CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-688

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-688
Submission Date	September 5. 2003
Brand Name	SENSIPAR™
Generic Name	Cinacalcet HCl
Reviewers	S.W. Johnny Lau and Sang M. Chung
Team Leader	Hae-Young Ahn
OCPB Division	DPE II (HFD-870)
ORM Division	Metabolic and Endocrine (HFD-510)
Sponsor	Amgen
Relevant IND	56.010
Submission Type: Code	Original: P
Formulation; Strengths	30, 60, and 90 mg film coated tablets
Indications	To treat [redacted] secondary hyperparathyroidism in chronic kidney disease patients; to treat hypercalcemia in primary hyperparathyroidism and parathyroid cancer patients

1 Executive Summary

The sponsor submitted NDA 21-688 to seek approval for the 30, 60, and 90 mg cinacalcet oral tablets to treat [redacted] secondary hyperparathyroidism from chronic kidney disease and treat hypercalcemia from primary hyperparathyroidism and parathyroid carcinoma. Cinacalcet decreases parathyroid hormone release via modulating calcium receptors on the parathyroid gland. Cinacalcet is the 1st calcimimetic to seek U.S. marketing approval.

Briefly, the cinacalcet clinical pharmacology and biopharmaceutics information follows: Cinacalcet is well absorbed upon oral administration in humans. Cinacalcet has a mean steady state volume of distribution of 913 - 1235 L and is [redacted] bound to plasma protein(s). The ratio of red blood cells cinacalcet concentration to plasma cinacalcet concentration is [redacted] at a blood cinacalcet concentration of 10 ng/mL. Cinacalcet terminal half-life is 30 – 40 hours upon oral administration. Mean plasma cinacalcet clearance is 60.9 – 77.1 L/hr.

Cinacalcet pharmacokinetics is proportional upon oral 25 – 200 mg cinacalcet once daily oral administration to chronic renal impaired patients. However, cinacalcet exposure does not increase beyond the 200 mg oral dose. Cinacalcet pharmacokinetics does not appear to change with time upon multiple once daily oral administration. In general, steady state plasma cinacalcet concentrations are reached after 4 days of once daily oral administration and the mean accumulation ratio is 1.5 – 2.1 and 1.7 – 2.1 for cinacalcet C_{max} and $AUC_{(0-24h)}$, respectively. The median accumulation ratio is 1.2 – 3.7 and 2.3 – 4.6 for cinacalcet C_{max} and $AUC_{(0-24h)}$, respectively, upon twice daily oral administration.

Cinacalcet is metabolized by multiple enzymes, primarily cytochrome P450 3A4, 2D6, and 1A2. Cinacalcet is a strong cytochrome P450 2D6 inhibitor in vitro. The major plasma cinacalcet metabolites were hydrocinnamic acid and hydroxy-hydrocinnamic acid. Glucuronides of the dihydrodiol metabolites are also present in plasma. The major urinary metabolites are glycine conjugates of hydroxy-hydrocinnamic acid and glucuronides of the dihydrodiol metabolites. The calcimimetic activity of hydrocinnamic acid and hydroxy-hydrocinnamic acid are unknown.

Glucuronides of the dihydrodiol metabolites shows 333-fold less potent calcimimetic activity than cinacalcet. Cinacalcet is extensively metabolized and the metabolites are renally excreted.

Cinacalcet C_{max} and $AUC_{(0\text{-}inf)}$ are increased 82% and 68%, respectively, under a high-fat meal as compared to that under fasting conditions. The low-fat meal vs. fasting conditions indicates that the C_{max} and $AUC_{(0\text{-}inf)}$ are increased 65% and 50%, respectively. Cinacalcet C_{max} and $AUC_{(0\text{-}inf)}$ upon high-fat meal are 11% and 12% higher, respectively, than that for a low-fat meal.

The efficacy endpoints for the secondary hyperparathyroidism are proportion of patients achieved a mean reduction of parathyroid hormone to ≤ 250 pg/mL, proportion of patients achieved a ≥ 30% reduction in mean parathyroid hormone, and % change in serum Ca x P (calcium phosphorus product).

Since the maximum proportion of parathyroid hormone suppression (I_{max}) by cinacalcet has not been reached, the IC_{50} can not be reliably estimated in secondary hyperparathyroidism patients.

The starting 30 mg cinacalcet dose is chosen because this is the lowest effective dose to lower parathyroid hormone and the 180 mg highest dose is chosen because this dose is safe and effective and higher doses will not increase exposure for secondary hyperparathyroidism patients. The 30 mg twice daily dose to 90 mg 4 times daily dose are determined per experience with earlier calcimimetic in primary hyperparathyroidism and parathyroid carcinoma patients.

Cinacalcet blocks 11.7% (mean) of the hERG channel at 500 ng/mL. A 3-month monkey study shows QT prolongation by cinacalcet, whereas a 12-month monkey study shows no significant QT prolongation by cinacalcet. A multivariate linear regression analysis adjusting for age, gender, race, history of diabetes, history of congestive heart failure, and baseline QTc demonstrates a weak association (correlation = - 0.227) that the magnitude of the increase in QTc averages 6 msec for each 1 mg/dL reduction in serum calcium.

Per meta-analysis and population pharmacokinetic analysis, age, body weight, and body mass index do not show impact on cinacalcet pharmacokinetics. However, female shows a 40% lower apparent clearance than that for male and smokers show a 38% higher apparent clearance than that for nonsmokers. Race is a significant covariate of the central volume of distribution. These differences may not be clinical relevant since cinacalcet dose is titrated for individuals.

No trend exists that cinacalcet exposure increases with increasing degree of renal impairment from normal subjects to hemodialysis patients. Hemodialysis does not alter cinacalcet pharmacokinetics. Cinacalcet pharmacokinetics for patients receiving continuous ambulatory peritoneal dialysis is similar to that for hemodialysis patients and healthy volunteers. Cinacalcet $AUC_{(0\text{-}inf)}$s between healthy volunteers and mild hepatic impairment patients are comparable. However, cinacalcet exposures for moderate and severe hepatic impairment patients are 2.4 and 4.2 times higher, respectively, than that for healthy volunteers upon single 50 mg cinacalcet administration.

Coadministration with 200 mg ketoconazole twice daily increases 90 mg cinacalcet's exposure by about 2.3 times. No evidence exists for a pharmacokinetic interaction between cinacalcet and either pantoprazole, calcium carbonate, or sevelamer HCl.

Coadministration with 25 or 100 mg cinacalcet increases amitriptyline and nortriptyline's exposure by about 20% in cytochrome P450 2D6 extensive metabolizers. Coadministration with 25 or 100 mg cinacalcet does not appear to increase amitriptyline and nortriptyline's exposure in cytochrome P450 2D6 poor metabolizers. No evidence exists for pharmacokinetic and pharmacodynamic interactions between cinacalcet and warfarin.

Cinacalcet HCl is a Biopharmaceutics Classification System class 4 drug. The clinically tested 30, 60, and 90 mg cinacalcet tablets for the secondary hyperparathyroidism studies are identical to the to-be-marketed cinacalcet tablets, except the clinical formulation contains — tablet film coating and the to-be-marketed formulation contains — tablet film coating. The tablet film coating difference is acceptable via SUPAC-IR.

A. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the Clinical Pharmacology and Biopharmaceutics data of NDA 21-688 and it is acceptable. However, the recommended in vitro dissolution specification for the 30, 60, and 90 mg cinacalcet tablets is "Not less than — (Q = —) of the labeled amount of cinacalcet is dissolved in — minutes."

B. Phase IV Commitments

The followings issues should be addressed as Phase IV commitments, if NDA 21-688 will be approved:

- —
- The sponsor should conduct a clinical cinacalcet drug interaction study with preferred in vivo CYP2D6 substrate such as desipramine (*J Clin Pharmacol* 2003;43:443) to address cinacalcet's inhibition potential on CYP2D6. **Reasons:** Study 980234 examined the effect of cinacalcet on amitriptyline and nortriptyline pharmacokinetics to assess cinacalcet's inhibition potential on CYP2D6. However, the metabolism of amitriptyline to nortriptyline is via CYP2C19 and does not reflect CYP2D6 activity (Levy et al. Metabolic Drug Interactions. page 234, 2000 edition, Lippincott Williams & Wilkins). The IC_{50}s for inhibiting the in vitro 1'-hydroxylation of bufuralol are 70 nM and 200 nM for cinacalcet (Study 100157) and quinidine (*Br J Clin Pharmacol* 1986;22:739), respectively.

Quinidine is a preferred in vitro CYP2D6 inhibitor and bufuralol is a preferred in vitro CYP2D6 substrate (*J Clin Pharmacol* 2003;43:443).

- The sponsor should conduct an in vitro drug metabolic enzymes induction study for cinacalcet in human liver cells. **Reasons:** From the 3 key clinical studies in secondary hyperparathyroidism patients, the seizure incidence is higher in the cinacalcet treatment group than that in the placebo group (1.7% vs. 0.4%). Cinacalcet may induce drug metabolic enzymes that caused lowering of concomitant anticonvulsants' exposure, which can increase seizure risk. Moreover, the sponsor has not conducted drug metabolic enzymes induction study for the NDA.

/S/

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

An Office Level Clinical Pharmacology and Biopharmaceutics Briefing for NDA 21-688 was conducted on February 10, 2004; participants included P. Beaston, T. Kehoe, G. Kuijpers, J. Mele, D. Hedin, L. Lesko, S. Huang, R. Powell, A. Selen, C. Sahajwalla, H. Malinowski, Y. Uyama, T. Chen, S. Nallani, H. Ahn, J. Vaidyanathan, and J. Lau.

FT signed by Hae-Young Ahn, Ph.D., Team Leader ______________________ 2/ /04

2 Table of Contents

List of Figures:

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List of Tables:

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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor develops cinacalcet, a calcimimetic to treat [redacted] secondary hyperparathyroidism (2° HPT) for chronic kidney disease patients and treat hypercalcemia in primary hyperparathyroidism (1° HPT) and parathyroid cancer patients. The dose for treating [redacted] 2° HPT is 30 – 180 mg once daily titrated to target parathyroid hormone concentrations (PTH). The dose for treating 1° HPT and parathyroid carcinoma is 30 mg twice daily to 90 mg 4 times daily titrated to lower serum calcium concentrations.

Basic Human Pharmacology of Cinacalcet

Cinacalcet is well absorbed orally since 80% of the orally administered radioactivity is recovered in urine and 15% of the orally administered radioactivity is recovered in feces.

Cinacalcet has a mean steady state volume of distribution, V_{ss}, of 913 - 1235 L after single intravenous administration of 2, 5, and 10 mg to healthy volunteers. Cinacalcet is [redacted] bound to human plasma protein(s). The ratio of red blood cells cinacalcet concentration to plasma cinacalcet concentration is [redacted] at a blood cinacalcet concentration of 10 ng/mL.

Cinacalcet is metabolized by multiple enzymes, primarily, CYP3A4, CYP2D6, and CYP1A2. Cinacalcet is a strong CYP2D6 inhibitor in vitro.

The major plasma cinacalcet metabolites are hydrocinnamic acid (P18) and hydroxy-hydrocinnamic acid (P13). Glucuronides of the dihydrodiol metabolites (P6 and P12) are also present in plasma. The major urinary metabolites are glycine conjugates of P13 and glucuronides of the dihydrodiol metabolites (U6, U10, and U12). The calcimimetic activity of P18 and P13 are unknown. U6 and U12 showed 333-fold less potent calcimimetic activity than cinacalcet. Cinacalcet terminal half-life is 30 – 40 hours. Cinacalcet is extensively metabolized and the metabolites are renally excreted. Mean plasma cinacalcet clearance, CL, is 60.9 – 77.1 L/hr after single intravenous administration of 2, 5, and 10 mg to healthy volunteers.

Cinacalcet pharmacokinetics (PK) is proportional upon oral 25 – 200 mg cinacalcet once daily oral administration to chronic renal impaired patients. However, cinacalcet exposure did not increase beyond the 200 mg oral dose.

Cinacalcet PK did not appear to change with time upon multiple once daily oral administration. In general, steady state plasma cinacalcet concentrations are reached after 4 days of once daily administration and the mean accumulation ratio is 1.5 – 2.1 and 1.7 – 2.1 for cinacalcet C_{max} and $AUC_{(0\text{-}24h)}$, respectively. The median accumulation ratio is 1.2 – 3.7 and 2.3 – 4.6 for cinacalcet C_{max} and $AUC_{(0\text{-}24h)}$, respectively, upon twice daily dosing.

At the 50 mg cinacalcet once daily oral administration, PK between 2° and 1° HPT patients is similar.

The starting dose was 30 mg cinacalcet because it is the lowest dose to appreciably lower PTH. The highest dose was 180 mg because it was safe and effective. Higher doses did not increase exposure for

2° HPT patients. The starting dose of 30 mg twice daily to 90 mg 4 times daily are determined per experience with earlier calcimimetic in 1° HPT and parathyroid carcinoma patients.

A multivariate linear regression analysis adjusting for age, gender, race, history of diabetes, history of congestive heart failure, and baseline QTc demonstrated a weak association (correlation = -0.227) that the magnitude of the increase in QTc averages 6 msec for each 1 mg/dL reduction in serum calcium.

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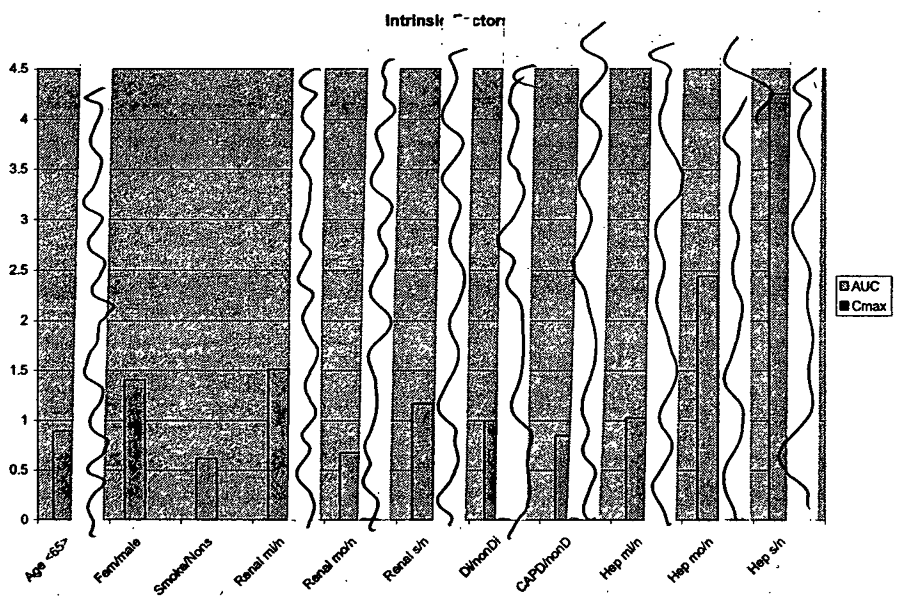
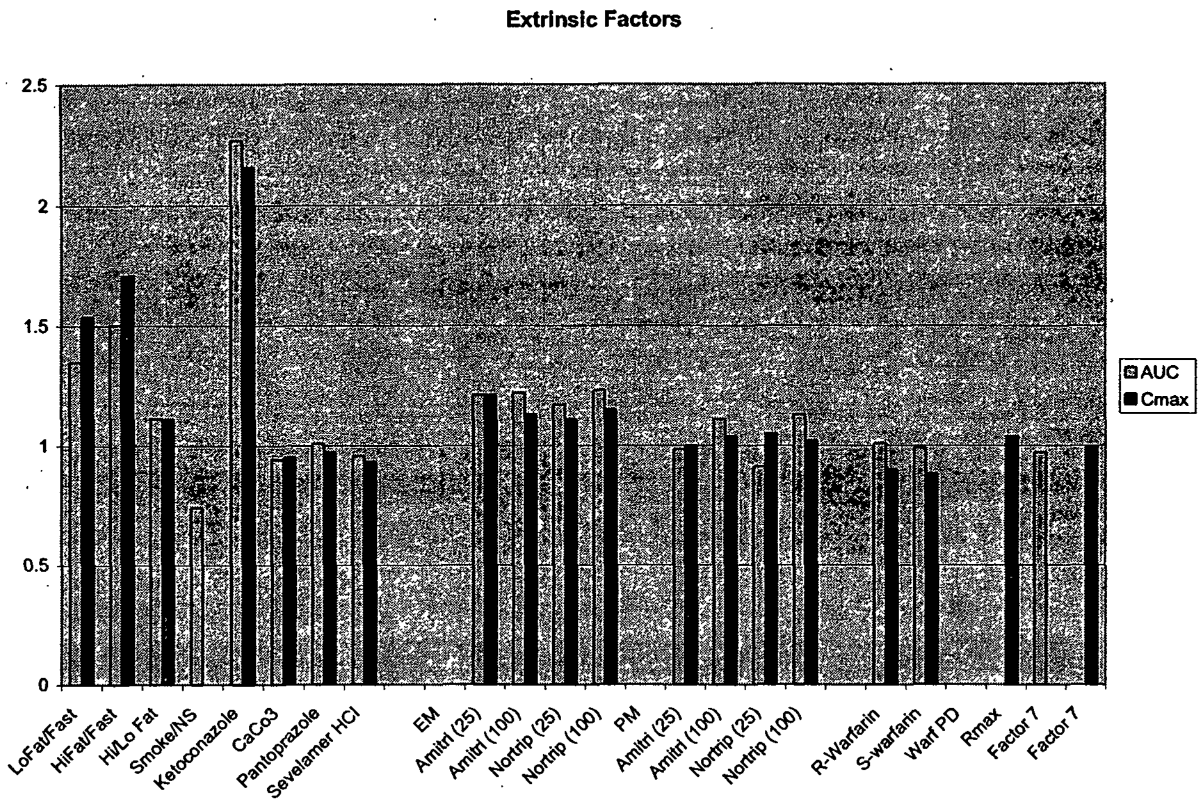


Age, body weight, and body mass index did not show impact on cinacalcet pharmacokinetics. However, female showed a 40% lower apparent clearance than that for male and smoker showed a 38% higher apparent clearance than that for nonsmokers. Race is a significant covariate for the central volume of distribution.

No trend existed that cinacalcet exposure increased with increasing degree of renal impairment from normal subjects to hemodialysis patients. Hemodialysis did not alter cinacalcet PK. Cinacalcet PK for patients on continuous ambulatory peritoneal dialysis is similar to that for hemodialysis patients and healthy volunteers.

Cinacalcet $AUC_{(0\text{-}inf)}$ between healthy volunteers and mild hepatic impairment patients were comparable. However, cinacalcet exposure for moderate and severe hepatic impairment patients were 2.4 and 4.2 times higher, respectively, than that for healthy volunteers.



Food-Drug interaction
Cinacalcet C_{max} and $AUC_{(0\text{-inf})}$ were increased 82% and 68%, respectively, under a high-fat meal as compared to that under fasting conditions. The low-fat meal vs. fasting conditions indicated that the C_{max} and $AUC_{(0\text{-inf})}$ were increased 65% and 50, respectively.

Drug-Drug Interaction
Cinacalcet AUC and C_{max} increased 2.3 and 2.2 times, respectively, when 90 mg cinacalcet was coadministered with 200 mg ketoconazole twice daily as compared to that for 90 mg cinacalcet alone.

Per the 90% confidence interval for cinacalcet C_{max} and $AUC_{(0\text{-inf})}$ ratios, no significant PK drug interaction was observed:

- when 80 mg pantoprazole daily was coadministered with 90 mg cinacalcet
- when 1500 mg $CaCO_3$ was coadministered with 100 mg cinacalcet
- coadministration of 2400 mg sevelamer HCl 3 times daily did not change the cinacalcet PK upon oral administration of a 90 mg cinacalcet tablet.

In CYP2D6 extensive metabolizers who received 50 mg amitriptyline, amitriptyline $AUC_{(0\text{-inf})}$ and C_{max} increased about 20% with coadministration of 25 mg or 100 mg cinacalcet. Nortriptyline $AUC_{(0\text{-inf})}$ increased 17 – 23% and C_{max} increased 11 - 15% with coadministration of 25 mg or 100 mg cinacalcet. In CYP2D6 poor metabolizers who received 50 mg amitriptyline, $AUC_{(0\text{-inf})}$ and C_{max} for both amitriptyline and nortriptyline did not appear to change with coadministration of 25 mg or 100 mg cinacalcet.

Both R-and S-warfarin PK were not affected when 30 mg cinacalcet twice daily was coadministered with 25 mg warfarin. Warfarin pharmacodynamic endpoints (maximal rise in prothrombin time and factor VII concentrations) were not affected when 30 mg cinacalcet was coadministered twice daily with 25 mg warfarin.

Cinacalcet HCl is a Biopharmaceutics Classification System class 4 drug.

Bioequivalence between the Clinically Tested and To-Be-Marketed Formulations
The clinically tested 30, 60, and 90 mg cinacalcet tablets for the 2° HPT studies are identical to the to-be-marketed cinacalcet tablets, except the tablet film coating was changed from [redacted] (clinical to to-be-marketed formulation). This change was justified per SUPAC-IR Guidance (± 1% for film coat changes) and similarity of the in vitro dissolution data between the clinical and to-be-marketed formulation [redacted]

Proposed In Vitro Dissolution Method and Specification

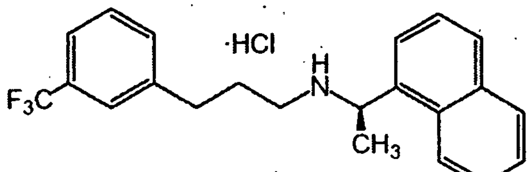
Apparatus	USP Type 2 [redacted]
Dissolution medium	[redacted]
Medium volume	[redacted]
Medium temperature	[redacted]
Stirring speed	[redacted]
Sampling time	[redacted]
Specifications	Not less than [redacted] (Q) of the labeled amount of cinacalcet is dissolved in [redacted] minutes

The proposed dissolution method is acceptable. However, the recommended specification for the 30, 60, and 90 mg cinacalcet tablets is "Not less than [redacted] (Q = [redacted]) of the labeled amount of cinacalcet is dissolved in [redacted] minutes."

4 Question-Based Review

4.1 General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of cinacalcet HCl?



$C_{22}H_{22}F_3N \cdot HCl$
(393.87)

Figure 1. Molecular structure of cinacalcet HCl. Figure 2. pH-solubility profile of cinacalcet HCl.

Cinacalcet (AMG 073) is the R enantiomer. Cinacalcet HCl's pH solubility profile follows: The maximum solubility is about from pH 3 to 5. Below pH 2, solubility decreases due to the common ion effect. Hence, cinacalcet HCl exhibits relatively low solubility in Above pH solubility decreases rapidly due to the unionized form's low solubility. Cinacalcet HCl

2. What is the formulation of the to-be-marketed 30, 60, and 90 mg cinacalcet oral tablet?

Table 1. Cinacalcet HCl Tablet Composition (mg/tablet).

Component	Reference to Standards	Function	% (w/w)[a]	30 mg	60 mg	90 mg
Core Tablet						
Cinacalcet HCl	HSE[b]	active	18.367[c]	33.06[c]	66.12[c]	99.18[c]
Pregelatinized starch	Ph Eur. USP/NF					
Microcrystalline cellulose	Ph Eur. USP/NF					
Povidone	Ph Eur. USP/NF					
Crospovidone	Ph Eur. USP/NF					
	Ph Eur. USP/NF					
Microcrystalline cellulose	Ph Eur. USP/NF					
Colloidal silicon dioxide	Ph Eur. USP/NF					
Crospovidone	Ph Eur. USP/NF					
Magnesium stearate	Ph Eur. USP/NF					
Core Tablet Total			100.00	180.00	360.00	540.00

(Continued)

[a] % (w/w) is identical regardless of dose strength.
[b] HSE = In-house Specification
[c] Molecular weights of the HCl salt and the free base are respectively; therefore, the free base accounts for 90.74% of the salt.
[d] The sum total of cinacalcet HCl and microcrystalline cellulose per tablet is fixed; therefore, as the amount of cinacalcet HCl varies in regard to potency, the amount of microcrystalline cellulose is adjusted to meet the fixed total amount.
[e]

Component	Reference to Standards	Function	% (w/w)[a]	30 mg	60 mg	90 mg
Film Coat Tablet						
Opadry® II Green[f,g,h]						
	Ph Eur, USP/NF					
Opadry® Clear[f,g,h]						
	Ph Eur, USP/NF					
Carnauba wax[g,h]	Ph Eur, USP/NF					
Ink Printed Tablet						
Opacode® Black[f,i]						

[a] % (w/w) is identical regardless of dose strength.

[e]

[f] ... of the film coats (clear and color) and black ink are incorporated by reference from 1. Information related to the Opadry® Clear and Opadry® II Green was filed ... 394 (page 3426) and 28 Aug 2002 (page 4495), respectively. Opacode® Black was filed on 10 March 2003 (page 4576). The letter of authorization from is provided in Module 1. Also provided in Table 2 is the qualitative and quantitat... osition of these materials from

[g] Final amount is typically less than stated.

[h] Amount applied is based on the core tablet weight.

[i]

Active and inactive ingredients for different strengths of the to-be-marketed tablets are proportionally similar.

3. What is cinacalcet's mechanism of action?

Cinacalcet binds to the calcium-sensing receptors of the parathyroid gland and amplifies the receptor sensitivity to extracellular calcium (calcimimetic), thereby decreasing parathyroid hormone (PTH) release. Cinacalcet is the biologically active R enantiomer.

4. What are cinacalcet's proposed therapeutic indications, dosage, and route of administration?

For treatment of secondary (2°) hyperparathyroidism (HPT) in chronic kidney disease patients the proposed starting oral dose is 30 mg cinacalcet once daily and should be titrated every 2 -4 weeks to a maximum dose of 180 mg cinacalcet once daily to achieve a target PTH: 1.5 – 5 times the upper limit of normal for dialysis patient and > 30% reduction of PTH concentrations for patients not receiving dialysis. For treatment of hypercalcemia in parathyroid carcinoma and

4.2 General Clinical Pharmacology

1. What are cinacalcet's clinical pharmacokinetic (PK) characteristics?

Absorption

Cinacalcet is well absorbed upon oral administration as evidenced via 80% of the orally administered radioactivity is recovered in urine (Study 980233, see the Metabolism section of this question below for details).

Study 100154 examined the permeability of cinacalcet across in vitro human colon carcinoma cells (Caco-2) for the apical-to-basolateral (A – B) and basolateral-to-apical (B – A) directions.

Table 2. Apparent permeability coefficients (P_{app}) across Caco-2 cell layers for various agents (mean ± SD; x 10^{-6} cm/sec).

n = 3	A - B	B - A	(B – A)/(A – B)
mannitol	1.65 ± 0.08	1.25 ± 0.18	0.76
verapamil	5.28 ± 0.58	21.7 ± 2.73	4.1
cinacalcet	3.2 ± 0.34	3.33 ± 0.10	1.04

Verapamil P_{app} (B – A)/ P_{app} (A – B) is 4.1, which is consistent with verapamil being a P-gp substrate. No significant difference exists in the P_{app} for cinacalcet across Caco-2 monolayers between the A – B and B – A directions. Hence, cinacalcet appears not to be a P-gp substrate.

Study 103270 examined the permeability of cinacalcet, aspirin, and mannitol across in vitro human Caco-2 cells from A- B direction. The P_{app} follows (**Table 3**):

n = 6 wells	Mean ± SD (x 10^{-6} cm/sec)
cinacalcet	5.8 ± 0.56
aspirin	8.14 ± 0.48
mannitol	0.99 ± 0.05

Mannitol P_{app} from both studies was higher than 0.5 x 10^{-6} cm/sec as reported in literature. Study 103270 also showed that transepithelial electrical resistance across the Caco-2 cell layers used for determining mannitol, aspirin, and cinacalcet fluxes were not significantly different between each group. The sponsor claimed that aspirin was a high permeability drug and concluded that cinacalcet was a high permeability drug per [redacted] Per the Biopharmaceutics Classification System (BCS) Guidance, 20 model drugs are recommended to be used to demonstrate suitability for an in vitro cell culture permeability method. Hence, the sponsor's conclusion of high cinacalcet absorptive permeability cannot be established based on 1 reference drug.

Cinacalcet's P-gp inhibition and induction potentials are unknown.

Distribution

Cinacalcet is [redacted] bound to human plasma protein(s) in vitro via [redacted] method (Study 100158). However, the plasma proteins that bind cinacalcet and their respective extent of binding are unknown. The ratio of red blood cells cinacalcet concentration to plasma cinacalcet concentration is [redacted] at a blood cinacalcet concentration of 10 ng/mL (Study 102739). Cinacalcet has a mean steady state volume of distribution, V_{ss}, of 913 - 1235 L after single intravenous administration of 2, 5, and 10 mg to healthy volunteers (Study 990751). The large V_{ss} suggests extensive cinacalcet tissue distribution.

Metabolism

Study 102724 examined the in vitro cytochrome P450 (CYP) isozymes that metabolized cinacalcet: 1) via cDNA expressed CYP isoforms, 2) metabolism inhibition via isoform selctive CYP inhibitors in pooled human liver microsomes, and 3) cinacalcet metabolism correlation analysis with known isoform specific CYP activities in a panel of human liver microsomes. Multiple CYP isozymes (1A2, 2C9, 2C19, 2D6, and 3A4) could metabolize cinacalcet with NADPH. Per the "% Inhibition via isoform-selective inhibitors" and "Correlation coefficient with isoform-specific activity" results, cinacalcet is primarily metabolized via CYP3A4 and to lesser extent via CYP2D6 and CYP1A2.

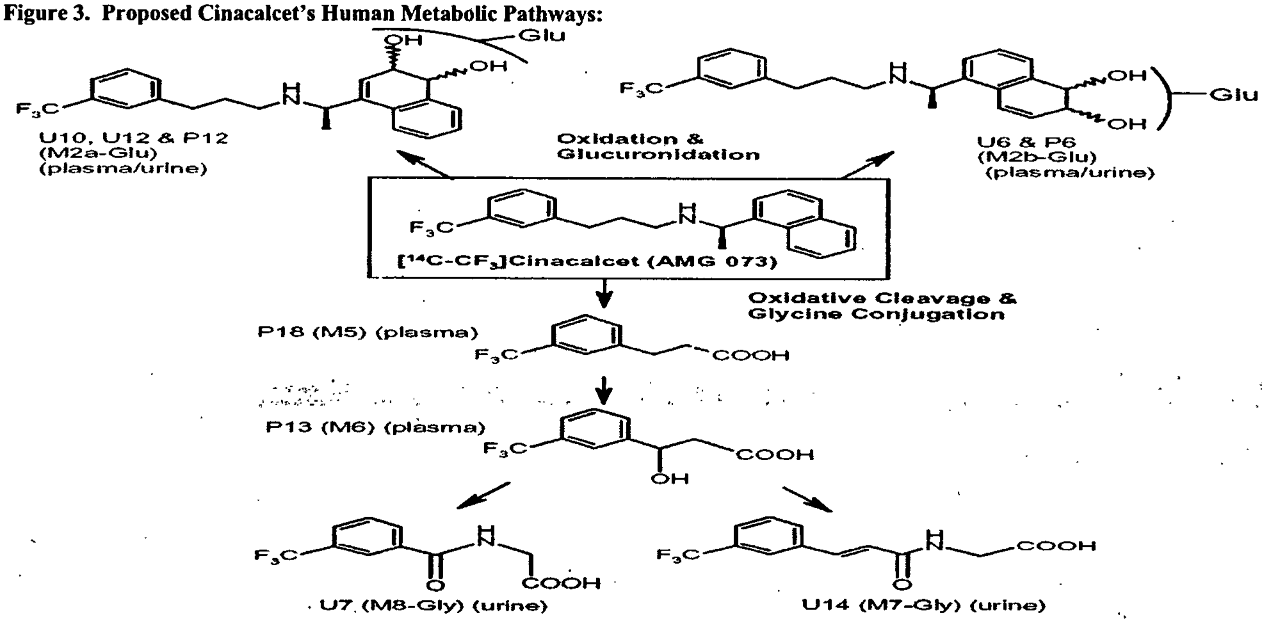
Study 100157 examined cinacalcet's in vitro CYP isozymes inhibition potential (**Table 4**):

CYP	IC_{50}	Substrate	Product	Positive Control Inhibitor
1A2	>300 µM	45 µM phenacetin	acetaminophen	100 µM furafylline
2C9	>300 µM	100 µM tobutamide	hydroxytobutamide	2 µM sulfaphenazole
2C19	~10 µM	30 µM S-mephenytoin	hydroxymephentoin	-
2D6	~70 nM	10 µM bufuralol HCl	1' hydroxybufuralol	-
3A4	~100 µM	1-5 µM midazolam	hydroxy midazolam	250 nM ketoconazole

Cinacalcet is a strong CYP2D6 inhibitor per its IC_{50} for CYP2D6 in pooled human liver microsomes.

Study 980233 examined the mass balance of a 75 mg cinacalcet capsule (———]-cinacalcet) upon oral administration to 5 smoking and 5 nonsmoking healthy men under fasting conditions. Blood, urine, feces, saliva, and any emesis samples were collected for about 192 hours postdose to determine radioactivity and PK parameters. Metabolites were identified via liquid chromatography and mass spectrometry. Caffeine phenotyping was conducted on Day 9. Blood samples were collected predose and 6 hours postdose for determination of paraxanthine to caffeine in plasma (metabolic ratio).

Figure 3. Proposed Cinacalcet's Human Metabolic Pathways:



Cinacalcet is extensively metabolized via multiple and rapid metabolic conversions. Oxidative N-dealkylation of cinacalcet is a major metabolic conversion, followed by β-oxidation and glycine conjugation. Hydrocinnamic acid (P18) and hydroxy-hydrocinnamic acid (P13) are the most abundant plasma metabolites. P18 and P13 will likely accumulate upon a 24-hour cinacalcet dosing interval (see Table 5 below).

Oxidation of the naphthalene ring on cinacalcet to form dihydrodiols is another major metabolic conversion and the dihydrodiols are rapidly conjugated with glucuronic acid. The glucuronide conjugates (P6 and P12) are then excreted in the urine as U6, U10 (U12's regioisomer), and U12. Plasma P6 and P12 metabolites will not likely accumulate upon a 24-hour cinacalcet dosing interval (see Table 5 below). U6, U10, U12, P6, and P12 are higher in smokers. However, U7 and U14 (urine glycine conjugates) from the N-dealkylation pathway is higher in nonsmokers. Plasma P18 and P13 concentrations from this pathway are also higher in nonsmokers.

Table 5. μg Equivalents of Cinacalcet in Plasma (Left Sub-table) and Urine (Right Sub-table) After Oral Administration of [^{14}C-CF_3]-Cinacalcet.

	Nonsmokers (n = 5)				Smokers (n = 5)			
Time (hr)	P6 (M2b-Glu)	P12 (M2a-Glu)	P13 (M6)	P18 (M5)	P6 (M2b-Glu)	P12 (M2a-Glu)	P13 (M6)	P18 (M5)
3	0.26	0.06	0.26	2.08	0.50	0.17	0.20	1.74
12	0.03	0.00	0.22	1.22	0.05	0.00	0.20	0.84
36	0.00	0.00	0.06	0.29	<0.01	0.00	0.05	0.17

Metabolite	Nonsmokers (n = 3)	Smokers (n = 3)
U6 (M2b-Glu)	20.85 (1.85)	26.78 (1.82)
U7 (M8-Gly)	14.14 (0.62)	13.77 (1.63)
U10 (M2a-Glu isomer)	2.81 (0.40)	5.18 (1.59)
U12 (M2a-Glu isomer)	8.37 (0.27)	6.46 (0.73)
U14 (M7-Gly)	20.36 (0.66)	13.33 (1.28)
Total	66.53	65.50

The amine part of cinacalcet molecule that contains naphthalene was not radiolabled. Hence, the qualitative and quantitative information on the amine part of cinacalcet molecule that contains naphthalene and its metabolites in plasma are unknown.

Table 6. Mean ± SD of Plasma Cinacalcet PK Parameters (Left Sub-table) and % Recovery of Radioactive Dose (Right Sub-table).

Pharmacokinetic Parameter	Nonsmokers (n = 5) Radioactivity Blood	Nonsmokers (n = 5) Radioactivity Plasma	Nonsmokers (n = 5) Cinacalcet Plasma	Smokers (n = 5) Radioactivity Blood	Smokers (n = 5) Radioactivity Plasma	Smokers (n = 5) Cinacalcet Plasma
t_{max} (hr)	3.20 ±0.837	2.80 ±0.447	3.00 ±0.000	2.80 ±0.447	2.60 ±0.548	2.90 ±0.894
C_{max} (μg equivalents/g)*	1.38 ±0.151	2.85 ±0.223	10.6 ±2.78	1.37 ±0.167	3.03 ±0.328	12.2 ±5.55
AUC0-inf (μg equivalents*hr/g)*	26.5 ±7.60	54.8 ±14.95	122 ±29.7	21.6 ±5.92	46.0 ±10.48	137 ±53.6
$t_{1/2}$ (hr)	13.3 ±3.36	15.7 ±2.45	34.3 ±8.61	12.1 ±2.51	15.6 ±3.13	41.0 ±18.54
CL/F (L/hr)	NA	NA	641 ±126.9	NA	NA	601 ±164.0

* Cinacalcet in plasma, ng/mL
* Cinacalcet in plasma, ng*hr/mL
NA = not applicable

Matrix	Nonsmokers (n = 5)	Smokers (n = 5)
Urine	83.2 ± 5.13	80.3 ± 5.00
Feces	13.1 ± 2.37	16.9 ± 2.50
Toilet Tissue	0.02 ± 0.03	0.07 ± 0.09
Saliva Wipe	ND	ND
Total	96.3 ± 3.43	97.4 ± 3.62

Drug-derived radioactivity and plasma cinacalcet concentration decline slowly, with mean cinacalcet $t_{1/2}$ of 34.3 and 41.0 hours in the nonsmoking and smoking subjects, respectively. Cinacalcet PK parameters between smokers and nonsmokers are similar. After adjusting for smoking status, there appeared to be a positive relationship between cinacalcet ln (CL/F) and ln (metabolic ratio) for both groups. The total mean radioactivity recovery in excreta exceeds 95% of the dosed radioactivity in both nonsmoking and smoking subjects. Renal excretion is the prevalent route (> 80%) of radioactivity elimination.

Per in vitro assays examining calcimimetic activity, U6 and U12 showed 333-fold less potent calcimimetic activity (calcitonin release) than cinacalcet in the rat medullary thyroid carcinoma cell line ( ) (Study R2002079).

Per the bioanalytical validation report 102326 for Study 20010169 (food effect study), there was no detectable stereoconversion when 90 mg cinacalcet (R enantiomer) was administered to healthy volunteers.

The % contribution of different CYP isozymes to cinacalcet clearance is unknown. Cinacalcet's metabolizing enzymes induction potential is unknown.

Excretion

Cinacalcet terminal half-life ranged from 30 – 40 hours. Per Study 980233 above, cinacalcet is extensively cleared via metabolism and its metabolites are mainly eliminated via urine. Mean plasma cinacalcet clearance, CL, is 60.9 – 77.1 L/hr after single intravenous administration of 2, 5, and 10 mg to healthy volunteers (Study 990751).

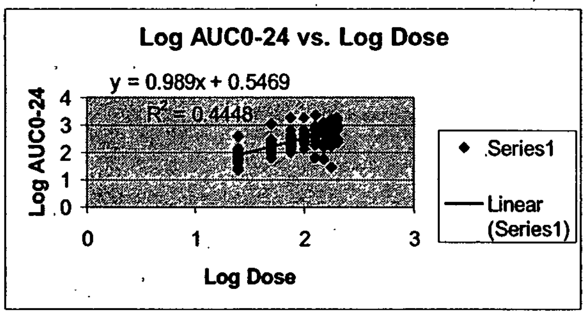
2. Is the cinacalcet PK proportional upon oral administration?

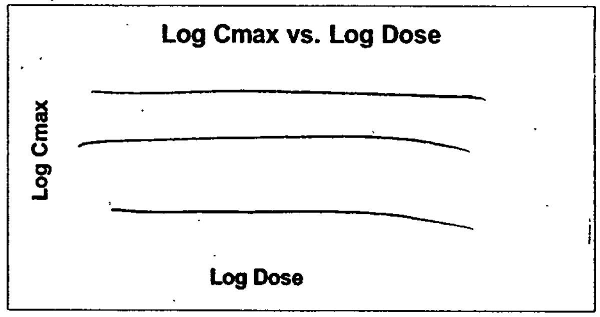
In Study 20000187, each chronic renal failure patient receiving hemodialysis received a 25 mg cinacalcet tablet daily with food as a starting dose for 7 days. In the absence of toxicity, each patient received a higher dose (previous dose + 25 mg) daily for 7 days. The patients received this escalating dose scheme up to 300 mg. Patients received a combination of 25 and 50 mg cinacalcet tablets for the respective doses. Predose blood samples were collected on Day 4, 6, and 7 of each dose group. On the last day of each dose (usually Day 7 or Day 8 if dialysis on Day 7), serial plasma samples were collected for 24 hours to assess cinacalcet PK.

Table 7. PK Parameters for Subjects with Chronic Renal Failure Receiving Hemodialysis.

Dose (mg)	n	AUC(0-24) (ng*hr/mL)		C_{max} (ng/mL)	
		Median	Range	Median	Range
25	16	76.8		7.22	
50	16	179		17.2	
75	16	253		21.6	
100	16	383		31.1	
125	15	427		36.5	
150	15	530		55.5	
175	13	648		56.6	
200	11	900		78.3	
225	12	570		58.6	
250	11	911		67.0	
275	9	930		72.1	
300	7	501		55.7	

Figure 4. Log Cinacalcet $AUC_{(0-24)}$ vs. Log Cinacalcet Dose Plot. Figure 5. Log Cinacalcet C_{max} vs. Log Cinacalcet Dose Plot.





Mean predose plasma cinacalcet concentrations did not notably increase beyond Day 4 and steady state appeared to be reached on Day 4. The slope of the log $AUC_{(0-24)}$ vs. log dose plot is 0.989 (95%CI: 0.787 – 1.19) from 25 – 200 mg cinacalcet dose. The slope of the log C_{max} vs. log dose plot is —— (95%CI: 0.783 – 1.18) from 25 – 200 mg cinacalcet dose. These slopes were about 1, which suggests that the PK is proportional upon oral 25 – 200 mg cinacalcet once daily administration to chronic renal impaired patients. Cinacalcet exposure did not increase beyond the 200 mg dose, which might be due to limited cinacalcet dissolution or absorption saturation in the gastrointestinal tract.

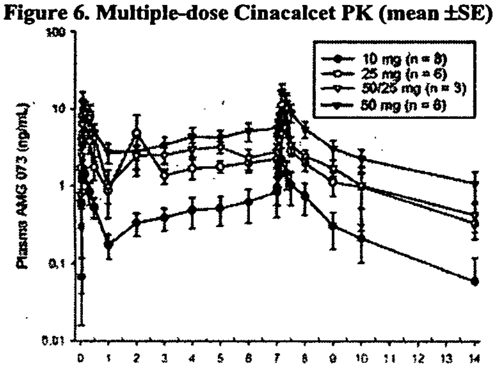
The sponsor did not formally establish PK proportionality for the 2, 3, and 4 times daily cinacalcet oral administration regimens for 1° hyperparathyroidism and parathyroid carcinoma patients.

3. How does chronic oral dosing alter cinacalcet PK?

Cinacalcet PK does not appear to change with time upon multiple dosing in the dose escalation study (Study 20000187 for PK proportionality above). Per Study 20000187, steady state plasma cinacalcet concentrations are reached after 4 days of once daily administration.

Study 980126 examined the single and multiple dose cinacalcet PK. Randomized patients with 2° HPT received a 5, 10, 25, 50, 75, or 100 mg cinacalcet doses as multiples of 5 and 25 mg cinacalcet —— (fasting conditions not required). Some patients continued with 10, 25, and 50 mg cinacalcet doses once daily for 8 consecutive days. For the single dose phase, serial plasma samples were collected for 72 hours postdose to assess cinacalcet PK. For the multiple dose phase, serial plasma samples were collected for 24 hours post 1st dose, the 24th hour sample during days 2 – 7, and serial plasma samples were collected for 14 days post last dose to assess cinacalcet PK. Mean (SD) accumulation ratio was 1.49 (0.57) – 2.09 (2.23) and 1.72 (0.37) – 2.10 (1.26) for cinacalcet C_{max} and $AUC_{(0-24h)}$, respectively, in 2° HPT patients upon once daily oral cinacalcet administration.

Figure 6. Multiple-dose Cinacalcet PK (mean ±SE) After Daily Administration to Subjects with 2° HPT.



[redacted]

The accumulation ratio for the 3 and 4 times daily cinacalcet oral administration regimens in [redacted] parathyroid carcinoma patients is unknown.

4. Does cinacalcet PK differ between 2° and 1° HPT patients?

The sponsor did not conduct any study to compare cinacalcet PK in 2° [redacted] patients. Hence, cinacalcet PK in 2° [redacted] patients were compared across Studies 990126 and 990125, respectively. The following **Table 8** details the mean PK parameters (SD) for 2 x 25 mg cinacalcet capsules once daily oral administration for these 2 studies:

	2° HPT	[redacted]
Day 1	N = 8	N = 12
$AUC_{(0-24h)}$, ng·h/mL	112 (65.0)	[redacted]
C_{max}, ng/mL	13.4 (7.0)	
T_{max}, h	2.92 (1.2)	
CL/F, L/h	567 (723)	[redacted]
$T_{1/2}$, h	26.6 (8.9)	
Day 8	N = 8	N = 12
$AUC_{(0-24h)}$, ng·h/mL	224 (130)	
C_{max}, ng/mL	17.4 (10.3)	[redacted]
T_{max}, h	5.67 (3.67)	
CL/F, L/h	303 (189)	[redacted]
$T_{1/2}$, h	37.9 (14.6)	
AR_{Cmax}	1.49 (0.57)	
AR_{AUC}	1.72 (0.37)	

AR_{Cmax} and AR_{AUC} are accumulation ratio for C_{max} and $AUC_{(0-24h)}$ on Day 8 divided by C_{max} and $AUC_{(0-24h)}$ on Day 1, respectively.

The PK upon 50 mg cinacalcet once daily administration appears to be similar between 2° [redacted] except the $T_{1/2}$ was shorter with the latter. [redacted]

5. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for cinacalcet efficacy?

For 2° HPT, the efficacy endpoints (in decreasing priorities) are the following:

- proportion of subjects achieved a reduction in mean PTH to ≤ 250 pg/mL
- proportion of subjects who achieved a ≥ 30% reduction in mean PTH during the efficacy assessment phase
- % change in serum Ca x P (calcium phosphorus product)

The sponsor chose these efficacy endpoints because:

- Relatively normal bone histology is associated with PTH concentrations about 2 – 4 times the upper limit of normal, corresponding to 100 – 250 pg/mL.
- A ≥ 30% reduction of PTH is considered clinically meaningful by many nephrologists and was the 1° endpoint in registration studies for vitamin D sterols for 2° hyperparathyrodism.

- Elevation of Ca x P is associated with increased risk of cardiac, visceral, and vascular calcifications.

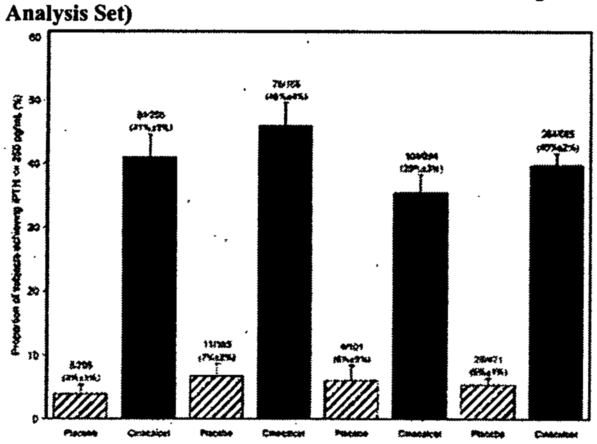
Cinacalcet daily dose was titrated up (30, 60, 90, 120, and 180 mg) based on PTH response and safety monitoring for 3 key clinical studies (20000172, 20000183, and 20000188). Results for these 3 studies follow:

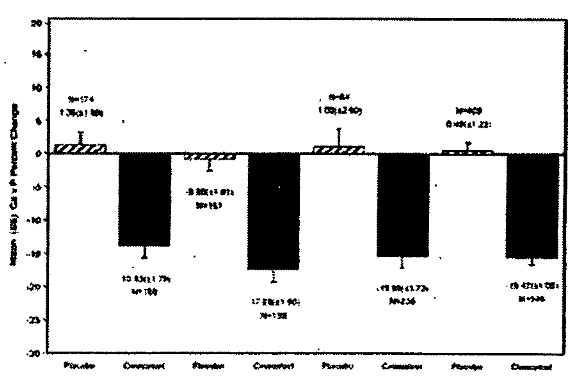
Table 9. Effects of Cinacalcet on iPTH, Serum Ca x P, Calcium, and Phosphorus (Controlled Phase 3 ESRD Studies - ITT Analysis Set)

	Study 20000172		Study 20000183		Study 20000188		Total	
	Placebo (N = 205)	Cinacalcet (N = 205)	Placebo (N = 165)	Cinacalcet (N = 166)	Placebo (N = 101)	Cinacalcet (N = 294)	Placebo (N = 471)	Cinacalcet (N = 665)
iPTH								
Baseline (pg/mL)	651 (28)	636 (24)	630 (25)	652 (29)	832 (48)	848 (40)	683 (18)	733 (21)
Evaluation Phase (pg/mL)	698 (33)	385 (25)	687 (32)	361 (29)	852 (55)	526 (30)	727 (22)	441 (17)
% Change	9.5 (2.8)	-38.4 (2.9)	8.7 (2.8)	-47.5 (2.8)	4.1 (3.4)	-40.3 (2.1)	8.1 (1.7)	-41.5 (1.4)
Primary Endpoint: Patients Achieving iPTH Target (≤ 250 pg/mL) (%)	4%	41%	7%	46%	6%	35%	5%	40%
Patients Achieving ≥ 30% Reduction in iPTH (%)	11%	61%	12%	68%	10%	59%	11%	62%
Ca x P								
Baseline (mg^2/dL^2)	61 (1.1)	62 (1.1)	61 (1.2)	61 (1.2)	61 (1.4)	60 (1.0)	61 (0.7)	61 (0.6)
Evaluation Phase (mg^2/dL^2)	60 (1.0)	52 (1.0)	59 (1.2)	50 (1.3)	58 (1.3)	50 (0.9)	59 (0.7)	51 (0.6)
% Change	1.5 (1.8)	-13.0 (1.7)	-0.7 (1.9)	-16.7 (2.1)	-1.4 (2.4)	-12.8 (1.7)	0.1 (1.2)	-13.8 (1.0)
Calcium								
Baseline (mg/dL)	9.9 (0.1)	9.8 (0.1)	9.9 (0.1)	10.0 (0.1)	10.0 (0.1)	9.8 (0.05)	9.9 (0.04)	9.9 (0.03)
Evaluation Phase (mg/dL)	9.9 (0.1)	9.2 (0.1)	9.9 (0.1)	9.2 (0.1)	10.1 (0.1)	9.1 (0.1)	10.0 (0.04)	9.2 (0.03)
% Change	0.5 (0.3)	-6.3 (0.6)	0.3 (0.4)	-7.5 (0.6)	0.9 (0.5)	-6.5 (0.6)	0.5 (0.2)	-6.7 (0.4)
Phosphorus								
Baseline (mg/dL)	6.2 (0.1)	6.3 (0.1)	6.2 (0.1)	6.1 (0.1)	6.1 (0.1)	6.1 (0.1)	6.2 (0.1)	6.2 (0.1)
Evaluation Phase (mg/dL)	6.0 (0.1)	5.7 (0.1)	6.0 (0.1)	5.4 (0.1)	5.8 (0.1)	5.5 (0.1)	6.0 (0.1)	5.5 (0.1)
% Change	1.1 (1.8)	-7.1 (1.7)	-0.9 (1.9)	-9.9 (2.0)	-2.2 (2.5)	-7.2 (1.6)	-0.3 (1.1)	-7.8 (1.0)

Data represent mean (standard error) or percent.

Figure 7. Proportion (± SE) of Subjects with a Reduction in Mean iPTH to ≤ 250 pg/mL (Controlled Phase 3 ESRD Studies – ITT Analysis Set). Figure 8. Mean (SE) Percent Change from Baseline in Ca x P (Controlled Phase 3 ESRD Studies – ITT Analysis Set)



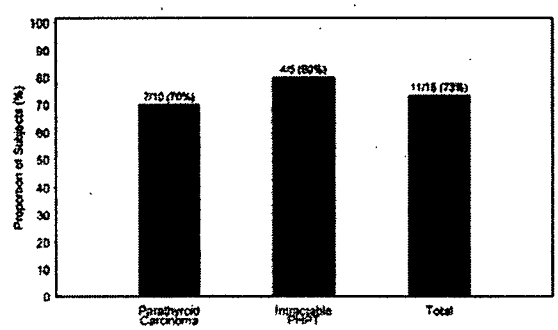


For ——— parathyroid carcinoma, the efficacy endpoint is the proportion of subjects with a 1 mg/dL reduction in serum calcium from baseline to end of the titration phase.

The cinacalcet dose was titrated up (30 mg twice daily, 70 mg twice daily, 70 mg 3 times daily, 70 mg 4 times daily, 90 mg twice daily, 90 mg 3 times daily, 90 mg 4 times daily) based on serum calcium concentration and adverse event assessment.

Figure 9. Proportion of Subjects with a Reduction from Baseline in Serum Calcium of ≥ 1 mg/dL at the End of the Titration Phase - LVCF (Study 20000204)

	Placebo			Cinacalcet		
	Baseline	Post-treatment	% Change	Baseline	Post-treatment	% Change
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Study 980125						
QD phase, 6 wks	10.5 (0.3)	10.3 (0.2)	-2.1 (1.2)	10.6 (0.1)	9.3 (0.1)	-10.6 (1.4)
BID phase, 2 wks	10.4 (0.3)	10.4 (0.7)	0.3 (2.9)	10.6 (0.2)	8.9 (0.2)	-16.1 (2.2)
Study 990120						
6 months	10.6 (0.1)	10.7 (0.1)	-0.2 (1.1)	10.7 (0.1)	9.3 (0.1)	-13.1 (1.1)
1 year	10.7 (0.1)	10.9 (0.1)	1.4 (0.9)	10.7 (0.1)	9.7 (0.1)	-9.8 (1.3)
Study 990100						
4 wks	11.4 (0.5)	10.9 (0.3)	-5.8 (1.8)	11.7 (0.4)	10.0 (0.7)	-16.2 (3.4)
Study 20000159						
1 year	N/A	N/A	N/A	10.8 (0.1)	9.8 (0.1)	-9.0 (0.9)
2 years	N/A	N/A	N/A	10.8 (0.1)	9.8 (0.1)	-8.5 (0.9)



6. Is there a PK/PD relationship for efficacy parameters?

The sponsor developed a population PK/PD model to describe the suppression of plasma PTH concentrations with plasma cinacalcet concentrations in 2° HPT patients.

$$PTH = PTH_{baseline} \times \left(1 - I_{max} \times \frac{C_{cinacalcet}}{IC_{50} + C_{cinacalcet}}\right)$$

The sponsor set the estimated maximum proportion of PTH suppression (I_{max}) to be 1.0 and estimated the 50% PTH suppression (IC_{50}) was about 10 ng/mL of plasma cinacalcet concentration. The I_{max} and IC_{50} estimates are not reliable, since most patients did not achieve maximum PTH suppression (I_{max}) and only the slope between PTH concentrations and cinacalcet concentrations can be reliably estimated.

7. How were cinacalcet doses selected for 2° and 1° HPT?

Because of large interindividual variability in cinacalcet PK and PD profiles, no fixed dose is likely to result in effectiveness with appropriate safety margin among all patients. Hence, a dose titration scheme was used to individualize dose.

The starting daily dose of 30 mg cinacalcet was chosen for 2° HPT patients because it was generally well tolerated and lower doses did not appreciably lower PTH concentrations (Study 980126). A maximum daily dose of 180 mg cinacalcet was chosen because cinacalcet exposure increased proportionally with dose over the range of 30 to 180 mg and then plateaus at doses above 180 mg (Study 20000187). Once-daily dosing within this range, with 30 mg titration increments, was safe and effective in most 2° hyperparathyroidism patients receiving dialysis, and in patients with chronic renal insufficiency (Studies 20000236 and 20010239).

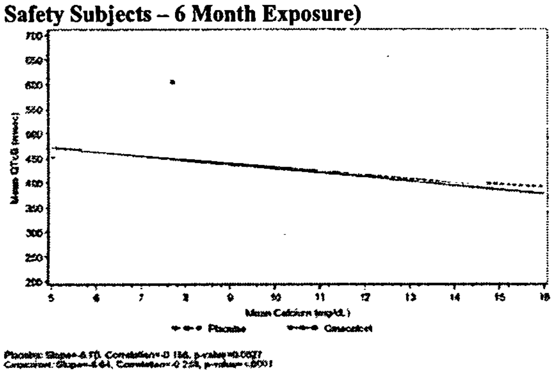
An unblinded Safety Monitoring Committee (SMC) evaluated the safety, PK, serum calcium, and PTH data after 8 days of dosing in these 3 cohorts. Cinacalcet PK was used to project drug concentrations expected at successive doses. After SMC's evaluation on the data for the 50-, 75-, and 100-mg cohorts, they determined that it was not appropriate to proceed to doses of 125, 150, and 175 mg because serum calcium was reduced to the normal range and, in some cases, below the normal range for the 24-hour dosing interval at doses of 50, 75, and 100 mg through Day 8 and because 3 of 8 subjects were withdrawn from the 100 mg group due to adverse events. Although PTH was reduced by approximately 50% to 60% at 2 hours postdose, PTH suppression was not maintained for 24 hours on each day of treatment. Preliminary PK/PD modeling suggested that twice daily dosing (at 12-hour intervals) with 30, 40, and 50 mg could provide a more prolonged suppression of PTH. Therefore, doses of 30, 40, and 50 mg BID were chosen for the twice daily phase of Study 980125.

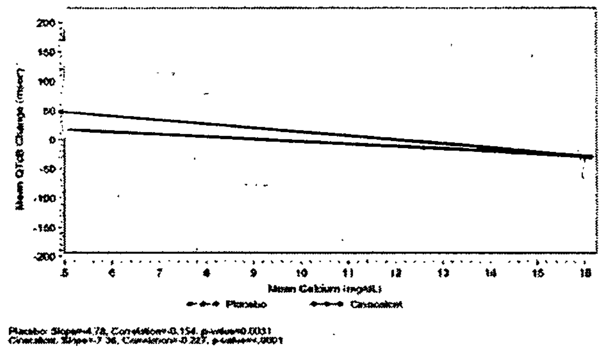
The higher dose range and the option of more frequent administration were based on experience with the 1st generation calcimimetic, R-568, in a subject with parathyroid carcinoma (Collins et al. Treatment of hypercalcemia secondary to parathyroid carcinoma with a novel calcimimetic agent. *J Clin Endocrinol Metab* **83**:1083-8 (1998)). Four times daily administration was selected based on expected efficacy, tolerance and compliance.

8. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? Is there a PK/PD relationship for safety parameters?
The most common adverse events (placebo, cinacalcet) of cinacalcet were nausea (19%, 31%), vomiting (15%, 27%), diarrhea (20%, 21%), and headache (17%, 16%) for Phase 3 clinical studies in end stage renal diseased patients. No exposure-safety relationship was explored for these adverse events.

Across Study 20000172's population (2° HPT), no relationship was observed between steady state, predose cinacalcet concentration and QTc interval. Further analysis within individual subjects showed no significant effect of changes in cinacalcet dose level on changes in QTc corrected either via Bazett's or Fidericia's method ($p = 0.417$ and $p = 0.405$, respectively). However, there was a significant but weak association between increases in QTc interval and reductions in serum calcium ($p < 0.001$; correlation = - 0.227). A multivariate linear regression analysis adjusting for age, gender, race, history of diabetes, history of congestive heart failure, and baseline QTc demonstrated that the magnitude of the increase in QTc averages 6 msec for each 1 mg/dL reduction in serum calcium.

Figures 10. QTc (Bazett's) Interval by Serum Calcium Levels at Week 14/18 (Phase 3 ESRD Safety Subjects – 6 Month Exposure). Figure 11. Change from Baseline in QTc (Bazett's) Interval by Serum Calcium Levels at Week 14/18 (Phase 3 ESRD Safety Subjects – 6 Month Exposure)





9. Does cinacalcet prolong QT interval?

Study 970035 examined the in vitro hERG channel blockade by cinacalcet at 500 ng/mL (about 10 times higher than the C_{max} for 90 mg cinacalcet dose). Cinacalcet blocked 11.7% (mean, SEM = 3.8%, n = 6) of the hERG channel. Dofetilide (10 μM, positive control) blocked 100% (mean, SEM = 0.0%, n = 3) of the hERG channel. The sponsor has not established the hERG channel IC_{50} for cinacalcet.

A slight prolongation of the QT interval, which was correlated with reduction in serum calcium concentrations, was observed in monkeys that had received repeated doses of cinacalcet for 3 months (Study 100020). In a 12-month, repeat-dose study in monkeys, no ECG abnormalities were detected that could be attributed to cinacalcet administration (Study 100188). Reduction in ionized calcium concentrations was associated with a slight prolongation in QT interval, which was not statistically different between control and cinacalcet-treated animals.

Only 3 Phase 1 clinical studies (970241, 990751, and 20000187) collected ECGs at various time points including the time of the anticipated cinacalcet C_{max}. Additionally, ECGs were obtained at cinacalcet steady state during the multiple-dose phase of Studies 970241 and 20000187. Bazett's and Fridericia's correction formulae were used for correction of the QT-interval data for Study 20000187. The proportion of subjects with an increase from baseline interval of < 30 msec, 30 to 60 msec, and > 60 msec and the interval mean, median, and range were calculated. Subjects receiving cinacalcet and subjects receiving placebo had similar QTc intervals at any time point. Participants in Study 20000187 received cinacalcet doses from 25 to 300 mg once daily for 7 days. In this study, the results for QTc were similar among all dose groups and between cinacalcet and placebo groups regardless of the correction formulae. Likewise, the results of the categorical analyses did not reveal differences or trends within or between treatment groups.

In general, the sponsor explained the observed cardiovascular effects upon cinacalcet administration in Phase 3 clinical studies as:

- hypocalcemia associated QT prolongation, which is due to ST segment prolongation (without clinical consequences) rather than changes in ______ (associated with ______). One patient in the placebo group (17210909 in the 20010240 extension study) experienced a transient episode of Torsade de Pointes during a

period of cardiac instability and resuscitative efforts and subsequently died due to cardiac arrest. Torsade de Pointes arrhythmia was not observed for any cinacalcet-treated patient in the phase 1, 2, and 3 clinical studies.
- dialysis associated syncope, which is not unexpected in dialysis population due to alterations of blood pressure and intravascular volume during dialysis

The sponsor has not conducted any study to evaluate cinacalcet's direct cardiac delaying repolarization potential in humans. Hence, the sponsor should conduct a clinical study with positive control to thoroughly evaluate cinacalcet's direct effect on QT prolongation in 1° HPT patients or healthy volunteers per the Preliminary Concept Paper "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs."

4.3 Intrinsic Factors

1. Do age, gender, body weight, smoking, and race affect cinacalcet PK?

Age, gender, body weight, smoking, and race effects on cinacalcet PK were analyzed via meta-analysis and population PK analysis. See Dr. Sang Chung's (clinical pharmacology and biopharmaceutics reviewer) review on meta-analysis and population PK analysis in Attachment. Majority of the plasma cinacalcet PK data for meta analysis were pooled from the 90 mg dose under fasting condition in healthy volunteers. Majority of the cinacalcet PK and PD (plasma PTH) data for population PK analysis were pooled from clinical studies with patients.

The results showed no impact of age, body weight, and body mass index on cinacalcet PK. Female and current smoker were identified as significant covariates on apparent clearance (CL/F). Apparent clearance was 40% lower in female than that in male and 38% higher in current smoker than that in nonsmoking 2° hyperparathyroidism patients. Race was not a significant covariate on the apparent clearance but central volume of distribution (V2/F) and intercompartmental clearance (Q/F). However, the sponsor concluded that those were not clinically significant with large inter-subject variability. Dose adjustment was not proposed per demographic factors because of individualization in dosing.

The sponsor did not propose labeling based on the results of meta-analysis and population PK analysis except geriatric patients as follows:

Exposure data for geriatric subjects (age≥65) were summarized in the following table and the sponsor's conclusion was acceptable based on the following results.

Table 11. Mean (SD) cinacalcet exposure (AUC and C_{max}) in age < 65 and age ≥ 65.

Age	Less than 65 (n=268)	Equal to or greater than 65 (n=12)
$AUC_{0\text{-}last}$	253.09 (175.87)	283.4 (192.35)
C_{max}	24.4 (15.05)	22.8 (15.28)

The sponsor did not study cinacalcet PK in humans < 18 years of age.

2. How does renal impairment affect cinacalcet PK?

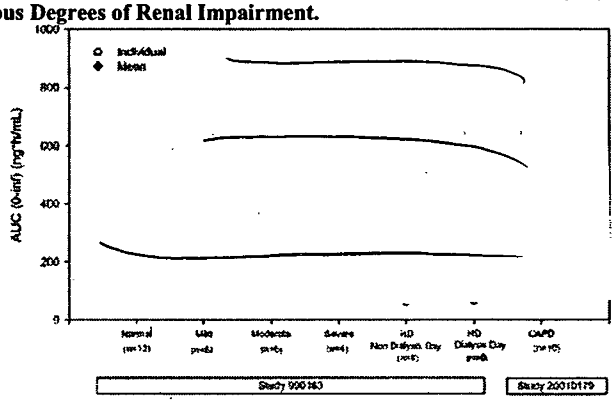
Study 990163 examined a 75 mg cinacalcet dose in healthy subjects and patients with mild, moderate, severe, and end stage renal disease (both off and on hemodialysis) under fasting conditions. In the hemodialysis patients group, the 1st cinacalcet dose was on a nondialysis day. After 2 weeks washout, the 2nd dose was 3 hours before hemodialysis. Classification of healthy and different stages of renal disease was per the Renal Guidance. Serial plasma samples were collected for 72 hours postdose to assess cinacalcet PK. Cinacalcet plasma protein binding was assessed for all subjects.

Study 20010179 examined a 75 mg cinacalcet dose in patients receiving continuous ambulatory peritoneal dialysis (CAPD) under fasting conditions ("add on" to Study 990163). Serial plasma samples were collected for 120 hours postdose to assess cinacalcet PK. Studies 990163 and 20010179's results are presented together below.

Table 12. Mean (SD) Single Dose PK Parameters in Subjects with Various Degrees of Renal Impairment. Figure 12. $AUC_{(0-inf)}$ in Subjects with Normal Renal Function vs. Subjects With Various Degrees of Renal Impairment.

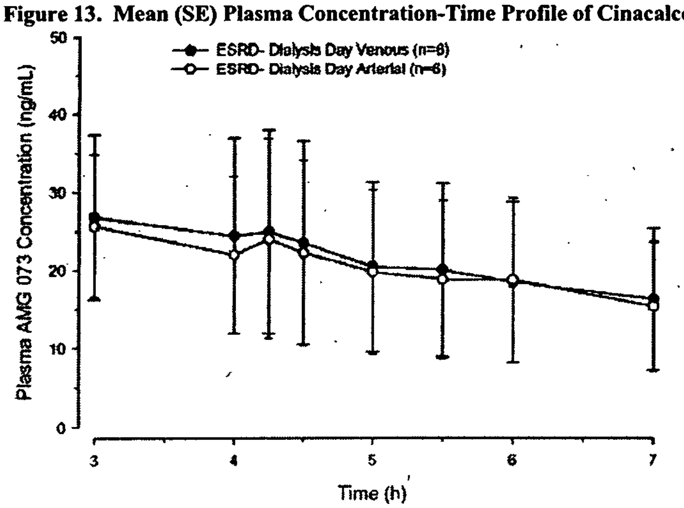
Study Number	990163						20010179[a]
Group	Normal (n=12)	Mild (n=6)	Moderate (n=6)	Severe (n=6)	HD Nondialysis Day (n=6)	HD Dialysis Day (n=6)	CAPD (n=10)
C_{max} (ng/mL)	28.6 (9.40)	40.1 (18.9)	14.8 (8.46)	20.6 (14.7)	25.0 (23.0)	30.1 (30 2)	22.9 (14.9)
t_{max}[b] (h)	6.00 (3.006.00)	6.00 (2 50-8.00)	5.00 (2.00-8.00)	6.00 (4.00-8.00)	2.30 (1.00-6.00)	3.50 (3.00-4.30)	3.25 (1.00-8.00)
AUC(0-t) (ng*h/mL)	272 (128)	423 (255)	178 (111)	286 (224)	282 (241)	281 (284)	228 (172)
AUC(0-inf) (ng*h/mL)	296 (143)	447 (264)	200 (126)	348 (302)	303 (254)	302 (298)	258 (187)
$t_{1/2,z}$ (h)	30.4 (8.48)	23.1 (13.8)	35.4 (9.56)	33.6 (14.1)	23.5 (10 7)	24.7 (7.11)	40 9 (23.1)
CL/F (L/h)	314 (148)	231 (140)	543 (348)	359 (198)	472 (418)	532 (457)	394 (199)

[a] Parameters are based on analysis of concentration-time values through 72 hours
[b] t_{max} is presented as median (range)
HD = Hemodialysis
CAPD = Continuous ambulatory peritoneal dialysis



HD= Hemodialysis
CAPD= Chronic ambulatory peritoneal dialysis

Figure 13. Mean (SE) Plasma Concentration-Time Profile of Cinacalcet in ESRD Subjects



No trend existed that cinacalcet exposure increased with increasing degree of renal impairment. Hemodialysis did not alter cinacalcet PK, which is consistent with cinacalcet's high plasma protein binding and large V_{ss}. Cinacalcet PK in patients receiving CAPD was similar to that in hemodialysis patients and healthy volunteers. Mean (SD) % cinacalcet plasma protein binding for the healthy volunteers and mild, moderate, severe, and dialysis patients were 94.7 (2.2), 94.7 (1.9), 92.7 (2.9), 93.1 (1.6), and 95.1 (1.4), respectively. Cinacalcet plasma protein binding did not appear to differ in these subject groups. Renal impairment does not appear to affect cinacalcet PK, which is consistent with cinacalcet being primarily eliminated via hepatic metabolism.

3. How does hepatic impairment affect cinacalcet PK?

Study 990162 examined volunteers with normal liver function and patients with various degrees of chronic liver diseases received a 50 mg cinacalcet ——— tablet under fasting conditions. Per Child Pugh Classification, the patients were classified to have mild, moderate, and severe hepatic impairment. Serial plasma samples were collected for 120 hours postdose to assess cinacalcet PK.

Table 13. Mean (SD) Cinacalcet PK Parameters in Healthy Volunteers and in Patients with Various Degrees of Hepatic Impairment After Receiving 50-mg Cinacalcet. Figure 14. Plasma Concentration-Time Profiles (Mean, SD) of Cinacalcet in Subjects with Various Degrees of Hepatic Impairment.

Parameter	Healthy Volunteers (n = 6)	Hepatically Impaired Patients: Mild (n = 6)	Moderate (n = 6)	Severe (n = 6)
AUC(0-inf) (ng*hr/mL)	181 (131)	186 (71.5)	442 (116)	769 (327)
C_{max} (ng/mL)	11.9 (6.62)	13.7 (6.20)	18.0 (3.17)	14.6 (3.60)
t_{max} (hr)	5.50 (2.17)	5.08 (2.65)	4.83 (2.98)	5.92 (2.58)
$t_{1/2}$ (hr)	49.2 (35.4)	36.9 (16.5)	65.3 (12.3)	83.6 (19.6)
CL/F (L/hr)	429 (282)	299 (98.4)	120 (31.5)	81.4 (51.0)
Protein bound (%)	96.4 (2.0)	96.9 (0.68)	97.1 (0.59)	94.7 (3.0)

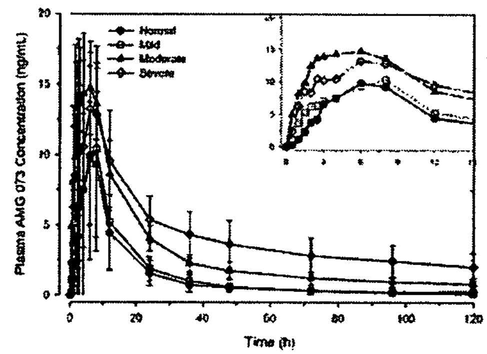
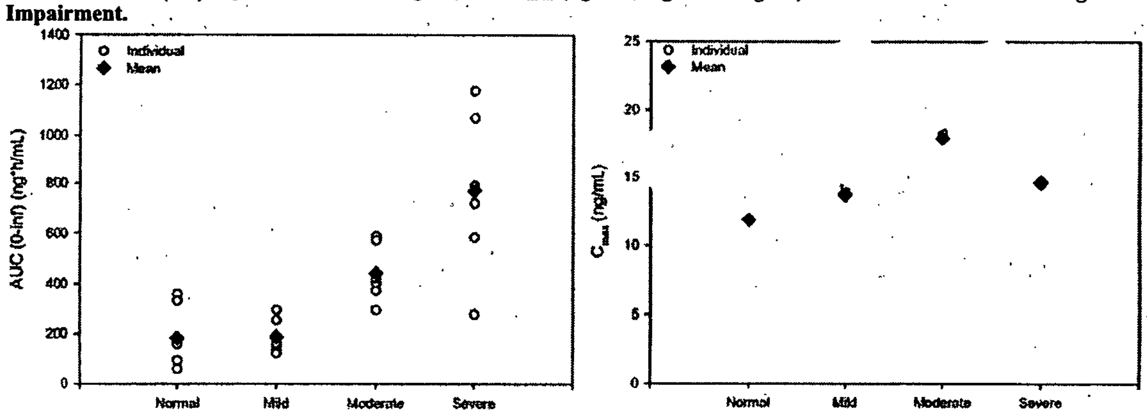


Figure 15. $AUC_{(0-inf)}$ (ng*h/mL; left sub-figure) and C_{max} (ng/mL; right sub-figure) in Patients with Various Degrees of Hepatic Impairment.



Mean cinacalcet $AUC_{(0-inf)}$ between healthy volunteers and mild hepatic impairment patients were comparable. However, mean cinacalcet $AUC_{(0-inf)}$ for moderate and severe hepatic impairment patients were 2.4 and 4.2 times higher, respectively, than that for healthy volunteers. Mean cinacalcet C_{max} for the hepatic impaired patients are 15 - 51% higher than that for healthy volunteers. Plasma protein binding among all subjects was similar. Use of cinacalcet in severely hepatic impaired patients should be monitored very carefully, because:

- circulating cinacalcet is primarily cleared via hepatic metabolism.
- Upon single dose administration, cinacalcet exposure increased 4.2-fold in severely hepatic impaired patients as compared to that for normal hepatic function subjects. Upon multiple dose administration, cinacalcet exposure in these patients may increase beyond the predictable accumulation index (2 fold for once daily dosing, 2 - 5 fold for twice daily dosing, and unknown higher fold for 3 and 4 times daily dosing) due to their lack of eliminating organ for cinacalcet.

4.4 Extrinsic Factors

1. How does food affect cinacalcet bioavailability?

Study 20010169 evaluated the effect of a high-fat meal and a low-fat meal on the oral bioavailability of 90 mg cinacalcet Phase III formulation tablet (the highest strength) in 29 healthy volunteers. The high-fat meal was per the Food Effect Guidance. The low-fat meal was 4 ounces of scrambled eggs, 2 slices of wheat toasts, 1 tablespoon jelly, 1 tablespoon margarine, 2 ounces of melon, and 4 ounces of apple juice. This was a crossover study with > 13 days washout between treatments. Serial plasma samples were collected for 72 hours postdose to assess cinacalcet PK.

Figure 16. Mean (SE) Plasma Concentration-time Profiles After Administration of a 90-mg Cinacalcet Phase III Formulation Tablet With a Low- and High-fat Meal and Under Fasted Conditions

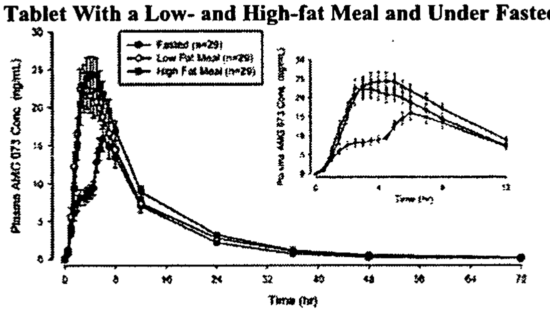


Table 14. Mean (SD) Pharmacokinetic Data with Point Estimates (90% Confidence Intervals) After Administration of a 90-mg Cinacalcet Phase III Formulation Tablet With a Low- and High-fat Meal and Under Fasted Conditions.

Parameter (units)	Fasted	Low-fat Meal	High-fat Meal
AUC(0-inf) (ng*hr/mL)	215	290	323
AUC(0-t) (ng·hr/mL)	189	261	296
C_{max} (ng/mL)	17.5	26.5	29.9
t_{max}[a] (hr)	6.00 (1.50-8.00)	3.50 (1.50-6.00)	4.00 (2.00-7.00)

[a] t_{max} presented as median (range)
Note: n = 29

Parameter	High-fat Meal vs Fasted	Low-fat Meal vs Fasted	High-fat Meal vs Low-fat Meal
AUC(0-inf)	168	150	112
AUC(0-t)	181	157	115
C_{max}	182	165	111

Values are expressed as a percentage
Note: n = 29

Cinacalcet C_{max} and $AUC_{(0-inf)}$ were increased 82% and 68%, respectively, under a high-fat meal as compared to that under fasting conditions. The low-fat meal vs. fasting conditions indicated that the C_{max} and $AUC_{(0-inf)}$ were increased 65% and 50%, respectively. Cinacalcet C_{max} and $AUC_{(0-inf)}$ upon high-fat meal was 11% and 12% higher, respectively, than that for a low-fat meal. Cinacalcet was administered with food or shortly after meals in clinical studies for both 2° and 1° hyperparathyroidism programs.

2. What are the drug-drug interaction studies for cinacalcet?

Coadministered drugs' effect on cinacalcet PK:

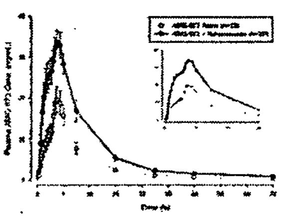
<u>A. Ketoconazole</u>

Randomized healthy volunteers received 200 mg oral ketoconazole twice daily for 5 days (Study 20000101). They received a single 100 mg ( ) cinacalcet dose with 200 mg ketoconazole under fasting conditions. During the crossover period, subjects received a 100 mg cinacalcet dose on Day 1. A washout of > 7 days separated the 2 periods. Serial plasma samples were collected for 72 hours postdose to determine cinacalcet PK.

A large unknown period effect existed, which did not relate to ketoconazole dose administration error. Both cinacalcet AUC and C_{max} increased > 3 times when cinacalcet was coadministered with ketoconazole during the 2nd period as compared to that when cinacalcet was administered alone during the 1st period. However, both cinacalcet AUC and C_{max} decreased 43% and 45%, respectively, when cinacalcet was coadministered with ketoconazole during the 1st period as compared to that when cinacalcet was administered alone during the 2nd period. The observation that cinacalcet exposure decreased with coadministration of ketoconazole is not consistent with in vitro metabolism data.

The ketoconazole-cinacalcet interaction study was repeated (Study 20010206). Randomized healthy volunteers received 200 mg oral ketoconazole twice daily for 7 days. They received a single 90 mg cinacalcet tablet with 200 mg ketoconazole on Day 5 under fasting conditions. During the crossover period, subjects received a 90 mg cinacalcet tablet (Phase III formulation) on Day 1. Fourteen days of washout separated the 2 periods. Serial plasma samples were collected for 72 hours postdose to determine cinacalcet PK.

Figure 17. Mean (SE) Plasma Cinacalcet Concentration-Time Profiles after Administration of cinacalcet Alone or cinacalcet with Ketoconazole. Table 15. Mean (SD) Cinacalcet PK Data, Point Estimates, and 90% Confidence Intervals.



Parameter	AMG 073 Plus Ketoconazole (n=20)	AMG 073 Alone (n=20)	Point Estimate[b] (90% CI)
AUC(0-t) (ng*h/mL)	517 (226)	255 (176)	220 (191-271)
AUC(0-inf) (ng*h/mL)	562 (230)	277 (191)	227 (192-267)
C_{max} (ng/mL)	39.1 (34.9)	22.7 (15.4)	216 (167-278)
t_{max}[a] (h)	5.50 (2.00 - 8.00)	5.00 (1.50 - 7.00)	---
$t_{1/2}$ (h)	31.2 (7.58)	29.3 (6.09)	---
CL/F (L/h)	190 (88.8)	556 (541)	---

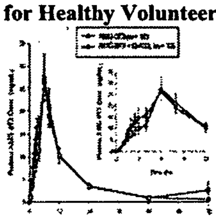
[a] t_{max} presented as median (range)
[b] Ratio (AMG 073 with ketoconazole: AMG 073 alone) of geometric means expressed as a percentage

No period effect existed in Study 20010206. Cinacalcet AUC and C_{max} increased 2.3 and 2.2 times, respectively, when 90 mg cinacalcet was coadministered with 200 mg ketoconazole twice daily as compared to that for 90 mg cinacalcet alone. This observation is consistent with in vitro metabolism data. Hence, cinacalcet dose adjustment may be required if a patient receiving cinacalcet initiates or discontinues therapy with a strong CYP3A4 inhibitor (eg, ketoconazole, erythromycin, or itraconazole).

B. Calcium Carbonate

Subjects received 100 mg (———————— tablets) cinacalcet alone and with 1500 mg (3 x 500 mg tablets) calcium carbonate under fasting conditions (Study 990791). A 21-day washout separated the 2 treatment periods. Serial plasma samples were collected for 72 hours to assess cinacalcet PK.

Figure 18. Mean (SE) Plasma Concentration-time Profiles of Cinacalcet in Healthy Volunteers Receiving 100 mg Cinacalcet Alone and 100 mg Cinacalcet Plus 1500 mg $CaCO_3$. Table 16. Mean (SD) Cinacalcet PK Parameters and Comparative Statistics for Healthy Volunteers Receiving 100 mg Cinacalcet and 100 mg Cinacalcet Plus 1500 mg $CaCO_3$.



Parameter (Units)	100 mg Cinacalcet	100 mg Cinacalcet + 1500 mg $CaCO_3$	Point Estimates (90% CI)
AUC(0-inf) (ng*hr/mL)	358 (150)	344 (175)	94.1 (81.0-109)
C_{max} (ng/mL)	27.7 (10.7)	26.4 (17.8)	94.8 (78.9-114)
t_{max} (hr)	5.33 (1.23)	5.42 (1.08)	102 (84.6-122)
CL/F (L/hr)	348 (159)	374 (182)	107 (92.6-125)
$t_{1/2}$ (hr)	20.9 (3.65)	19.2 (4.12)	91.1 (84.0-98.1)

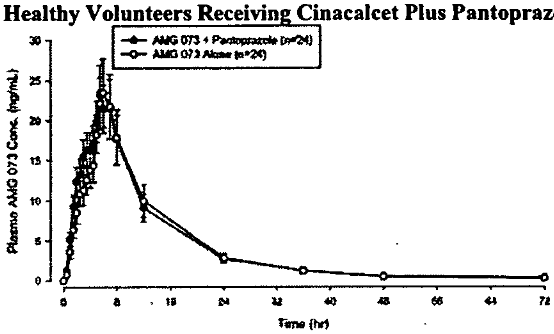
Note: n = 12
Note: Data is presented as point estimate (90% confidence interval) for the ratio of geometric means of cinacalcet + $CaCO_3$: cinacalcet alone

No significant drug interaction was observed when 1500 mg $CaCO_3$ was coadministered with 100 mg cinacalcet.

C. Pantoprazole

Cinacalcet was administered to healthy volunteers on 2 occasions as an oral 90-mg tablet (Phase III formulation) with a 13-day washout separating the 2 treatments (Study 20010207). Under fasting conditions, cinacalcet was administered on the final day (Day 3) of once daily 80 mg (2 x 40 mg tablets) pantoprazole dosing, and alone on Day 1 of the crossover period. Serial plasma samples were collected for 72 hours to assess cinacalcet PK.

Figure 19. Mean (SE) Plasma Cinacalcet Concentration-time Profiles after Administration of Cinacalcet Plus Pantoprazole or Cinacalcet Alone to Healthy Volunteers. Table 17. Mean (SD) Cinacalcet PK Parameters and Comparative Statistics for Healthy Volunteers Receiving Cinacalcet Plus Pantoprazole or Cinacalcet Alone.



Parameter (Units)	Cinacalcet + Pantoprazole (n = 24)	Cinacalcet Alone (n = 24)	Point Estimate [b] (90% CI)
AUC(0-inf) (ng*hr/mL)	305 (252)	294 (256)	101 (92.6-110)
C_{max} (ng/mL)	25.8 (18.4)	26.5 (20.9)	97.3 (87.3-109)
t_{max}[a] (hr)	5.50 (2.00-12.0)	5.50 (2.50-12.0)	---
$t_{1/2}$ (hr)	11.2 (8.91)	9.42 (7.38)	---
CL/F (L/hr)	614 (628)	632 (802)	---

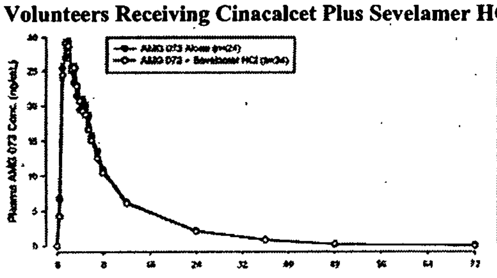
[a] t_{max} is presented as median (range)
[b] Cinacalcet + pantoprazole: Cinacalcet alone, presented as a percentage

No significant drug interaction was observed when 80 mg pantoprazole daily was coadministered with 90 mg cinacalcet.

D. Sevelamer HCl

Healthy volunteers received a 90 mg cinacalcet tablet (Phase III formulation) with 2400 mg sevelamer HCl (Study 20010205) after a 10-hour fast with consumption of a low-fat, low-caloric breakfast immediately followed dose administration. They received 2400 mg sevelamer HCl 2 more times on Day 1 and 3 times on Day 2. On a separate occasion separated by a 21-day washout, subjects received a 90 mg cinacalcet tablet alone under the same conditions previously.

Figure 20. Mean (SE) Plasma Cinacalcet Concentration-time Profiles After Administration of Cinacalcet Plus Sevelamer HCl or Cinacalcet Alone to Healthy Volunteers. Table 18. Mean (SD) Cinacalcet PK Parameters and Comparative Statistics for Healthy Volunteers Receiving Cinacalcet Plus Sevelamer HCl or Cinacalcet Alone.



Parameter (Units)	Cinacalcet + Sevelamer HCl (n = 24)	Cinacalcet Alone (n = 24)	Point Estimate [a] (90% CI)
AUC(0-Inf) (ng*hr/mL)	260 (	271	95.6 (87.3-105)
C_{max} (ng/mL)	36.4 (	37.8	93.2 (80.4-108)
t_{max}[b] (hr)	2.00	1.75	--
$t_{1/2}$ (hr)	9.09 (	9.53	--

[a] Cinacalcet plus sevelamer HCl: cinacalcet alone
[b] t_{max} presented as median (range)

Coadministration of 2400 mg sevelamer HCl 3 times daily did not change the cinacalcet PK upon oral administration of a 90 mg cinacalcet tablet.

E. Others

The effect of coadministering CYP3A4 inducers with cinacalcet is unknown. The effect of coadministering CYP2D6 inhibitors with cinacalcet is unknown.

Cinacalcet's effect on coadministered drugs' PK:

A. Amitriptyline

Study 980234 examined the effect of 25 and 100 mg (4 x 25 mg) cinacalcet) on amitriptyline PK (a 50 mg amitriptyline tablet) in a double-blind fashion. Randomized healthy men received 50 mg amitriptyline under fasting conditions on 3 occasions with: i) placebo, ii) 25 mg cinacalcet, and iii) 100 mg cinacalcet. A 14 day washout separated each occasion. Plasma samples were collected for 72 hours and 144 hours postdoses to assess cinacalcet and amitriptyline/nortriptyline (amitriptyline's metabolite) PK, respectively. Before the study, subjects received 30 mg oral dextromethorphan to phenotype for CYP2D6. Per the dextromethorphan to dextorphan urinary metabolic ratio, 15 subjects were extensive metabolizers and 3 were poor metabolizers.

Figure 21. Mean (SE) Plasma Amitriptyline and Nortriptyline Concentration-time Profiles for Extensive Metabolizers Receiving Cinacalcet.

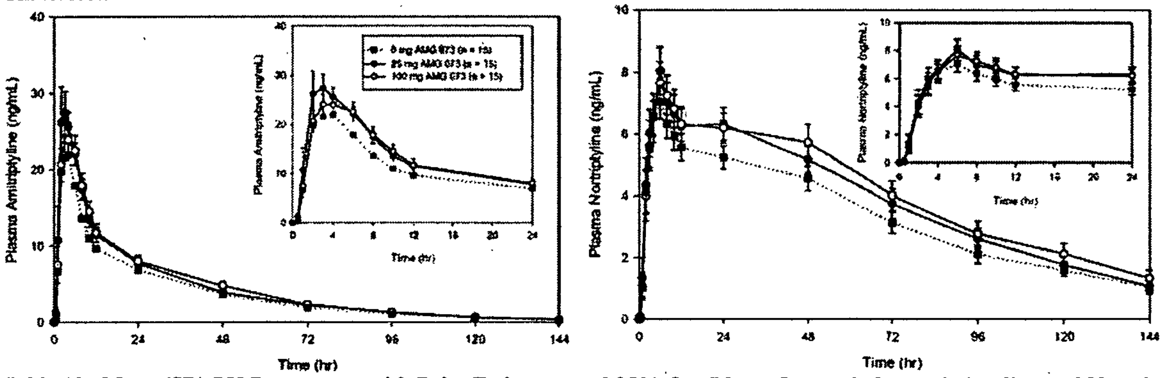


Table 19. Mean (SD) PK Parameters with Point Estimates and 95% Confidence Intervals for Amitriptyline and Nortriptyline in Extensive Metabolizers Receiving Cinacalcet.

Analyte	Amitriptyline (n = 15)			Nortriptyline (n = 15)		
Cinacalcet Dose (mg)	Placebo	25	100	Placebo	25	100
AUC(0-inf) (ng*hr/mL)	539 (204)	643 (216)	658 (256)	556 (221)	641 (245)	690 (289)
C_{max} (ng/mL)	26.8 (7.41)	33.3 (14.0)	30.0 (7.98)	7.33 (2.17)	8.24 (2.86)	8.58 (2.74)
t_{max} (hr)	2.87 (1.19)	3.13 (1.46)	3.33 (1.56)	5.53 (1.46)	11.1 (12.1)	11.1 (12.2)
CL/F (L/hr)	109 (51.7)	89.9 (43.8)	88.2 (36.6)	ND	ND	ND
$t_{1/2}$ (hr)	27.6 (7.40)	29.8 (8.21)	27.0 (7.47)	45.8 (17.9)	45.9 (10.1)	45.8 (13.8)

ND: Not determined

	Amitriptyline (n = 15)		Nortriptyline (n = 15)	
	25 mg Cinacalcet vs. Placebo	100 mg Cinacalcet vs. Placebo	25 mg Cinacalcet vs. Placebo	100 mg Cinacalcet vs. Placebo
AUC(0-inf)	1.21 (1.10-1.34)	1.22 (1.11-1.35)	1.17 (1.04-1.32)	1.23 (1.09-1.38)
C_{max}	1.21 (1.04-1.40)	1.13 (0.98-1.31)	1.11 (0.99-1.24)	1.15 (1.03-1.28)

Note: Data is presented as point estimate (95% confidence interval) for the ratio of geometric means of amitriptyline + cinacalcet: amitriptyline alone

In CYP2D6 extensive metabolizers, amitriptyline $AUC_{(0\text{-inf})}$ and C_{max} increased about 20% with coadministration of 25 mg or 100 mg cinacalcet. Nortriptyline $AUC_{(0\text{-inf})}$ increased 17 – 23% and C_{max} increased 11 - 15% with coadministration of 25 mg or 100 mg cinacalcet.

Figure 22. Mean (SE) Plasma Amitriptyline and Nortriptyline PK Profiles for Poor Metabolizers Receiving Cinacalcet (Separated by Dose).

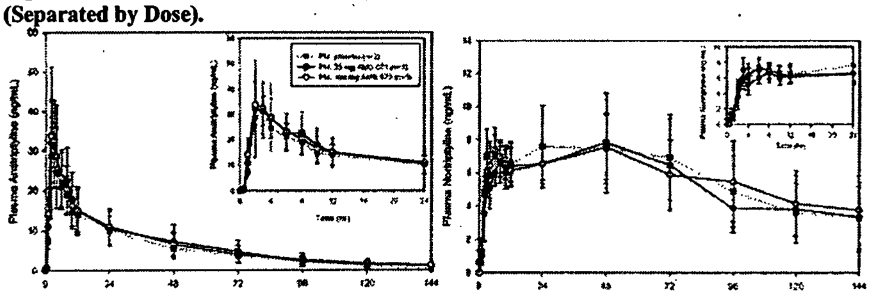


Table 20. Mean (SD) PK Parameters with Point Estimates and 95% Confidence Intervals for Amitriptyline and Nortriptyline in Poor Metabolizers Receiving Cinacalcet.

Analyte	Amitriptyline (n = 3)			Nortriptyline (n = 3)		
Dose (mg)	Placebo	25	100	Placebo	25	100
$AUC_{(0-inf)}$ (ng*hr/mL)	841 (498)	984 (878)	1000 (769)	1310 (1170)	1160 (972)	1400 (1110)
C_{max} (ng/mL)	31.9 (9.47)	36.9 (27.4)	34.5 (18.4)	8.51 (3.93)	8.92 (4.41)	8.41 (3.07)
t_{max} (hr)	2.33 (0.577)	2.33 (0.577)	2.33 (0.577)	25.0 (22.5)	25.0 (22.5)	20.7 (23.7)
CL/F (L/hr)	76.5 (45.8)	91.1 (77.4)	72.7 (48.1)	ND	ND	ND
$t_{1/2}$ (hr)	38.2 (13.5)	31.5 (7.49)	35.7 (10.2)	71.9 (46.6)	64.8 (30.7)	84.7 (43.3)

ND: Not determined

	Amitriptyline (n = 3)		Nortriptyline (n = 3)	
	25 mg Cinacalcet vs. Placebo	100 mg Cinacalcet vs. Placebo	25 mg Cinacalcet vs. Placebo	100 mg Cinacalcet vs. Placebo
AUC(0-Inf)	0.985 (0.67-1.70)	1.11 (0.64-1.91)	0.91 (0.75-1.11)	1.13 (0.93-1.37)
C_{max}	1.00 (0.58-1.72)	1.04 (0.60-1.79)	1.05 (0.91-1.20)	1.02 (0.84-1.12)

Note: Data is presented as point estimate (95% confidence interval) for the ratio of geometric means of amitriptyline + cinacalcet: amitriptyline alone

In CYP2D6 poor metabolizers, $AUC_{(0\text{-}inf)}$ and C_{max} for both amitriptyline and nortriptyline did not appear to change with coadministration of 25 mg or 100 mg cinacalcet.

The mean amitriptyline $AUC_{(0\text{-}inf)}$ with coadministration of placebo for extensive and poor metabolizers are 539 and 841 ng·hr/mL, respectively. The mean amitriptyline $AUC_{(0\text{-}inf)}$ with coadministration of 25 mg and 100 mg cinacalcet are 643 and 656 ng·hr/mL, respectively, for extensive metabolizers. Same observations existed for nortriptyline (also metabolized via CYP2D6). Hence, cinacalcet is an in vivo CYP2D6 inhibitor (amitriptyline $AUC_{(0\text{-}inf)}$ with coadministration of cinacalcet were within that upon coadministration of placebo for extensive and poor metabolizers), which is consistent with in vitro metabolism data. However, it is hard to see the full impact of cinacalcet's in vivo CYP2D6 inhibition potential via amitriptyline. Amitriptyline is metabolized via CYP2D6, 3A4, 1A2, and 2C19 (Levy et al. Metabolic Drug Interactions. page 234, 2000 edition, Lippincott Williams & Wilkins). Other CYPs may increase amitriptyline metabolism (shunting) when CYP2D6 is inhibited. The sponsor should study cinacalcet's in vivo CYP2D6 inhibitory effect via desipramine, preferred CYP2D6 probe substrate (Bjornsson et al. *J Clin Pharmocol* **43**:443-69 (2003)).

Due to the strong in vitro inhibition of CYP2D6 by cinacalcet, dose adjustments of concomitant medications may be required when cinacalcet is coadministered with drugs that are predominantly metabolized by CYP2D6 and have a narrow therapeutic index (eg, flecainide, vinblastine, thioridazine, and most tricyclic antidepressants).

B. Warfarin

Randomized healthy volunteers received 30 mg (________ tablets) cinacalcet or placebo twice daily for 8 days (Study 990778). They received a 25 mg racemic warfarin tablet on Day 5 or Day 34 of each crossover treatment period under fasting conditions. At least 20 days separated the 2 treatment periods. Serial blood samples were collected for 144 hours to assess R-warfarin and S-warfarin PK as well as prothrombin time and factor VII PD effect.

Figure 23. Mean (SD) Plasma Concentration of R-Warfarin (right side) and S-Warfarin (left side) After Cinacalcet Plus Warfarin and Placebo Plus Warfarin.

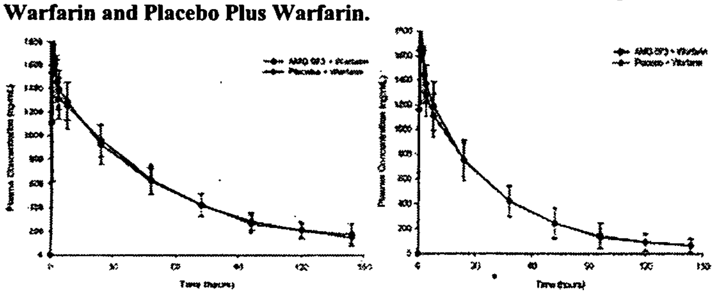


Table 21. Mean (SD) Comparative Statistics of R-Warfarin (right side) and S-Warfarin (left side) PK Parameters for Healthy Subjects Receiving Multiple Doses of Cinacalcet or Placebo.

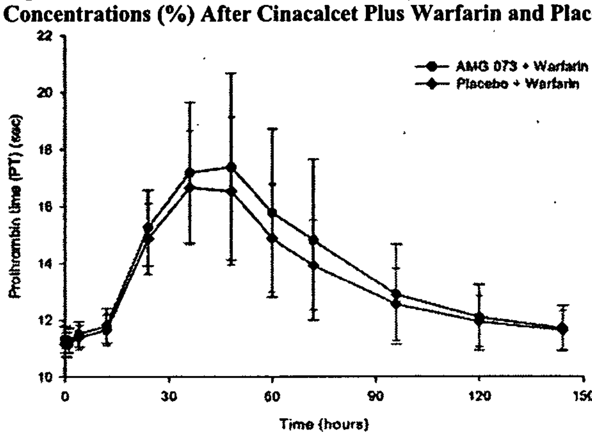
Parameter (Units)	Cinacalcet + Warfarin	Placebo + Warfarin	Point Estimates (90% CI)
AUC(0-inf) (ng*hr/mL)	89434.0	87820.7 (	101 (94.8-107)
C_{max} (ng/mL)	1728.2	1936.8	89.9 (84.0-96.3)
t_{max}* (hr)	2.00 (0.50, 4.00)	1.00 (0.50, 3.00)	–

* t_{max} is presented as median (range)
Note: Data is presented as point estimate (90% confidence interval) for the ratio of geometric means of cinacalcet + warfarin: warfarin alone

Parameter (Units)	Cinacalcet + Warfarin	Placebo + Warfarin	Point Estimates (90% CI)
AUC(0-inf) (ng*hr/mL)	60772.7	59730.5	98.9 (94.4-104)
C_{max} (ng/mL)	1770.5	2012.7	88.2 (82.6-94.1)
t_{max}* (hr)	2.00 (0.50, 8.00)	1.00 (0.50, 2.12)	–

\# t_{max} is presented as median (range)
Note: Data is presented as point estimate (90% confidence interval) for the ratio of geometric means of cinacalcet + warfarin: warfarin alone

Figure 24. Mean (SD) PT After Cinacalcet Plus Warfarin and Placebo Plus Warfarin. Figure 25. Mean (SD) Factor VII Concentrations (%) After Cinacalcet Plus Warfarin and Placebo Plus Warfarin.



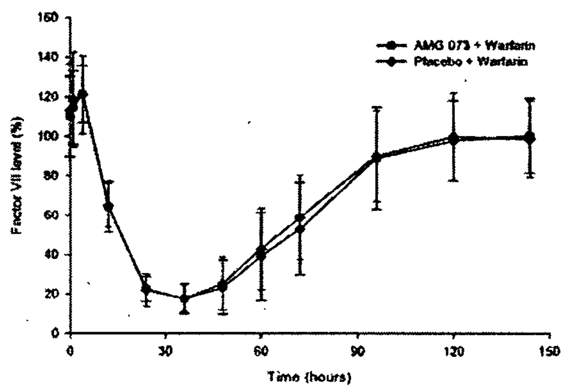


Table 22. Summary of Pharmacodynamic Parameters for Prothrombin Time and Factor VII After Multiple-Dose Administration of Cinacalcet or Placebo to Healthy Volunteers.

Parameter	Cinacalcet + Warfarin	Placebo + Warfarin	Point Estimates (90% CI)
	Prothrombin Time		
R_{max}	17.7 (3.11)	16.9 (2.33)	104 (102-105)
	Factor VII		
AUC(0-t)	9463.8 (2146.64)	9692.6 (2035.74)	97.0 (93.4-101)
max	127.0 (17.41)	128.2 (21.20)	99.6 (96.2-103)

AUC(0-t) = area under the curve from time 0 to the last measurable plasma concentration
max = observed maximal change in clotting factor VII
R_{max} = maximal rise
Note: Data is presented as point estimate (90% confidence interval) for the ratio of geometric means of cinacalcet + warfarin: warfarin alone

Both R-and S-warfarin PK were not affected when 30 mg cinacalcet twice daily was coadministered with 25 mg warfarin. Warfarin PD endpoints (maximal rise in prothrombin time and factor VII concentrations) were not affected when 30 mg cinacalcet twice daily was coadministered with 25 mg warfarin. Study 990778's design was used in Duursema et al. Model to detect warfarin-drug interactions in man. *Drug Invest.* 4:395-401 (1992) and Priskorn et al. Investigation of multiple dose citalopram on the pharmacokinetics and pharmacodynamics of racemic warfarin. *Br. J. Clin. Pharmacol.* 44:199-202 (1997). CYP2C9 is the major enzyme for metabolizing S-warfarin to its 7-hydroxy metabolite (Levy et al. Metabolic Drug Interactions. page 406 2000 edition). S-warfarin pharmacokinetics is not affected in the presence of multiple cinacalcet coadministration, which suggests that cinacalcet is not a CYP2C9 inducer.

4.5 General Biopharmaceutics

1. What class does cinacalcet HCl belong to the Biopharmaceutics Classification System (BCS)?

Cinacalcet HCl belongs to BCS class 4. It is a low solubility drug per BCS. Ninety mg cinacalcet (highest dose strength) would dissolve in about . at pH 1; see Section 4.1, Question

1 above). It is a low permeability drug per BCS. Eighty percent of the orally administered radioactivity is recovered in urine (Study 980233; see Section 4.2, Question 1, Metabolism section above), whereas the BCS guidance recommends ≥ 90% of the administered drug is recovered in urine to be classified as a high permeability drug.

2. Does difference exist between the to-be-marketed formulation and the pivotal clinical study formulation?

2° HPT Indication:

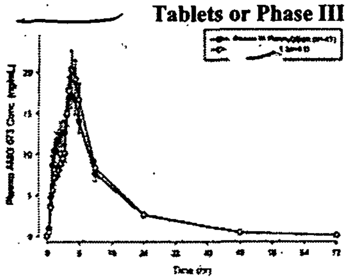
The 30, 60, and 90 mg cinacalcet tablets (Phase III formulation) used in key clinical studies (20000172, 20000183, 20000188, and 20010240) are identical to the to-be-marketed cinacalcet tablets, except that the tablet film coating was changed from (clinical to to-be-marketed formulation). This change was discussed in a meeting with the sponsor on December 5, 2002 and the change was acceptable. Per SUPAC Guidance for oral immediate release products' film coat changes (±1%) and similarity of in vitro dissolution data between the clinical and to-be-marketed formulation, the change to tablet film coating does not necessitate in vivo bioequivalence study documentation.

1° HPT and Parathyroid Cancer Indications:

Phase III formulation were used in 4 key clinical studies. The 15, 25, and 50 mg tablets were used in Studies 990120 and 990160. is different from the to-be-marketed formulation. The 30, 50, 70, and 90 mg cinacalcet tablets (Phase III formulation) were used in Studies 20000204 and 20000159.

can be linked to the to-be-marketed formulation via Studies 20010105 and 20000187. Study 20010105 examined the bioequivalence of cinacalcet when administered as a single 90-mg dose of tablets (15 mg + 25 mg + 50 mg) and a single 90-mg tablet of the Phase III Formulation tablet. Subjects received a single 90 mg cinacalcet dose on 2 occasions. This was a crossover study with 14 days washout between occasions. Serial plasma samples were collected for 72 hours postdose to assess cinacalcet PK.

Figure 26. Mean (SE) Plasma Cinacalcet Concentration-time Profile after Administration of 90-mg Tablets or Phase III Formulation Tablets. Table 23. Comparative Statistics of Cinacalcet PK Parameters after Administration of 90-mg Tablets or Phase III Formulation Tablets.



Parameter	Phase III Formulation (n = 41)	Formulation X (n = 41)	Point Estimate [a] (90% CI)
AUC(0-inf) (ng*h/mL)	245	255	96.0
C_{max} (ng/mL)	20.9	22.1	98 0
t_{max} [b] (hr)	5.50	6.00	-
$t_{1/2}$ (hr)	10.3	10.7	-
CL/F (L/hr)	543	537	-

[a] Ratio (Phase III Formulation: tablets) of geometric means expressed as a percentage

[b] Median (range)

Per the 90% CI for cinacalcet C_{max} and $AUC_{(0-inf)}$ ratio, the total of 15, 25, and 50 mg of tablets are bioequivalent to a 90 mg Phase III Formulation tablet

Different strengths of tablets are not proportionally similar in formulation.

Table 24. Composition of Tablet Strengths.

Ingredient	w/w %[a] 5mg	15mg	25mg	50mg
Cinacalcet HCl[b]				
Pregelatinized starch				
Microcrystalline cellulose				
Povidone				
Microcrystalline cellulose				
Colloidal silicon dioxide				
Talc				
Crospovidone				
Magnesium stearate				
Total core tablet				
Opadry® II Green				
Opadry® Clear				

[a] All tablet strengths have the same tablet core weight of 200 mg

[b] Molecular weights of the HCl salt and the free base are respectively; therefore, the free base accounts for 90.74% of the salt

Study 20000187 (see Question 2 in Section 4.2 above) used various combinations of 25 and 50 mg cinacalcet tablets to establish PK proportionality of 25 - 200 mg cinacalcet oral doses.

Phase III Formulation and Phase III Formulation All Phase III formulation tablet strengths are weight proportional. The 30, 50, 60, 70, and 90 mg strengths were manufactured for the Phase II and III studies, and the 30, 60, and 90 mg strengths were selected for commercialization.

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3. What is the proposed in vitro dissolution method and specifications for the 30, 60, and 90 mg cinacalcet tablets?

The sponsor's proposed in vitro dissolution method and specification for the 30, 60, and 90 mg cinacalcet oral tablets follow (Table 25):

Apparatus	USP Type 2 [redacted]
Dissolution medium	[redacted]
Medium volume	
Medium temperature	[redacted]
Stirring speed	[redacted]
Sampling time	[redacted] minutes
Specifications	Not less than [redacted] (Q) of the labeled amount of cinacalcet is dissolved i [redacted] minutes

The sponsor's proposed in vitro dissolution method is acceptable. This dissolution method is used for the stability program of cinacalcet oral tablets, which was accepted during a telephone conference on November 19, 2001 with the sponsor (see IND 56,010 serial 132's review).

The sponsor's proposed single point in vitro dissolution specification approach is acceptable. The in vitro dissolution results of the clinical lots (F0822001 (90 mg), F0824001 (60 mg), and F0823001 (30 mg) in mean ± SD (range)) were 95.9 ± 1.0 ([redacted] 96.4 ± 3.9 ([redacted]), and 99.1 ± 1.2 [redacted] , respectively, at [redacted] minutes. Moreover, the commercial lots' ([redacted] tablet film coating) in vitro dissolution results also match that for the clinical lots. Per these results, the recommended in vitro dissolution specification for the 30, 60, and 90 mg cinacalcet tablets is "Not less than [redacted] (Q = [redacted]) of the labeled amount of cinacalcet is dissolved in [redacted] minutes."

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4.6 Bioanalytical

1 Are the bioanalytical methods properly validated?

Study	V0791AMG073-R	100861	100990	101377	100486	365791	102326 R-isomer	102326	102326 achiral
LOQ, ng/mL									
Recovery, %									
Linearity, ng/mL									
Accuracy, %									
Intraassay									
Interassay									
Precision, %CV									
Intraassay									
Interassay									

LOQ = lower limit of quantification; * = dilution; ξ = intraday; ¥ = interday; † = relative extraction from plasma to water. Studies 100308 and 101768 are cross-validation between the sponsor's original assay and assay and both studies met the acceptance criteria for Equivalence test.

For Study 980234, plasma amitriptyline and nortriptyline concentrations were determined via LC/MS. were used as internal standards for amitriptyline and nortriptyline, respectively. The amitriptyline and nortriptyline LOQ were and their linear range were . No further validation information was available.

For Study 990778, plasma R- and S-warfarin concentrations were determined via an HPLC-UV bioanalytical assay. The LOQ for both R- and S-warfarin were . The sponsor claimed that the validation of this assay included linearity, precision, accuracy, LOQ, specificity, separation, and stability. However, the bioanalytical report (6438-253) was not available.

5 page(s) of revised draft labeling has been redacted from this portion of the review.

A-14

6. Attachment

Meta-analysis and population pharmacokinetic analysis

1. Title: Review on Meta-analyses

2. Table of Contents

3. Executive summary

The sponsor assessed the effect of demographic factors (i.e., age, body weight, sex, or race) on cinacalcet exposure using meta-analyses of pooled data from clinical studies. Two methods were employed for the analyses: averages were compared (method 1) after sampling of cinacalcet exposure data by covariates from the pooled data, and population pharmacokinetic method (method 2) was used to characterize relationship between the covariates and cinacalcet exposure.

Brief summary of findings based on the method 1 was described in the NDA summary but detailed results were not provided in CPB section. Most plasma cinacalcet pharmacokinetic data were pooled for the method 1 from comparable dosing (i.e., 90mg dosing under fasting condition) in healthy subjects.

Population pharmacokinetic approaches followed recommendations in the current Guidances including model selection and validation criteria. Plasma cinacalcet and PD (i.e., plasma PTH) data were collected for the method 2 from clinical studies with patients.

The results showed no impact of age, body weight, and body mass index on cinacalcet pharmacokinetics. Female and current smoker were identified as significant covariates on apparent clearance (CL/F) based on the method 2; apparent clearance was 40% lower in female than that in male and 38% higher in current smoker than that in non-smoking secondary HPT patients. Race was not a significant covariate on the apparent clearance but central volume of distribution (V2/F) and intercompartmental clearance (Q/F). However, the sponsor concluded that those covariate effects on cinacalcet exposure were not clinically significant with large inter-subject variability, and dose adjustment will not be recommended based on demographic factors because of individualization in dosing.

The sponsor did not propose labeling based on the results of meta-analyses except geriatric patients as follows:

> The pharmacokinetics of SENSIPAR™ are similar in patients greater than, or less than, 65 years of age.

There is no major CPB issue.

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4. Individual Study Review

4-1. Meta-analysis using conventional approach (method 1)

The effect of covariates on cinacalcet exposure (AUC and C_{max}) was explored based on samplings of exposure data by covariates from the pooled-data. Pharmacokinetic data were pooled from primarily 9 studies (Study 20010118, 20010169, 20000150, 20000241, 20000224, 20010105, 20010205, 20010206, and 20010207). These studies were chosen based on the comparable dosing (i.e., 90mg under fasting condition) in healthy subjects. Additional 2 studies (Study 990163, and 20010179) were added in the analysis for age effect on cinacalcet exposure and data from patients were included. Number of subjects in the pooled data were 234 (female=80, male=154) from the 9 studies. Additional 46 subjects were added for the age effect, and 34 subjects were identified as patients with renal impairment. Exposure data from severe or ESRD patients were indicated with red circle in figure 1 and 2, and it appeared to be no apparent exposure difference to the exposure in others.

There was no apparent association between age/body weight and cinacalcet exposure ($AUC_{0\text{-}last}$ and C_{max}) as summarized in figure 1 and 2.

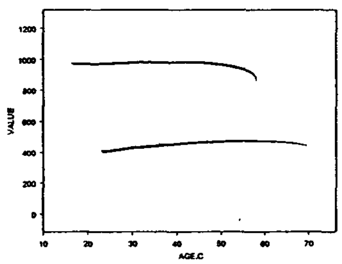

Figure 1 Relationship between age and plasma cinacalcet $AUC_{0\text{-}last}$ (red circle indicates data from ESRD with CAPD; Study 20010179). Total number of subjects was 280 from 11 clinical studies.

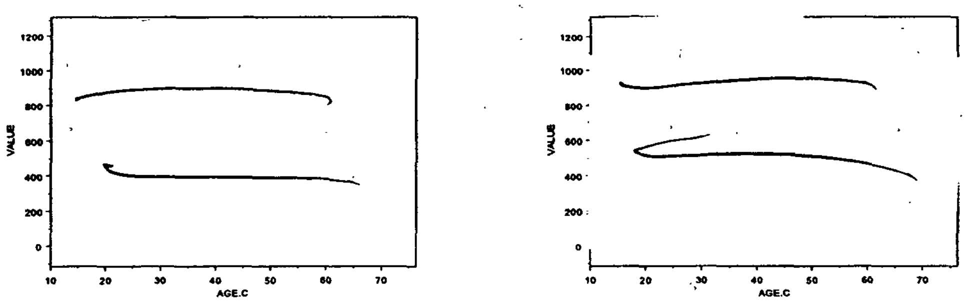

Figure 2 Relationsl

The sponsor proposed labeling on geriatric patients as follow:

However, exposure comparison results based on age categories to support the above labeling were not provided in CPB section. Exposure data for geriatric subjects (age≥65) were summarized by this reviewer in the following table and the sponsor's conclusion was acceptable based on the results.

Table 1 **Mean (SD) cinacalcet exposure (AUC and C_{max}) in age less than 65 and age equal to or greater than 65**

Age	Less than 65 (n=268)	Equal to or greater than 65 (n=12)
AUC_{0-last}	253.09 (175.87)	283.4 (192.35)
C_{max}	24.4 (15.05)	22.8 (15.28)

The sponsor concluded that there was no clinical significance of gender or race effect on cinacalcet exposure though female showed higher AUC (29% in average) than that in male, and AUC in other races was also higher than that in White (40% in average) (table 2 and 3). Other race included several ethnicities (i.e., Hispanic, or Asian pacific islanders) with small number of subjects.

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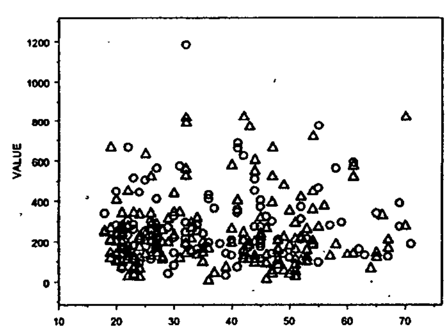
Table 2 **Gender effect on mean (SD) cinacalcet exposure (AUC and C_{max})**

	Female (n=80)	Male (n=154)
AUC_{0-last}	323 (203)	250 (172)
C_{max}	27.7 (14.8)	22.3 (14.7)

Table 3 **Race effect on mean (SD) cinacalcet exposure (AUC and C_{max})**

	White (n=191)	Black (n=24)	Other (n=19)
AUC_{0-last}	265 (174)	282 (176)	372 (275)
C_{max}	23.6 (14.4)	21.9 (10.6)	32.5 (22.2)

The exposure difference by gender was remaining even after body weight normalization; mean body weight difference between female and male was in average about 16% (71(13)kg vs. 83(17)kg). However, there was no apparent association between gender and cinacalcet AUC as summarized in figure 3. Mean (SD) AUC in female with age equal to or greater than 60 (n=8) was 273.8 (160.36) and it was not greater than that in total female. In addition, individualization will be recommended for dosing. In these regards, the sponsor's conclusions on no clinical significance effect of gender and race on cinacalcet were acceptable.



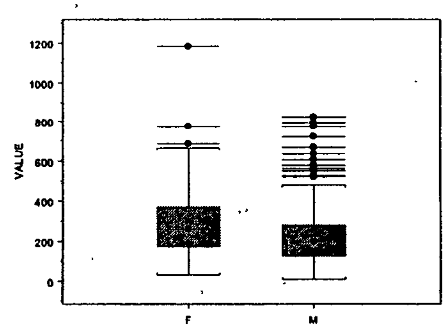


Figure 3 Gender (female in circle and male in triangle) association in the relationship between age and $AUC_{0\text{-}last}$ (left panel) and box plot for gender vs. $AUC_{0\text{-}last}$ (right panel)

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4-2. Meta-analysis using population pharmacokinetics (method 2)

Population pharmacokinetic approach was employed to estimate covariates effect on cinacalcet exposure using pooled data from clinical studies with secondary HPT patients (HPT/ESRD) or primary HPT patients.

4-2-1 Patients with secondary hyperparathyroidism (HPT/ESRD)

Cinacalcet exposure data for the final analyses were collected from mainly clinical studies with patient of HPT/ESRD (Study 980126, 20000187, 990101, 990102, 990740, and 20000237). Two studies were from Phase I (Study 980126, and 20000187) and others were from Phase II clinical trials. Except Study 980126, dosing was multiple doses, and dose-titration studies.

The population modeling was validated using two Phase III data (Study 20000172 (n=200), and 20000183 (n=160)).

Data set for the final model were from 218 patients and excluded data from dosing below 20mg and above 200mg because cinacalcet pharmacokinetics were linear between 20mg to 200mg according to the results of non-compartmental analyses.

Population PK model was developed using NONMEM and selection of optimal model was based on primarily significant objective function value (OBJ) change and conventional goodness-of-fit (GOF) results. Final structural PK model for the secondary HPT with ESRD was selected as 2-compartment with delayed first-order absorption and first-order elimination (figure 4). Residual error was assumed to be additive and proportional components. The stepwise additive modeling procedure was used to explore the covariate effect on the structural parameters using information criteria and conventional GOF results. NONMEM control record for the final population PK model was attached in the Appendix.

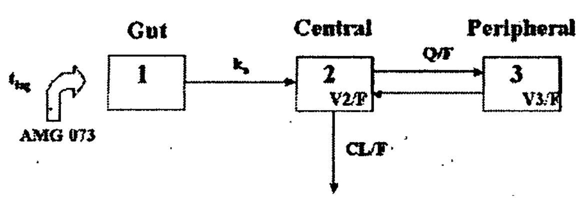

Figure 4 **Structural PK model for secondary HPT with ESRD**

The results of population PK estimates were summarized in the following tables.

Table 4 **Cinacalcet population PK parameters in secondary HPT/ESRD with inter-individual variability**

Parameter	Units	Parameter Estimate (SE)	Inter-individual Variance (SE)	Inter-individual variability (%CV)
Ka	h^{-1}	1.30 (0.25)	0.814 (0.252)	90.2
CL/F	L/h	234 (19)	0.302 (0.050)	55.0
V2/F	L	2650 (390)	0.516 (0.074)	71.8
V3/F	L	14700 (2200)	0 FIX (NA)	0 FIX
Q/F	L/h	160 (24)	0.339 (0.111)	58.2
Tlag	h	0.431 (0.025)	0.0199 (0.0139)	14.1

CL/F = oral clearance
V2/F = central volume of distribution
V3/F = peripheral volume of distribution
Q/F= intercompartmental clearance
Ka = first-order absorption rate constant
Tlag = absorption lag-time
NA = not applicable

Table 5 **Summary of residual error estimates from the final structure PK model**

Residual Error	Parameter Estimates (SE)
Proportional	Variance=0.240 (0.058); CV=49.0%
Additive	Study 980126: Variance=0.862 (0.722); SD=0.928 ng/mL
	Multiple-dose Study: Variance=3.77 (1.90); SD=1.94 ng/mL

The results of fixed-effect parameters from the final population PK model were summarized in the following tables.

Table 6 **Fixed-effect PK parameters (SE) of cinacalcet in secondary HPT/ESRD patients**

Parameter (unit)	Regression Model*	Parameter Estimates (SE)
Ka (h^{-1})	$Ka=\theta_1$	θ_1= 1.22 (0.27)
CL/F (L/h)	$CL/F=\theta_2*(1-SEX+\theta_7*SEX)*(1-SMOK+\theta_8*SMOK)$	θ_2=290 (26) θ_7=0.589(0.115) θ_8=1.36 (0.22)
V2/F (L)	$V2/F=\theta_3*(RAC1+ RAC2*\theta_9 +RAC3*\theta_{10} +RAC4*\theta_{11})$	θ_3=1870 (270) θ_9=1.61(0.30) θ_{10}=1.32 (0.42) θ_{11}=0 663 (0.240)
V3/F (L)	$V2/F=\theta_4$	θ_4=14600 (3100)
Q/F (L/h)	$Q/F=\theta_5*(RAC1+ RAC2*\theta_{12} +RAC3*\theta_{13} +RAC4*\theta_{14})$	θ_5=63.9 (24.6) θ_{12}=2.50 (0.60) θ_{13}=0.834 (0 339) θ_{14}=0 0639 (0.1520)
Tlag (h)	$Tlag=\theta_6$	θ_6=0.431 (0.026)

*Covariate coding: SEX = 0 for males, 1 for females
SMOK = 0 for non- and former-smokers, 1 for concurrent smokers
RAC1 = 1 for Caucasian, 0 otherwise
RAC2 = 1 for African American / Black, 0 otherwise
RAC3 = 1 for American Indian / Hispanic, 0 otherwise
RAC4 = 1 for Asian / Pacific Islander 0 otherwise

Table 7 **Summary of variance parameter estimates and residual variability in the final population PK model**

	Parameter	CL/F Males	CL/F Females	V2/F	V3/F	Q/F	Ka	Tlag
Inter-individual Variability	Variance	0.394 (0.099)	0.215 (0.084)	0.474 (0.076)	0 FIX (NA)	0.251 (0.106)	0.796 (0.218)	0.0220 (0.0149)
	%CV	62.8	46.4	68.8	0 FIX	50.1	89.2	14.8
Inter-occasion Variability	Variance	0.0506 (0.0153)		NA	NA	NA	NA	NA
	%CV	22.5		NA	NA	NA	NA	NA

NA- not applicable

Residual Error	Parameter Estimates (SE)
Proportional	Variance=0.239 (0.041); CV=48.9%
Additive	Study 980126: Variance=0.808 (0.669); SD=0.899 ng/mL
	Multiple-dose Study: Variance=3.00 (1.67); SD=1.73 ng/mL

The PK and PD (PTH level) were explored using population PK/PD modeling. Maximum suppression (I_{max}, eq. 1) from baseline was chosen based on preliminary direct relationship between plasma concentration and PTH level (figure 5), and significant OBJ change among several PD models. The estimated I_{max} was restricted to be less than or equal to 1.

$$PTH = PTH_{baseline} \times \left(1 - I_{max} \times \frac{C_{cinacalcet}}{IC_{50} + C_{cinacalcet}}\right) \qquad \textbf{Equation 1}$$

The PK and variance parameters were fixed and demographic covariate effect on PD were not assessed.

The population PD parameter estimates were summarized in the following table.

Table 8 **Population PD parameter estimates in the secondary HPT/ESRD patients**

Parameter	Unit	Parameter Estimate (SE)	Inter-individual Variance (SE)	Inter-individual variability (%CV)
$PTH_{baseline}$	pg/mL	508 (21)	0.292 (0.037)	54.0
Imax	—	1.00 FIX (NA)	—	—
IC50	ng/mL	10.6 (1.2)	1.27 (0.21)	113

NA = not applicable

4-2-2 Patients with

primary hyperparathyroidism (pHPT)

The population approaches were the same as those for secondary PTH/ESRD patients. Covariates and PD modeling were not attempted in the population analysis due to the limited sample size. Plasma cinacalcet data were merged from three clinical studies; Study 980125 (n=39), 990120 (n=37), and 990160 (n=6). Parameter estimates were summarized in the following table.

Table 9 **POP PK parameter estimates in primary HPT patients.**

Parameter	Units	Parameter Estimate (SE)	Inter-Individual Variance (SE)	Inter-Individual Variability (%CV)

CL/F = oral clearance
V2/F = central volume of distribution
V3/F = peripheral volume of distribution
Q/F= intercompartmental clearance
Ka = first-order absorption rate constant
Tlag = absorption lag-time
NA = not applicable

4-2-3 Summaries of findings by population PK analyses

- Estimated inter-individual variability in structural PK parameters were relatively large (i.e., 55% for CL/F)
- Gender and current smoker were identified as significant covariates for cinacalcet CL/F
    - female CL/F is about 40% lower than that in male.
    - CL/F of current smokers was modestly higher (36%) than that in non-smokers.
- Race was a covariate for V2/F and Q/F.
- There was no effect of age, body weight, BMI on cinacalcet exposure.
- The estimated population IC_{50} was 10.6 mg/ml with relatively large inter-individual variability (113% CV).
- The results of parameter estimated indicated comparable cinacalcet PK between primary and secondary HPT patients.

There was no major issue on the modeling and summaries of results. However, interpretation of results from the population PK/PD modeling should be limited by the modeling conditions. In general, most individual data indicated PTH suppression by cinacalcet was not in the maximum response (I_{max}) as showed in the following figure from a representative subject.

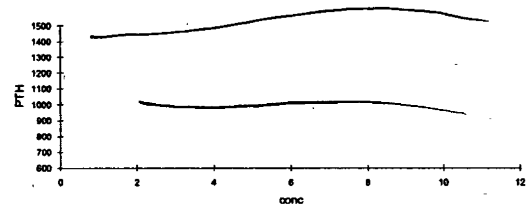

Figure 5 **Relationship between plasma cinacalcet concentration and PTH concentration in a patient.**

Therefore, utility of IC_{50} from the results should be limited within a defined condition.

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5. Labeling Comment
(Underlined text indicates addition and ~~strikethrough text~~ indicates deletion.)

The sponsor proposed labeling for geriatric patients as follows:

The labeling recommendation by the reviewer is as follows:

> The pharmacokinetics of SENSIPAR™ in geriatric patients (age ≥ 65, n=12) is similar to that for patients who are < 65 years of age (n=268) according to the results of meta-analysis.

15 page(s) of revised draft labeling has been redacted from this portion of the review.

A-15