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Safety

Disposition: As shown in the table below, 90% of placebo-treated subjects and 97% of cinacalcet-treated subjects experienced adverse events during the study.

Study 20000236: Disposition

	Placebo n (%)	Cinacalcet n (%)
Subjects evaluable for safety	31	30
Deaths on study	0 (0)	0 (0)
Severe adverse events*	3 (10)	11 (37)
Serious adverse events	3 (10)	1 (3)
Withdrawal due to adverse events	2 (6)	2 (7)
All adverse events	28 (90)	29 (97)

* Includes severe, life-threatening and fatal adverse events

Exposure: A total of 61 (30 cinacalcet, 31 placebo) received study medication (see table below). The mean (range) number of days of exposure to study drug was 106 (19 to 116) days for the cinacalcet group and 105 (22, 115) days for the placebo group. The mean (range) cumulative dose of cinacalcet was 7293.7 ( ) mg.

Study 20000236: Summary of Exposure to Study Drug

	Placebo (N=31)	Cinacalcet (N=30)
Number of days of exposure		
Mean	105.4	106.4
SD	19.9	20.0
Min, Max	22 , 115	19 , 116
Cumulative dose of cinacalcet (mg)		
Mean	0.0	7293.7
SD	0.0	3272.6
Min, Max		

Study 20000236: Summary of Exposure to Study Drug		
	Placebo	Cinacalcet
Dose compliance (%)		
Mean	98.1	95.0
SD	3.5	7.9
Min, Max		

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

Deaths: No deaths occurred during the study.

Serious Adverse Events: Serious adverse events were reported by 3 (10%) placebo-treated subjects and one (3%) cinacalcet-treated subjects. None of the serious adverse events occurred in more than one subject.

Subject Incidence of Serious Adverse Events by Preferred Term		
	Placebo	AMG 073
	(N = 31)	(N = 30)
	n (%)	n (%)
Subjects	3 (10)	1 (3)
Events		
Fever	0 (0)	1 (3)
Infection	0 (0)	1 (3)
Overdose-No Sequelae	1 (3)	0 (0)
Pain Chest, Non-Cardiac	1 (3)	0 (0)
Hypotension Postural	1 (3)	0 (0)
Cerebrovascular Disorder	1 (3)	0 (0)

Adverse Events Leading to Withdrawal: A total of 4 subjects withdrew from the study due to adverse events [2 (7%) from the cinacalcet group and 2 (6%) from the placebo group]. In the cinacalcet group, both withdrawals were due to hypocalcemia in one subject who had a baseline calcium of 10.2, and an initial low calcium of 7.3 mg/dL with symptoms at week 5, on the 70mg dose. He continued to have calcium levels from 7.3 – 8.2 mg/dL despite supplementation and ultimately withdrew from the study at week 15. A second subject, receiving cinacalcet withdrew from the study due to nausea and vomiting while on the 50mg dose. In the placebo group, one subject withdrew due to nausea and anorexia and a second subject withdrew due to a cerebrovascular event.

Adverse Events: Ninety-seven percent of subjects in the cinacalcet group and 90% of subjects in the placebo group reported at least 1 adverse event during the study (see table below). Ninety-seven percent of subjects in the cinacalcet group and 90% of subjects in the placebo group reported at least 1 adverse event during the study. The most common adverse events reported by cinacalcet-treated subjects were (cinacalcet, placebo) hypocalcemia (47%, 0%), nausea (27%, 23%), myalgia (23%, 23%), diarrhea (20%, 16%), and vomiting (17%, 10%).

20000236: Adverse Events, by Body System		
	Placebo	Cinacalcet
Subjects Receiving Dose	31	30
Subjects Reporting AEs	28 (90)	29 (97)
Events:		
Body as a whole	12 (39)	16 (53)

20000236: Adverse Events, by Body System		
	Placebo	Cinacalcet
Gastrointestinal	18 (58)	20 (67)
Nervous	13 (42)	12 (40)
Cardiovascular	5 (16)	0 (0)
Myo/Endo/Pericardial	1 (3)	1 (3)
Respiratory	9 (29)	6 (20)
Endocrine/Metabolic	7 (23)	16 (53)
Musculoskeletal	12 (39)	13 (43)
Infectious	2 (6)	2 (7)
Blood and Lymphatic	1 (3)	4 (13)
Skin and Appendages	6 (19)	5 (17)
Urinary Disorders	4 (13)	3 (10)
Reproductive	1 (3)	0 (0)
Vascular Disorders	1 (3)	0 (0)
Vision Disorders	2 (6)	2 (7)
Hearing / Vestibular	1 (3)	2 (7)
Psychiatric	2 (6)	1 (3)

Adverse Events of Special Interest:

Convulsions: There were no reports of seizure activity during the study.

GI Adverse Events: Gastrointestinal adverse events are common with cinacalcet treatment. Nausea was reported in 27% of cinacalcet-treated patients and 23% of placebo treated patients. Vomiting was reported in 17% of cinacalcet-treated patients and 10% of placebo-treated patients. Diarrhea was reported in 20% of cinacalcet-treated patients and 16% of placebo treated patients. Dyspepsia was reported in 4 (13%) of cinacalcet-treated subjects and 1 (4%) of placebo-treated subjects. There were no reports of esophagitis, gastritis or gastric ulcer.

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

Laboratory: Safety laboratory assessments were performed at screening and follow-up. Shift tables demonstrated no evidence of a treatment effect in hematologic and blood chemistry variables. Specific relevant laboratory evaluations are discussed below.

Serum Calcium: Mean (SE) serum calcium concentrations at baseline were 9.5 (0.1) mg/dL and 9.4 (0.1) mg/dL in the cinacalcet and placebo groups, respectively. At week 16, mean serum calcium concentrations were 8.3 mg/dL in the cinacalcet group and 9.3 mg/dL in the placebo group. These values represent a 13% decrease from baseline in the cinacalcet group and a 2% decrease in the placebo group.

Serum Phosphorus: The mean (SE) serum phosphorus concentrations at baseline were 4.2 (0.1) mg/dL in the cinacalcet group and 4.1 (0.1) mg/dL in the placebo group. Modest increases in serum phosphorus occurred in the cinacalcet group, reflective of reductions in plasma iPTH concentrations. At week 16, the mean (SE) serum phosphorus concentrations were 4.9 (1.2)

mg/dL in the cinacalcet group and 4.3 (1.2) mg/dL in the placebo group (normal range: 2.2 to 5.1 mg/dL).

Creatinine Clearance: The mean (SE) CrCl at baseline was 34.8 (1.6) mL/min in the cinacalcet group and 33.1 (1.9) mL/min in the placebo group. The mean CrCl was stable during the study in both treatment groups.

Ca x P: The mean (SE) Ca x P values at baseline were 39.6 (1.1) $(mg/dL)^2$ in the cinacalcet group and 38.9 (1.2) $(mg/dL)^2$ in the placebo group. Ca x P values and percentage change from baseline were similar between treatment groups throughout the study. At week 16, the mean (SE) Ca x P value was 41.0 (1.4) $(mg/dL)^2$ for the cinacalcet group and 40.0 (1.6) $(mg/dL)^2$ for the placebo group. At week 16, Ca x P had increased by 5% in the cinacalcet group and by 2% in the placebo group.

Vitamin D (1,25[OH]2D3): The mean (SE) 1,25(OH)2D3l at baseline was 31.3 (3.4) pg/mL in the cinacalcet group and 30.1 (2.9) pg/mL in the placebo group. The mean 1,25(OH)2D3 levels were stable during the study in both treatment groups.

Bone Alkaline Phosphatase (BALP): Median baseline BALP concentrations were 16.4 and 18.6 ng/mL in the cinacalcet and placebo groups, respectively (normal range: 2.9 to 20.1 ng/mL). At week 16, median BALP was 33% lower than baseline in the cinacalcet group and 6% higher than baseline in the placebo group.

Urine Calcium: Mean (range) baseline values for urine calcium excretion were below normal at baseline: 42.0 (4.2 to 228.6) mg/24 hours in the cinacalcet group and 39.7 (4.9 to 153.4) mg/24 hours in the placebo group (normal range: 50 to 300 mg/24 hours). At week 16, the mean 24-hour urine calcium values were increased from baseline in both treatment groups but remained in the normal range with mean values of 63.2 (10.2 to 303.9) and 49.7 (7.9 to 373.5) mg/24 hours in the cinacalcet and placebo groups, respectively.

Urine Phosphorus: Mean baseline 24-hour urine phosphorus excretion was 753.4 (range: 320.0 to 1244.0) mg/24 hours in the cinacalcet group and 683.7 (range: 291.0 to 1038.0) mg/24 hours for the placebo group (normal range: 400 to 1300 mg/24 hours). At week 16 (the end of the efficacy-assessment phase) the mean 24-hour urine phosphorus excretion was 759.4 (range: 119.0 to 3218.0) and 758.5 mg/24 hours (range: 278.0 to 1374.0) mg/24 hours in the cinacalcet and placebo groups, respectively.

Urine Protein: Mean (SE) 24-hour urine protein excretion at baseline was 2089 (325) mg/24 hours in the cinacalcet group and 2060 (531) mg/24 hours in the placebo group. At week 16, the corresponding values were 1643 (297) mg/24 hours in the cinacalcet group and 2385 (691) mg/24 hours in the placebo group. The mean percentage change from baseline at week 16 was a decrease of 12% (with a median decrease of 30%) in the cinacalcet group and an increase of 32% (with a median decrease of 16%) in the placebo group.

Other Safety Tests:

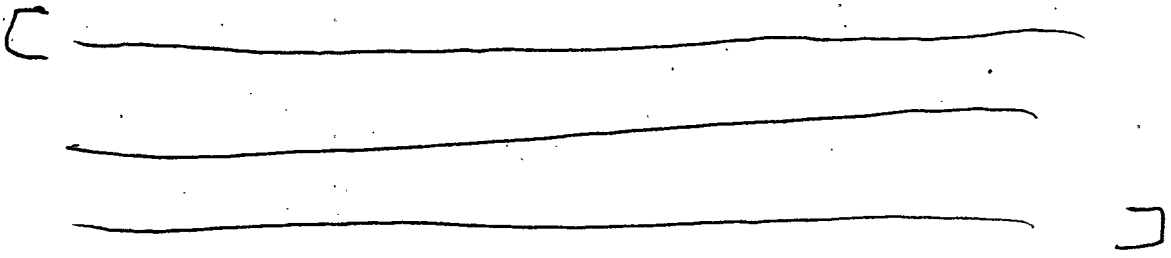
Vital Signs: Mean blood pressure measurements were stable throughout the study and did not differ between treatment groups. Any notable changes from baseline in vital signs and physical findings were recorded as adverse events.

ECGs: Investigator interpretation of ECGs was categorized on the case report form as normal; abnormal; not clinically significant; and abnormal, clinically significant. The majority of subjects (83% in the cinacalcet group and 68% in the placebo group) had an abnormal, but not clinically significantly abnormal ECG at baseline. No subject in either treatment group developed clinically significant abnormalities during the study.

Safety Conclusions: Sixty-one subjects (30 cinacalcet, 31 placebo) received study drug and were evaluable for safety. No subject died during the study. The overall incidence of serious adverse events and the incidence of adverse events were comparable between the cinacalcet and placebo groups. Two cinacalcet subjects and 2 placebo subjects withdrew due to an adverse event.

With cinacalcet treatment, reductions in serum calcium levels were observed, 8.3 versus 9.3 mg/dL at end of study for the cinacalcet and placebo groups, respectively. Serum calcium concentrations decreased 13% from baseline in the cinacalcet group and a 2% in the placebo group. Mean serum phosphorus concentrations increased slightly in the cinacalcet group but remained in the normal range. At baseline Ca x P levels were similar between treatment groups and remained stable throughout the study. Increases in 24-hour urine calcium were observed; however, no subjects had values above the normal range. Similarly, modest decreases in urine phosphorus excretion occurred. No changes in GFR were observed in this study.

Discussion and Conclusions: Secondary hyperparathyroidism (HPT) is a common and serious sequela of chronic renal disease. Approximately 75 - 100% of patients with Stage 3 or 4 CKD have evidence of renal osteodystrophy[14]. Treatment of secondary HPT to prevent renal osteodystrophy is one of the major goals of therapy in CKD patients.



The most common adverse events were hypocalcemia, nausea, myalgia, and diarrhea; these events were generally mild to moderate in severity and infrequently resulted in

[14] Elder G. Pathophysiology and recent advances in the management of renal osteodystrophy. J Bone Miner Res 2002; 17:2094-2105.

discontinuation of therapy. One subject withdrew due to a serum calcium < 7.5 mg/dL. The median dose of cinacalcet was 90mg and a higher incidence of hypocalcemia was observed in this study than in Study 20010239, which is reviewed below.

Study 20010239: 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

[redacted]

Objectives: [redacted]

Study Design: [redacted]

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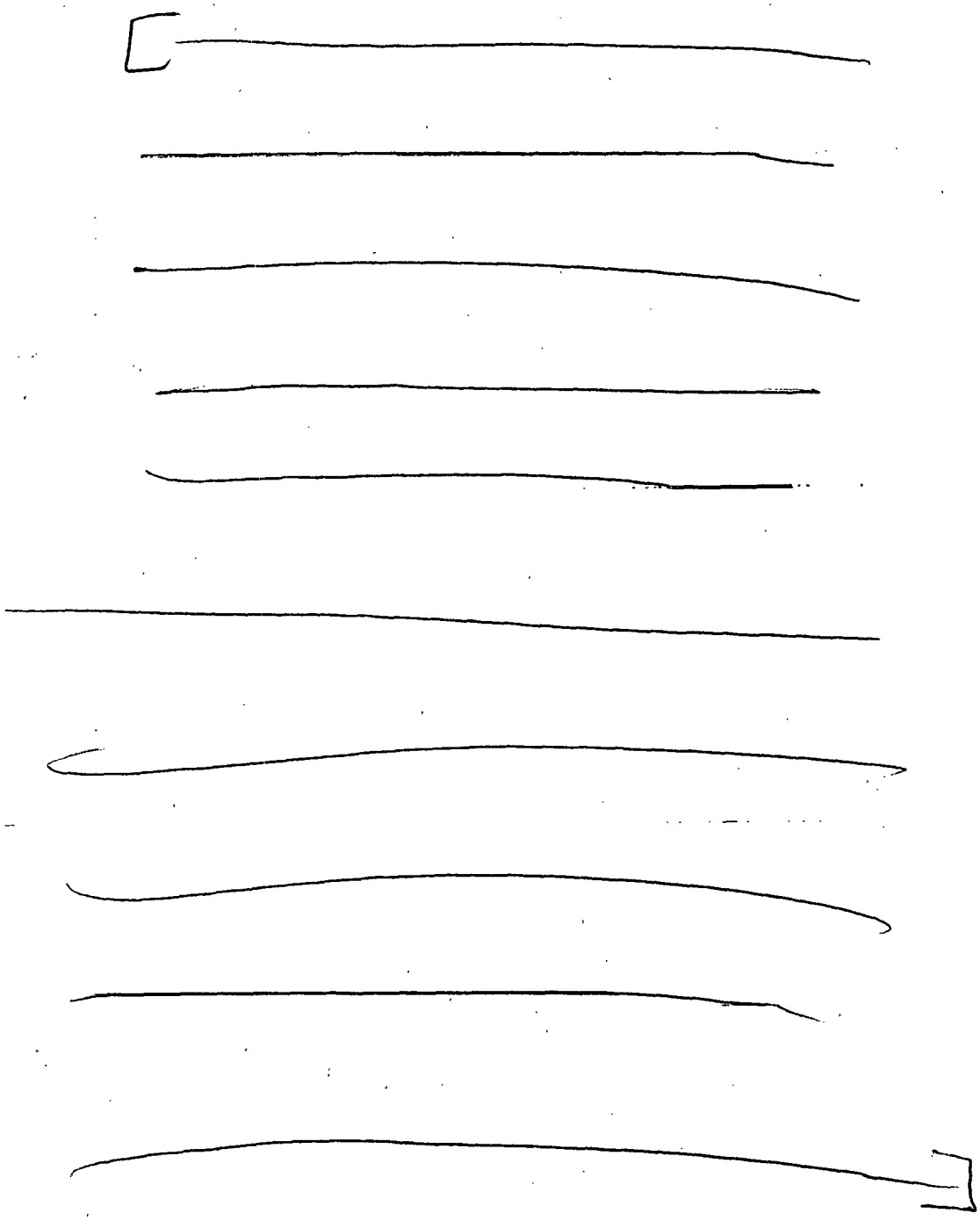

Safety

Disposition: As shown in the table below, 96% of placebo-treated subjects and 100% of cinacalcet-treated subjects experienced adverse events during the study.

Study 20010239: Disposition		
	Placebo n (%)	Cinacalcet n (%)
Subjects evaluable for safety	27	27
Deaths on study	2 (7)	0 (0)
Severe adverse events*	7 (26)	5 (19)
Serious adverse events	6 (22)	3 (11)
Withdrawal due to adverse events	1 (4)	5 (19)
All adverse events	26 (96)	27 (100)

* Includes severe, life-threatening and fatal adverse events

Exposure: A total of 54 (27 cinacalcet, 27 placebo) received study medication (see table below). The mean (range) number of days of exposure to study drug was 102 (6 to 133) days for the cinacalcet group and 102 (4, 135) days for the placebo group. The mean (range) cumulative dose of cinacalcet was 5044.4 [redacted] mg.

Study 20010239: Summary of Exposure to Study Drug		
	Placebo (N=27)	Cinacalcet (N=27)
Number of days of exposure		
Mean	101.6	102.3
SD	45.7	40.9
Min, Max	4 , 135	6 , 133
Cumulative dose of cinacalcet (mg)		
Mean	0.0	5044.4
SD	0.0	3669.7
Min, Max	[redacted]	
Dose compliance (%)		
Mean	87.9	92.4
SD	21.2	10.1
Min, Max	[redacted]	

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

Deaths: Two deaths occurred during the study. Both subjects received placebo treatment. One 58 year old mane died of cardiac failure on day 22. The second subject was an 87 year old man who suffered a myocardial infarction and died on Day 6 of the trial.

Serious Adverse Events: Three subjects (11%) in the cinacalcet group and 6 subjects (22%) in the placebo group reported serious adverse events. In the cinacalcet group one subject experienced abdominal pain, one subject experienced peripheral edema and hypertension, and a third subject was hospitalized with pulmonary edema; it was coincidentally noted that this subject was hypocalcemic (serum calcium of 7.2 to 7.8 mg/dL). In the placebo group, 2 subjects experienced serious adverse events of pulmonary edema and 2 subjects experienced cardiac failure. One subject each reported serious adverse events of myocardial infarction and atrial fibrillation. An additional placebo subject experienced multiple serious adverse events culminating in a fatal event of cardiac failure.

Adverse Events Leading to Withdrawal: A total of 6 subjects withdrew from the study due to adverse events [5 (19%) from the cinacalcet group and 1 (4%) from the placebo group]. In the

cinacalcet group, one subject withdrew because of nausea and 4 subjects withdrew because of hypocalcemia. At baseline, iPTH ranged from 119 to 594 pg/mL in these subjects, with a mean percent reduction in PTH of 85% at Week 1. In 3 of the 4 subjects, no symptoms were associated with the low serum calcium values, whereas the fourth experienced paresthesia. In each case, serum calcium increased to normal levels shortly after discontinuation of study drug. One subject withdrew from the placebo group because of cardiac failure.

Adverse Events: All subjects in the cinacalcet group and 96% of subjects in the placebo group reported at least 1 adverse event during the study. The most common adverse events were (cinacalcet, placebo) nausea (33%, 7%), myalgia (26%,15%), and diarrhea (22%, 15%) (see table below).

20010239: Adverse Events, by Body System

	Placebo	Cinacalcet
Subjects Receiving Dose	27	27
Subjects Reporting AEs	26 (96)	27 (100)
Events:		
Body as a whole	12 (44)	12 (44)
Gastrointestinal	11 (41)	15 (56)
Liver and Biliary	1 (4)	0 (0)
Nervous	9 (33)	9 (33)
Cardiovascular	3 (11)	3 (11)
Heart Rate / Rhythm	3 (11)	0 (0)
Myo/Endo/Pericardial	2 (7)	1 (4)
Respiratory	11 (41)	7 (26)
Endocrine/Metabolic	3 (11)	7 (26)
Musculoskeletal	8 (30)	11 (41)
Infectious	1 (4)	1 (4)
Blood and Lymphatic	1 (4)	0 (0)
Skin and Appendages	4 (15)	8 (30)
Urinary Disorders	3 (11)	2 (7)
Reproductive	0 (0)	2 (7)
Vascular Disorders	1 (4)	0 (0)
Vision Disorders	0 (0)	1 (4)
Hearing / Vestibular	0 (0)	1 (4)
Psychiatric	0 (0)	1 (4)

Adverse Events of Special Interest:

Convulsions: There were no reports of seizure activity during the study.

GI Adverse Events: Gastrointestinal adverse events are common with cinacalcet treatment. Nausea was reported in 33% of cinacalcet-treated patients and 7% of placebo treated patients. Vomiting was reported in 15% of cinacalcet-treated patients and 7% of placebo treated patients. Diarrhea was reported in 22% of cinacalcet-treated patients and 15% of placebo treated patients. Dyspepsia was reported in 2 (7%) of cinacalcet-treated subjects and 1 (4%) of placebo-treated subjects. There were no reports of esophagitis, gastritis or gastric ulcer.

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

Laboratory: Safety laboratory assessments were performed at screening and follow-up. Shift tables demonstrated no evidence of a treatment effect in hematologic and blood chemistry variables. Specific relevant laboratory evaluations are discussed below.

Serum Calcium: The mean (SD) serum calcium concentration at baseline was 9.7 (0.5) mg/dL and 9.7 (0.5) mg/dL in the cinacalcet and placebo groups, respectively. At Week 18, mean serum calcium concentrations were 9.0 mg/dL in the cinacalcet group and 9.6 mg/dL in the placebo group, which was within the normal range. These values represent a 7% decrease from baseline in the cinacalcet group and a 0.1% decrease in the placebo. Below is the shift table for decreases in calcium concentration.

Study 20010239: Shift Table for Change in Serum Calcium

Treatment Group	Baseline Grade	Maximum Grade for Decreased Value			
		1	2	3	4
mg/dL		7.6 – 8.4	6.5 – 7.6	5.7 – 6.5	< 5.7
Cinacalcet	0	9 (33%)	13 (48%)	0 (0%)	0 (0%)
N^d= 27	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Placebo	0	2 (8%)	0 (0%)	0 (0%)	0 (0%)
N^d= 27	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	4	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Ionized Calcium: Ionized calcium concentrations were determined in a subset of subjects who participated in this study. Reductions in ionized calcium in subjects treated with cinacalcet mirror reductions in serum calcium.

Serum Phosphorus: The mean (SD) serum phosphorus concentration at baseline was 4.1 (0.5) mg/dL in the cinacalcet group and 4.0 (0.7) mg/dL in the placebo group. Modest increases in serum phosphorus occurred in the cinacalcet group, reflective of reductions in plasma iPTH concentrations. At week 18, the mean serum phosphorus concentrations were 4.6 mg/dL in the cinacalcet group and 4.2 mg/dL in the placebo group (normal range: 2.2 to 5.1 mg/dL).

Glomerular Filtration Rate: The mean (SD) GFR at baseline was 22.6 (7.1) mL/min/1.73m^2 in the cinacalcet group and 23.1 (6.6) mL/min/1.73m^2 in the placebo group. The mean GFR was stable during the study in both treatment groups.

Ca x P: The mean (SD) Ca x P value at baseline was 39.6 (5.5) (mg/dL)^2 in the cinacalcet group and 38.8 (6.4) (mg/dL)^2 in the placebo group. Ca x P values and percent change from baseline were similar between treatment groups throughout the study. At week 18, the mean (SD) Ca x P value was 41.6 (8.7) (mg/dL)^2 for the cinacalcet and 40.2 (11.0) (mg/dL)^2 for the placebo group. The mean percent change in Ca x P was 7% in the cinacalcet group and 3% in the placebo group.

Urine Calcium: Mean (range) baseline values for urine calcium excretion were below normal at baseline: 34.9 (0.9 to 185.3) mg/24 hours in the cinacalcet group and 33.7 (4.3 to 126.9) mg/24 hours in the placebo group (normal range: 50 to 300 mg/24 hours). At week 18, the mean 24-hour urine calcium values were increased from baseline but remained in the normal range with mean values of 74.0 (5.8 to 295.7) and 53.9 (5.0 to 203.7) mg/24 hours in the cinacalcet and placebo groups, respectively. No subjects in either treatment group experienced 24-hour urine calcium values above the normal range during the study.

Mean (SD) baseline values for the ratio of spot urine calcium to creatinine were 0.03 (0.04) for the cinacalcet group and 0.03 (0.05) in the placebo group. At week 18, mean values were 0.04 and 0.03 in the cinacalcet and placebo groups, respectively. Mean percent change in fasting spot urine calcium/creatinine ratios was 59.6% and 38.9%, and median percent change was -5.9% and 29.0% in the cinacalcet and placebo groups, respectively.

Urine Phosphorus: Mean (SD) baseline 24-hour urine phosphorus excretion was 538.4 (220.5) mg in the cinacalcet group and 614.4 (278.4) mg/24 hours for the placebo group (normal range: 400 to 1300 mg/24 hours). At week 18, the end of the efficacy-assessment phase, the mean 24-hour urine phosphorus excretion was 497.4 (range: 107.0 to 956.0) mg/24 hours and 678.3 (range: 244.0 to 1337.0) mg/24 hours in the cinacalcet and placebo groups, respectively.

Urine Protein: Mean (SD) 24-hour urine protein excretion at baseline was 1131 (1225) mg in the cinacalcet group and 2200 (2883) mg/24 hours in the placebo group. At week 18, the corresponding values were 929 (989) mg/24 hours in the cinacalcet group and 1742 (2265) mg/24 hours in the placebo group. The mean (median) percentage change from baseline was 25.5% (-19.7%) in the cinacalcet group and 15.5% (14.6%) in the placebo group.

Other Safety Tests:

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

ECGs: Investigator interpretation of ECGs was categorized on the case report form as normal; abnormal, not clinically significant; and abnormal, clinically significant. The majority of subjects (63% [17/27] cinacalcet, 67 % [18/27] placebo) had an abnormal ECG at baseline. Of these, 4 (15%) subjects in the cinacalcet group and 1 (4%) subject in the placebo group had baseline ECGs that were considered clinically significantly abnormal.

Safety Conclusions: In this 18 weeks in this randomized, placebo-controlled trial, the most frequent cinacalcet dose was 30 or 60 mg once daily, although doses of 90 to 180 mg were used by approximately 20% of the subjects. Two deaths were reported in the placebo group during the study. Overall, adverse event rates were similar between treatment groups, with the cinacalcet group experiencing fewer serious adverse events than the placebo group. More subjects receiving cinacalcet compared to the placebo group reported gastrointestinal adverse events, primarily nausea and diarrhea. Four subjects in the cinacalcet group withdrew due to a serum calcium < 7.8 mg/dL on the lowest dose of study drug.

Serum calcium concentrations were 9.6 (0.5) mg/dL in the cinacalcet group and 9.7 (0.5) mg/dL in the placebo group. With cinacalcet treatment, reductions in serum calcium levels were observed, although mean levels remained in the normal range: 9.0 versus 9.6 mg/dL at end of study for the cinacalcet and placebo groups, respectively). Mean serum phosphorus concentrations increased slightly in the cinacalcet group but remained in the normal range. At baseline Ca x P levels were similar between treatment groups and remained stable throughout the study. Increases in 24-hour urine calcium were observed; however, no subjects had values above the normal range. Similarly, modest decreases in urine phosphorus excretion occurred. No changes in GFR were observed in this study.

Discussion and Conclusions: Secondary hyperparathyroidism (HPT) is a common and serious sequelae of chronic renal disease. Approximately 75 - 100% of patients with Stage 3 or 4 CKD have evidence of renal osteodystrophy[15]. Treatment of secondary HPT to prevent renal osteodystrophy is one of the major goals of therapy in CKD patients.

This study demonstrates that cinacalcet is effective in reducing plasma levels of iPTH in subjects with secondary HPT due to Stage 3 or 4 chronic kidney disease. Intact PTH levels were reduced 32% with cinacalcet treatment, compared with an increase of 6% in the placebo treated group. Significantly more cinacalcet-treated subjects (56%) than placebo treated subjects (19%) achieved the primary endpoint, a $\geq$ 30% reduction in iPTH (p = 0.006). Baseline stage of renal disease, when determined by GFR, was not a significant predictor for change in iPTH.

The most common adverse events were nausea, myalgia, and diarrhea. Hypocalcemia is recognized as a consequence of cinacalcet therapy. Four subjects withdrew from the study with serum calcium < 7.8 mg/dL on the lowest dose of study drug. Overall, there was a 7% decrease serum calcium in the cinacalcet group and a 0.1% decrease in the placebo.

<u>Study 20000204</u>: An Assessment of the Calcimimetic Agent AMG 073 for the Treatment of Subjects with Parathyroid Carcinoma or Intractable Primary Hyperparathyroidism

Objective: The primary objective of this study was to evaluate the ability of cinacalcet hydrochloride to reduce serum calcium concentrations in subjects with parathyroid carcinoma or intractable primary hyperparathyroidism (PHPT).

Study Design: This was a multicenter, open-label, dose-titration study.

The study consisted of 3 phases: a 30-day screening period, a variable length dose-titration phase, and a maintenance phase. Study medication has been administered for up to 64 weeks (data collection closed 31 January 2004).

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[15] Elder G. Pathophysiology and recent advances in the management of renal osteodystrophy. J Bone Miner Res 2002; 17:2094-2105.

Subject Population: The study population consisted of subjects with parathyroid carcinoma or intractable primary HPT. Intractable primary hyperparathyroidism was defined as unresolved primary HPT after unsuccessful parathyroidectomy or contraindication for parathyroidectomy.

Inclusion Criteria:

- Had either of the following:
  -parathyroid carcinoma
  -intractable primary HPT with a serum calcium concentration > 12.5 mg/dL
- Agreed to use, in the opinion of the principal investigator, highly effective contraceptive measures throughout the study (all women were required to have a negative serum pregnancy test within 30 days before study day 0)
- Gave informed consent for participation in the study before any study-specific procedure, including screening and study drug administration,

Exclusion Criteria:

- Undergoing therapy with flecainide or tricyclic antidepressants (except amitriptyline, which was allowed)
- Undergoing concurrent cancer chemotherapy for an indication other than parathyroid carcinoma
- Diagnosed with a malignancy (within the last 5 years) other than parathyroid carcinoma or nonmelanomatous skin cancers or in situ cervical cancer
- Diagnosed with hypercalcemia of nonparathyroid malignancy
- Unable to swallow or absorb orally administered medications in tablet form
- Known hypersensitivity to cinacalcet or tablet excipients
- Currently enrolled in, or < 30 days since completing, other investigational device or drug trial(s), or was receiving other investigational agent(s)
- Breast feeding or lactating
- Diagnosed with any condition, including a psychiatric disorder, that would interfere with compliance with the protocol unless an acceptable responsible caregiver was identified
- Previously enrolled in this study
- Unable to give truly informed consent

COMMENT: The inclusion and exclusion criteria appear appropriate. Because severe hypercalcemia in patients with parathyroid carcinoma and intractable primary hyperthyroidism is associated with significant morbidity and mortality, the use of an open label trial design is appropriate for this subset of patients.

Study Medication and Dose Titration: Study medication was administered orally, with a meal or shortly thereafter, BID at 12-hour intervals. The initial dose was 30 mg BID for 2 weeks. Subsequent dosages in the titration sequence were 50 mg BID, 70 mg BID, 90 mg BID, 70 mg 3 times daily (TID), 90 mg TID, 70 mg 4 times daily (QID), and 90 mg QID. Dosage could be increased every 2 weeks during the titration phase. Dosage escalation continued until the serum

calcium concentration was ≤ 10 mg/dL, the subject reached the highest possible dosage, or adverse events precluded further dosage increases.

Hypocalcemia: If, at any time during the study, the subject experienced symptoms of hypocalcemia or had a serum calcium measurement < 8.0 mg/dL, study medication was to have been withheld until the symptoms resolved and/or serum calcium concentration was ≥ 8.4 mg/dL. Study medication was then to be resumed at the next lower dose. If the subject was receiving 30 mg, the subject was to have been withdrawn from the study.

Concomitant Therapy: Other investigational agents were not permitted. Investigators were permitted to prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, with the exception of any excluded medications. Without jeopardizing the subject's safety, the concomitant medication regimen was to be kept as stable as possible during the study. Concomitant medications were not collected on the case report form.

Cinacalcet results in a clinically significant inhibition of the cytochrome P450 enzyme CYP2D6. Thus, CYP2D6 substrates having narrow therapeutic windows, such as flecainide or tricyclic antidepressants (except amitriptyline, which was allowed), were excluded. If a subject required such excluded medications while on study, the sponsor was to be contacted to determine whether the subject was permitted to continue in the study.

COMMENT: The prohibition of drugs that may interact with the study medication was appropriate. Failure to document the use of concomitant medications during this study limits the ability to note any potential interaction of drugs.

Efficacy Measures: The key assessments in this study included measurements of serum calcium, plasma iPTH, bone markers (serum BALP and NTx), adverse events, patient reported outcomes (PRO), and pharmacokinetics.

Primary Efficacy Endpoint:

- The primary endpoint for evaluation of cinacalcet clinical effects was the proportion of subjects experiencing a reduction of serum calcium by ≥ 1 mg/dL at the end of the titration phase.

Secondary Efficacy Endpoints:

- The proportion of subjects experiencing a reduction of serum calcium concentration to ≤ 10.3 mg/dL at the end of titration phase
- Absolute concentrations, changes from baseline, and percentage changes from baseline in serum calcium, plasma iPTH, and serum NTx and BALP
- The safety and tolerability of cinacalcet as assessed by the incidence, severity, and seriousness of adverse events, changes in clinically relevant laboratory tests, and physical examination
- Changes in PRO scale scores and summary scores
- The pharmacokinetic profile of cinacalcet (based on plasma cinacalcet concentrations)

COMMENT: There is no support in the literature for the clinical significance of the primary efficacy endpoint.

Safety Endpoints: Included standard laboratory measures (CBC, chemistry) and queries for adverse events. EKG data were not collected during this study.

COMMENT: Laboratory monitoring appeared appropriate. The lack of EKG data is concerning. Given the limited data evaluating for QT prolongation and the potential for the study drug to cause large shifts in serum calcium levels, monitoring EKGs in these patients would have been preferred.

Study Methods:

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.

Withdrawal criteria: Any subject had the right to withdraw from the study at any time and for any reason.

The investigator and Amgen also had the right to withdraw subjects from the study in the event of any of the following:

- Significant protocol violation or noncompliance, either on the part of the subject or investigator
- Significant adverse event or unacceptable toxicity
- Decision by the investigator or Amgen that discontinuation was in the subject's best medical interest
- Unrelated medical illness or complication
- Loss to follow-up

Statistical Analysis: (For a complete discussion of the statistical analysis please refer to Ms. J. Mele's review.)

Sample size calculation was based on the results of a study of subjects with mild-to-moderate primary HPT (study 990120), 79% of cinacalcet-treated subjects had a reduction in serum calcium of ≤ 1 mg/dL at the end of the titration phase. was assumed for sample size considerations. It was assumed that although subjects in this study had more severe disease, a similar result would be expected. An enrollment of 50 subjects was calculated to give an estimated 95% confidence interval (CI) of between 67% and 90% for the proportion of subjects achieving this endpoint.

Protocol Amendments: The protocol was amended once, primarily to clarify the background and rationale for the protocol. In addition, it was clarified that the contents of the PRO

questionnaire included the SF-36 and the 6-item MOS Cognitive Functioning scale. The only change in the protocol that affected study conduct was the elimination of the requirement for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) assessments during screening. This change resulted in the deletion of the inclusion criteria requiring that AST and ALT not be > 3 times the upper limit of normal.

Pharmacokinetic modeling and formal pharmacokinetic/pharmacodynamic analyses that were specified in the protocol were not conducted because of the limited dataset. Instead, pharmacokinetic and pharmacodynamic data were tabulated, and the relationship between cinacalcet concentration and effect was explored graphically.

Descriptive statistics used to summarize safety and efficacy data were to include 95% CIs. However, because the number of subjects who participated in the study was small, 95% CIs were not included in the statistical analyses.

Efficacy and safety results were presented separately for subjects with parathyroid carcinoma and intractable primary HPT and also combined for the entire subject population.

COMMENT: The restriction for hepatic insufficiency was removed, presumably because the drug is titrated. However, given the limited experience in this patient population, documentation and PK studies in patients with different hepatic function may have been informative. This, combined with the lack of documentation for concomitant medications, raises concerns for much higher doses at first exposure than may be expected.

Results:

Subject Population: Fifteen subjects (10 subjects with parathyroid carcinoma and 5 subjects with intractable primary HPT) from 10 study centers in the United States. The demographics are summarized in the following table:

Baseline Demographic Characteristics (ITT Subjects)

	Parathyroid Carcinoma 10	Intractable Primary HPT 5	Total 15
Sex			
Female	4		5
Male	6		10
Race			
White or Caucasian	10		14
Black or African American	0		1
Age (years)			
Mean	47.5		54.1
SD	15.6		17.7
Range	24 to 71		24 to 88
Parathyroid Surgery			
Yes	10		12
No	0		3
Kidney Stone			
Yes	4		6
No	6		9
Bisphosphonate Use			
Yes	10		14
No	0		1

COMMENT: The number of subjects is small and well short of the proposed 50 subjects. The difference in mean age between the two groups reflects the difference in age at presentation for the two diseases. The occurrence of kidney stones is consistent with the hypercalcemia in these patients. The determination of intractable primary hyperparathyroidism in the 5 subjects was not discussed – including why surgery or re-operation was not appropriate.

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Selected Baseline Laboratory Values	Parathyroid Carcinoma N = 10	Intractable Primary HPT N = 5	Total N = 15
Serum Calcium (mg/dl)			
n	10		15
mean	14.74		13.96
SD	1.81		1.86
range			
iPTH (pg/ml)			
n	9		14
mean	917.78		682.79
SD	343.18		432.71
range			
Serum Phosphorus (mg/dl)			
n	9		14
mean	2.74		2.56
SD	0.61		0.62
range			
Bone Specific Alkaline Phosphatase (ng/ml)			
n	10		15
mean	122.70		105.03
SD	171.53		154.18
range			
N-telopeptide (nM)			
n	10		15
mean	162.70		134.71
SD	154.88		150.84
range			

COMMENT: The baseline laboratory studies are consistent with the two diseases studied.

Subject Disposition: Eight subjects withdrew from the study. One subject with intractable primary HPT was participating in the titration phase and 5 subjects with parathyroid carcinoma and 1 subject with intractable primary HPT were participating in the maintenance phase. Subject disposition is summarized in the following table:

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Subjects Disposition (ITT Subjects)			
	Parathyroid Carcinoma n (%)	Intractable Primary HPT n (%)	Total n (%)
Enrolled	10 (100)		15 (100)
Received Study Drug	10 (100)		15 (100)
Titration Phase			
Started	10 (100)		15 (100)
Ongoing	0		1 (7)
Discontinued	4 (40)		7 (47)
Completed	6 (60)		7 (47)
Maintenance Phase			
Started	6 (60)		7 (47)
Ongoing	5 (50)		6 (40)
Discontinued	1 (10)		1 (7)
Completed	0		0
Total Discontinued	5 (50)		8 (53)

COMMENT: The number of drop outs in this study leaves few subjects to provide data for efficacy analysis.

Protocol Violations: Key protocol deviations that occurred during the study included missed assessments of serum calcium, plasma iPTH, and PRO. Two eligibility deviations also occurred. Subject 0101 (with parathyroid carcinoma) had a chest X-ray performed as part of the subject's standard care before the informed consent was signed for this study. Because the chest X-ray was a study-specific screening procedure, the performance of the X-ray was considered an eligibility deviation. Subject 1301, a 59-year-old woman who had been postmenopausal for 10 years, had a positive serum beta HCG pregnancy test at screening. The subject was not pregnant.

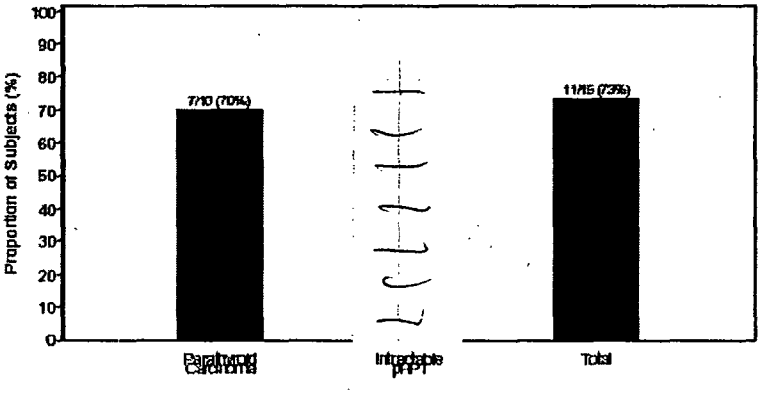
COMMENT: None of the protocol deviations should affect the interpretation of the effects on serum calcium. The missed PRO assessments appeared to have affected the interpretation of this secondary endpoint.

Extent of Exposure to Treatment: Mean (SD, range) exposure to study drug was 162 days (± 138, 36 to 452) for subjects with parathyroid carcinoma

Efficacy:

Primary Endpoint Analysis: The primary endpoint was defined as the proportion of subjects experiencing a reduction of serum calcium by ≥ 1 mg/dl at the end of the titration phase. The proportion of subjects meeting this criterion is summarized in the following figure:

Figure 9-1. Proportion of Subjects Who Achieved a≥ 1 mg/dL Reduction From Baseline in Serum Calcium at the End of Titration



pHPT: primary HPT

COMMENT: As stated in the general discussion, no clinical trials have demonstrated that this endpoint is clinically meaningful. Furthermore, the above figure over estimates the efficacy of cinacalcet in this population. Of the 10 subjects with parathyroid carcinoma and 5 subjects with intractable primary hyperparathyroidism, only 4 subjects (3 with parathyroid carcinoma and 1 with intractable primary hyperparathyroidism) completed the titration phase and entered the maintenance phase. Furthermore, it does not demonstrate durability of effect. While there was durability of effect in some subjects, other subjects had serum calcium levels increase despite increasing doses of cinacalcet.

Secondary Endpoint Analysis: The secondary endpoint was defined as the proportion of subjects having a reduction of serum calcium to ≤ 10.3 mg/dL at the end of the titration phase. No subjects with parathyroid carcinoma met this criterion although 2 subjects had transient decreases into the normal range during the titration phase.

COMMENT: The subject reported to have reached a normalized serum calcium had the lowest serum calcium level of the group at entry to the study and died in the 4th week of the titration phase (33 days into the study).

Graphic representations of the serum calcium levels for all subjects are shown in the 2 figures below:

Figure 9-2. Serum Calcium Concentrations During the Titration Phase for Parathyroid Carcinoma Subjects

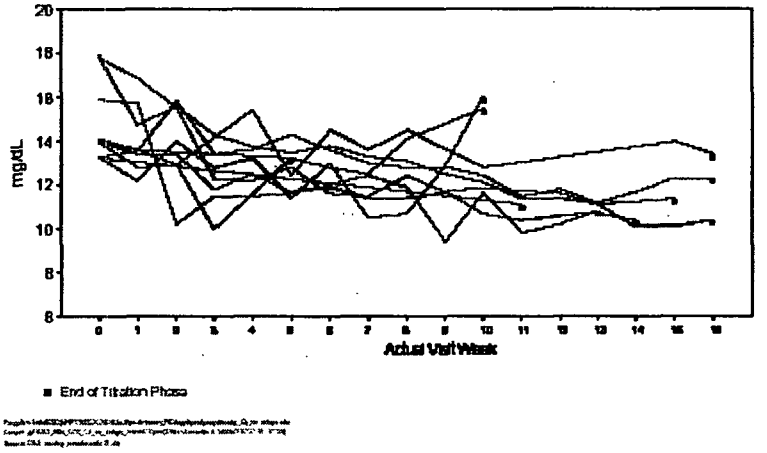
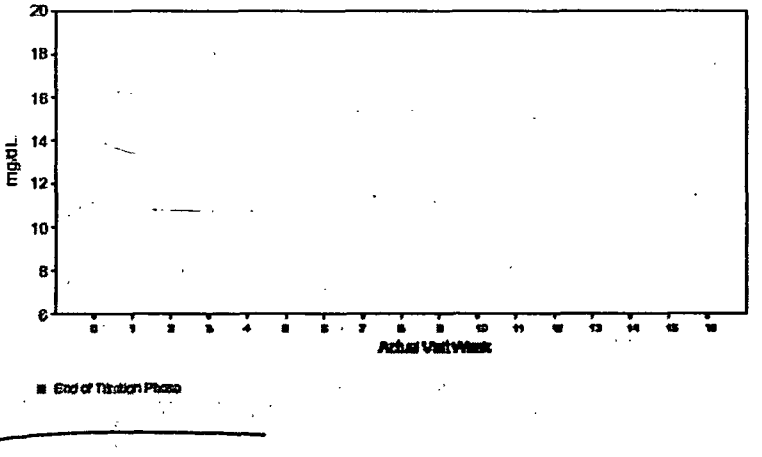


Figure 9-3. Serum Calcium Concentrations During the Titration Phase for Intractable Primary HPT Subjects



Individual data: Because of the limited number of subjects and data, the baseline serum calcium, serum calcium at the end of the titration phase, dosage at the end of the titration phase, last values are reported for all subjects in the following table. If the subject was discontinued, the reason for discontinuation (if known) was listed. All data were reported as of the end of the data collection date (31 January 03). For completeness, the additional data reported (as of 31 July 03) are included. [Data for subjects enrolled after 31 January 03 are not included.]

Individual Data for Patients in Study 2000204								
Subject ID	Baseline Calcium (mg/dL)	EOTP Visit Week	Dosage at EOTP Visit	EOTP Calcium (mg/dL)	Last Study Week[c]	Dosage at Last Visit	Last Calcium (mg/dL)	Status
Subjects with parathyroid carcinoma								
0101	14.0	5	70 mg BID	12.8	5	70 mg BID	12.8	Died study day 36
0201	14.0	14	70 mg QID	10.4	30	90 mg TID	10.8	Died study day 230
0301	14.1	16	90 mg TID	13.4	24	90 mg QID	15.0	
					(40	90 mg QID	15.0	Off study)
0401	17.9	16	90 mg TID	10.4	48	90 mg TID	10.5	
					(88	90 mg TID	10.6	Ongoing)
0403	15.9	14	70 mg QID	10.8	14	70 mg QID	10.8	
					(38	70 mg TID	10.7	Ongoing)
0601	13.2	2	30 mg BID	11.1	2	30 mg BID	11.1	Noncompliance
1201	13.3	11	70 mg TID	15.2	11	70 mg TID	15.2	Consent withdrawn
1301	17.8	16	90 mg QID	11.0	16	90 mg QID	11.0	
					(40	90 mg QID	10.8	Ongoing)
1303	13.3	10	70 mg TID	16.0	10	70 mg TID	16.0	Died study day 97
1304	13.9	16	90 mg QID	12.3	16	90 mg QID	12.3	Ongoing
Subjects with intractable primary HPT								

ETOP = end of treatment phase

COMMENT: The individual data demonstrate the subject variability for the efficacy of cinacalcet in subjects with parathyroid carcinoma and intractable primary hyperparathyroidism. In general, the daily dose used by subjects with parathyroid carcinoma was greater than that of subjects with intractable primary hyperparathyroidism. Despite failure to reach the goal of serum calcium ≤ 10.3 mg/dL, not all subjects reached the maximum allowable dose under the protocol (90 mg QID). It is not clear if this limitation in dose is related to adverse events.

Because of the limited data available, further evaluation of the additional secondary endpoints (serum n-telopeptide and bone specific alkaline phosphatase) was not done. The limited completion of the patient reported outcomes (PRO) assessments makes conclusions regarding functional improvement related to treatment difficult.

EFFICACY CONCLUSIONS: The severe hypercalcemia from parathyroid carcinoma and intractable primary hyperparathyroidism is associated with significant morbidity and mortality. To date medical therapy is limited to treatment of acute increases in serum calcium and long-term therapy is lacking. Despite the small data set presented in this application, efficacy has been demonstrated in some patients with these diseases. The

failure of subjects to achieve normalized calcium may reflect that dosing regimens – interval or dose has not been adequately studied.

SAFETY: Fifteen subjects were evaluable for safety.

Deaths: Four deaths occurred during this study. The causes of death were cardiac arrest, hypotension, and respiratory insufficiency for subjects with parathyroid carcinoma and arrhythmia for the subject with intractable primary hyperparathyroidism.

Adverse events: All subjects experienced at least 1 adverse event. The most common adverse events were nausea and headache.

Adverse Events			
	Parathyroid Carcinoma n (%)	Intractable Primary HPT n (%)	Total n (%)
Subjects evaluable for safety			
All Adverse Events	10 (100)	5 (100)	15 (100)
Severe, life-threatening and fatal adverse events	5 (50)	3 (60)	8 (53)
Serious adverse events	5 (50)	3 (60)	8 (53)
All Treatment Related Adverse events	9 (90)	4 (80)	13 (87)
Severe, life-threatening and fatal adverse events	2 (20)	1 (20)	3 (20)
Serious adverse events	1 (10)	0	1 (7)
Discontinuation due to adverse events	1 (10)	1 (20)	2 (13)
Deaths on study	3 (30)	1 (20)	4 (27)

Serious Adverse Events: Serious adverse events occurred in 8 subjects and are summarized in the following table:

Serious Adverse Events			
	Parathyroid Carcinoma (N = 10)	Intractable Primary HPT (N = 5)	Total (N = 15)
Preferred Term	n (%)	n (%)	n (%)
Number of Subjects Reporting Serious Adverse Events	5 (50)	3 (60)	8 (53)
Hypercalcemia	2 (20)	1 (20)	3 (20)
Arrhythmia	0 (0)	1 (20)	1 (7)
Cardiac Arrest	1 (10)	0 (0)	1 (7)
Coronary Artery Disorder	0 (0)	1 (20)	1 (7)
Dehydration	1 (10)	0 (0)	1 (7)
Dyspnea	1 (10)	0 (0)	1 (7)
Fibrillation Atrial	1 (10)	0 (0)	1 (7)
Hypotension	1 (10)	0 (0)	1 (7)
Nausea	1 (10)	0 (0)	1 (7)
Pneumonia	1 (10)	0 (0)	1 (7)
Respiratory Insufficiency	1 (10)	0 (0)	1 (7)
Spinal Cord Compression	1 (10)	0 (0)	1 (7)
Vascular Disorder	0 (0)	1 (20)	1 (7)
Vomiting	1 (10)	0 (0)	1 (7)

Adverse Events Leading to Withdrawal: Two subjects were withdrawn from the study because of adverse events. One subject with parathyroid carcinoma was discontinued because of nausea and vomiting and one subject with intractable primary hyperparathyroidism was discontinued because of hypercalcemia.

COMMENT: The adverse events related to subject 1303 are not clear – this subject is listed as having been discontinued from treatment because of adverse events (nausea and vomiting) starting on study day 15 at dose 50 mg BID but also having died from hypotension on study day 97 at dose 90 mg TID.

Adverse Events: All adverse events are listed in the following table:

All Adverse Events			
Preferred Term	Parathyroid Carcinoma (N = 10) n (%)	Intractable pHPT (N = 5) n (%)	Total (N = 15) n (%)
Number of Subjects Reporting Adverse Events	10 (100)	5 (100)	15 (100)
Nausea	6 (60)	2 (40)	8 (53)
Vomiting	5 (50)	2 (40)	7 (47)
Anorexia	2 (20)	1 (20)	3 (20)
Asthenia	1 (10)	2 (40)	3 (20)
Dysphagia	1 (10)	2 (40)	3 (20)
Headache	3 (30)	0 (0)	3 (20)
Hypercalcemia	2 (20)	1 (20)	3 (20)

All Adverse Events			
Preferred Term	Parathyroid Carcinoma (N = 10) n (%)	Intractable pHPT (N = 5) n (%)	Total (N = 15) n (%)
Paresthesia	3 (30)	0 (0)	3 (20)
Alopecia	2 (20)	0 (0)	2 (13)
Dyspepsia	1 (10)	1 (20)	2 (13)
Fracture	1 (10)	1 (20)	2 (13)
Infection Upper Respiratory	1 (10)	1 (20)	2 (13)
Pneumonia	2 (20)	0 (0)	2 (13)
Somnolence	2 (20)	0 (0)	2 (13)
Spinal Cord Compression	2 (20)	0 (0)	2 (13)
Weight Decrease	2 (20)	0 (0)	2 (13)
Allergic Reaction	0 (0)	1 (20)	1 (7)
Anemia	1 (10)	0 (0)	1 (7)
Anxiety	1 (10)	0 (0)	1 (7)
Arrhythmia	0 (0)	1 (20)	1 (7)
Arthralgia	1 (10)	0 (0)	1 (7)
Bronchitis	1 (10)	0 (0)	1 (7)
Cardiac Arrest	1 (10)	0 (0)	1 (7)
Cataract	1 (10)	0 (0)	1 (7)
Constipation	1 (10)	0 (0)	1 (7)
Coronary Artery Disorder	0 (0)	1 (20)	1 (7)
Cough Dry	1 (10)	0 (0)	1 (7)
Dehydration	1 (10)	0 (0)	1 (7)
Depression	1 (10)	0 (0)	1 (7)
Dizziness	1 (10)	0 (0)	1 (7)
Dyspnea	1 (10)	0 (0)	1 (7)
Edema	1 (10)	0 (0)	1 (7)
Edema Periorbital	1 (10)	0 (0)	1 (7)
Edema Peripheral	1 (10)	0 (0)	1 (7)
Fatigue	1 (10)	0 (0)	1 (7)
Fibrillation Atrial	1 (10)	0 (0)	1 (7)
Flatulence	0 (0)	1 (20)	1 (7)
Gastro-Intestinal Disorder	0 (0)	1 (20)	1 (7)
Hair Texture Changed	1 (10)	0 (0)	1 (7)
Hematemesis	1 (10)	0 (0)	1 (7)
Hemorrhage Conjunctival	1 (10)	0 (0)	1 (7)
Hypocalcemia	0 (0)	1 (20)	1 (7)
Hypotension	1 (10)	0 (0)	1 (7)
Influenza-Like Symptoms	1 (10)	0 (0)	1 (7)
Insomnia	0 (0)	1 (20)	1 (7)
Laryngitis	1 (10)	0 (0)	1 (7)
Malaise	1 (10)	0 (0)	1 (7)
Migraine	1 (10)	0 (0)	1 (7)
Muscle Weakness	1 (10)	0 (0)	1 (7)
Myalgia	1 (10)	0 (0)	1 (7)
Pain Abdominal	0 (0)	1 (20)	1 (7)
Pain Chest, Non-Cardiac	1 (10)	0 (0)	1 (7)
Pain Limb	1 (10)	0 (0)	1 (7)
Pain Skeletal	1 (10)	0 (0)	1 (7)
Palpitation	1 (10)	0 (0)	1 (7)
Polyuria	1 (10)	0 (0)	1 (7)

All Adverse Events			
Preferred Term	Parathyroid Carcinoma (N = 10) n (%)	Intractable pHPT (N = 5) n (%)	Total (N = 15) n (%)
Pruritus	0 (0)	1 (20)	1 (7)
Renal Calculus	0 (0)	1 (20)	1 (7)
Respiratory Insufficiency	1 (10)	0 (0)	1 (7)
Skin Dry	1 (10)	0 (0)	1 (7)
Taste Perversion	1 (10)	0 (0)	1 (7)
Thinking Abnormal	1 (10)	0 (0)	1 (7)
Thirst	1 (10)	0 (0)	1 (7)
Vascular Disorder	0 (0)	1 (20)	1 (7)

Concomitant Medications – No information on concomitant medications was collected during this study.

SAFETY COMMENTS: As with the efficacy data, the safety data are limited by the small number of subjects. The most common side effects (nausea, vomiting, and headache) are similar to that seen in studies of cinacalcet in patients with CKD. Four subjects died during this study, two relatively early in the titration phase. Given the baseline level of illness in this population, deaths are not unexpected. However, it is concerning that one subject (with intractable primary hyperparathyroidism) who died early in the titration phase was hypocalcemic at last measure. This patient who had the lowest serum calcium at entry (11.8 mg/dL) was on the lowest dose of study drug (30 mg BID) which was not held with the onset of the hypocalcemia. Furthermore, this patient was noted to have died of an arrhythmia but no EKG data were obtained during this study. Amgen has been asked to provide additional information on the patients who died during the study.

SUMMARY COMMENTS: The hypercalcemia that occurs in patients with parathyroid carcinoma and some patients with primary hyperparathyroidism is associated with significant morbidity and mortality and the current medical treatments are insufficient for long-term management of these patients.

The results of this small Phase 2 study demonstrate that cinacalcet is effective in lowering serum calcium in some of these patients, although normalization of calcium was not achieved. The limited experience with dose titration, concomitant medications, and safety data cautions against the use of this medication in patients without careful selection and monitoring.

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MEDICAL OFFICER

Eric Colman
2/27/04 01:05:37 PM
MEDICAL OFFICER