean	427.92	435.22
SE	3.85	2.13
Median	425.00	434.00

As outlined in the table below, subjects were also categorized with regard to change in QTc from baseline (< 30, 30 to 60, > 60 msec). The proportion of subjects in each category was similar between treatment groups, except for a higher incidence in the cinacalcet group of QTcB increases of 30 – 60 msec at week 26 and end of study. The occurrence of an absolute QTc > 500 msec was similar in the 2 treatment groups (7% in the cinacalcet-treated group, compared to 5% in the placebo group). The occurrence of a QTc increase > 60 msec from baseline at any time during the study was 11% in the cinacalcet-treated group, compared to 9% in the placebo-treated group. The proportion of subjects with a normal QTcB at baseline and an increase in QTcB beyond the upper limit of normal during the study was 36% in the cinacalcet group compared with 24% in the placebo group.

Proportion of Subjects with Each Category of QTcB Change from Baseline (Safety Subjects)		
	Placebo	Cinacalcet
	(N = 101)	(N = 291)
	n/N1 (%)	n/N1 (%)
Week 18		
Decrease	37/ 76 (49)	87/226 (38)
Increase < 30 msec	22/ 76 (29)	73/226 (32)
Increase 30-60 msec	15/ 76 (20)	52/226 (23)
Increase > 60 msec	2/ 76 (3)	14/226 (6)
Week 26		
Decrease	36/ 73 (49)	80/212 (38)
Increase < 30 msec	24/ 73 (33)	68/212 (32)
Increase 30-60 msec	7/ 73 (10)	49/212 (23)
Increase > 60 msec	6/ 73 (8)	15/212 (7)
End of Study		
Decrease	44/ 88 (50)	105/258 (41)
Increase < 30 msec	28/ 88 (32)	82/258 (32)
Increase 30-60 msec	9/ 88 (10)	55/258 (21)
Increase > 60 msec	7/ 88 (8)	16/258 (6)
Maximum During Study		
Decrease	32/ 88 (36)	75/258 (29)
Increase < 30 msec	31/ 88 (35)	86/258 (33)
Increase 30-60 msec	17/ 88 (19)	69/258 (27)
Increase > 60 msec	8/ 88 (9)	28/258 (11)

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: Three hundred ninety-two subjects (291 cinacalcet, 101 placebo) received study drug and were evaluable for safety. Deaths occurred in five subjects (3 placebo-treated and 2 cinacalcet-treated subjects). Causes of death were consistent causes of death in the general population of patients with ESRD. Serious adverse events were reported by 26% placebo-treated subjects and 27% cinacalcet-treated subjects were similar between the groups. The proportion of subjects who withdrew from the study due to adverse events was slightly higher in the cinacalcet group than the placebo group (13% in the cinacalcet group and 8% in the placebo group. Ninety-one percent of subjects in the cinacalcet group and 93% of subjects in the placebo group reported at least 1 adverse event during the study. The most common adverse events were nausea, diarrhea, vomiting, upper respiratory infection, headache, myalgia, and abdominal pain. The gastrointestinal adverse events, namely nausea and vomiting were significantly higher in cinacalcet-treated subjects.

Three (1%) 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. Other possible etiologies include cytochrome p450 enzyme induction causing a decrease in anti-seizure medication levels and a direct effect

from this highly lipophilic drug. Significant decreases in testosterone levels were seen in men treated with cinacalcet. Chronic renal failure is known to cause hypothalamic-pituitary dysfunction affecting the sex steroid axis as well as gonadal dysfunction. The calcium-sensing receptor has been shown to exist on anterior pituitary cells as well as in the testes themselves. The etiology of the decrease in serum testosterone levels with cinacalcet treatment is unclear.

No differences were noted between treatment groups in routine laboratory measurements. Studies in monkeys showed perturbations in thyroid and sex hormone (testosterone) levels. In this study, the majority of subjects in both treatment groups exhibited low to low-normal free T4 levels with normal TSH levels, which is consistent with the sick euthyroid profile characteristic of patients with ESRD. No subject in either group met the definition of hyperthyroidism or hypothyroidism during the study.

Evaluation of ECGs indicated a greater prolongation in the QTc interval in cinacalcet-treated subjects compared with placebo subjects. It is unclear if the increase in QT interval is solely related to change in calcium level or if there is an independent drug effect. The incidence of QTc prolongation > 60 msec or an absolute QTcB > 500 msec was similar between treatment groups. This effect may be solely due to the decreases in serum calcium levels, although it is not clear if there is an additional direct effect from the drug itself.

Discussion and Conclusions: Current therapy for secondary HPT includes pharmacologic doses of vitamin D 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%; $p < 0.001$). As well, 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. At the end of study (week 26), subjects were distributed across all dose levels of cinacalcet, with 41% of subjects receiving 180 mg. 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 $p < 0.001$).

Current K/DOQI guidelines[11] list the target range of iPTH in dialysis patients as 150 – 300 pg/mL and a mean Ca x P ≤ 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).

Gastrointestinal adverse events are common side effects of cinacalcet use. An unanticipated decrease in testosterone levels in cinacalcet-treated subjects was observed. This effect is thought to possibly be related to a direct drug effect, though it is unclear if the effect is central or at the level of the testes. As well, an increase in the occurrence of seizures was also observed with cinacalcet treatment. Decreases in serum calcium levels may be the cause of the increase in seizure activity. Lower calcium levels may also be the cause of the QTc interval prolongation seen. With both the seizure activity and the QT effect, it has not been clearly determined if there is direct effects of the drug.

Study 20010141: A Multicenter, Randomized, Placebo-controlled, Double-blind, 12-month Study to Assess the Effects of an Oral Calcimimetic Agent (AMG 073) on Renal Osteodystrophy in Hemodialysis Patients with Secondary Hyperparathyroidism

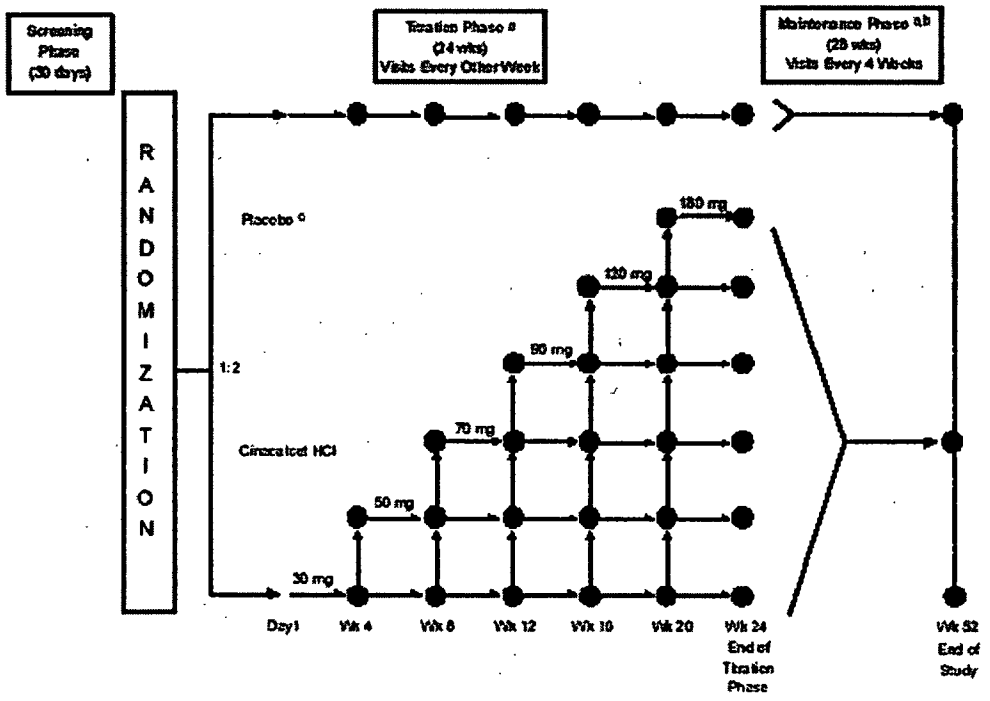
This 52-week, multicenter, randomized, double-blind study was designed to evaluate the effects of cinacalcet on renal osteodystrophy (metabolic bone disease) in hemodialysis patients with secondary hyperparathyroidism

Objectives: The primary objective of this study was to evaluate the effects of cinacalcet compared with placebo on renal osteodystrophy as assessed by bone histomorphometry

Study Design: This was a randomized, double-blind, placebo-controlled, multicenter, 12 month study. Seventeen centers in the United States and Europe participated in the study. After a 30-day screening period, subjects with end stage renal disease who qualified for the study were randomized in a 2:1 ratio to cinacalcet or placebo. Throughout the study, investigators could prescribe concomitant therapy considered necessary

The study consisted of 3 phases (see figure below): a 30-day screening phase, a 24-week dose-titration phase (visits every other week), and a 28-week maintenance phase (visits every 4 weeks). Eligible subjects were randomized (2:1) to receive cinacalcet or placebo and began treatment with 30 mg study drug once daily. No baseline stratification factors were used. During the titration phase, sequential dose increases occurred every 4 weeks based on iPTH response, serum calcium values, and safety monitoring. Possible sequential daily doses were 30, 50, 70, 90, 120, and 180 mg of cinacalcet or placebo. Dose changes also were permitted during the maintenance phase.

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



Population: The study population consisted of subjects with end stage renal disease on maintenance hemodialysis.

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 (both men and women). All subjects were to notify the principal investigator if they or their partner suspected a pregnancy
- iPTH determination of ≥ 300 pg/mL (31.8 pmol/L) obtained within the 30 day screening period
- Met the following criteria (central laboratory) taken within 30 days before day 1 and before dialysis (abnormal tests could be repeated once at the discretion of the investigator):
  - Serum calcium ≥ 8.4 mg/dL (2.1 mmol/L) reported as a corrected value by the central laboratory
  - Hemoglobin (Hb) > 9 g/dL or hematocrit (Hct) > 27%.
- In-center hemodialysis for ≥ 1 month before day 1.
- Able to comprehend and willing to give written informed consent for participation in the study before any study-specific procedures were performed.

Exclusion Criteria

- Had an unstable medical condition, defined as having been hospitalized within 30 days before day 1, or were otherwise unstable in the judgment of the investigator
- Pregnant or breastfeeding
- Parathyroidectomy in the previous 6 months
- Received vitamin D sterol therapy for < 30 days before day 1 or required a change in vitamin D sterol brand or dose level within 30 days before day 1 (for subjects prescribed vitamin D sterols).
- Received, within 21 days before day 1, therapy with flecainide, systemic glucocorticoids (> 5 mg/day, prednisone equivalent), lithium, thioridazine, haloperidol, calcitonin, or tricyclic antidepressants (e.g., imipramine, desipramine). (The tricyclic antidepressant amitriptyline is permitted.)
- Received within 90 days before day 1, therapy with bisphosphonates or fluoride. (Unchanged doses of estrogen [> 1 year] or thyroid replacement therapy [≥ 3 months] were permitted.)
- Known to abuse alcohol, or use illicit drugs, within 12 months before day 1.
- Myocardial infarction (MI) within 6 months before day 1.
- Ventricular rhythm disturbance requiring current treatment.
- Currently enrolled in or had not yet completed ≥30 days before day 1, other invasive investigational device or drug study, or receiving other investigational agents (experimental dialysis machines were acceptable).
- Seizure within 12 months before day 1.
- History (within 5 years) of malignancy of any type, other than non-melanomatous skin cancers or in situ cervical cancer.
- Gastrointestinal disorder that could be associated with impaired absorption of orally administered medications.
- Evidence of treatment for or active sarcoidosis, tuberculosis, or other diseases known to cause hypercalcemia, within five years of starting the study.
- Inability to swallow tablets.
- A disorder that interfered with the understanding and giving of informed consent or compliance with protocol requirements.

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-, 50-, 70- and 90-mg free-base equivalents or placebo, which were graduated in size, smallest to largest. During the titration phase, the dose of cinacalcet or placebo could be increased to the next dose level at the week 4, 8, 12, 16, and 20 study visits. Possible sequential doses during the study were 30, 50, 70, 90, 120 and 180 mg cinacalcet or placebo. Depending on the dose specified, subjects received 1 to 2 tablets. Changes in phosphate binders 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: Efficacy was evaluated by bone histomorphometry and the change from baseline in iPTH, BALP, serum N-Tx, and Ca x P. Safety was assessed by the nature, frequency, severity, and relationship to treatment of adverse events, changes in laboratory parameters, vital signs, and physical exams. Patient-reported outcomes were assessed by SF-36 (the Medical Outcomes Study 36-Item Short Form Health Survey) scale scores, and measurement of physical activity was assessed by accelerometry.

Primary Efficacy Endpoint

- A comparison between treatment groups using end-of-study values and changes from baseline to the end of the study for the following bone histomorphometry parameters: activation frequency, BFR/BS, fibrosis surface/BS, woven osteoid surface/BS, osteoblast number, and osteoclast number.

Secondary Efficacy Endpoints

- The absolute values and percentage change from baseline in iPTH, BALP, serum N-Tx, and Ca x P concentrations
- The feasibility of measuring physical activity by quantitative 3-dimensional accelerometry

Safety Endpoints:

- The nature, frequency, severity, and relationship to treatment of adverse events; and changes in laboratory parameters (including clinical chemistry and hematology)

Study Methods:

Bone Histomorphometry: The following bone turnover parameters were assessed: activation frequency, BFR, fibrosis surface (percentage of bone surface covered with fibrous tissue), woven osteoid surface (percentage of the bone surface that is woven bone), osteoblast number, and osteoclast number. In addition, preservation of bone mineralization also was assessed in each bone biopsy specimen by measuring the following parameters: mineralization lag time (the time interval between collagen matrix synthesis by osteoblasts and the onset of mineralization), osteoid thickness, and osteoid surface. Aluminum surface also was evaluated. A blinded assessment of each subject's bone biopsy sample was performed by Dr. [redacted] to determine whether the subject had mild or severe hyperparathyroid bone disease, osteomalacia, adynamic bone disease, or mixed uremic osteodystrophy (osteomalacia and hyperparathyroid bone disease).

iPTH Measurement: [redacted] was used to analyze the samples for the primary, secondary and safety endpoints. Measurement of iPTH was done with duplicate

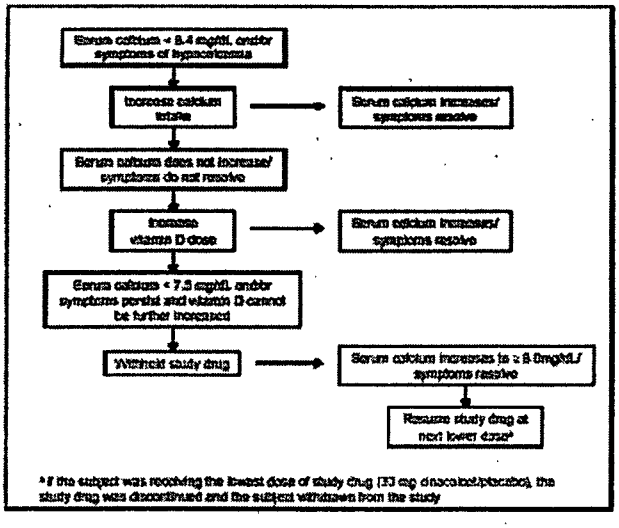
plasma samples to allow comparison of results obtained with the iPTH and biPTH assays. All iPTH levels used in the primary analysis were obtained utilizing the manual IRMA methodology.

Dose Titration: Subjects could be titrated up to the next sequential dose level of study drug Week 4, 8, 12, 16, and 20 study visits. If the central laboratory iPTH value was > 200 pg/mL, the subject's dose of study medication was increased, provided that the serum calcium was ≥ 7.8 mg/dL and the subject was not experiencing an adverse event that precluded a dose increase. During the maintenance phase, at Week 28-, 32-,36-, 40-, 44-, and 48, a subject's dose could be adjusted according to the same titration rules.

Dose reductions could occur at any time during the study. If iPTH values were < 100 pg/mL for 2 consecutive study visits, study medication was reduced to the next lower dose. If the subject was already receiving the lowest dose (30 mg Cinacalcet or placebo), vitamin D sterol therapy could be decreased. If the subject was not taking vitamin D sterols, the subject continued to receive the lowest dose of study drug.

If a subject experienced an intolerable adverse event that was considered related to the study drug, study drug was decreased to the next lower dose. If a subject experienced symptoms of hypocalcemia and/or a serum calcium concentration < 8.4 mg/dL, phosphate binders were increased at the discretion of the investigator to resolve the symptoms or to increase serum calcium concentration to ≥ 8.4 mg/dL. If these measures were not sufficient, the vitamin D sterol dose was increased. If serum calcium concentration decreased below 7.5 mg/dL or symptoms of hypocalcemia persisted, and the investigator did not wish to further increase vitamin D sterol dosage, study medication was withheld until the symptoms resolved and serum calcium concentration was ≥ 8.0 mg/dL. Study medication was then resumed at the next lower dose. If the subject was receiving the lowest dose of study medication (30 mg Cinacalcet or placebo), study medication was discontinued and the subject was withdrawn from the study.

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



Protocol Specified Guidelines for Changes in Vitamin D therapy: If the serum calcium concentration was ≥ 11 mg/dL, the serum phosphorus concentration was ≥ 6.5 mg/dL (2.1 mmol/L), or the Ca x P was ≥ 70 $(mg/dL)^2$ (5.65 [mmol/L]2), the investigator could modify diet or change dose or brand of phosphate binders to reduce these concentrations. If these measures were not sufficient, the vitamin D sterol dose could have been withheld or reduced until the serum calcium, serum phosphorus, and Ca x P were < 11.0 mg/dL, 6.5 mg/dL, and 70 $(mg/dL)^2$, respectively. If the subject had been withdrawn from vitamin D sterol therapy, vitamin D sterol could have been restarted at the investigator's discretion. If iPTH increased by ≥ 50% from the baseline value for 2 consecutive study visits on the highest dose of study drug, vitamin D sterols could be increased.

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 pregnancy, parathyroidectomy, or kidney transplant. Withdrawn patients were not replaced.

Statistical Analyses:
Activation frequency was considered to have the most variability of all bone turnover parameters examined and was used to calculate sample size. A difference of 0.4/year between the treatment groups in activation frequency was considered clinically significant; standard deviation (SD) for this parameter was estimated as 0.5/year. A sample size of 45 subjects (2:1 randomization) would provide a 95% confidence interval (CI) of (0.08, 0.72) for the difference between placebo and cinacalcet in activation frequency.

The statistical analysis plan was amended once (29 May 2003). Analyses of the primary and secondary endpoints were not affected. The key revisions of the amendment were:

- Clarified the analyses of iPTH and biPTH
- Added several exploratory analyses and amended the sign-off page to reflect changes to the study team
- Redefined the primary iPTH dataset and added sensitivity analyses for iPTH related endpoints after Amgen's identification of inconsistencies in global procedures to measure iPTH and questionable iPTH values during a global audit of
- Clarified the correlation analyses for percentage changes from baseline in biochemical markers with changes from baseline in bone histomorphometric variables because some subjects had zero values for bone histomorphometric parameters at baseline
- Added a summary of the ratio of osteoblasts to osteoclasts using descriptive statistics

Protocol Amendments: The protocol was amended once (2 January 2002). The key revisions of the amendment were:

- The bone biopsy procedures for antibiotic dosing were changed because the antibiotic declomycin is not available to European centers. Instead, double tetracycline labeling was used.
- In addition, the bone biopsy procedures for sample storage were changed at the request of the bone histomorphologist.

Results

Patient Disposition: As shown in the table below, 79 subjects were screened and 48 subjects were enrolled in this study at 17 centers in the United States and Europe. Thirty-two subjects were randomized to receive cinacalcet and 16 subjects were randomized to receive placebo. Twenty (63%) subjects in the cinacalcet group and 13 (81%) subjects in the placebo group completed the study.

20010141: Patient Disposition

	Placebo	Cinacalcet
Enrolled	16	32
No treatment	0	0
At least one dose	16	32
Withdrew - Total	3 (19)	12 (38)
Withdrew - AE	0	5
Deaths	2	3
Withdrew - Other	1	4
Completed Titration Phase (Weeks 1-24)	16 (100)	28 (88)
Completed Study	13 (81)	20 (63)

Protocol Violations: Five (10%) subjects had eligibility deviations in this study. The most common eligibility deviation was a change in vitamin D sterol dose in the 30 days before study day 1. Overall, 67% of subjects (56% of placebo-treated subjects and 72% of cinacalcet -treated subjects) had at least one protocol deviation during the study. Compliance with study drug was > 80% and similar in both the cinacalcet and placebo groups

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

Demographics: Baseline subject demographics were well balanced across the treatment groups (see table below). The mean age was 51 years. Overall, 60% of subjects were male and 65% of subjects were black. Fifteen percent of enrolled subjects were ≥ 65 years of age. Baseline iPTH, biPTH, serum N-Tx, BALP, Ca x P, serum calcium, and serum phosphorus concentrations all were similar between treatment groups. Baseline serum N-Tx concentrations were markedly elevated (normal range: 5.4 to 24.2 nmol bone collagen equivalents [BCE]) because N-Tx is excreted by the kidney and therefore, accumulates in renal failure. Baseline vitamin D and phosphate binder use were similar between treatment groups, except for slightly less phosphate binder use in the placebo group.

Study 20010141: Demographics

	Placebo	Cinacalcet
N	16 (%)	32 (%)
Age (yrs.)	52.1 ± 12.8	50.3 ± 11.9
≥ 65	3 (19)	4 (13)
≥ 75	0 (0)	0 (0)

Study 20010141: Demographics		
	Placebo	Cinacalcet
Sex		
Male	11 (69)	18 (56)
Female	5 (31)	14 (44)
Race		
Caucasian	5 (31)	8 (25)
Black	11 (69)	20 (63)
Other	0 (0)	4 (13)
Baseline Labs		
iPTH (pg/mL)	672.2 ± 351.4	676.4 ± 417.6
biPTH (pg/mL)	383.0 ± 230.4	394.8 ± 295.0
Ca x P (mg/dL)^2	62.62 ± 10.64	65.92 ± 12.87
Serum Ca (mg/dL)	9.80 ± 0.91	9.86 ± 0.79
Serum Phos (mg/dL)	6.41 ± 1.11	6.71 ± 1.40
BALP (ng/mL)	40.11 ± 32.17	32.74 ± 25.66
N-Tx (nmol BCE)	538.0 ± 594.2	588.5 ± 569.7
Baseline Vitamin D Use		
Yes	9 (56)	16 (50)
No	7 (44)	16 (50)
Baseline Phosphate Binder Use		
Yes	13 (81)	31 (97)
No	3 (19)	1 (3)

Baseline height, weight, blood pressure, and selected medical history were generally similar between treatment groups. The incidence of diabetes was slightly higher in the placebo group (44%) compared with the cinacalcet group (25%).

Primary Efficacy Outcomes

Bone Histomorphometry Parameters

Nineteen subjects in the cinacalcet group and 13 subjects in the placebo group had both baseline and end-of-study bone biopsies. No subject in either treatment group had aluminum present on their bone surface. Results are outlined in the table below (normal levels for each parameter in parentheses)

20010141: Bone Biopsy Results				
	Placebo		Cinacalcet	
	Baseline	End of Study	Baseline	End of Study
Activation Frequency (0.49 – 0.72/year)				
Mean (SE)	1.41 (0.28)	1.29 (0.14)	1.54 (0.24)	1.03 (0.14)
Mean Change (SE)	- 0.12 (0.30)		- 0.51 (0.30)	
% Change (SE)	- 5.39 (0.30)		-7.47 (0.30)	
Bone Formation Rate (1.8 – 3.9 mm^3 / cm^2 / yr)				
Mean (SE)	6.51 (1.20)	5.47 (0.65)	6.60 (0.90)	4.72 (0.65)
Mean Change (SE)	- 1.04 (1.17)		- 1.88 (1.17)	
% Change (SE)	- 15.38 (28.71)		13.93 (28.71)	
Fibrosis Surface / Bone Surface (0%)				
Mean (SE)	6.99 (1.73)	9.12 (1.20)	4.69 (1.13)	2.70 (1.20)
Mean Change (SE)	2.13 (1.44)		- 1.99 (1.44)	
% Change (SE)	38.72 (9.90)		- 68.43 (9.90)	

20010141: Bone Biopsy Results				
	Placebo		Cinacalcet	
	Baseline	End of Study	Baseline	End of Study
Woven Osteoid Surface / Bone Surface (0%)				
Mean (SE)	7.23 (2.37)	11.04 (2.78)	4.64 (1.34)	8.58 (2.78)
Mean Change (SE)	3.82 (3.46)		3.94 (3.46)	
% Change (SE)	6.64 (29.91)		8.26 (29.91)	
Osteoblast Number (1 – 200 / 100mm)				
Mean (SE)	580.29 (125.7)	575.00 (91.02)	486.2 (84.4)	283.93 (91.02)
Mean Change (SE)	- 5.29 (123.58)		- 202.31 (123.58)	
% Change (SE)	13.06 (48.74)		52.82 (48.74)	
Osteoclast Number (0.1 – 53 / 100mm)				
Mean (SE)	122.34 (81.66)	61.46 (8.67)	100.95 (20.0)	37.17 (8.67)
Mean Change (SE)	- 60.88 (19.36)		- 63.79 (19.36)	
% Change (SE)	- 47.67 (17.87)		- 36.61 (17.87)	

Activation Frequency: Baseline activation frequencies were 1.54/year in the cinacalcet group and 1.41/year in the placebo group. Both groups had a mean reduction in activation frequency (0.51/year in the cinacalcet group and 0.12/year in the placebo group).

Bone Formation Rate: Baseline BFR values were 6.6 (0.90) mm^3/cm^2/year in the cinacalcet group and 6.51 mm^3/cm^2/year in the placebo group. The mean end-of-study BFR was 4.53 mm^3/cm^2/year in the cinacalcet group and 5.33 mm^3/cm^2/year in the placebo group, representing a mean reduction from baseline of 1.88 mm^3/cm^2/year in the cinacalcet group and 1.04 mm^3/cm^2/year in the placebo group.

Fibrosis Surface: Baseline fibrosis surface values were 4.69% and 6.99% for subjects in the cinacalcet and placebo groups, respectively. The mean fibrosis surface at the end of the study was 2.70% in the cinacalcet group and 9.12% in the placebo group, representing a reduction from baseline by a mean of 2.0% in the cinacalcet group compared with an increase 2.1% in the placebo.

Woven Osteoid Surface: Baseline woven osteoid surface values were 4.64% and 7.23% for subjects in the cinacalcet and placebo groups, respectively. No trend or difference between treatment groups was observed for woven osteoid surface at the end of the study: The mean woven osteoid surface at the end of the study was 8.58% in the cinacalcet group and 11.04% in the placebo group, representing a increase from baseline by a mean of 3.9% in the cinacalcet group and 3.8% in the placebo group.

Osteoblast Number: Baseline number of osteoblasts was 486/100 mm and 580/100 mm for subjects in the cinacalcet and placebo groups, respectively. The mean number of osteoblasts at end of the study was 284/100 mm in the cinacalcet group and 575/100 mm in the placebo group, representing a reduction from baseline by a mean of 202/100 mm in the cinacalcet group compared with 5/100 mm in the placebo group.

Osteoclast Number: The mean (SE) baseline number of osteoclasts was 101/100 mm and 122/100 mm for subjects in the cinacalcet and placebo groups, respectively. The mean number

of osteoclasts at the end of the study was 37/100 mm in the cinacalcet group and 61/100 mm in the placebo group; the number of osteoclasts decreased by approximately 60/100 mm in both treatment groups at the end of the study.

Bone Mineralization Parameters

A mineralization defect (osteomalacia) is characterized by elevations in MLT, osteoid thickness, and osteoid surface. As outlined in the table below, at the end of the study, mean values for mineralization parameters in both treatment groups were within the normal range (listed in parentheses for each parameter).

Study 20010141: Bone Mineralization Parameters				
Mineralizing Lag Time (< 50days)				
Mean (SE)	33.03 (7.05)	46.15 (7.15)	29.74 (5.82)	49.07 (15.63)
Mean Change (SE)	11.24 (8.30)		19.02 (17.64)	
% Change (SE)	84.97 (36.54)		133.55 (93.08)	
Osteoid Thickness (4 – 20 μm)				
Mean (SE)	11.88 (0.92)	11.98 (1.20)	11.11 (0.77)	11.42 (1.03)
Mean Change (SE)	0.11 (1.52)		0.30 (1.30)	
% Change (SE)	10.02 (13.61)		12.43 (11.99)	
Osteoid Surface/Bone Surface (1 – 39%)				
Mean (SE)	27.96 (3.16)	37.96 (4.31)	31.05 (3.05)	27.22 (3.71)
Mean Change (SE)	10.01 (5.80)		- 3.83 (3.90)	
% Change (SE)	81.14 (42.82)		- 3.55 (12.78)	

Mineralization Lag Time: Mean (SE) baseline MLTs were 29.74 (5.82) days and 33.03 (7.05) days for subjects in the cinacalcet and placebo groups, respectively. The mean MLT at the end of the study remained in the normal range (49 days in the cinacalcet group and 46 days in the placebo group). The change in baseline was 19 days in the cinacalcet group and 11 days in the placebo group. Four (22%) subjects in the cinacalcet group and 5 (42%) subjects in the placebo group had an elevated MLT (> 50 days) at the end of the study, compared with 3 (17%) and 1 (8%), respectively, at baseline.

Osteoid Thickness: Mean (SE) baseline osteoid thickness was 11.11 (0.77) μm and 11.88 (0.92) μm for subjects in the cinacalcet and placebo groups, respectively. The mean osteoid thickness at the end of the study was 11.42 μm in the Cinacalcet group and 11.98 μm in the placebo group, and no trends in absolute change from baseline were observed for either treatment group (0.30 μm cinacalcet, 0.11 μm placebo).

Osteoid Surface: Mean (SE) baseline osteoid surface was 31.05 (3.05)% and 27.96 (3.16)% for subjects in the cinacalcet and placebo groups, respectively. The mean osteoid surface at the end of the study was 27% in the cinacalcet group and 38% in the placebo group, corresponding to a 4% decrease in the cinacalcet group compared with a 10% increase in the placebo group.

Renal Osteodystrophy Class: Classification of renal osteodystrophy occurred at baseline and end of study. Mild hyperthyroid bone disease is defined as elevated activation frequency/BFR. Severe hyperthyroid bone disease is defined as elevated activation frequency/BFR in the

presence of significant fibrosis. Mixed uremic osteodystrophy is defined as normal or elevated activation frequency/BFR in the presence of an elevated mineralization lag time (MLT). Adynamic bone disease is defined as low bone turnover (activation frequency/BFR below the lower limit of normal), with normal levels of osteoid thickness and osteoid surface. Osteomalacia is defined as reduced bone turnover with elevation of MLT.

At baseline, 16 (84%) of 19 subjects in the cinacalcet group and 11 (85%) of 13 subjects in the placebo group had mild hyperparathyroid bone disease. Of the subjects with mild hyperparathyroid bone disease at baseline, 12 subjects in the cinacalcet group and 7 subjects in the placebo group did not change their classification during the study. Two subjects in the cinacalcet group and 4 subjects in the placebo group developed mixed uremic osteodystrophy. One subject in the placebo group had adynamic bone disease at baseline and improved to mixed uremic osteodystrophy at the end of the study. In the cinacalcet group, one subject had adynamic bone disease at baseline and at the end of the study. This subject did exhibit some improvement in bone turnover parameters (increases toward normal in activation frequency and BFR, which led to a reduction in MLT).

Three subjects in the cinacalcet group developed adynamic bone disease. In two of these subjects, there was over suppression of iPTH. In one subject, iPTH was < 100 pg/mL at 9 time points during the study while in the second subject iPTH was < 100 pg/mL at 5 time points during the study. The third subject who developed adynamic bone disease had a baseline iPTH of 1502 pg/mL with a lowest level of 547 pg/mL. This subject was immobilized during a 3-week hospitalization which may have contributed to his bone disease. In all subjects bone alkaline phosphatase values fell to . In these 3 subjects, decreased fibrosis surface was observed, and numbers of osteoblasts and osteoclasts were within the normal range at the end of the study.

20010141: Proportion of Subjects With Each Class of Renal Osteodystrophy at Baseline and End of Study

	Placebo		Cinacalcet	
Unit: n (%)	(N=13)		(N=19)	
	Baseline	End of Study	Baseline	End of Study
Normal Bone Histology	0 (0)	0 (0)	0 (0)	0 (0)
Mild Hyperparathyroid Bone Disease	11 (85)	7 (54)	16 (84)	13 (68)
Severe Hyperparathyroid Bone Disease	1 (8)	2 (15)	1 (5)	0 (0)
Mixed Uremic Osteodystrophy	0 (0)	4 (31)	1 (5)	2 (11)
Adynamic Bone Disease	1 (8)	0 (0)	1 (5)	4 (21)
Osteomalacia	0 (0)	0 (0)	0 (0)	0 (0)

Secondary Efficacy Outcomes

The absolute values and percentage change from baseline in iPTH, BALP, serum N-Tx, and Ca x P concentrations

iPTH: Mean (SE) baseline iPTH concentrations were 676 (74) and 672 (88) pg/mL for subjects in the cinacalcet and placebo groups, respectively. At the end of the study, mean plasma iPTH concentrations were reduced by 54% in the cinacalcet group compared with an increase of 36% in the placebo group, corresponding to a mean plasma iPTH concentration of 271 pg/mL in the cinacalcet group and 961 pg/mL in the placebo group.

BioIntact PTH: The concentration of PTH is an important measure for effective clinical management of patients with chronic renal failure. Recent investigations have shown that current PTH assays (including the Nichols IRMA assay) detect a large PTH fragment (amino acids 7-84) in addition to the full-length molecule (1-84). A new second generation PTH assay, the bio-intact PTH (biPTH) assay, which detects only the full-length molecule, has become now available. Published data indicate that PTH values obtained with the iPTH and biPTH assays are highly correlated, and that a conversion factor can help interpret the biPTH assay results [12]. To enable correlation of the results of the new biPTH assay with the existing gold standard iPTH assay, duplicate plasma samples were collected for measurement of PTH concentrations using both assays. At baseline and during the maintenance phase, iPTH and biPTH values were positively correlated with biPTH values comprising approximately 55% of iPTH values ($r = 0.83$ for placebo and $r = 0.84$ for cinacalcet at baseline and $r = 0.99$ for placebo and $r = 0.83$ for cinacalcet at the end of the study. Treatment with cinacalcet did not change the relationship between iPTH and biPTH, as evidenced by similar regression equations for both treatment groups at baseline and the end of the study. Reductions in mean PTH concentrations in the cinacalcet group compared with the placebo group also were demonstrated using biPTH assay. As shown in the table below, similar conclusions were reached regarding the efficacy of cinacalcet treatment using either PTH assay.

Study 20010141: Comparison of biPTH and iPTH Assay Results

	Placebo (N=16)		Cinacalcet (N=32)	
	iPTH	**biPTH**	**iPTH**	**biPTH**
Mean (SE) baseline PTH (pg/mL)	672.2 (87.9)	383.0 (57.6)	676.4 (73.8)	394.8 (52.2)
Mean (SE) end of study PTH (pg/mL)	1011 (198.9)	686.2 (155.3)	360.7 (74.8)	208.2 (49.7)
Mean (SE) percent change in PTH[a]	48.8 (15.4)	91.5 (27.3)	-51.4 (5.8)	-48.3 (7.8)
Subjects achieving target PTH[ab]	6.3%	6.3%	53.1 %	62.5 %
≥ 30% Reduction at End of Study[a]	6.3%	6.3%	78.1 %	71.9 %

[a] At Week 52. For subjects with no week 52 value, the last post-baseline value was used

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

Bone-specific Alkaline Phosphatase: At baseline, the median bone-specific alkaline phosphatase (BALP) concentrations were 24.6 and 30.5 ng/mL in the cinacalcet and placebo groups, respectively. At the end of the study, median BALP concentrations decreased by 32% in the cinacalcet group compared with a 26% increase in the placebo group, corresponding to median BALP concentrations of 18.8 ng/mL in the cinacalcet group and 72.2 ng/mL in the placebo group. The proportion of subjects in the cinacalcet group with BALP concentrations reduced to within the normal range [redacted] increased from 26% (5/19) subjects at baseline to 47% (9/19) subjects at the end of the 1-year study. The proportion of subjects in the placebo group with BALP concentrations within the normal range was unchanged from baseline to the end of the study (31% [4/13]).

[12] Goodman, et al. Parathyroid hormone (PTH), PTH-derived peptides, and new PTH assays in renal osteodystrophy. Kidney International, Vol. 63 (2003), pp. 1–11

Serum N-Telopeptide: At baseline, median serum N-Tx concentrations were 400.0 and 325.0 nmol BCE in the cinacalcet and placebo groups, respectively. At the end of the study, median serum N-Tx concentrations decreased by 44% in the cinacalcet group compared with a 25% increase in the placebo group, corresponding to median serum N-Tx concentrations of 230.0 nmol BCE in the cinacalcet group and 440.0 nmol BCE in the placebo group. Although median serum N-Tx concentrations throughout the study were reduced in the cinacalcet group compared with the placebo group, no subjects in the cinacalcet group had serum N-Tx concentrations within the normal range during the study.

Calcium x Phosphorus Product: Mean (SE) baseline Ca x P concentrations were 65.9 (2.3) $(mg/dL)^2$ in the cinacalcet group and 62.6 (2.7) $(mg/dL)^2$ in the placebo group. At the end of the titration phase (week 24), mean (SE) Ca x P concentrations were 54.9 (2.7) $(mg/dL)^2$ in the cinacalcet t group and 60.3 (3.1) $(mg/dL)^2$ in the placebo group. At the end of the study, mean (SE) Ca x P concentrations were 55.8 (4.2) $(mg/dL)^2$ in the cinacalcet group and 52.0 (3.3) $(mg/dL)^2$ in the placebo group.

Serum Calcium: Mean (SE) baseline serum calcium concentrations were 9.9 (0.1) mg/dL in the cinacalcet group and 9.8 (0.2) mg/dL in the placebo group. Mean serum calcium concentrations in the cinacalcet group decreased to a nadir (10% reduction) at Week 10 then remained relatively stable through the end of the study. At the end of the study (Week 52), mean serum calcium concentration were reduced by 5% in the cinacalcet group compared with an increase of 2% in the placebo group, corresponding to mean (SE) serum calcium concentrations of 9.4 (0.3) mg/dL in the cinacalcet group compared with 9.9 (0.3) mg/dL in the placebo group.

Serum Phosphorus: Mean (SE) baseline serum phosphorus concentrations were 6.7 (0.2) mg/dL in the cinacalcet group and 6.4 (0.3) mg/dL in the placebo group. Greater variability was observed in serum phosphorus concentrations compared with serum calcium concentrations in both treatment groups. Throughout the maintenance phase, the reduction in mean serum phosphorus concentrations was sustained in the cinacalcet group (approximately 10% reduction at each time point). In the placebo group, mean serum phosphorus concentrations remained at baseline levels until week 48; at week 52, a 14% reduction in serum phosphorus was observed.

Dose Distribution: Cinacalcet treatment was titrated based on an individual subject's iPTH response and tolerability. At the end of the study, subjects were distributed across all dose levels of cinacalcet, with 31% of subjects receiving 180 mg (see table below). In the placebo group, 88% of subjects were at the 180-mg placebo dose level.

Study 20010141: Summary of Test Article Dose Level

	Placebo (N=16)	Cinacalcet (N=32)
Daily dose (mg) at end of titration - n(%)		
30	0 (0)	5 (16)
50	0 (0)	5 (16)
70	0 (0)	3 (9)
90	1 (6)	5 (16)
120	3 (19)	7 (22)
180	12 (75)	7 (22)

Study 20010141: Summary of Test Article Dose Level		
	Placebo	Cinacalcet
	(N=16)	(N=32)
Daily dose (mg) at end of study - n(%)		
30	0 (0)	6 (19)
50	0 (0)	2 (6)
70	0 (0)	3 (9)
90	1 (6)	7 (22)
120	1 (6)	4 (13)
180	14 (88)	10 (31)
Dose taken most frequently (over whole study) - n(%)		
30	0 (0)	7 (22)
50	0 (0)	5 (16)
70	0 (0)	3 (9)
90	1 (6)	4 (13)
120	1 (6)	5 (16)
180	14 (88)	8 (25)

Vitamin D and Phosphate Binder Use: The proportion of subjects receiving vitamin D increased from 50% at baseline to approximately 65% during the study in the cinacalcet group and remained relatively stable (approximately 55%) for the placebo group. The most common reason for vitamin D dose changes in the cinacalcet group was a serum calcium < 8.4 mg/dL or symptoms of hypocalcemia. The proportion of subjects receiving phosphate binders at each scheduled visit remained relatively stable through the end of the study (approximately 95% in the cinacalcet group and 85% in the placebo group).

Patient Reported Outcomes Evaluations: High completion rates for both physical activity and PRO assessments at all time points suggest that conducting these assessments in this population is feasible. However, based on the analyses conducted, a significant relationship between changes in physical activity and changes in PRO was not apparent. The relatively small sample size and the variability of the measures make additional conclusions difficult.

Efficacy Conclusions: Bone biopsy with double tetracycline labeling is the most accurate way to determine the presence and type of bone disease associated with chronic kidney disease. In this study at baseline, the most predominant type of bone abnormality was mild hyperparathyroid bone disease in approximately 85% of enrolled subjects. One subject (5% cinacalcet, 8% placebo) in each treatment group had adynamic bone disease at baseline. Improvements in mean bone turnover parameters were observed in the cinacalcet-treated group as reflected by reductions in activation frequency, BFR, fibrosis surface, and the number of osteoblasts and osteoclasts. The placebo group also showed some improvement in bone turnover, reflected by reductions in activation frequency, BFR, and osteoclast numbers. No trend or difference between treatment groups was observed for woven osteoid surface. Mean values for mineralization parameters (MLT, osteoid thickness, and osteoid surface) were normal in both treatment groups at baseline and end of study. However, four (22%) subjects in the cinacalcet group and 5 (42%) subjects in the placebo group had an elevated MLT (> 50 days) at the end of the study, compared with 3 (17%) and 1 (8%), respectively, at baseline.

In the cinacalcet group over the 1-year study duration, decreases from baseline in iPTH, biPTH, BALP, and serum N-Tx concentrations were observed; in the placebo group, concentrations of these biochemical parameters remained stable or increased. As observed in other cinacalcet studies in ESRD subjects with secondary HPT, mean Ca x P, serum calcium, and serum phosphorus concentrations were reduced in the cinacalcet group compared with the placebo group.

Safety

Disposition: As shown in the table below, 100% of placebo-treated subjects and 97% of cinacalcet-treated subjects experienced adverse events during the study.

Study 20010141: Disposition		
	Placebo n (%)	Cinacalcet n (%)
Subjects evaluable for safety	16	32
Deaths on study	2 (13)	3 (9)
Severe adverse events [a]	9 (56)	16 (50)
Serious adverse events	8 (50)	18 (56)
Withdrawal due to adverse events	0	4 (13)
All adverse events	16 (100)	31 (97)

[a] Includes severe, life-threatening and fatal adverse events

Exposure: A total of 48 (32 cinacalcet, 16 placebo) received study medication (see table below). The mean (range) number of days of exposure to study drug was 307 (19 to 371) days for the cinacalcet group and 350 (196, 374) days for the placebo group. The mean (range) cumulative dose of cinacalcet was 22,932 (mg.

Study 20010141: Summary of Exposure to Study Drug		
	Placebo (N=16)	Cinacalcet (N=32)
Number of days of exposure		
Mean	349.9	307.4
SD	44.2	96.7
Min, Max	196 , 374	19 , 371
Cumulative dose of cinacalcet (mg)		
Mean	0.0	22932.5
SD	0.0	14642.0
Min, Max		
Dose compliance (%)		
Mean	90.1	85.6
SD	8.8	17.7
Min, Max		

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

Deaths: Five deaths occurred during the study, 3 (9%) in the cinacalcet group and 2 (13%) in the placebo group. Two subjects receiving cinacalcet died of cardiac arrest. One was a 49-year-old man with a baseline serum calcium of 9.3 mg/dL who had a strong past medical history of cardiovascular disease including prior coronary artery bypass graft, and cardiac arrhythmias. He suffered a gastrointestinal hemorrhage on Day 10 and subsequently experienced a cardiac arrest

at home and died on Day 20. The last on-study serum calcium measurement was 9.3 mg/dL on Day 15. The second subject was a 52-year-old man with a baseline serum calcium of 9.9 mg/dL who also had a strong past medical history of cardiovascular disease including prior myocardial infarction and left bundle branch block. On Day 251 the subject experienced a cardiac arrest and died. The last on-study serum calcium measurement was 8.2 mg/dL on Day 225. Most of the subject's serum calcium concentrations were between 7.7 and 8.7 mg/dL with the lowest recorded serum calcium was 7.3 mg/dL. One subject receiving cinacalcet died of sepsis. One such each, receiving placebo, died of intracranial hemorrhage and pulmonary embolism.

Serious and Severe Adverse Events: Serious adverse events were experienced by 18 (56%) subjects in the cinacalcet group and 8 (50%) subjects in the placebo group. The most common serious adverse events were (cinacalcet, placebo) thrombosis vascular access (13%, 0%) and hemorrhage GI (9%, 0%). One subject in the cinacalcet group developed a serious allergic reaction, which was attributed to radiocontrast dye. Serious adverse events related to the gastrointestinal system were reported for 25% of subjects in the cinacalcet group and 0% of subjects in the placebo group.

Adverse Events Leading to Withdrawal: Four (13%) subjects in the cinacalcet group and 0 (0%) subjects in the placebo group withdrew because of adverse events. Adverse events that most commonly resulted in withdrawal involved the gastrointestinal system, with 1 subject each who withdrew due to dyspepsia, nausea, and vomiting. One subject withdrew from the study because of a renal mass that was considered by the investigator to be serious but not related to study drug.

Adverse Events Leading to Dose Alteration: A total of 4 (25%) subjects in the placebo group and 7 (22%) subjects in the cinacalcet group had adverse events leading to study drug dose alteration. One subject in each group had hypocalcemia requiring dose alteration. In the cinacalcet group, gastrointestinal adverse events led to dose alteration in 4 (13%) subjects.

Adverse Events: Ninety-seven percent of subjects in the cinacalcet group and 100% of subjects in the placebo group reported at least 1 adverse event during the study (table below). The most common adverse events were (cinacalcet, placebo) nausea (44%, 44%), abdominal pain (44%, 19%), and vomiting (41%, 31%).

20010141: Adverse Events by Body System

	Placebo	Cinacalcet
Subjects Receiving Dose	16	32
Subjects Reporting AEs	16 (100)	31 (97)
Events:		
Body as a whole	12 (75)	23 (72)
Gastrointestinal	13 (81)	25 (78)
Liver and Biliary	3 (19)	2 (6)
Nervous	12 (75)	17 (53)
Cardiovascular	8 (50)	8 (25)
Heart Rate / Rhythm	4 (25)	3 (9)
Myo/Endo/Pericardial	2 (13)	3 (9)
Respiratory	13 (81)	15 (47)

20010141: Adverse Events, by Body System		
	Placebo	Cinacalcet
Endocrine/Metabolic	7 (44)	5 (16)
Musculoskeletal	14 (88)	22 (69)
Infectious	4 (25)	7 (22)
Blood and Lymphatic	1 (6)	5 (16)
Skin and Appendages	7 (44)	14 (44)
Urinary Disorders	3 (19)	4 (13)
Reproductive	2 (13)	2 (6)
Vascular Disorders	3 (19)	11 (34)
Vision Disorders	3 (19)	2 (6)
Hearing / Vestibular	2 (13)	1 (3)
Psychiatric	3 (19)	4 (13)

Adverse Events of Special Interest:

Hypocalcemia: Three adverse events of asymptomatic hypocalcemia (2 cinacalcet, 1 placebo) were reported. For the 2 subjects in the cinacalcet group: One subject had a serum calcium concentration of 7.6 mg/dL on Day 132, and the event resolved on the same day. A second subject had a serum calcium concentration of 7.2 mg/dL on Day 71, and the event resolved 14 days later. In the placebo group, one subject had a serum calcium concentration of 6.1 mg/dL on day 228, and the event resolved 2 days later.

Convulsions: No adverse events involving seizures were reported in this study.

GI Adverse Events: As discussed above, gastrointestinal adverse events were the most common events reported events occurring in 81% of the placebo-treated group and 78% of the cinacalcet-treated group.

Cataracts: One subject receiving placebo developed cataracts during the study. No cataracts were reported in subjects receiving cinacalcet.

Laboratory: Safety laboratory assessments were performed at screening and follow-up. No trends indicative of treatment-related effects in clinical chemistry or hematology were noted. Shift tables also demonstrated no trends 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. Any notable changes from baseline in vital signs and physical findings were reported as adverse events.

Safety Conclusions: In this 12-month study, cinacalcet was safe and generally well tolerated at doses up to 180 mg once daily. The incidence of serious adverse events and deaths was similar across treatment groups. Gastrointestinal adverse events, namely abdominal pain and vomiting occurred more often in cinacalcet-treated subjects and led to study discontinuation in 1 subject and study drug dose alteration in 4 subjects. Asymptomatic hypocalcemia was observed and managed by adjustments to the doses of calcium-

containing phosphate binders, vitamin D sterols, or study drug. No unexpected trends indicative of a treatment effect were noted in clinical laboratory measurements.

Discussion and Conclusions: Cinacalcet amplifies the sensitivity of the parathyroid gland CaR to extracellular calcium and thereby reduces PTH concentrations. In this study, similar to results of the phase 3 studies, cinacalcet reduced PTH, Ca x P, serum calcium and phosphorus in ESRD subjects with secondary HPT. Treatment secondary HPT to prevent renal osteodystrophy, which can develop early in CKD and progress throughout the disease stages, is one of the major goals of therapy in CKD patients diagnosed with secondary HPT. In the presence of elevated PTH, hyperparathyroid bone disease (osteitis fibrosa) develops. The disease is characterized by a marked increase in bone turnover (bone formation and resorption). A consequence of reduction in elevated PTH levels is a decrease in the rates of bone turnover and adynamic bone disease.

Three subjects in the cinacalcet group developed adynamic bone disease, which appeared to result from over suppression of iPTH (< 100 pg/mL) in 2 subjects and immobilization (during a 3-week hospitalization) complicated by hypercalcemia in 1 subject. The current K/DOQI guidelines[13] list the target range of iPTH in dialysis patients as 150 – 300 pg/mL. These levels should, if followed, prevent the occurrence of unintended adynamic bone disease in CKD patients with secondary HPT.

Study 20000236: A Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of a Calcimimetic Agent (AMG 073) in Subjects with Secondary Hyperparathyroidism of Chronic Renal Insufficiency

This was a randomized, double-blind, placebo-controlled, multicenter study of the efficacy and safety of cinacalcet in subjects with secondary hyperparathyroidism of chronic renal insufficiency

Objectives:

Study Design:

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