Enrollment Criteria:

For study 20000204: The study population consisted of patients with parathyroid carcinoma or intractable primary hyperparathyroidism and serum calcium of > 12.5 mg/dl.

For study 990120: The study population consisted of patients with primary hyperparathyroidism and with an iPTH concentration of > 45 pg/mL and serum calcium concentration > 10.3 mg/dL and ≤ 12.5 mg/dL.

COMMENT: Intractable primary hyperparathyroidism was not clearly defined in study 20000204. The degree of primary hyperparathyroidism in study 990120 was not clearly defined or discussed. The criteria for enrollment did not include failed or contraindicated surgery although several patients appeared to fall into the former category. The patients by inclusion had milder hypercalcemia than those defined as having intractable primary HPT in study 20000204.

Study Medication and Dose Titration: All medications were administered orally, with a meal or shortly thereafter, BID at 12-hours intervals. In study 20000204 all patient started on cinacalcet 30 mg BID for Weeks 1-2 and doses were titrated every 2 weeks 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. Serum calcium levels were checked every 8 weeks in the maintenance phase, additional increases in dose could be made if serum calcium had increased and the patient was not at the maximum study dose. In study 990120 all patients randomized to cinacalcet started on 30 mg BID for Weeks 1-4 and doses were titrated sequentially (weeks 4 and 8) to 40, or 50 mg, BID. Serum calcium levels were checked every 4 weeks during the maintenance phase.

Dose Titration:

For all studies, a patient's dose was NOT increased if any of the following criteria applied: The highest dose of study medication was reached.

- The subject was experiencing symptoms of hypocalcemia.
- The subject was experiencing an adverse event that precluded a dose increase.

Study 20000204:

- The serum calcium was < 10.0 mg/dL

Study 990120:

- The serum calcium was < 8.4 mg/dL (2.1 mmol/L)

Treatment of Hypocalcemia: For all studies, if a patient experienced symptoms of hypocalcemia and/or a serum calcium < 8.0 mg/dL the study medication was held until symptoms resolved and or the serum calcium concentration was ≥ 8.4. Study medication was then to resume at the next lower dose. If the patient was receiving 30 mg BID or placebo, the patient was to have been withdrawn from the study.

Withdrawal criteria: Any patient had the right to withdraw from any of these studies at any time and for any reason. Patients could be withdrawn from the study in the event of severe hypercalcemia (≥ 12.5 mg/dL) or parathyroidectomy in study 990120; or, protocol violation or noncompliance, adverse event or unacceptable toxicity in either study. Patients continued to be enrolled into study 20000203 at the time of submission. The open-label continuation phase of study 990120 (study 20000159) was ongoing at the time of submission.

Primary Efficacy Endpoint

Study 20000204:

- 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.

Study 990120:

- The primary endpoint of this study was the proportion of subjects with the mean of the maintenance phase serum calcium measurements ≤ 10.3 mg/dL and with a mean decrease of at least 0.5 mg/dL.

Secondary Efficacy Endpoints

Study 20000204:

- 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)

Study 990120:

- The safety and tolerability of cinacalcet as measured by incidence of adverse events, significant changes in vital signs, electrocardiograms (ECGs), physical and ophthalmologic examinations, and significant changes from baseline in serum chemistry, hematology, coagulation, urinary calcium/creatinine ratio, and urinalysis values.
- The maintenance phase mean for serum calcium was evaluated by the following: change from baseline, percent change from baseline, and the proportion of subjects maintaining a 12-week maintenance phase mean reduction of serum calcium from baseline of at least 0.5 mg/dL.
- The maintenance phase mean for plasma iPTH was evaluated by the following: change from baseline, percent change from baseline, the proportion with baseline > 65 pg/mL who decrease to ≤ 65 pg/mL, and the proportion of all subjects with iPTH ≤ 65 pg/mL.

- The proportion of all subjects with maintenance phase mean serum calcium ≤ 10.3 mg/dL and maintenance phase mean iPTH ≤ 65 pg/dL.
- The change from baseline and percent change from baseline in maintenance phase mean for the following variables: serum BALP, serum 1,25(OH)2D3, serum NTx, serum phosphorus, urinary calcium/creatinine ratio, urinary DPD/creatinine ratio, and urinary NTx/creatinine ratio.
- The percent change from baseline in BMD at weeks 24 and 52 as assessed by DXA scans of proximal femur (total femur and femoral neck), lumbar spine (L1-L4), forearm (ultra distal radius and 1/3 radius), and total body.
- The pharmacokinetic profile of cinacalcet as determined with population-based methods: correlations between the pharmacokinetic parameters (area-under the- plasma-concentration time curve from 0 to infinity [AUC(0-inf)]), minimum plasma cinacalcet concentrations [Cmin], and maximum plasma cinacalcet concentrations [Cmax]) and the clinical measurements of iPTH and serum calcium were computed.
- The proportions of subjects completing part or all of the QOLSAQ at baseline, end of titration phase (week 12), end of maintenance phase (week 24), week 36, and end of follow-up phase (week 52).
- The internal consistency reliability, discriminant validity, criterion validity, and responsiveness of the Medical Outcomes Short Form-36 (SF-36), Brief Symptom Inventory (BSI), and Visual Analogue Scale (VAS).
- The change in patient HRQOL between week 24 and baseline (exploratory).
- The total HRQOL as measured by area-under-the-quality-of-life time curve from baseline to the end-of-study (AUC_QOL) (exploratory)

Statistical Analyses: For study 20000204,

Results

Patient Disposition: The disposition of patients is provided in the below table.

Disposition by study, patient population, and treatment*				
	20000204		990120	
	Parathyroid Carcinoma	Intractable Primary HPT	Primary HPT	
Treatment	Cinacalcet		Cinacalcet	Placebo
Enrolled	10	5	40	38
No treatment	0			
Titration Phase				
discontinued	4			
completed	6			
ongoing	0			
Maintenance Phase				
discontinued	1			
completed	0			
ongoing	5			
Deaths	3			

Demographics: Baseline patient demographics are presented in the following table:

Demographics by study, patient population, and treatment*				
	20000204		990120	
	Parathyroid Carcinoma	Intractable Primary HPT	Primary HPT	
Treatment	Cinacalcet		Cinacalcet	Placebo
Number Enrolled	10	5	40	38
Age (years)	47.5 ± 15.6			
Sex				
male	6			
female	4			
Race				
Caucasian	10			
Black	0			
other	0			
Baseline Labs				
serum calcium (mg/dL)	14.74 ± 1.81			

*Values reported in means ± SD

COMMENT: The ranges in age, gender, and baseline labs are consistent with the differences in the presentation of the different diseases: younger age with highest serum calcium and [redacted] in the patients with parathyroid carcinoma, and older age in the [redacted] with lower levels of serum calcium and [redacted] in the milder disease (study 990120).

Efficacy Outcomes

Study 20000204: Because of the small number of patients in this study a description of the data are provided, no statistical analysis is presented.

Ten patients with parathyroid carcinoma entered the titration phase with a range of exposure to cinacalcet of 2 to 16 weeks. The range of change for serum calcium from baseline to the last measurement in the titration phase was -7.5 to 2.7 mg/dL. Three patients entered the maintenance phase with a range of exposure of 16 to 48 weeks. The range of change from baseline to the last measurement in the maintenance phase was -74 to 0.9 mg/dL.. The final dosage reported range from 70 mg BID to 90 mg QID.

Study 990120: The primary efficacy outcome assessment

Medical Officer Conclusions: These studies demonstrate that cinacalcet is effective in reducing serum calcium levels in patients with parathyroid carcinoma; however, normalization of serum calcium was not maintained in these patients. The clinical significance of these changes in serum calcium in terms of morbidity or mortality is unknown.

[redacted]

VI.C.4. Exploratory Bio-intact PTH Analyses

The concentration of iPTH is an important measure for effective clinical management of patients with chronic renal failure. The Nichols first generation immunoradiometric iPTH assay is the current gold-standard assay for PTH measurement. PTH levels were used for titration of study medication and for efficacy analyses in all of the cinacalcet studies. Recent investigations have shown that the Nichols assay detects 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, is 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 [2]. Amgen collected duplicate plasma samples in two studies (20000172 and 20010141) for measurement of PTH concentrations using both assays to allow comparison of results obtained.

As shown in the table below, biPTH values are approximately 50% lower than values obtained with the iPTH assay. Reductions in mean PTH concentrations in the cinacalcet group compared with the placebo group were demonstrated using both the iPTH and biPTH assay.

Study 20000172: Comparison of biPTH and iPTH Assay Results

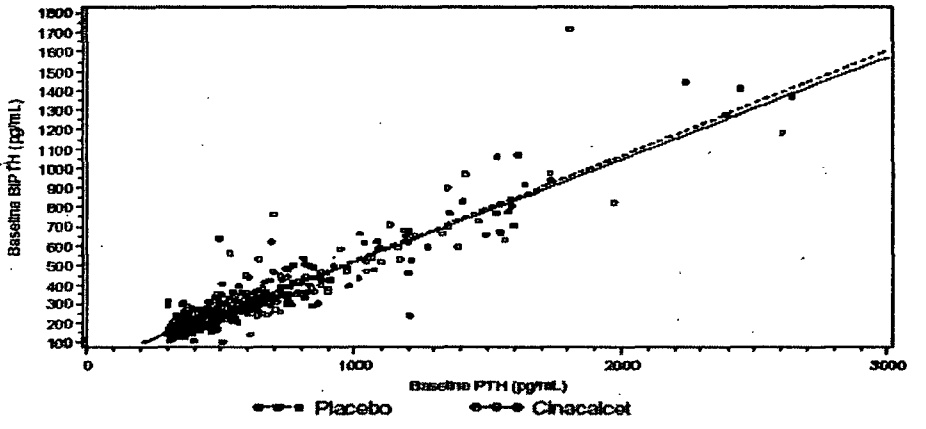
	Placebo (N = 205)		Cinacalcet (N = 205)	
	biPTH	**iPTH**	**biPTH**	**iPTH**
Mean (SE) baseline PTH (pg/mL)	337 (16)	651 (28)	326 (14)	636 (24)
Mean (SE) percentage change in PTH[a]	23% (3.6%)	10% (2.8%)	-38% (3.1%)	-38% (2.9%)
> 30% reduction in mean PTH[a] (n%)	10%	11%	56%	61%
Subjects achieving target PTH[a,b] (n%)	8%	4%	45%	41%

a During the efficacy-assessment phase (LVCF)
b The target biPTH and iPTH concentrations were = 140 pg/mL and = 250 pg/mL, respectively

As shown in the figure below, baseline iPTH and biPTH values were highly correlated (r = 0.89 for cinacalcet and r = 0.95 for placebo). Similar correlations were present during the efficacy-assessment phase (r = 0.96 for cinacalcet and r = 0.95 for placebo). 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 during the efficacy-assessment phase.

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

Figure 14.4.1. Correlation Analysis of iPTH and biPTH Values at Baseline (Randomized Subjects)



Placebo: Correlation= 0.950, p-value=<.0001 Cinacalcet: Correlation= 0.887, p-value=<.0001

Similar results were achieved in the 52-week study 20010141, as shown below. Values were again highly correlated at baseline (r = 0.83 for placebo and r = 0.84 for cinacalcet) and at the end of the study (r = 0.99 for placebo and r = 0.83 for cinacalcet).

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) % change in PTH[a]	48.8 (15.4)	91.5 (27.3)	-51.4 (5.8)	-48.3 (7.8)
Subjects achieving target PTH[a,b] (n%)	6.3%	6.3%	53.1 %	62.5 %
> 30% reduction in mean PTH[a] (n%)	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

Medical Officer Conclusions: The bio-intact PTH (biPTH) assay is highly correlated with the current gold standard iPTH assay and may offer a more accurate assessment of intact PTH levels in patients with secondary HPT associated with renal disease. PTH levels remain an integral part of the clinical management of osteodystrophy associated with renal disease. Current National Kidney Foundation clinical guidelines and recommendations for titration of therapeutic interventions rely upon the iPTH assay. Data presented here are consistent with published literature, showing that biPTH values are approximately 50% of the values derived from the iPTH assays. Based on these data, one could postulate that target biPTH ranges used to initiate therapy would be 75 – 150 pg/mL. However, until the relationship between iPTH levels, measured by the biPTH assay, and renal bone disease, assessed by biopsy, is defined, the management of renal osteodystrophy will likely remain guided by iPTH levels measured with the iPTH assay.

VI.C.5. Bone Histomorphometry

Three studies assessing the safety and efficacy of cinacalcet use in end stage renal disease obtained bone histomorphometry data. Study 990740 was a phase-2 study that obtained bone

biopsy on a total of 6 subjects (2 placebo, 4 cinacalcet). Study 990126 was a subset of study 990101 that obtained bone biopsies on a total of 9 subjects (3 placebo, 6 cinacalcet). This review focuses on study 20010141 which obtained bone biopsy on 35 subjects (13 placebo, 22 cinacalcet). Please see the Appendix for the complete reviews of the individual trials.

Study 20010141:

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. Subjects with end stage renal disease on hemodialysis were randomized in a 2:1 ratio to cinacalcet or placebo. The study consisted of 3 phases: 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). No baseline stratification factors were used.

Study Methods: 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 [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).

Study Medication: All medications were administered orally with a starting dose of 30 mg cinacalcet or placebo. 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. Study drug dose changes also were permitted during the maintenance phase. Possible sequential doses during the study were 30, 50, 70, 90, 120 and 180 mg cinacalcet or placebo. Changes in phosphate binders were permitted throughout the study. Changes in vitamin D therapy were only permitted based on protocol-specified guidelines.

Dose Titration: Subjects could be titrated up to the next sequential dose level of study drug at 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, a subject's dose could be adjusted according to the same titration rules.

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.

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.

Results

Patient Disposition: As shown in the table below, 32 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. Compliance with study drug was > 80% and similar in both the cinacalcet and placebo groups.

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 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
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
Serum Ca (mg/dL)	9.80 ± 0.91	9.86 ± 0.79
Serum Phos (mg/dL)	6.41 ± 1.11	6.71 ± 1.40
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)

Primary Efficacy Outcomes

Bone Histomorphometry Parameters

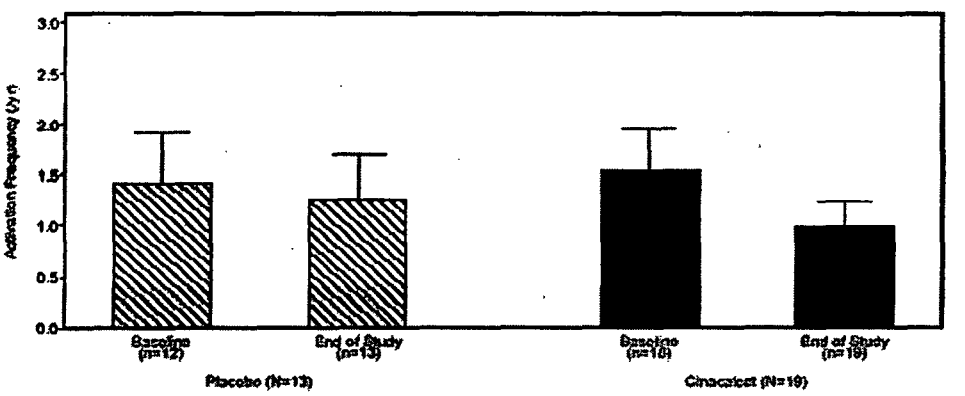
Nineteen subjects in the cinacalcet group and 13 subjects in the placebo group had both baseline and end-of-study bone biopsies. No subject in either treatment group had aluminum present on their bone surface. Results are outlined in the table below (normal levels for each parameter in parentheses)

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)	
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)	

20010141: Bone Biopsy Results				
	Placebo		Cinacalcet	
	Baseline	End of Study	Baseline	End of Study
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)	
Mineralizing Lag Time (< 50 days)				
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)	

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).

Figure 9-8. Mean (95% Confidence Intervals) Activation Frequency at Baseline and End of Study (Analysis Set)



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. At the end of the study, mean values for mineralization parameters in both treatment groups were within the normal range (MLT [< 50 days], osteoid thickness [4-20 μm], and osteoid surface [1-39%]).

Renal Osteodystrophy Class: Classification of renal osteodystrophy occurred at baseline and end of study. 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 (defined as a normal or elevated activation frequency/BFR in the presence of an elevated MLT).

Adynamic bone disease was defined as low bone turnover (activation frequency/BFR below the lower limit of normal), with normal levels of osteoid thickness and osteoid surface. One subject in the placebo group had adynamic bone disease at baseline and 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 as biomechanical forces are known to play a role in the stimulation of osteoblasts. In all subjects bone alkaline phosphatase values fell too. 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)

Medical Officer 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. A consequence of over-suppression of PTH is the occurrence of adynamic bone disease, as seen with several subjects in this study. The current the NKF-K/DOQI guidelines[3] recommend iPTH target ranges of 150 – 300 pg/mL. In this trial, 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.

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

VI.D. Efficacy Conclusions

Secondary HPT is a common and serious sequelae of chronic renal disease. Current therapies for the HPT associated with renal disease includes phosphate binders (calcium and non-calcium based) and vitamin D. Calcium-based phosphate binder and vitamin D use is limited by their propensity to increase serum calcium and phosphorus.

In subjects with secondary HPT associated with end stage renal disease, cinacalcet is more effective than placebo in reducing plasma levels of iPTH. This effect was demonstrated in a population of patients of which many were being treated with standard phosphate-binder and vitamin D therapies. Therapy was more effective in those subjects with less severe HPT, with a 12% response rate in subjects with iPTH at baseline of greater than 800 pg/mL, compared with a 61% response rate in subjects with a baseline iPTH 300-500 pg/ml. A higher proportion of subjects in both groups achieved a 30% reduction in baseline iPTH levels (62% in the cinacalcet-treated group vs. 11% in the placebo-treated group).

In subjects with secondary HPT associated with Stage 3 or 4 chronic kidney disease (pre-dialysis),

In renal disease, the Ca x P ion product has been associated with a variety of adverse sequelae, including increased risk of cardiac, visceral, and vascular calcifications. In subjects with secondary HPT associated with end stage renal disease, the mean Ca x P value at baseline was 61 $(mg/dL)^2$ for subjects in both treatment groups. Over the course of the studies, the mean Ca x P value was reduced by 14% in the cinacalcet group, compared with a 0.1% increase in the placebo group. The proposed NKF-K/DOQI target for Ca x P is ≤ 55 $(mg/dL)^2$. The mean Ca x P value during the efficacy-assessment phase was 51 $(mg/dL)^2$ for the cinacalcet group vs. 59 $(mg/dL)^2$ for the placebo group.

One of the main effects of cinacalcet treatment is lowering of serum calcium levels. In subjects with secondary HPT associated with end stage renal disease, the mean serum calcium concentration was reduced by 7 % in the cinacalcet group, compared with a < 1% increase in the placebo group.

VII. Integrated Review of Safety

COMMENT: Because of the differences in patients with secondary hyperparathyroidism and primary hyperparathyroidism, both in the mechanism of the disease and protocol designs, an integrated review of safety for these 2 groups in inappropriate. Because only one study was performed in patients with parathyroid carcinoma an integrated review is not necessary. Please see the appendix for a complete review of study 20000204.

VII.A. Description of Patient Exposure

As shown in the following table, the average number of weeks patients were treated with doses of 30 mg – 120 mg was approximately 7 weeks. Subjects were exposed to 180 mg of cinacalcet for nearly 13 weeks on average.

		Cinacalcet					
Exposure (weeks)	Placebo (N = 470)	30 mg (N = 656)	60 mg (N = 590)	90 mg (N = 472)	120 mg (N = 363)	180 mg (N = 272)	Any Dose (N = 656)
Exposure							
n	470	656	590	472	363	272	656
Total Weeks	14174	4586	3877	3426	2443	3484	17501
Mean (SE)	30.2 (0.7)	7.0 (0.3)	6.6 (0.2)	7.3 (0.3)	6.7 (0.3)	12.8 (0.6)	26.7 (0.5)
Median (Min, Max)	26.0 (1, 56)	4.0 (1, 52)	4.0 (1, 45)	4.0 (1, 40)	4.0 (1, 43)	10.0 (1, 45)	26.0 (1, 59)

VII.B. Methods and Specific Findings of Safety Review

The focus of this safety review is the pooled data from the core studies 20000172, 20000183, and 20000188, 6-month, placebo-controlled phase 3 trials of patients with ESRD receiving dialysis. Analyses of data from study 20010240, a double-blind, six-month extension of patients who completed studies 20000172, 20000183, and 20000188, is also examined. A total of 1136 patients were enrolled into the core 6-month studies (1126 received at least one dose of study medication), with 266 of them rolling over into the 6-month extension study.

A total of 115 subjects with pre-dialysis CKD were enrolled into two studies, 20000236 and 20010239, and treated with cinacalcet or placebo for 16 and 18 weeks, respectively. In general, this review will only discuss the safety data from these two studies if they differ significantly from the findings from ESRD studies 172, 183, and 188.

VII.B.1.Deaths: All deaths that occurred on-study and within 30 days of discontinuation, withdrawal, or completion of the study were recorded.

Core 6-Month Studies

A total of 15 (3%) subjects randomized to receive placebo and 14 (2%) randomized to cinacalcet died during the core 6-month studies. The causes of death in the cinacalcet-treated patients were not unusual for a population of patients with CKD requiring dialysis.

VII.B.2. Other Serious Adverse Events

Core 6-Month Studies

For the purposes of this review, a serious adverse event (experience) or reaction was any untoward medical occurrence that at any dose resulted in death, was life-threatening, required or prolonged hospitalization, resulted in significant disability/incapacity, or was a congenital anomaly/birth defect.

The overall incidence of SAEs was 31% in the placebo group and 29% in the cinacalcet group. No individual serious adverse event occurred in more than 2% of subjects. The most common

serious adverse events included (placebo, cinacalcet) vascular access thrombosis (2%, 2%), pneumonia (2%, 2%), sepsis (2%, 2%), and non-cardiac chest pain (<1%, 2%).

Serious events of cardiac arrest occurred in 1% of subjects in each treatment group (6 placebo, 9 cinacalcet). Cardiac arrest was fatal in 10 subjects (3 [< 1%] placebo and 7 [1%] cinacalcet).

6-Month Extension Study

The incidence of serious adverse events was similar across treatment groups in the phase 3 extension study (32% placebo, 34% cinacalcet). The most common serious adverse events were (placebo, cinacalcet) infection (3%, 3%), vascular access thrombosis (2%, 3%), gastrointestinal hemorrhage (1%, 3%), cardiac chest pain (4%, 2%), pulmonary edema (3%, 2%), access infection (3%, 1%), and cardiac arrest (3%, 1%).

VII.B.3. Dropouts and "Other Significant Adverse Events"

Core 6-Month Studies

Withdrawals due to adverse events occurred in 8% of subjects receiving placebo compared with 15% of subjects receiving cinacalcet. The most common individual events leading to withdrawal (placebo, cinacalcet), were nausea (1%, 5%), vomiting (< 1%, 4%), diarrhea (< 1%, 2%), and abdominal pain (< 1%, 2%).

6-Month Extension Study

The most common causes of withdrawal due to adverse events were (placebo, cinacalcet) nausea (1%, 6%), vomiting (<1%, 5%), diarrhea (<1%, 2%) and abdominal pain (<1%, 2%). See Appendix XI.A.1.

CKD Pre-Dialysis Studies

Of note, in studies 236 and 239, none of the placebo patients withdrew because of hypocalcemia, whereas 4/47 (7%) cinacalcet subjects withdrew due to low serum calcium levels.

Because nausea and vomiting are the most commonly-reported drug-related adverse events in patients taking cinacalcet, a more detailed analysis of these events is provided below. Other adverse events of special interest because of either preclinical or phase 3 findings include hypocalcemia, seizures, cardiac repolarization, and serum testosterone levels.

Nausea And Vomiting

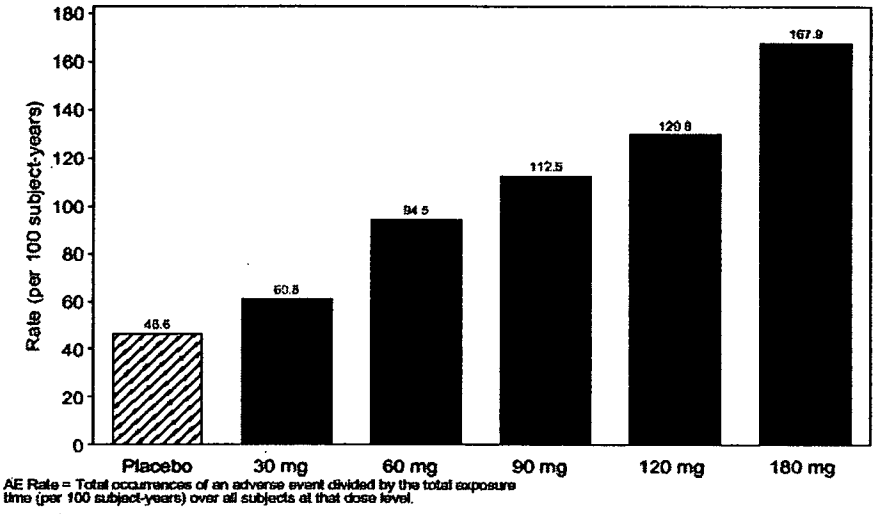
Core 6-Month Studies

The incidence of nausea in the cinacalcet groups was slightly higher during the first two months of treatment (9%) compared with subsequent 4-week intervals of drug therapy (3% to 7%). The incidence of vomiting, on the other hand, ranged from less than 1% to 8% during all 4-week intervals of treatment.

When nausea and vomiting were analyzed by severity, more cinacalcet-treated patients vs. placebo-treated subjects had moderate or severe experiences.

The mean duration of nausea in days was 18 and 22 for placebo and cinacalcet, respectively. The median duration of nausea in days was 2 and 4, respectively, with ranges of 1 to 185 and 1 to 186 days, respectively. The mean duration of vomiting in days was 11 and 16 for placebo and cinacalcet, respectively. The median duration was 1 and 3 days, respectively, with ranges of 1 to 183 and 1 to 186, respectively.

As noted earlier in the review, there was no dose-response for nausea in cinacalcet-treated patients, but there was a clear dose-response for vomiting, as shown in the following figure.



The following table provides information regarding actions taken in response to reports of nausea and vomiting. Not surprisingly, more actions had to be taken in response to the nausea and vomiting in the cinacalcet-treated patients than the placebo-treated subjects.

Subject Incidence of Nausea and Vomiting by Action Taken (Phase 3 ESRD Safety Subjects)

Preferred Term / Action Taken	Placebo N = 470 n (%)	Cinacalcet N = 656 n (%)
Nausea	91 (19)	204 (31)
Test Article Dose Altered	9 (2)	49 (7)
Test Article Discontinued	5 (1)	36 (5)
Hospitalization	1 (<1)	5 (<1)
Medication Taken	24 (5)	48 (7)
Removed from Study	5 (1)	33 (5)
Other Action	14 (3)	27 (4)
No Action Taken	63 (13)	100 (15)

Subject Incidence of Nausea and Vomiting by Action Taken (Phase 3 ESRD Safety Subjects)		
	Placebo	Cinacalcet
Vomiting	69 (15)	178 (27)
Test Article Dose Altered	5 (1)	40 (6)
Test Article Discontinued	3 (<1)	31 (5)
Hospitalization	2 (<1)	6 (<1)
Medication Taken	17 (4)	47 (7)
Removed from Study	3 (<1)	29 (4)
Other Action	11 (2)	23 (4)
No Action Taken	48 (10)	103 (16)

Hypocalcemia

For each 1 g/dL decrease in albumin below 4 g/dL, the serum calcium value was increased by 0.8 mg/dL. Because a reduction in serum calcium is an expected effect of cinacalcet, an algorithm for evaluation and treatment of hypocalcemia was pre-defined (see Appendix XI.A.2.). All blood samples were taken pre-dialysis.

Core 6-Month Studies

The mean baseline serum calcium levels were 9.9 mg/dL in both treatment groups. The mean weekly serum calcium level remained stable in the placebo group and decreased by approximately 5% to 7% below baseline in the cinacalcet group.

Approximately 25% of placebo patients and 65% of cinacalcet patients developed at least one serum calcium level < 8.4 mg/dL. A similar pattern of hypocalcemia in drug vs. placebo-treated patients was noted in analyses stratified by baseline iPTH levels and Ca x P products.

In the event that a patient developed a serum calcium level < 8.4 mg/dL, the protocol specified that investigators had the option of, first increasing calcium intake (i.e., phosphate binder), second, increasing the dose of vitamin D, and third, withholding study drug.

As shown in the following table, a slightly larger percentage of patients treated with cinacalcet compared with placebo, had increases in their doses of calcium-based phosphate binders in response to hypocalcemia.

	Placebo N = 470 n (%)	Cinacalcet N = 656 n (%)
Serum calcium <8.4 mg/dL	116	433
Action Taken		
Calcium containing phosphate binder increase	39 (34)	175 (40)
Vitamin D increase	50 (43)	188 (43)
Neither of above actions taken	48 (41)	153 (35)

In an analysis of the percentage of patients who developed 2 consecutive serum calcium levels below 7.5 mg/dL, 0.9% of placebo patients and 5% of cinacalcet subjects met this criterion.

The incidence of 2 consecutive low serum calcium levels was similar for the 30 mg through the 180 mg doses of cinacalcet.

Shown in the Appendix XI.A.3 is a list of adverse events that could be associated with hypocalcemia. Forty percent of cinacalcet and 39% of placebo subjects reported an adverse event possibly associated with hypocalcemia. The only adverse events from this list that occurred with an incidence of at least 2% in the cinacalcet group and a higher incidence than placebo were (placebo vs. cinacalcet): myalgia (14% vs. 15%), asthenia (4% vs. 7%), hypoesthesia (3% vs. 4%), paresthesia (1% vs. 4%), and muscle weakness (1% vs. 2%).

6-Month Extension Study

During the 6-months of extended placebo-controlled treatment, 5% of cinacalcet-treated patients and none of the placebo patients developed at least one episode of hypocalcemia.

Pre-Dialysis CKD Studies

In study 236, 47% of cinacalcet patients and none of the placebo patients developed hypocalcemia. In study 239, 15% of cinacalcet and 4% of placebo subjects developed hypocalcemia.

In an analysis of pooled data from the two pre-dialysis studies, the mean baseline serum calcium levels were approximately 9.5 in both groups. The mean changes from baseline to Week 16 were –0.2 mg/dL and –1.0 mg/dL in the placebo and cinacalcet groups, respectively.

Six percent of cinacalcet subjects and none of the placebo subjects developed a serum calcium level below 7.5 mg/dL. Of these 6%, 37 % had a serum calcium level between 7.5 mg/dL – 8.0 mg/dL at more than 2 lab draws, 29% had a serum calcium level between 7.5 mg/dL – 8.0 mg/dL at the next lab draw; and 18% had a serum calcium level between 7.5 mg/dL – 8.0 mg/dL at 2 lab draws.

COMMENT: The much higher incidence of hypocalcemia in the cinacalcet-treated patients in study 236 compared with study 239 was due to lower baseline levels of iPTH and a more aggressive treatment scheme.

Seizures

Core 6-Month Studies

According to Amgen, a comprehensive search of the phase 3 database was conducted to identify adverse events that could indicate seizure. The search included the following WHOART preferred terms: Aura Convulsions, Convulsions Aggravated, Convulsions Febrile, Convulsions Grand Mal, Convulsions Local, Convulsions Neonatal, Epileptic Aura, Status Epilepticus.

Five percent of patients in the cinacalcet and placebo groups reported having a history of seizures at baseline. Eleven (2%) of the cinacalcet subjects experienced at least one seizure,

whereas 2 (0.4%) of the placebo subjects had at least one seizure during the trials (nominal p = 0.054) (see Appendix XI.A.4). Five of the 11

cinacalcet-treated subjects who experienced an on-study seizure had a previous history of a seizure disorder. Of these 5 subjects, 3 had one or more clinical conditions that were *possible* confounding factors, such as subdural hematoma secondary to head trauma; ventriculo-peritoneal shunt and concurrent urinary tract infection; isoniazid administration; promethazine administration; cefazolin administration;. Despite a history of convulsions, only 2 of the 5 subjects were on anticonvulsant medications at the time of study enrollment. The 2 placebo subjects who experienced convulsions had a history of convulsions and were on anticonvulsant medications at the time of study enrollment.

In toxicology studies, convulsions associated with acute and severe reductions in serum calcium were observed in rats and dogs at the highest cinacalcet dose levels. As shown in the Table in the Appendix, 4 of the cinacalcet subjects had low serum calcium levels at some point prior to or following the reported seizure.

Of the 11 cinacalcet subjects who reportedly suffered an on-study seizure, 2 were receiving 30 mg, 3 were receiving 60 mg, 2 were receiving 90 mg, 3 were receiving 120 mg and 1 was receiving 180 mg at the time of the seizure.

No studies have been done to examine whether cinacalcet induces the activity of enzymes that metabolize common anti-seizure medications.

COMMENT: With the available data, it's not possible to accept or reject the hypothesis that cinacalcet increases the risk for seizure. If the drug does in fact increase the risk for seizure, it most likely does so by way of hypocalcemia. Despite the uncertainty of a cause and effect relationship between cinacalcet and seizures, several measures should be taken in response to the findings from the phase 3 CKD studies. First, a series of *in vitro* enzyme induction studies should be conducted to determine whether cinacalcet increases the activity of enzymes known to metabolize common anti-seizure medication. Second, the Warnings section of the labeling should include a clear description of the seizure findings from Studies 172, 183, and 188, along with a recommendation that serum calcium levels be closely monitored, particularly in patients with a known seizure disorder. Third, following approval, Amgen should commit to providing the Division with regular (i.e., semi-annual) analyses of all seizure data from cinacalcet clinical trials and MedWatch reports.

VII.B.4. Laboratory Findings

Core 6-Month Studies

Chemistry Parameters: The following table provides the mean percent changes from baseline to Week 26 in various routine chemistry parameters. The only parameter that was significantly different between groups was alkaline phosphatase. The reduction in the cinacalcet group likely reflects the reduction in bone formation, and the expected decrease in bone specific alkaline phosphatase levels. This would be considered a favorable response to cinacalcet treatment.

Serum Chemistry Parameters – Mean Percent Change From Baseline to Week 26		
	Placebo	Cinacalcet
Alk Phos*	13.2%	3.1%
Total Bilirubin	9.2%	8.3%
BUN	4.7%	3.1%
Creatinine	7.4%	-1.0%
Sodium	-0.18%	-0.01%
Potassium	0.8%	3.2%
Bicarbonate	4.7%	7.1%
SGOT	7%	16%
SGPT	15%	32%

*P<0.001

Hematology Parameters: The mean values for hematocrit, hemoglobin, platelets, and white blood cells were the same at baseline in both treatment groups. The mean values for these parameters changed very little from baseline to Week 26 within and between treatment groups.

Shift Analyses

Aside from serum creatinine and calcium , there were no clinically significant differences between placebo and cinacalcet in the shift analyses of routine chemistry and hematology parameters.

While 22% of cinacalcet-treated patients who had a grade 3 increase (>2.5-5.0xUL) in serum creatinine at baseline had at least one grade 3 abnormality during the trials, only 10% of placebo-treated subjects met these criteria.

Two of 470 placebo patients and 8 of 656 cinacalcet patients developed at least one SGPT value that was > 2x ULN. Two of 656 subjects and none of the placebo patients developed at least one SGPT value that was > 3x ULN.

The narratives for the two cinacalcet patients who developed SGPT values > 3x ULN are provided below.

Subject 16302 was a 64-year-old man with past medical history significant for diabetes mellitus, hypertension, peripheral vascular disease, myocardial infarction, coronary artery disease, and congestive heart failure. The subject had been maintained on hemodialysis for 1.5 years prior to study enrollment. Baseline PTH and serum calcium were 972 pg/mL and 10.6 mg/dL, respectively. At entry into the study, the subject was randomized to Cinacalcet and achieved a daily dose of 90 mg. Day 1 SGOT/SGPT values were 15/19 U/L. The subject was hospitalized for hyperkalemia during week 9. The following day, he experienced a cardiac arrest that was considered unrelated to study drug and was removed from study. The week 10 (early termination) SGOT/SGPT values were 203/680 U/L. The elevated liver enzymes were not reported as an adverse event. Concomitant medications during the study included, but were not limited to paracetamol, and acetylsalicylic acid. Elevated liver enzymes after a severe episode of hypotension, such as occurs during cardiac arrest (i.e, shock liver) are common due to low perfusion of liver tissue. Subject 16302 terminated from study 20000172 early on [redacted] 2002. At this time, elevations in both SGPT and SGOT for subject 16302 were observed (680 U/L and 203 U/L,

respectively). On ——— 2002, the SGPT and SGOT levels were both within normal limits (39 U/L and 18 U/L, respectively).

Subject 13910 was a 44-year-old woman with past medical history significant for diabetes mellitus, hypertension, peripheral vascular disease, coronary artery disease and congestive heart failure. The subject had been maintained on hemodialysis for 6 months prior to study enrollment. Baseline PTH and serum calcium were 674 pg/mL and 9.3 mg/dL, respectively. At entry into the study, the subject was randomized to Cinacalcet and achieved a daily dose of 180 mg. Day 1 SGOT/SGPT values were12/8 U/L, respectively. Week 16 and 26 SGOT/SGPT values were 10/10 and 193/208 U/L, respectively. The elevated liver enzymes were not reported as an adverse event. The subject received several medications known to be associated with increased liver enzymes (i.e., Augmentin™, Skelaxin™, and Elavil™) within several weeks prior to the assessment of liver enzymes. The subject also experienced rejection of a prior kidney transplant and kidney removal 2 weeks before the elevated liver enzymes. The elevation in SGPT for subject 13910 was observed while the subject participated in study 20000188. The subject completed study 20000188 on ——— 2003 and enrolled in open-label study 20020158 where the subject continued to receive cinacalcet. The SGPT and SGOT levels resolved spontaneously while on treatment, and were within normal limits (9 U/L and 21 U/L, respectively) at week 8 of the study 20020158, the first time they were measured after the elevated levels in study 20000188 were reported. The subject was receiving a cinacalcet dose of 120 mg at this time.

The largest absolute value observed for SGOT was 199 U/L in a cinacalcet subject. The narrative for this patient is provided below.

Subject 11407 was a 64-year-old woman with past medical history significant for hypertension. The subject had been maintained on hemodialysis for 4 years prior to study enrollment. Baseline PTH and serum calcium were 587 pg/mL and 10.0 mg/dL respectively. Day 1 SGOT and SGPT were 29 and 28 U/L, respectively. At entry into the study, the subject was randomized to cinacalcet and achieved a daily dose of 120 mg. The subject was hospitalized week 21 for dehydration. SGOT was 11 U/L at week 16 and 228 U/L at week 26. SGPT was 10 U/L at week 16 and 109 U/L at week 26. The elevated liver enzymes at week 26 were reported as an adverse event, considered related to study drug. Repeat liver function tests 4 days later while the subject was still receiving cinacalcet in the extension study (20020158) were within normal limits. Concomitant medication during the study included paracetamol, panadeine with codeine, rofecoxib, midodrine, and celecoxib. The subject also received a second dose (first dose given one month prior) of hepatitis B vaccine the same day the liver enzymes were elevated. Dehydration and concomitant administration of midodrine and hepatitis B vaccine were considered possible contributing factors.

COMMENT: Given the multiple potential confounding factors described in the cases above, it is unlikely that cinacalcet was the sole cause of the elevated transaminase levels. The safety database does not include any evidence that cinacalcet is a significant hepatotoxin.

VII.B.5. Vital Signs

Core 6-Month Studies

Systolic Blood Pressure: The mean baseline systolic blood pressures in the placebo and cinacalcet groups were 144 mmHg and 143 mmHg, respectively. The mean changes from baseline to Week 26 were 0.0 mmHg and –1.0 mmHg, respectively.

Diastolic Blood Pressure: The mean baseline diastolic blood pressures in the placebo and cinacalcet groups were 79 mmHg and 80 mmHg, respectively. The mean changes from baseline to Week 26 were 1.0 mmHg and 0.0 mmHg, respectively.

Heart Rate: The mean heart rates in the placebo and cinacalcet groups were 78 bpm and 79 bpm, respectively. The mean changes from baseline to Week 26 were –0.4 bpm and –2.4 bpm, respectively.

Body Weight: The mean body weights in the placebo and cinacalcet groups were 78 kg and 79 kg, respectively. The mean percent changes from baseline to Week 26 were 0.6% and 0.5%, respectively.

VII.B.6. Electrocardiograms

Although in vitro and preclinical studies do not provide consistent evidence that clinical doses of cinacalcet prolong the QT interval, one would expect the drug to have a degree of QT prolonging action because it tends to lower serum calcium levels.

In a HERG channel assay, relative to 100% block from the positive control drug Dofetilide, the mean channel block from 500 ng/mL of cinacalcet was 12%.

Electrocardiogram (ECG) data were collected on a large portion of the 1126 patients who took part in the three, 6-month phase 3 CKD – dialysis studies. The mean QT_{cb} intervals at baseline were 426 ms and 427 ms in the placebo and cinacalcet patients, respectively. The mean changes in QT_{cb} from baseline to Endpoint were 4.4 ms and 5.7 ms in the placebo and cinacalcet groups, respectively. It is important to note that the follow up ECGs were obtained at trough levels of study drug.

The following table provides the percentage of patients within each category of change in QT_{cb} from baseline to Endpoint.

Category of Change in QT_{cb} from Baseline to Endpoint

Endpoint	Placebo n = 470	Cinacalcet n = 656
Decrease	46%	42%
Increase < 30 ms	34%	37%
Increase 30 – 60 ms	15%	17%
Increase > 60 ms	5%	4%
> 450 ms (♂) > 470 ms (♀)	21%	24%
> 500 ms	3%	3%

The following table provides the proportion of subjects with normal baseline QT_{cb} intervals but prolonged QT_{cb} intervals [> 450 ms (♂) > 470 ms (♀)] by serum calcium levels at Week 14/18 and Week 26.

Proportion of subjects with normal baseline QT_{cb} intervals but prolonged QT_{cb} intervals by serum calcium levels		
Calcium Level	**Placebo n = 470**	**Cinacalcet n = 656**
Week 14/18		
< 7.5 mg/dl	0.3%	0.9%
≥ 7.5 to < 8.4 mg/dl	0.6%	6%
≥ 8.4 to 10.3 mg/dl	7%	9%
> 10.3 mg/dl	3%	2%
Week 26		
< 7.5 mg/dl	0%	0.2%
≥ 7.5 to < 8.4 mg/dl	1%	3%
≥ 8.4 to 10.3 mg/dl	9%	11%
> 10.3 mg/dl	3%	2%

The table below provides the proportion of subjects with QT_{cb} intervals > 500 ms by serum calcium levels at Week 14/18 and Week 26.

Proportion of subjects with QT_{cb} intervals > 500 ms by serum calcium levels		
Calcium Level	**Placebo n = 470**	**Cinacalcet n = 656**
Week 14/18		
< 7.5 mg/dl	0%	0.2%
≥ 7.5 to < 8.4 mg/dl	0.2%	2%
≥ 8.4 to 10.3 mg/dl	2%	1%
> 10.3 mg/dl	0.5%	0.2%
Week 26		
< 7.5 mg/dl	0%	0.2%
≥ 7.5 to < 8.4 mg/dl	0%	2%
≥ 8.4 to 10.3 mg/dl	3%	0.6%
> 10.3 mg/dl	0.5%	0.4%

In a multivariate logistic regression analysis, the following variables were statistically significant predictors of QT_{cb} at Week 26: baseline QT_{cb}, serum calcium, age, history of diabetes, Black race, and history of CHF. Gender, treatment with placebo or cinacalcet, and study (172, 183, 188) were not significant predictors of QT_{cb} in this statistical model.

COMMENT: Based on cinacalcet's mechanism of action to lower serum calcium levels, one would predict that the drug would be associated with a prolongation of the QT interval. And the data from the phase 3 CKD – dialysis studies do suggest that cinacalcet increases the mean QT_c interval by a very small amount compared with placebo. There were no significant differences between groups in the percentage of patients who developed QT_{cb} values > 500 ms, however.

A few caveats need to be considered when evaluating these data. The ECGs were obtained at trough, rather than peak drug levels; the nadir for PTH concentrations is 2-6 hours post-dose and corresponds with the C_{max} for cinacalcet; the nadir for serum calcium levels is unknown because the changes are generally very small and transient (one can assume that the calcium nadir follows the nadir for PTH); and the Endpoint ECGs were obtained in patients who were taking cinacalcet doses ranging from 30 mg to 180 mg QD.

The preclinical and clinical data, while admittedly not ideal, do not indicate that cinacalcet has the potential to significantly prolong cardiac repolarization. If properly designed, a thorough QT study would allow one to separate the intrinsic effect of Cinacalcet on the QT interval (if one exists) vs. effects due to changes in serum calcium concentrations – the mechanism likely to explain any QT prolongation.

Given the weak signal for QT prolongation and the significant percentage of CKD – dialysis patients who were able to concomitantly lower iPTH and the Ca x P ion product while on cinacalcet vs. placebo, the risk-to-benefit profile in dialysis patients supports the post-approval conduct of a thorough QT study, particularly if approval is limited to dialysis patients and those with parathyroid carcinoma.

Cardio-Renal Consult

The following comments are excerpted from a consult conducted by Dr. Norman Stockbrigde of the Division of Cardio-Renal Drug Products.

"Doses in phase I-III studies ranged up to 180 mg once-daily or 90 mg four-times-daily. Peak levels are reached after about 4 hours and the primary half-life is about 6 hours. Factors potentially affecting plasma levels include renal failure, 3A4 inhibition, and 1A2 inhibition.

Sparse QT data were obtained in numerous studies. For post-phase I studies, the synopses are not adequate to describe the timing of the ECGs. Most or all of the QT data appear to have come from automated reading. The sponsor's analyses of QTcB by dose or plasma level detected no signal (mean or outlier), although it is not possible to quantify the magnitude of mean signal that could have been missed. The sponsor was, however, able to detect an effect of serum calcium on QTcB, about -10 ms per mg/dL. As the sponsor acknowledges, this effect may not be innocuous.

Safety data apparently reveal no adverse events with a clear relationship to QT effects, not surprising for a database as small as this.

A thorough evaluation of QT effects would appear to be quite relevant. Such a study ought to include a dosing regimen that challenges tolerability, allows for production of metabolites, has ECGs timed to, at least, peak plasma levels of parent and major metabolites, and includes an assay validation. To differentiate effects of hypocalcemia from true drug effects, this study might need external control of plasma calcium levels."

VII.B.7. Special Studies

Hormone Evaluation

In a one-year monkey study in which animals received placebo or cinacalcet 5 mg/kg/day, 50 mg/kg/day, or 100 mg/kg/day, decreased levels of serum testosterone and T3 and increased levels of T4 were noted. Levels of TSH did not change.

To further investigate these observations, levels of TSH, T4, testosterone, LH, and FSH were evaluated at baseline and Weeks 16 and 26 in clinical study 188, one of the 6-month phase 3 trials of ESRD patients.

TSH: In male patients, the mean baseline levels of TSH were similar, 1.59 uU/ml and 1.61 uU/ml, in placebo and cinacalcet, respectively. The mean changes from baseline to Week 26 were 0.08 uU/ml and 0.09 uU/ml, respectively. In female patients, the mean baseline levels of TSH were 1.92 uU/ml and 6.75 uU/ml in the placebo and cinacalcet groups, respectively (3 subjects in the Cinacalcet group had extremely high TSH values leading to a significant increase in the mean baseline value).

Of the patients with TSH levels within normal at baseline, none of the cinacalcet subjects had an above normal level at Weeks 16 and 26, while one placebo subject had an above normal TSH value at Week 16 or 26. Two cinacalcet and two placebo subjects with normal baseline TSH levels had levels below normal at Weeks 16 and 26.

T4: The mean baseline T4 levels were approximately 0.85 ng/dL in the male and female placebo and the male and female cinacalcet subjects. At Week 26 the mean levels of T4 decreased by 0.03 ng/dL in male placebo patients and increased by 0.02 ng/dL in male cinacalcet subjects. At Week 26 the mean T4 levels decreased by 0.05 ng/dL in female placebo subjects and increased by 0.03 ng/dL in female cinacalcet subjects. Five percent of cinacalcet subjects who had normal baseline T4 levels had an abnormally low value at Week 26, while 4% of placebo subjects with normal baseline T4 level had a low level at Week 26.

None of the patients in either treatment group had abnormal TSH and T4 values at Week 26.

COMMENT: These data on thyroid hormones do not confirm the findings from the preclinical study in non-human primates.

Serum Testosterone: In a long-term monkey study, serum testosterone levels were noted to have decreased significantly in the Cinacalcet compared with the placebo-treated animals. To evaluate this finding further, Amgen measured serum levels of total testosterone, free testosterone, LH, and FSH in 240 men who participated in Study 188.

Baseline levels of total and free testosterone were similar in the two groups. The median changes from baseline to Week 26 in total testosterone were 2 pg/ml and –49 pg/ml in the placebo and Cinacalcet groups, respectively (nominal p=0.0004); the median changes from Baseline to Week

26 in free testosterone were –8 pg/ml and –18 pg/ml in the placebo and Cinacalcet groups, respectively (nominal p=0.02).

Baseline levels of LH were similar in the two groups: approximately 11.3 mIU/ml. The mean values at Week 26 were 12.3 mIU/ml and 9.9 mIU/ml in the placebo and Cinacalcet groups, respectively. There were very small, insignificant changes in the levels of FSH from baseline to Week 26 in both groups.

COMMENT: Abnormalities in the hypothalamic-pituitary-gonadotropin axis are well documented in male patients with CKD receiving dialysis. Reduced libido and erectile dysfunction are two common manifestations of this altered endocrine milieu. The data presented above confirm the preclinical findings and indicate that treatment of male patients with cinacalcet lowers total and free testosterone. Given the abnormal endocrine profile of male dialysis patients, it may be difficult to assess the clinical significance of modest cinacalcet-induced reductions in testosterone levels. Nevertheless, future long-term studies (i.e., > 1 year) should, at a minimum, include assessments of bone mineral density and sexual function in male dialysis patients taking cinacalcet.

VII.C. 120-Day Safety Update

Significant safety data from 6 ongoing cinacalcet trials are provided in this report. October 1, 2003, is the cutoff date.

At the time of the original NDA submission, 4 open-label, uncontrolled clinical studies were ongoing: 2 studies in subjects with secondary HPT (studies 20000130 and 20020158), 1 study in subjects with primary HPT (study 20000159), and 1 study in subjects with parathyroid carcinoma or intractable primary HPT (study 20000204). In addition, subject enrollment was ongoing for studies 20020158 and 20000204. For these studies, safety data were provided up to prespecified cutoff dates (28 February 2003 for studies 20000130, 20000159, and 20020158 and 31 January 2003 for study 20000204). Subsequently, 2 additional open-label clinical studies in subjects with secondary HPT were initiated (studies 20020389 and 20020390), which have currently enrolled a total of 65 subjects.

Because the studies are currently ongoing, the presentation of safety information in this document is limited to deaths, serious adverse events, and adverse events leading to withdrawal. The serious adverse event information summarized here has been derived from the current Amgen safety database, and not all information has been source document verified.

For study 20000204, a study supporting the use of cinacalcet in the treatment of hypercalcemia in subjects with parathyroid carcinoma or intractable primary HPT, 14 additional subjects have enrolled since the original data cutoff for the NDA, which included 15 subjects. An analysis has been conducted for the key safety and efficacy data that includes all 29 subjects who have participated in the study to date.

A total of 667 patients (255 newly exposed) have been exposed to study drug during this Safety Update period. The vast majority of these patients have secondary HPT.

The following table provides the number of deaths, serious AEs, and AEs leading to study withdrawal – all patients are receiving cinacalcet in the ongoing studies.

	Number (%) of Subjects Reporting Events		
	Deaths	Serious Adverse Events	Adverse Events Leading to Withdrawal
Secondary HPT studies			
20000130 (N = 83)	0	35 (42)	3 (4)
20020158 (N = 460)	28 (6)	169 (37)	22 (5)
20020389 (N = 1)	0	0	0
20020390 (N = 64)	0	8 (12)	0
Primary HPT studies			
20000159 (N = 38)	0	4 (10)	1 (3)
20000204 (N = 21)	0	6 (28)	3 (14)
Total (N = 667)	28 (4)	222 (44)	29 (4)

N = number of subjects participating in the study during the reporting period
n = number of subjects reporting events

Hypocalcemia is an expected adverse event with use of cinacalcet. A review of investigator-reported preferred terms determined that serious adverse events of hypocalcemia were reported for 3 subjects (< 1%; 3/608) with secondary HPT receiving dialysis. These events were considered by the investigator to be related to study drug and are described below.

- Subject 17211704 (study 20020158): A 31-year-old woman with a history of hypertension was randomized into the 6-month study 20000172 (baseline serum calcium was 10.5 mg/dL) and reached a maximum dose of 180 mg of cinacalcet. She continued on 180 mg cinacalcet after enrolling in the 6-month 20010240 double-blind extension study. After completing study 20020240, the subject continued to receive cinacalcet during the open-label study 20020158 (baseline serum calcium was 9.6 mg/dL). The subject was hospitalized for hypocalcemia during week 26 of study 20020158 (180 mg cinacalcet; total cinacalcet exposure was approximately 1.5 years). Local laboratory serum calcium values at the time of the hospitalization ranged from 6.8 to 7.0 mg/dL. Symptoms included oral and bilateral palmar paresthesia and hypotension. Treatment included a reduction in the dose of cinacalcet to 120 mg and an increase in the calcium concentration of the subject's dialysis solution. The investigator reported that there was a reasonable possibility that the hypocalcemia may have been related to cinacalcet; subsequent investigation also determined that a low calcium dialysis solution may have been inadvertently used during dialysis just before the event. The patient remained on study, the dose of cinacalcet was subsequently increased to the previous amount of 180 mg/day, and serum calcium was 9.5 and 9.4 mg/dL at weeks 28 and 44, respectively.

- Subject 18335101 (study 20020158): A 40-year-old man with a history of hypertension was randomized to placebo in the 6-month study 20000183 (baseline serum calcium was 9.7 mg/dL). The subject subsequently enrolled into study 20020158 and received cinacalcet (baseline serum calcium was 9.7 mg/dL). He was hospitalized with nausea, vomiting, and difficulty walking approximately 5 weeks after initiating cinacalcet and 3 days after commencing metoclopramide at a dose of 10 mg three times daily. Serum calcium at admission was 8.7 mg/dL. Metoclopramide and cinacalcet were discontinued, biperiden and calcium were administered, and the patient received peritoneal dialysis.

Within 5 hours, the serum calcium was 11.5 mg/dL. Persistent cervical and jaw muscle spasms described as tetany and orolingual paresthesias led to tracheostomy. Over the next 4 days, the tracheostomy was closed and the subject's serum calcium ranged from 8.3 to 11.4 mg/dL, and the serum calcium at the time of discharge was 7.4 mg/dL. The investigator reported that there was a reasonable possibility that the events may have been related to cinacalcet. Metoclopramide has a 1 in 500 event rate of extrapyramidal symptoms, which may rarely include tetany.

- Subject 18813101 (study 20020158): A 49-year-old man with a history of hypertension, and alcoholic liver cirrhosis was randomized to placebo in the 6-month study 20000188 (baseline serum calcium was 9.3 mg/dL). He subsequently enrolled into study 20020158 and received cinacalcet (baseline serum calcium was 9.3 mg/dL). During week 13, he was hospitalized with bilateral leg pain and numbness, difficulty walking, hyperkalemia, hypocalcemia, and hypertension. The dose of cinacalcet at the time of the events was 120 mg. Corrected serum calcium was 8.0 mg/dL upon hospitalization. One week before hospitalization, the corrected serum calcium was 8.6 mg/dL. On-study serum calcium ranged from 7.7 (weeks 3, 20) to 9.2 mg/dL (week 8). Treatment included calcium replacement therapy (calcium acetate 2000 mg), dialysis, antihyperkalemics, and antihypertensives. The investigator reported that the subject's underlying ESRD and noncompliance with oral calcium and vitamin D supplements were possible etiologies and that the events may also have been related to cinacalcet. Cinacalcet was discontinued during these events, and the serum calcium concentration was 8.4 mg/dL at hospital discharge. At week 20, the subject was removed from study by the investigator for hypocalcemia (serum calcium was 7.7 mg/dL) and an abnormal gait.

Nausea and vomiting were two common AE that led to withdrawal from the studies.

Of the 667 subjects participating in cinacalcet clinical trials since the NDA data cutoff, 255 subjects have been newly exposed to cinacalcet. A total of 28 (4%) subjects died during this reporting period, all of whom were subjects with secondary HPT. The causes of death were consistent with this subject population's baseline comorbid conditions and with causes of death in patients with ESRD (e.g., cardiovascular events and infectious events). The incidence and causes of death were also similar to those described in the original NDA. The most frequently reported serious adverse events during this period, included events of infection, cardiovascular disease, gastrointestinal disorders, and vascular access complications. These serious adverse events are similar in nature and frequency to serious adverse events reported in the original NDA. The most common adverse events leading to withdrawal involved the gastrointestinal system, which was similar to that reported in the NDA.

COMMENT: The safety information presented in this Safety Update is consistent with the safety profile of cinacalcet that emerged from the data from the original NDA submission.

VII.D. Safety Conclusions

Nausea and vomiting were the two most commonly reported adverse events and the most frequent reasons for premature withdrawal from the trials. Vomiting was dose-related, nausea was not.

The risk of hypocalcemia (< 8.4 mg/dL) is clearly increased in patients treated with cinacalcet. The risk does not appear to be dose-related, but is does appear higher in pre-dialysis vs. dialysis

patients. This is particularly true in pre-dialysis patients with relatively mild elevations in iPTH who are aggressively treated (i.e., goal iPTH < 65 pg/ml). In one study, nearly 50% of the cinacalcet patients developed hypocalcemia (serum calcium levels less than 7.5 mg/dl), whereas none of the placebo subjects became hypocalcemic.

There was an imbalance between the cinacalcet and placebo groups in the number of patients who reportedly suffered a "seizure" during the studies of patients with CKD who were receiving dialysis. It is unknown if this imbalance is a chance finding or reflects a true drug-induced risk, perhaps by way of hypocalcemia.

Regarding cardiac repolarization, limitations of the preclinical and clinical data do not allow for a comprehensive assessment of cinacalcet's potential to significantly prolong the QT interval. It is unclear if the minor QT prolongation observed in the phase-3 trials is due to lowering of serum calcium levels or to direct effects of cinacalcet or its metabolites.

VIII. Dosing, Regimen, and Administration Issues

The dosing of cinacalcet is much more complicated than that for most other drugs. This is due to the fact that the dose is titrated not only against a single endpoint, such as serum iPTH, but must also take into account changes in serum calcium and phosphate, and also adjustments in the doses of concomitantly used phosphate binders and vitamin D sterols.

One of the striking features of the cinacalcet phase-3 data was the wide range of doses patients with CKD and parathyroid carcinoma were taking at the end of the studies. For example, at the completion of the three, 6-month CKD – dialysis studies, 40% of patients were receiving 180 mg once-daily of cinacalcet, while the remaining 60% of subjects were equally divided among the 30 mg, 60 mg, 90 mg, and 120 mg doses. This may reflect a host of factors, including baseline iPTH and serum calcium levels, varying sensitivities to cinacalcet-induced nausea and vomiting, and varying rates of use of concomitant medications such as calcium supplements, phosphate binders, and vitamin D sterols.

IX. Use in Special Populations

IX.A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

A good gender distribution was achieved in the seven trials evaluating the safety and efficacy of cinacalcet use for treatment of primary HPT, secondary HPT associated with chronic renal insufficiency and secondary HPT associated with end stage renal disease. In the total population of 1339 subjects, 40% were women and 60% were men.

IX.B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Study participants ranged in age from 18 to 93 years. In the seven trials evaluating the safety and efficacy of cinacalcet, 27% of subjects were ≥ 65 years old and 10% were ≥ 75 years old. The racial distribution (55% Caucasian, 33% Black and 12% Other) in the overall study population is appropriately mixed. In the secondary HPT population, the distribution of Black subjects is slightly higher (35%), which is consistent with the distribution seen in patients with ESRD and