Office of Clinical Pharmacology Review

NDA or BLA Number	21688 (pediatrics) / [redacted]
Link to EDR	• NDA 21688: \\CDSESUB1\evsprod\NDA021688\0109 • NDA [redacted] \\CDSESUB1\evsprod\NDA [redacted] \0001
Submission Date	December 2, 2016
Submission Type	Priority
Brand Name	SENSIPAR®
Generic Name	Cinacalcet HCl
Dosage Form and Strength	[redacted] Approved: 30, 60 and 90 mg tablets for administration orally
Route of Administration	Oral
Proposed Indication	[redacted] Approved: sHPT in adult patients with CKD on dialysis [redacted]
Applicant	Amgen
Associated IND	56010
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1. EXECUTIVE SUMMARY

The applicant submitted an efficacy supplement for cinacalcet HCl (SENSIPAR®) (NDA 21688, Sequence No. 0109) seeking (b) (4) The pediatric studies were conducted to satisfy the Written Request for SENSIPAR®. A New Drug Application (NDA) was also submitted (NDA (b) (4)) (b) (4)

The proposed starting dose in pediatric sHPT is 0.20 mg/kg based on the dry weight, and the dose can be titrated, no more frequently than every 4 weeks, to achieve a desired target parathyroid hormone (PTH) range. The maximum dose is 2.5 mg/kg/day, not to exceed a total daily dose of 180 mg.

SENSIPAR® has been approved for the treatment of sHPT with CKD on dialysis in adult patients. The recommended starting oral dose for adult patients is 30 mg oral tablet once daily with food or shortly after a meal. Dose of SENSIPAR® in adults can be adjusted, no more frequently than every 2 to 4 weeks, based on responses of intact parathyroid hormone (iPTH), serum calcium and serum phosphorus up to 180 mg once daily.

The sponsor did not fulfil the required minimum number of subjects who completed cinacalcet treatment for the efficacy and safety assessment per the agreement in Written Request (n=15 required; n=5 completed). Therefore, the pediatric exclusivity will not be granted.

1.1 Recommendations

Office of Clinical Pharmacology (OCP) has reviewed NDA 21688 supplement 109 and NDA (b) (4) The clinical pharmacology information including the exposure-response analysis submitted does not provide adequate data to support efficacy and safety of cinacalcet in pediatric population. The comments and recommendations are shown below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	**Deficiency for (b) (4):** • The primary efficacy and safety study required in Written Request (Study 20070208) was prematurely terminated due to a death. • The efficacy (i.e., iPTH change from baseline > 30%) was

	not shown following SENSIPAR in pediatric patients (refer details to the clinical and statistical reviews)
General dosing instructions	The proposed starting dose in pediatric sHPT is 0.20 mg/kg based on the dry weight, and the dose can be titrated, no more frequently than every 4 weeks, to achieve a desired target PTH range. The maximum dose is 2.5 mg/kg/day, not to exceed a total daily dose of 180 mg. The proposed starting dose is acceptable from a clinical pharmacology perspective.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Clinical pharmacology information supports the proposed starting dose of 0.2 mg/kg. Body weight based dosing may have lower hypocalcemia risk relative to that of dosing without body weight consideration as it shows less variability in exposure. However, the clinical relevance of body weight based dosing has not been demonstrated as the effectiveness of SENSIPAR has not been shown with dosing based on body weight brackets in pediatric patients.
Labeling	As the effectiveness of SENSIPAR has not been demonstrated in pediatric patients, (b) (4) Descriptive data will be stated in Section 8 of the label.
Bridge between the to-be-marketed and clinical trial formulations	The sponsor assessed relative bioavailability of cinacalcet oral capsule after the capsule contents were sprinkled onto applesauce or swallowed whole capsule with applesauce, referencing to the commercial oral tablets. Cinacalcet exposure with oral capsule following content sprinkled onto applesauce met bioequivalence (BE) criteria to that of the reference formulation. However, cinacalcet exposure following oral capsule swallowed intact with applesauce was not BE to the reference formulation. The (b) (4) oral capsule formulation was used in Phase 3 trials. Therefore, the PK bridging information is to refer clinical pharmacology information for oral capsule to commercial approved tablet.
Other (specify)	**Potential deficiency for (b) (4):** (b) (4)

	(b) (4)

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Cinacalcet is an allosteric modulator of the calcium sensing receptor (CaR) on the surface of parathyroid cells. Cinacalcet reduces serum parathyroid hormone (PTH) as it increases the sensitivity of the CaR to extracellular calcium concentration.

Cinacalcet (SENSIPAR®) has been approved since October 4, 2004 for the treatment of secondary hyperparathyroidism (sHPT) in patients with chronic kidney disease (CKD) on dialysis, for the treatment of hypercalcemia in patients with parathyroid carcinoma, and for severe hypercalcemia in patient with primary HPT who are unable to undergo parathyroidectomy.

Cinacalcet exposure was increased up to 82% when administered with food. Cinacalcet is known to undergo extensive metabolism with approximately 80% renal excretion as primarily metabolites. Responsible CYP isoforms are CYP1A2, 2C9, C19 and 3A4, and drug interaction is generally not significant (e.g., 27% AUC increase by ketoconazole). Its terminal half-life is 30 to 40 hours and steady-state is reached within 7 days. Hepatic impairment increases cinacalcet AUC up to 4.2-fold. Renal impairment including hemodialysis or peritoneal dialysis does not significantly affect cinacalcet exposure.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

SENSIPAR® tablets should be taken with food or shortly after a meal. Tablets should be taken whole and not divided. The recommended starting dose is 30 mg once daily for the sHPT in adult patients with CKD on dialysis. SENSIPAR® can be titrated no more frequently than every 2 to 4 weeks through sequential doses of 30, 60, 90, 120, and 180 mg once daily as necessary to achieve targeted intact parathyroid hormone (iPTH) levels, which should be measured no earlier than 12 hours after most recent dose.

For pediatric sHPT patients with CKD on dialysis, capsules are proposed to be administered orally by sprinkling contents on to a small amount of soft food or liquid or through nasogastric or gastrostomy tubes with a small amount (at least 5 ml) of water using polyvinyl chloride (PVC) tubing. Capsules should not be swallowed whole. Starting dose is proposed to be 0.20 mg/kg once daily based on the patient's dry weight and dose can be increased no more frequently than every 4 weeks as necessary to achieve targeted iPTH levels, which should be assessed at least 12 hours after dosing with SENSIPAR®.

2.2.2 Therapeutic individualization

The proposed pediatric initial dose is 0.20 mg/kg based upon dry body weight, which is without the excess fluid that builds up between dialysis treatments. Dose adjustments are dependent upon iPTH, total serum calcium, and the subject's safety status. If permitted by these parameters, subjects will be eligible for a dose increase once in 4 weeks.

The followings were specific instructions for a dose adjustment in the pivotal clinical trials (e.g., Study 20070208).

Increase to the next dose level if all of the following criteria are met:

- Plasma iPTH ≥ 300 pg/mL (31.8 pmol/L), and
- Corrected serum calcium is ≥ 8.4 mg/dL (2.1 mmol/L), and
- Subject has not reached the highest dry weight based dose, and
- Subject is not experiencing an adverse event such as symptomatic hypocalcemia, severe nausea, vomiting or diarrhea, or other event deemed by the investigator to be likely to be due to treatment that requires a dose decrease or precludes a dose increase.

Decrease the dose to the next lower dose level, if any of the following criteria have been met:

- The iPTH is < 150 pg/mL (15.9 pmol/L) and ≥ 100 pg/mL (10.6 pmol/L), or
- The corrected total serum calcium is < 8.4 mg/dL (2.1 mmol/L) and ≥ 8.0 mg/dL (2.0 mmol/L), or
- The subject is experiencing an adverse event such as mild nausea, vomiting, diarrhea, or any other adverse event deemed by the investigator to be possibly due to treatment that

requires a dose decrease, and does not require withholding the dose, per investigator assessment.

Withhold the dose at any time during the study if any of the following criteria have been met:

- Symptoms of hypocalcemia, regardless of the calcium level, or
- Corrected total serum calcium is < 8.0 mg/dL (2.0 mmol/L), or
- iPTH < 100 pg/mL (10.6 pmol/L), or
- The subject is experiencing symptoms of hypocalcemia, such as anxiety, muscular cramping or stiffness, twitching, tingling, paresthesia of the mouth or extremities, abdominal cramping, arrhythmias, hypotension, or convulsions, or other adverse events such as moderate or severe nausea, vomiting or diarrhea, or any other event deemed by the investigator to be likely to be due to treatment that requires a dose withhold, per investigator assessment.

2.3 Outstanding Issues

- **Adequate efficacy and safety data are not available**

The pivotal efficacy study (Study 20070208), which was one of studies required in Written Request, was prematurely terminated due to a death. Further, the efficacy of cinacalcet (i.e., iPTH change from baseline > 30%) was not shown following SENSIPAR in pediatric patients as compared to placebo (refer details to the clinical and statistical reviews).

- **Oral capsule to be used as content sprinkled**

According to the current regulatory guidelines/rules, an oral capsule is not considered as acceptable formulation for its content sprinkled. There is also a concern that the proposed packaging (i.e., capsules for sprinkling) might result in medication errors or risks when swallowed whole (e.g., chocking). The terminology 'capsule for sprinkle' is not acceptable and drug products should not be packaged in a container/closure system than implies or allows other than intended route of administration. Therefore, labeling for oral capsule content sprinkling onto food is not acceptable (refer details to the DMEPA/clinical review). The sponsor should consider an appropriate re-packaging of cinacalcet powder (e.g., sachet presentations).

- **Product specification for tubes**

Product specification did not meet the regulatory goal post for stability following nasogastric or gastrostomy tubes (refer details to the OPQ review). Therefore, labeling for gastric tubes is not acceptable.

2.4 Summary of Labeling Recommendations

- Proposed labeling by the sponsor (~~strikethrough~~ text indicates deletion, underlined text (b) (4) addition)

(b) (4)

- Recommendation by the review team (~~strikethrough~~ text indicates deletion, underlined text (b) (4) addition)

Sponsor's proposed labeling is not acceptable since (b) (4)
Descriptive information will be described in Section 8.

(b) (4)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The submission is under the priority review since studies have been conducted to satisfy the Written Request (WR, refer details in Appendix). The (b) (4) received an Orphan Drug Designation status on September 7, 2016 (Designation Request # 15-5113) (b) (4). The applicant is pursuing 6 month pediatric exclusivity and (b) (4) of exclusivity for the (b) (4)

The sponsor conducted 4 studies as required by the Written Request (Table 1). For a pediatric appropriate formulation, the sponsor developed oral capsules for sprinkling in soft food (Table 2). Although oral capsules were used in Phase 3 trials, the sponsor assessed relative bioavailability of cinacalcet after oral capsule administration referencing that of commercial approved tablets using the highest oral capsule strength (i.e., 5 mg) (Study 20070293).

Table 1 Summary of studies described in the Written Request (WR)

Study	Subjects (number of subjects)	Dosing Regimen	Primary endpoint(s)
20090005 • Phase 1 study (WR Study 1)	28 days to <6 years with CKD and 2nd HPT receiving dialysis (n=5 for 28 days to <3, n=9 for ≥3 to <6)	Single dose (0.25 mg/kg) using 5 mg capsule	PK, PD
20070208 • Phase 3 efficacy and safety study (WR Study 2)	6 to < 18 years old with CKD and secondary HPT receiving dialysis (n=43; 21 for PL, 22 cinacalcet)	Starting dose of 0.20 mg/kg based on dry weight, and the dose was titrated upward according to plasma iPTH and serum calcium levels. The maximum dose was 4.2 mg/kg, not to exceed a total dose of 180 mg for any subject. Formulation: 5 mg capsule, or commercial tablets for higher dose were used for cinacalcet treatment.	• efficacy of cinacalcet for reducing from baseline in the plasma iPTH by ≥ 30% over 30 weeks • PK was evaluated • the study was prematurely terminated due to a death
20110100 • Phase 3 safety study (WR Study 3)	28 days to <6 years with CKD and 2nd HPT receiving dialysis (n=18; 8 before PCH-cohort1, 10 after PCH – cohort2) (n= 4 completed, (3 for 26 wks, 1 in cohort 1 for 12 wks)	• Starting dose of 0.25 mg/kg, maximum allowed daily dose was 4.2 mg/kg (cohort 1) • Lower starting dose of 0.2 mg/kg, maximum daily cinacalcet dose to 2.5 mg/kg/day (cohort 2) *to add criteria for dose adjustment based on ionized calcium due to hypocalcemia concerns.* • For 5 mg capsules, the contents were either sprinkled on soft food and administered orally or mixed into sucrose syrup and administered orally or via nasogastric/gastrotomy tubes over 26 weeks	Proportion of subjects who develop corrected serum calcium levels < 9.0 mg/dL (2.25 mmol/L) for ages 28 days to < 2 years, and < 8.4 mg/dL (2.1 mmol/L) for ages ≥ 2 to < 6 years. Trough cinacalcet concentrations were measured.

20130356 • Phase 3 open-label study (WR Study 4)	6 to < 18 years old with CKD and sHPT receiving dialysis (n=48, 24 for cinacalcet + SOC*, 24 for SOC)	Starting dose of 0.20 mg/kg based on dry weight. Doses were: 2.5, 5, 10, 15, 30, 60, 90, 120, or 180 mg once daily for 20 weeks. Formulation: 5 mg capsule or 30 mg tablet	efficacy of cinacalcet for reducing from baseline in mean plasma iPTH by ≥ 30% from week 11 to 15 No PK assessment

* SOC: Standard of care, which included the use of vitamin D sterols (calcitriol and its analogs), calcium supplementation and phosphate binders

Table 2 (b) (4)

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The sponsor conducted two single dose studies in pediatric patients (Study 20090005, a study in WR, and Study 20030227, a preliminary study) to support study designs for dose-finding studies. Blood samples for PK and PD (e.g., iPTH and Ca) were collected from two pediatric Phase 3 studies for population analysis (Study 20070208 and Study 20110100, both in WR). Using available pediatric and historic adult data, the sponsor conducted population PK/PD analysis to support of efficacy in subjects less than 6 years of age (Report 122055). To support (b) (4) in subjects < 1 year old, the sponsor conducted physiologically-based PK (PBPK) modelling to predict the PK of cinacalcet (Report 122086). Finally, the sponsor conducted relative bioavailable study for oral capsules referencing the commercial approved tablets in healthy adult volunteers (Study 20070293). Overall clinical development program is summarized in

Figure 1.

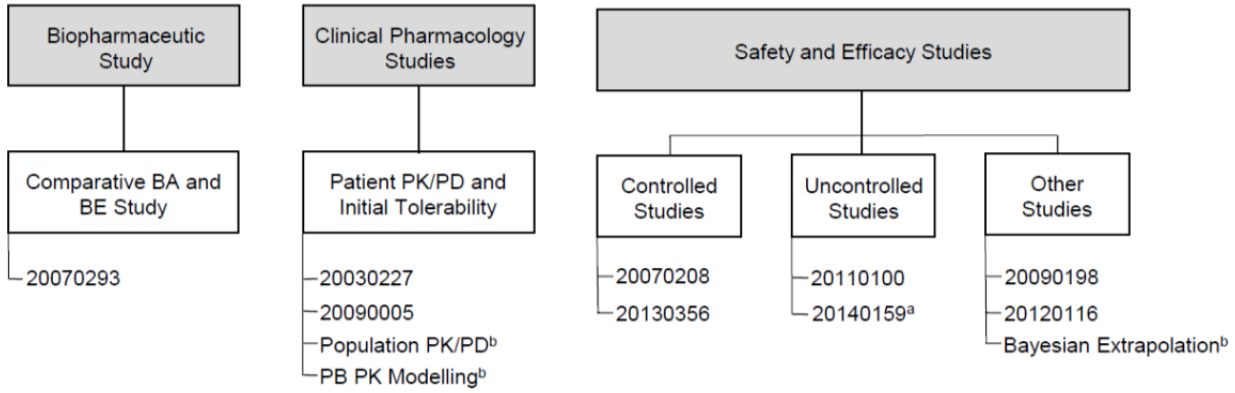


Figure 1 Schematic summary of clinical pharmacology programs
BA = bioavailability; BE = bioequivalence; PB = physiologically-based; PD = pharmacodynamic; PK = pharmacokinetic
[a] Ongoing study; interim analysis provided
[b] Cross-study analysis

The sponsor conducted two separate studies following the same dose for all subjects (i.e., 15 mg using half of 30 mg tablet, Study 20030227) and body weight based dose (i.e., 0.25 mg/kg using 5 mg capsule, Study 2009005) in pediatric patients. The body weight dosing was less variable in exposure compared to that of dosing without body weight consideration (Figure 2), and it may reduce exposure related potential safety concern for hypocalcemia. In general, cinacalcet concentrations after body weight based dose in the pediatric patients (age ranged from 8 to 61 months) were not significantly higher (Cmax; 2.83±1.98, Figure 3) than those after 30 mg tablet in adult healthy subjects (Cmax; 5.94±3.29 ng/mL, Study 20070293). Steady-state concentrations following daily body weight dosing were within expected range consistent with a 30-40 hours terminal half-life (Figure 4). Although cinacalcet exposure was not significantly

different among different administration methods (i.e., gastrotomy or nasogastric tubes, or oral administration, Figure 3), data are not sufficient to evaluate the impact of different administration methods on exposure due to limited sample size.

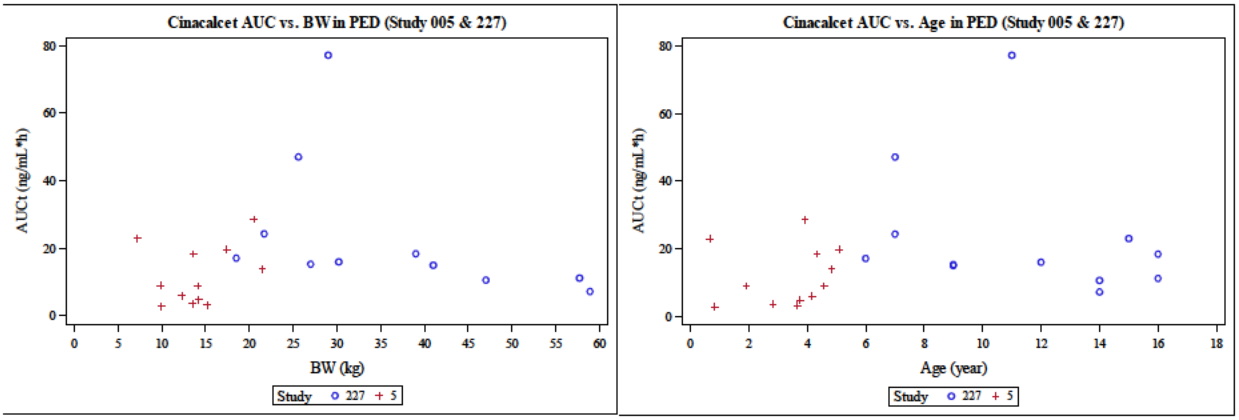


Figure 2 Relationship between body weight (left) or age (right) and cinacalcet AUC following single doses in Study 20030227 (15 mg) and 20090005 (0.2 mg/kg)

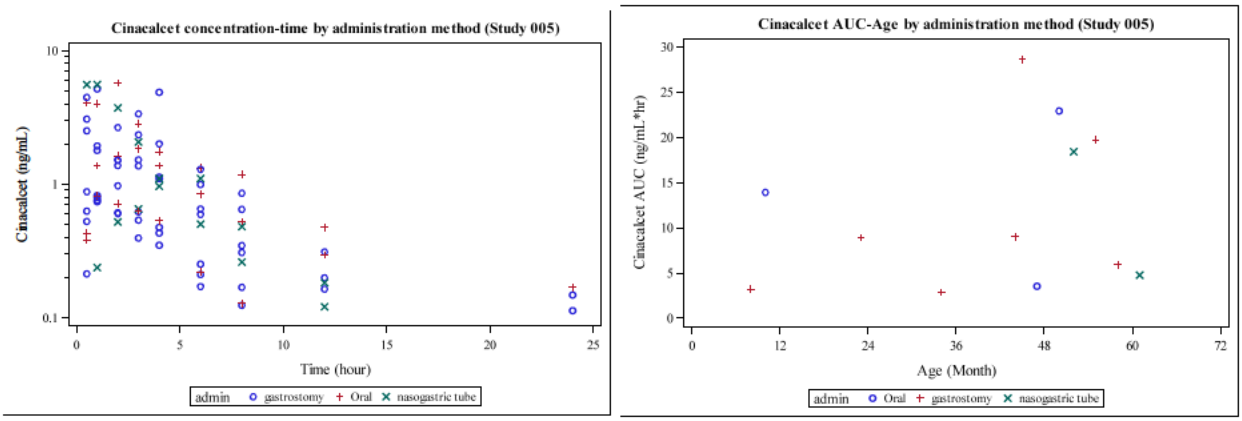


Figure 3 Cinacalcet concentration-time profiles (left) or AUC vs. age (right) following different administration methods (Study 20090005).

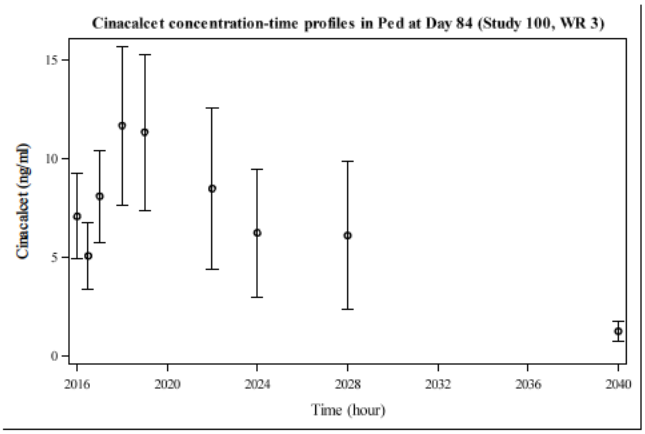
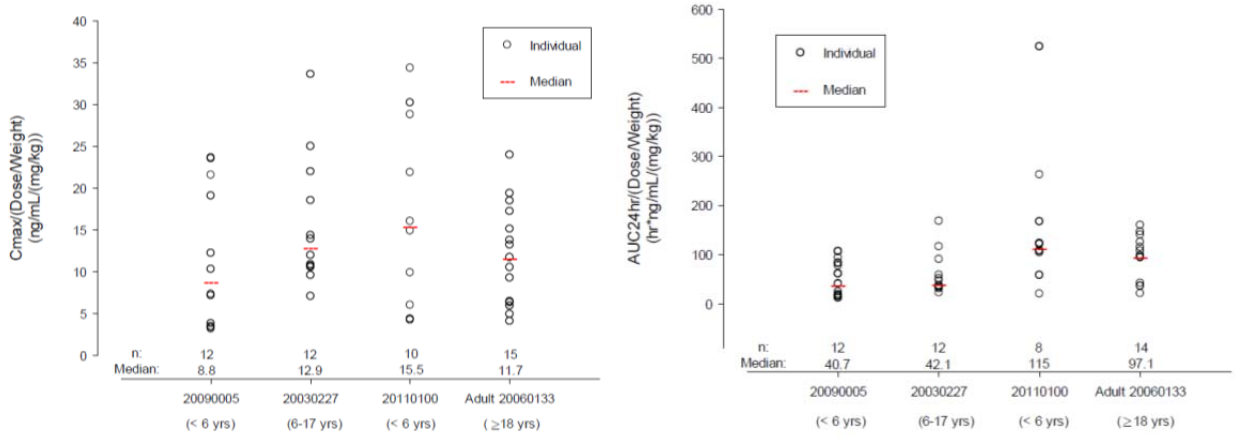


Figure 4 Cinacalcet concentration-time profiles following body weight based dosing at Week 12 (n=10, Study 20110100, Phase 3) (see summary of PK parameter in Appendix 1.1.4)

The sponsor conducted pooled PK data analysis across studies and results indicate that cinacalcet exposure was comparable across studies for pediatrics and adults (Figure 5).



Age range: 28 days to < 6 years old for Studies 20090005 and 20110100; 6 to < 18 years old for Study 20030227.

Figure 5 Dose- and weight-normalized cinacalcet Cmax (left) and AUC(0-24hr) across studies for pediatric and adult subjects (Study 2009005, 20030227, 20110100 and 20060133) (Source: Figure 11 and 12, 2.7.2)

The sponsor developed a population PK/PD model to describe cinacalcet PK and to evaluate the relationship between cinacalcet exposures and efficacy marker (iPTH) and safety marker (cCa). Covariates associated with exposure-response relationships were also evaluated in comparison with those in adults. Simulation was also performed to evaluate functions of multiple daily oral administration of cinacalcet in pediatrics patients with 28 days to 6 years of age. Cinacalcet plasma concentration and iPTH and cCa were pooled from 4 adults (20000172, 20000187, 970241, and 980126) and 4 pediatric studies (20070208, 20110100, 20030227 and 20090005), and doses ranging from 1 to 200 mg were administered orally in those studies. The dataset consisted of 3363 cinacalcet PK from 248 subjects and 8169 iPTH and 7074 cCa measurements from 444 subjects (Report 122055, see Table 13, Appendix 1.1.5 for study designs including number of subjects from each study).

- Population PK analysis results indicate that 2-compartment linear model with delayed first order absorption and first order elimination adequately describes cinacalcet pharmacokinetics (Appendix 1.1.5)
  - There were no statistically significant covariates were identified as predictors of PK variability using the final model
- A semi-mechanistic PK/PD model was introduced to describe the PK-PTH-calcium relationship (Appendix 1.1.5)

- The exposure of cinacalcet following multiple daily dosing showed linear or no time-dependent PK within dose range of 1 to 200 mg.
- The final model seems adequately describes the observed interactions between cinacalcet exposures, PTH and serum calcium. Inter-individual variability in cinacalcet PK parameters was quite high (58-88 CV%) and that in PD parameters were higher.
- No significant covariates on either PK or on PD were identified, thus it is not feasible to evaluate any dose adjustment scheme based on any covariate even on those related to baseline disease characteristic (iPTH, cCa, phosphorus, serum creatinine) with the PKPD modeling.
- Dose dependent response in iPTH and cCa was observed. The maximum median reduction in median iPTH was predicted to be <60% of baseline and <5% maximum median reduction in serum cCa at the highest simulated dose of 60 mg.
- The starting dose of 0.2 mg/kg appears to be reasonable since it minimizes safety concerns for hypocalcemia. Model-based simulations showed that the 0.2 mg/kg starting dose in pediatric patients is expected to generate minimal levels of PTH suppression (<10%) and negligible Ca suppression (<1%). Furthermore, this simulation is in good agreement with observed data from Study 20090005 where starting dose of 0.25 mg/kg was utilized. However, the simulation results with which the sponsor claims the target therapeutic response in iPTH could be achieved following multiple oral doses of >15 mg in pediatrics subjects with ages between 28 days and 6 years are not convincing due to large inter-individual variabilities resulting in wide prediction intervals.
- Although no covariates for PKPD model were identified, the sponsor introduced simulation to evaluate the effect of various rules for dose titration or dose withhold, e.g., monitoring corrected calcium weekly, removal of ionized calcium rule, or modified ionized calcium rules to compare number of dose withholds and the proportion of subjects receiving higher doses at the end of treatment. However, it is hard to utilize simulation to apply to an alternative dose-titration or dose-withhold rules due to the high inter-individual variability.

The sponsor conducted physiologically based pharmacokinetic modeling (PBPK) to predict the impact of age-dependent changes on cinacalcet PK for pediatric patients aged less than 1 year using SIMCYP® Simulator and pediatric module (Version 14.1) with introduction of in vivo ontogeny (Study 122086, refer further details in Appendix). The prediction results of cinacalcet PK in pediatric patients aged less than 1 year using the proposed PBPK modeling are not acceptable due to the following:

- Empirical modeling approach (i.e., using a minimal, one-compartment model with adjustment through sensitivity analysis) to provide reasonable prediction for two-compartment characteristics of cinacalcet PK

- The sponsor introduced *in vivo* ontogeny to improve age related pharmacokinetic changes to the default *in vitro* ontogeny of SIMCYP®. Validity/generalizability of *in vivo* ontogeny should be illustrated using additional drug examples.

There were extremely limited observations of cinacalcet concentrations in subjects below 1 year old (e.g., observations from approximately 8 months old subject). Therefore, predictability of the age-dependent change on cinacalcet PK for pediatric patients aged less than 1 year is not fully validated and thus not acceptable for extrapolation of efficacy and supporting an indication for age between 28 days to 1 year, especially in the consideration that cinacalcet efficacy and safety is inconclusive in pediatrics.

Overall, the proposed body weight dosing is acceptable from the clinical pharmacology perspective as it provides comparable exposure between pediatric and adult subjects. However, there were no adequate data to provide insight of inconclusive efficacy and safety data in older age group (approximately 6 to <18 years), and thus it is not acceptable for the exposure-response analysis to use as the pivotal bridging of indicated ages (i.e., from 28 days to <18 years).

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

While the proposed body weight dosing approach was acceptable based on PK/PD, the efficacy and safety was inconclusive in pediatric patients (Figure 6, refer details to statistical/clinical reviews).

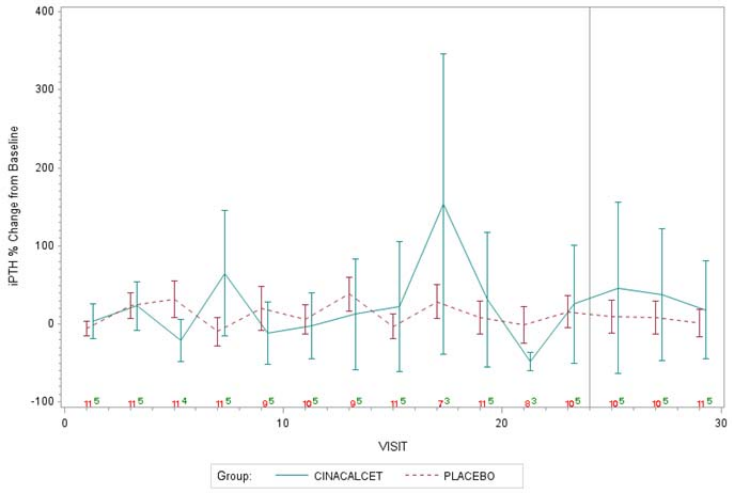


Figure 6 iPTH (%change from baseline) over visit from subject completed Efficacy Assessment Period (Study 20070208) (Source; Statistical Review by Dr. Sinks)

There might be potential difference in dosing between the proposed pediatric starting dose (i.e., 0.20 mg/kg) and actual doses administered due to body weight bracket for dosing (

Table 3) to accommodate available dosage form strengths (i.e., 1, 2.5, and 5 mg oral capsule). The actual dose administered to a pediatric patient using the brackets was significantly lower for some pediatric patients compared to that of nominal body weight based dose (Figure 7). For example, starting dose should be 9.8 mg for a patient with 49 kg body weight and the actual starting dose for the patient was 5 mg, which was approximately 50 % of nominal dose by body weight.

Further, the actual dosing scheme resulted in less than ¼ of starting dose in some pediatric patients compared to that of adult as 1) the proposed starting dose (0.2 mg/kg) was already approximately half the adult starting dose on the body weight basis (e.g., 0.5 mg/kg = 30 mg for 60 kg adult), and 2) starting dose in some pediatric patients was about 50% lower due to age brackets compared to that of nominal dose based on body weight.

Overall, the proposed dosing based on body weight bracket may result in significant between-subject variability in cinacalcet exposure due to body weight brackets. However, it may not attribute to lack of efficacy since the iPTH % change from baseline in subjects discontinued early was not apparently worse than that of subjects completed efficacy assessment phase (EAP) (refer biostatistics review). There were safety concerns due to hypocalcemia when a starting dose of 0.25 mg/kg was used (Study 20110100), thus indicating that 0.2 mg/kg was acceptable starting dose.

Table 3 Summary of possible pediatric starting dose and dose titration in clinical trials

Dry weight (kg)	Starting Daily Dose[a] (mg)	Possible Dose Titration[b]					
		Titration Step					
		1	2	3	4	5	6
12.5 to 14	2.5	5	10	15	30	30	30
> 14 to 21	2.5	5	10	15	30	60	60
> 21 to 25	2.5	5	10	15	30	60	90
> 25 to 28	5	10	15	30	60	90	90
> 28 to 49	5	10	15	30	60	90	120
> 49 to < 75	10	15	30	60	90	120	180
≥ 75	15	30	60	90	120	180	180

Source: Table 1 CSR 20070208, Section 16.1.1

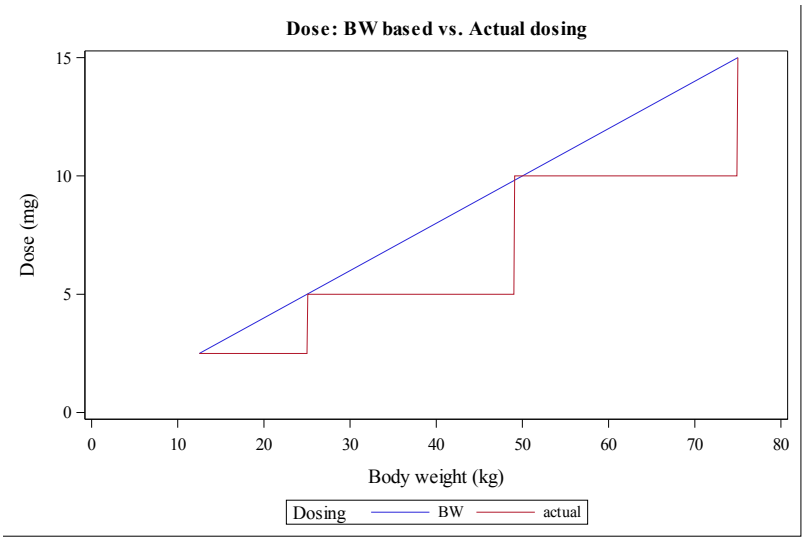


Figure 7 Difference in doses between nominal dose based on dry body weight (blue line) and dose administered (red line)

3.3.4 Are there the pivotal bridging for the proposed age appropriate formulation and use??

The sponsor developed a pediatric friendly formulation (capsules to be opened and sprinkled on soft food) and assessed its relative bioavailability compared to that of 30 mg commercial tablet in healthy adult volunteers (Study 20070293).

Cinacalcet exposure after 5 mg capsules (6 x 5 mg capsules) sprinkled onto and consumed with applesauce was bioequivalent to that of 30 mg tablet (Table 4). However, cinacalcet Cmax after swallowing intact capsule with applesauce did not meet bioequivalence criteria (Table 4). See appendix for details.

Table 4 Geometric Least Squares Means, Point Estimates, and 90% Confidence Intervals for the Ratio for Geometric Least Squares Means for Pharmacokinetic Parameter Estimates Following Administration of 30 mg Cinacalcet Given as 3 Different Cinacalcet Treatment Options to Healthy Adult Volunteers

	Geometric Least Square Mean[a]			Point Estimate[b] (90% CI)		
Parameter	A (N = 42)	B (N = 42)	C (N = 40)	A/B	C/B	C/A
AUC_{0-t} (ng*hr/mL)	41.6	46.8	46.6	0.889 (0.836, 0.946)	0.997 (0.935, 1.062)	1.121 (1.052, 1.194)
AUC_{0-inf} (ng*hr/mL)	45.2	50.7	50.7[a]	0.891 (0.839, 0.947)	1.000 (0.940, 1.065)	1.123 (1.054, 1.195)
C_{max} (ng/mL)	4.3	5.0	5.2	0.863 (0.796, 0.935)	1.037 (0.955, 1.126)	1.202 (1.107, 1.304)

[a] N = 38

[b] Point estimate and 90% confidence intervals (CI) are for the respective ratio of log-transformed AUC_{0-t}, AUC_{0-inf}, and Cmax values converted back to the original scale

A = 6 x 5 mg capsule whole; B = 1 x 30 mg tablet; C = 6 x 5 mg capsule sprinkled; AUC_{0-t} = area under plasma cinacalcet concentration-time curve from 0 to the last quantifiable concentration; AUC_{0-inf} = area under the plasma cinacalcet concentration-time curve from time 0 to infinity; C_{max} = maximum observed plasma cinacalcet concentration.

Source: Table 3, 2.7.1

The above study results support the bridging of dosing condition between adults and pediatrics as cinacalcet capsules were opened, and the contents were either sprinkled on soft food to be eaten by the subject in clinical trials (Study 20070293).

Sponsor has also proposed administration through nasogastric tubes, and provided CMC data to support the route of administration. In the clinical trials, oral capsules were opened, and the contents were suspended into sucrose syrup to create a liquid suspension and administered through the subject's feeding tube. (b) (4)

4. APPENDICES

4.1 Written Request (Amendment 5)

REVISED WRITTEN REQUEST – AMENDMENT 5

BACKGROUND:

These studies investigate the potential use of cinacalcet hydrochloride in the treatment of secondary hyperparathyroidism (HPT) in pediatric patients with chronic kidney disease (CKD) receiving dialysis. In 2007, approximately 2200 pediatric patients with CKD required maintenance dialysis in the United States.

Secondary HPT develops early in the course of CKD and progresses with worsening kidney function. Current treatment options include vitamin D sterols to reduce parathyroid hormone (PTH) levels, which may result in hypercalcemia and hyperphosphatemia. Hyperphosphatemia is controlled by a calcium-based phosphate binder; however, use is limited because calcium based phosphate binders also cause hypercalcemia. Hypercalcemia is a risk factor for soft tissue and vascular calcification. Therefore, calcium-based phosphate binders are not recommended for use in children with vascular calcifications.

Manifestations of secondary HPT in children include fractures, bone pain, bone deformities, and decreased bone mass; these manifestations are similar to those seen in adults. Of particular interest in the pediatric population is the role of secondary HPT in alteration of bone architecture, which may lead to growth retardation.

Cinacalcet hydrochloride has been shown to be safe and effective in simultaneously controlling PTH, calcium, and phosphorus, in adults on dialysis, and has the potential to meet this unmet medical need in the pediatric population. Although efficacy has been demonstrated in clinical trials in adults, there is not enough evidence to fully extrapolate efficacy from adult studies without additional supportive studies demonstrating a dose response in the pediatric population. Disturbances of calcium and phosphate metabolism pose an important threat especially to younger CKD patients, because childhood and adolescence are crucial times for development of the skeletal and vascular system.

Because there is not a product available for the treatment of children, and because the benefit of cinacalcet hydrochloride has not been demonstrated for children (clinical equipoise), a controlled trial is an appropriate trial design.

To obtain needed pediatric information on cinacalcet, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

Efficacy in pediatric patients ages 28 days to < 6 years with chronic kidney disease and secondary hyperparathyroidism receiving dialysis should be extrapolated from information gathered from adults and the studies outlined in this WR. An exposure-response analysis supporting this extrapolation must be submitted in response to this WR.

- *Clinical studies:*

Study 1: A single-dose PK/PD study in pediatric patients ages 28 days to < 6 years with chronic kidney disease and secondary hyperparathyroidism receiving dialysis.

Study 2: A 30-week, randomized, double-blind, placebo-controlled, safety and efficacy study with a 30-week, open-label, safety extension in pediatric patients ages 6 years to < 18 years with chronic kidney disease and secondary hyperparathyroidism receiving dialysis. This study will include an assessment of pharmacokinetic (PK) parameters using a sparse sampling design. Study 2 has been terminated early and will be analyzed with available data.

Study 3: A 26-week or time-until-transplantation (whichever comes first), open-label, safety study in pediatric patients ages 28 days to < 6 years. The final protocol including starting dose, dose titration scheme, and exclusion criteria will have to be approved by the Agency before this study is initiated.

Study 4: A 20-week, randomized, open-label, controlled study in pediatric subjects between the ages of 6 and < 18 years, with secondary hyperparathyroidism and chronic kidney disease who are receiving either hemodialysis or peritoneal dialysis.

- *Extension protocol:* An open-label extension protocol to Study 4 to assess longer term safety of cinacalcet for at least 7 additional months. A protocol will be submitted prior to fulfillment of the terms of this Written Request. Interim results will be submitted with the marketing application. While not a term of the Written Request, final results of this extension study will be submitted upon completion of the protocol.

In addition to the above studies, the following two items must also be submitted:

1) a summary of the published literature on use of cinacalcet in pediatric patients.

2) a summary of demographic and drug-use data from any national registry with greater than 6,000 registered pediatric dialysis patients. This summary is to include any available safety information about differences between patients treated with and without cinacalcet.

- *Indication to be studied:* the treatment of secondary hyperparathyroidism in pediatric patients with chronic kidney disease receiving dialysis.

- *Objective of each study:*

Study 1: To characterize the single-dose PK and PD profiles and collect data on the safety and tolerability of cinacalcet in pediatric patients ages 28 days to < 6 years with chronic

kidney disease and secondary hyperthyroidism receiving dialysis.

Study 2: In pediatric patients ages 6 years to < 18 years with chronic kidney disease and secondary hyperparathyroidism receiving dialysis:

- To demonstrate the efficacy of cinacalcet for reducing the plasma intact parathyroid hormone (iPTH) level
- To evaluate the long-term safety of cinacalcet in pediatric patients
- To characterize the PK profile and collect data on the safety and tolerability of cinacalcet in pediatric patients

Study 3: In pediatric patients ages 28 days to < 6 years with chronic kidney disease and secondary hyperparathyroidism receiving dialysis:

- To evaluate the safety and tolerability of cinacalcet in pediatric patients ages 28 days to < 6 years
- To characterize the PK profile in pediatric patients

Study 4: To evaluate the efficacy of cinacalcet for reducing the plasma intact parathyroid hormone (iPTH) level by ≥30% in pediatric patients ages 6 years to < 18 years with chronic kidney disease and secondary hyperparathyroidism receiving dialysis.

- *Patients to be studied:*
  - *Age groups in which studies will be performed*:
    - *Study 1*
      - 28 days to < 6 years
    - *Study 2*
      6 years to < 18 years stratified by age into the following cohorts:
      - 6 to < 12 years
      - 12 to < 18 years
    - *Study 3*
      28 days to < 6 years
    - *Study 4*
      6 years to < 18 years stratified by age into the following cohorts:
      - 6 to < 12 years
      - 12 to < 18 years

      At least 12 patients enrolled in Study 4 must be from the younger age

group and at least 10 of these patients must complete 12 weeks of the study and be included in the primary endpoint determination.

- *Number of patients to be studied:*
  - *Study 1*

    The study must be prospectively powered to achieve 80% power to detect a 0.48 mg/dL reduction from baseline in serum calcium in pediatric patients ages 28 days to < 6 years.

  - *Study 2*

    At least 40 patients should be enrolled in the study. The study will include an analysis of data of at least 14 patients who completed the double-blind portion of the study and at least 2 patients who completed the open label extension. With these available data, at least 25% of patients completing the double-blind phase will be 6 years to 12 years of age.

  - *Study 3*

    A minimum of 15 patients must complete this 26-week study. Patients who terminate the study prematurely to undergo a kidney transplant may be considered completers to satisfy this study requirement minimum if they have been enrolled in the study for at least 12 weeks.

  - *Study 4*

    At least 48 patients should be randomized (1:1 allocation). At least 40 patients must complete 12 weeks of the study and be included in the primary endpoint determination.

Representation of ethnic and racial minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*
  - *Pharmacokinetic endpoints:*

    Study 1

    The PK analysis must include estimates of the exposure (AUC), half-life, Cmax, and Tmax in pediatric patients 28 days to < 6 years of age.

    Study 2

The PK analysis must be performed for patients whose PK samples are collected in the treatment arm of the double-blind phase. For patients on hemodialysis, PK blood samples should be collected at baseline (pre-dose) and in the sampling windows of 1to < 3 hours post-dose or 3-24 hours post-dose. In addition, a trough sample and a sample in sampling windows of 1to < 3 hours postdose or 3-24 hours post-dose should be collected for every subsequent titration visit. Collection of post-dose PK samples should be well balanced between two sampling windows. Only trough samples need to be obtained from patients on peritoneal dialysis. PK samples must be collected from at least 80% of patients. The exact timing of blood samples must be documented.

PK parameters including apparent clearance (CL/F) and apparent volume of distribution (V/F) must be determined. The data may be obtained using a population PK analysis approach.

Study 3
PK parameters including apparent clearance (CL/F) and apparent volume of distribution (V/F) must be determined. The data may be obtained using a population PK analysis approach.

- *Pharmacodynamic endpoints:*

Study 1
At least three blood samples for iPTH and calcium must be collected up to at least 48 hours. The timings of these samples must be matched with the PK sampling nominal time points.

Study 2
Measurement of iPTH, calcium, phosphorus, and albumin must be performed to determine the changes in these endpoints across the course of therapy.

Study 3
Measurement of iPTH, calcium, phosphorus, and albumin must be performed at baseline and as needed to direct the course of therapy.

Study 4
Measurement of iPTH, calcium, albumin, and phosphorus must be performed to determine changes in these endpoints across the course of therapy.

- *Efficacy endpoints:*

Study 2

- The primary efficacy endpoint will be achievement of a ≥ 30% reduction from baseline in mean iPTH during the efficacy assessment phase (EAP).
- Important secondary endpoints must include
  - Achievement of a mean iPTH value ≤ 300 pg/mL during the efficacy assessment phase (EAP).
  - Growth velocity calculated from baseline to week 30 (end of controlled phase) and from week 30 to week 60 (end of study). Height data collection must meet current endocrinological standards.

Study 3

- Important secondary endpoints must include
  - Proportion of patients that have any decreases in iPTH of > 30% from baseline at two consecutive measurements.
  - Proportion of patients that have any normal iPTH values between 200 and 300 pg/mL at two consecutive measurements.

Study 4

- The primary efficacy endpoint will be the proportion of patients who achieve a ≥ 30% reduction from baseline in mean iPTH at weeks 11 and 15.
- Important secondary endpoints must include week 17 to 20 measurements of:
  (1) The proportion of patients who achieve a ≥ 30% reduction from baseline in mean iPTH and
  (2) the proportion of patients who achieve a mean iPTH value ≤ 300 pg/mL.

- *Safety endpoints:*

Study 1, Study 2, and Study 3, Study 4

- Safety outcomes must include:
  - Nature, frequency, severity, and relationship to treatment of all adverse events reported throughout the study
  - Patient incidence of hypocalcemia throughout the study (For Study 3, the primary endpoint will be the proportion of patients 0 to <2 years of age who develop corrected serum calcium levels <9.0 mg/dL and the proportion of patients ≥2 years to <6 years of age

who develop serum calcium levels <8.4 mg/dL)
- Vital signs and changes in laboratory parameters, including clinical chemistry.
- ECGs in a subset of patients
- The following adverse events must be actively monitored: hypocalcemia, seizures, and infections. All adverse events must be monitored until symptom resolution or until the condition stabilizes.
- All adverse events must be captured when spontaneously reported.

- *Exposure-response analysis*
  Study 1, Study 2, and Study 3
  The exposure-response analyses for studies 1, 2, and 3 must be performed for safety endpoints and effectiveness or pharmacodynamic endpoints (e.g., iPTH): a) to assess for the supportive evidence of effectiveness and b) to support the dosing recommendations.

- *Known drug-safety concerns and monitoring:*
  - Hypocalcemia – serum calcium concentration will be measured within one week after every dose change during the studies. Patients will be monitored and treated for signs and symptoms of hypocalcemia. Study 4 will include additional risk management strategies to mitigate the risk of hypocalcemia which will be prespecified in the study protocol.
  - Testosterone – testosterone levels in serum will be monitored during Studies 2 and 3 in male patients.
  - Tanner stage for both males and females will be measured at screening, week 30 (end of controlled phase of study 2), and at week 60 (end of Study 2).
  - Bone Health – linear growth velocity will be monitored. In addition, biomarkers of bone metabolism and DXA of the mid-shaft radius will be monitored in a subset of study participants in both treatment arms in Study 2.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

- *dosage form: capsules, tablets, and an age-appropriate formulation as necessary*
- *route of administration: oral*
- *regimen*

Study 1 – This study should explore doses based on mg/kg units. The doses must be selected such that the plasma concentrations are reasonably quantifiable using the available bioanalytical method to allow the estimation of PK and PD parameters.

Study 2 – The starting dose will be ≤0.20 mg/kg and titrated upward every 4 weeks based on plasma iPTH and serum calcium not to exceed the adult maximum dose of 180 mg.

Study 3 – The starting dose and dose titration must be approved by the Agency before the study is initiated.

Study 4 - The starting dose will be ≤0.20 mg/kg/day and titrated once monthly based on iPTH, serum calcium, ionized calcium and subject safety information. The maximum dose in this study will be 2.5 mg/kg/day based on screening dry weight or 180 mg/day, whichever is lower.

Use an age-appropriate formulation in the studies described above. If an age appropriate formulation is not currently available, you must develop and test an age appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), the Agency will publish a second notice indicating you have not marketed the new pediatric formulation if:

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation

that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Statistical information, including power of study(ies) and statistical assessments:

Study 1: Descriptive statistics must be provided for AUC, half-life, C_{max}, and T_{max}.

Study 2: Has been terminated early and will be analyzed with available data.

Study 3: The primary analysis population for the endpoint, the proportion of patients who develop corrected serum calcium levels < 8.8 mg/dL, must consist of all patients who received at least one dose of study medication and have at least one measured serum calcium level while on the study medication.

Study 4: Forty-eight patients will be randomized to receive cinacalcet plus standard of care or standard of care alone (1:1 allocation ratio). The primary analysis population should consist of all randomized patients. A plan for the statistical analysis is required to be included in the study protocol.

Studies 1, 2 3, and 4: Demographic and safety data must be tabulated and a descriptive analysis of safety data must be provided.

- *Labeling that may result from the studies*: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate

that cinacalcet is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

Format and types of reports to be submitted: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All postmarket reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the postmarket adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the Guidance addendum. You are encouraged to contact the Division of Metabolism and Endocrinology Products for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product*

Applications and Related Submissions Using the eCTD Specifications available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before **November 25, 2016**. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
10/14/2015

Reference ID: 3832575

4.2 Additional information (e.g., study design, PK) from individual studies

1.1.1 Study 20070293

The bioequivalence of 5 mg cinacalcet capsule was assessed reference 30 mg commercial formulation cinacalcet tablet in a conventional, open-label, randomized, single-dose (30 mg), 3-period, 3-treatment crossover study with healthy adult volunteers (Study 20070293).

Following an overnight fast of at least 10 hours, the following treatments were administered as randomized by treatment sequences with 4 mL of applesauce and 240 mL of water;

- Treatment A: 6 of the 5 mg capsules swallowed whole with applesauce,
- Treatment B: 1 commercial formulation 30 mg tablet swallowed whole with applesauce (reference), or
- Treatment C: contents of 6 of the 5 mg capsules sprinkled onto and consumed with applesauce

Pharmacokinetic parameters were summarized in Table 5 and results of statistical analysis for bioequivalence assessment were summarized in Table 6. Cinacalcet exposure (i.e., AUC and Cmax) following treatment C was bioequivalence to that of treatment B (reference) (Table 6). However, Cinacalcet exposure following treatment A was not bioequivalent to that of treatment B or C as Cmax of treatment A was not within the bioequivalence criteria (Table 6).

Table 5 Arithmetic Mean (SD) Serum Cinacalcet Pharmacokinetic Parameter Estimates Following Administration of 30 mg Cinacalcet Given as 3 Different Treatment Options to Healthy Adult Volunteers

	Treatment		
Parameter	A (N = 42)	B (N = 42)	C (N = 40)
AUC_{0-t} (ng*hr/mL)	53.3 (36.7)	58.3 (37.3)	57.6 (34.3)
AUC_{0-inf} (ng*hr/mL)	57.6 (40.2)	63.5 (41.7)	61.2[a] (34.4)
C_{max} (ng/mL)	5.30 (3.18)	5.94 (3.29)	6.16 (3.44)
t_{max} (hr)[b]	5.0 (2.0 – 8.0)	2.8 (1.0 – 6.0)	3.0 (1.0 – 6.0)
$t_{1/2}$ (hr)	19.8 (13.6)	22.6 (15.2)	20.7 (12.1)

[a] N = 38

[b] t_{max} is expressed a median (range)

A = 6 x 5 mg capsule whole; B = 1 x 30 mg tablet; C = 6 x 5 mg capsule sprinkled; AUC_{0-t} = area under plasma cinacalcet concentration-time curve from 0 to the last quantifiable concentration; AUC_{0-inf} = area under the plasma cinacalcet

concentration-time curve from time 0 to infinity; C_{max} = maximum observed plasma cinacalcet concentration; t_{max} = time to C_{max}; $t_{1/2}$ = terminal elimination half-life.
Source: Table 2, 2.7.1

Table 6 Geometric Least Squares Means, Point Estimates, and 90% Confidence Intervals for the Ratio for Geometric Least Squares Means for Pharmacokinetic Parameter Estimates Following Administration of 30 mg Cinacalcet Given as 3 Different Cinacalcet Treatment Options to Healthy Adult Volunteers

	Geometric Least Square Mean[a]			Point Estimate[b] (90% CI)		
Parameter	A (N = 42)	B (N = 42)	C (N = 40)	A/B	C/B	C/A
AUC_{0-t} (ng*hr/mL)	41.6	46.8	46.6	0.889 (0.836, 0.946)	0.997 (0.935, 1.062)	1.121 (1.052, 1.194)
AUC_{0-inf} (ng*hr/mL)	45.2	50.7	50.7[a]	0.891 (0.839, 0.947)	1.000 (0.940, 1.065)	1.123 (1.054, 1.195)
C_{max} (ng/mL)	4.3	5.0	5.2	0.863 (0.796, 0.935)	1.037 (0.955, 1.126)	1.202 (1.107, 1.304)

[a] N = 38

[b] Point estimate and 90% confidence intervals (CI) are for the respective ratio of log-transformed AUC0-t, AUC0-inf, and Cmax values converted back to the original scale

A = 6 x 5 mg capsule whole; B = 1 x 30 mg tablet; C = 6 x 5 mg capsule sprinkled; AUC_{0-t} = area under plasma cinacalcet concentration-time curve from 0 to the last quantifiable concentration; AUC_{0-inf} = area under the plasma cinacalcet concentration-time curve from time 0 to infinity; C_{max} = maximum observed plasma cinacalcet concentration.
Source: Table 3, 2.7.1

Reviewer's Comments:

- Two subjects did not finish assigned treatment at period 3. Conclusion for the bioequivalence of 5 mg capsule following content sprinkled onto applesauce (Test C) to 30 mg tablet was the same between balanced (excluding data from 2 subjects who did not complete all assigned treatment(s), yellow highlighted row, Table 7) and unbalanced PK data (Table 6).
- Variability of cinacalcet exposure was high with CV (%)>30 for both Cmax and AUClast following any treatments in the study (Table 8). It appears that cinacalcet capsule content sprinkled onto applesauce does not significantly change cinacalcet exposure variability compared to that of commercial tablet.
- The cinacalcet capsule formulation is thus considered bioequivalent to cinacalcet tablet formulation.

- Since the capsule formulation was used in pivotal pediatric clinical trials, this BE study was not considered as pivotal bridging study and hence no OSIS inspection was requested for the clinical and bioanalytical study sites.

Table 7 Ratios of Geometric Least Squares Means, and 90% Confidence Intervals for the Ratio for Geometric Least Squares Means for Pharmacokinetic Parameter Estimates using balanced data (without data from two subjects who did not complete all treatments*)

Dependent	Reference	Test	Ratio (%)	90% CL (lower, upper)
Cmax	B	A	87.28	80.32, 94.85
	B	C	104.24	95.92, 113.27
AUC	B	A	90.02	84.47, 95.93
	B	C	100.24	94.06, 106.82

* Subject 293001057 due to conmed at Period 3 and 293001080 due to unable to return at period 3

Table 8 Cinacalcet exposure variability (CV %) by treatments

Treatment	Cmax	AUC
A	60.0	68.8
B (reference)	55.3	63.9
C	55.9	59.6

1.1.2 Study 20090005 (WR Study 1)

Cinacalcet pharmacokinetics was evaluated in a single, open-label study in pediatric subjects 28 days to <6 years old with CKD and secondary HPT (sHPT) receiving dialysis (see study design in Figure 8).

Subject received 0.25 mg/kg cinacalcet. The dose is approximately half the adult starting dose on an mg/kg basis, and is lower than the mean dose of 0.39 mg/kg (range: 0.28 to 0.81 mg/kg) previously studied in 12 subjects age 6 to <18 years (Study 20030227).

Cinacalcet was supplied as 5 mg capsules for this study. The capsules were opened and the contents were mixed with purified water or United States Pharmacopeia-National Formulary (USP-NF) sucrose syrup. The water preparation was only for administration through either nasogastric or gastric tubes. The syrup preparation could be used for either oral or nasogastric/gastric tube administration.

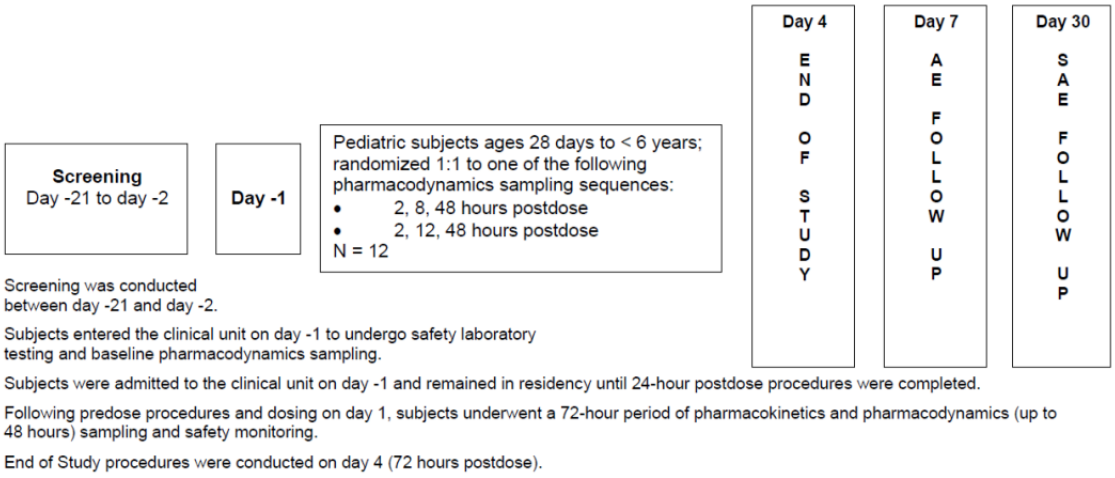


Figure 8 Schematic summary of study design and treatments (Study 005)

Table 9 Number of subjects (upper), dose (middle) and PK parameters (lower) by age groups

	Age Group: 28 days to < 3 years Subjects (N = 4)	Age Group: ≥ 3 years to < 6 years Subjects (N = 8)	Total Subjects (N = 12)
Age (months)			
n	4	8	12
Mean	18.8	51.5	40.6
SD	12.1	6.2	18.0
Median	16.5	51.0	46.0
Q1, Q3	9.0, 28.5	46.0, 56.5	28.5, 53.5
Min, Max	8, 34	44, 61	8, 61

	Age Group: 28 days to < 3 years Subjects (N = 4)	Age Group: ≥ 3 years to < 6 years Subjects (N = 8)	Total Subjects (N = 12)
Average Dose Delivered (mg)			
n	4	8	12
Mean	2.53	3.98	3.49
SD	0.66	0.87	1.05
Median	2.45	3.70	3.40
Q1, Q3	2.10, 2.95	3.30, 4.70	2.75, 4.10
Min, Max	1.8, 3.4	3.0, 5.4	1.8, 5.4

	Age Group: 28 days to < 3 years Subjects (N=4)		Age Group: ≥ 3 years to < 6 years Subjects (N=8)		Geometric Mean Ratio Cohort 1/ 2[b]	
Parameter (unit)	n	Mean[a]	n	Mean[a]	Mean	90% CI
$AUC_{0\text{-}inf}$(h*ng/mL)	4	6.60	7	10.40	0.63	(0.27 , 1.51)
$AUC_{0\text{-}last}$(h*ng/mL)	4	5.78	8	10.97	0.53	(0.22 , 1.27)
C_{max}(ng/mL)	4	1.34	8	2.77	0.48	(0.21 , 1.10)
$T_{1/2}$(h)	4	2.60	7	3.59	0.72	(0.40 , 1.31)
T_{max}(h)	4	0.94	8	1.41	0.67	(0.28 , 1.58)

Table 10 Descriptive Statistics of Pharmacokinetics Parameter Estimates for Cinacalcet in Plasma after Oral Administration of 0.25 mg/kg Cinacalcet to Pediatric Subjects < 6 Years of Age with CKD Receiving Dialysis (Study 005)

Parameter	t_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (hr•ng/mL)	AUC_{inf} (hr•ng/mL)	$t_{1/2,z}$ (hr)
Subjects 28 Days to < 3 Years of Age					
N	4	4	4	4	4
Mean (SD)	NR	1.51 (0.820)	7.21 (5.27)	8.31 (6.28)	2.73 (0.952)
Median	0.75	1.36	6.04	6.68	2.60
Min - Max	0.50-3.1	0.797-2.51	2.84-13.9	3.29-16.6	1.83-3.87
CV%	NR	54.5	73.1	75.7	34.9
Subjects ≥ 3 to < 6 Years of Age					
N	8	8	8	7	7
Mean (SD)	NR	3.50 (2.09)	14.1 (9.49)	12.9 (8.60)	4.26 (3.09)
Median	1.0	3.97	13.7	9.66	2.95
Min - Max	0.50-4.0	0.818-5.75	3.52-28.6	3.90-25.4	2.06-10.6
CV%	NR	59.9	67.3	66.5	72.6
All Subjects < 6 Years of Age					
N	12	12	12	11	11
Mean (SD)	NR	2.83(1.98)	11.8(8.74)	11.3(7.86)	3.70(2.57)
Median	1.0	2.18	8.96	9.66	2.95
Min - Max	0.50-4.0	0.797-5.75	2.84-28.6	3.29-25.4	1.83-10.6
CV%	NR	70.0	74.1	69.8	69.4

Source: Table 11-1, CSR Study 005

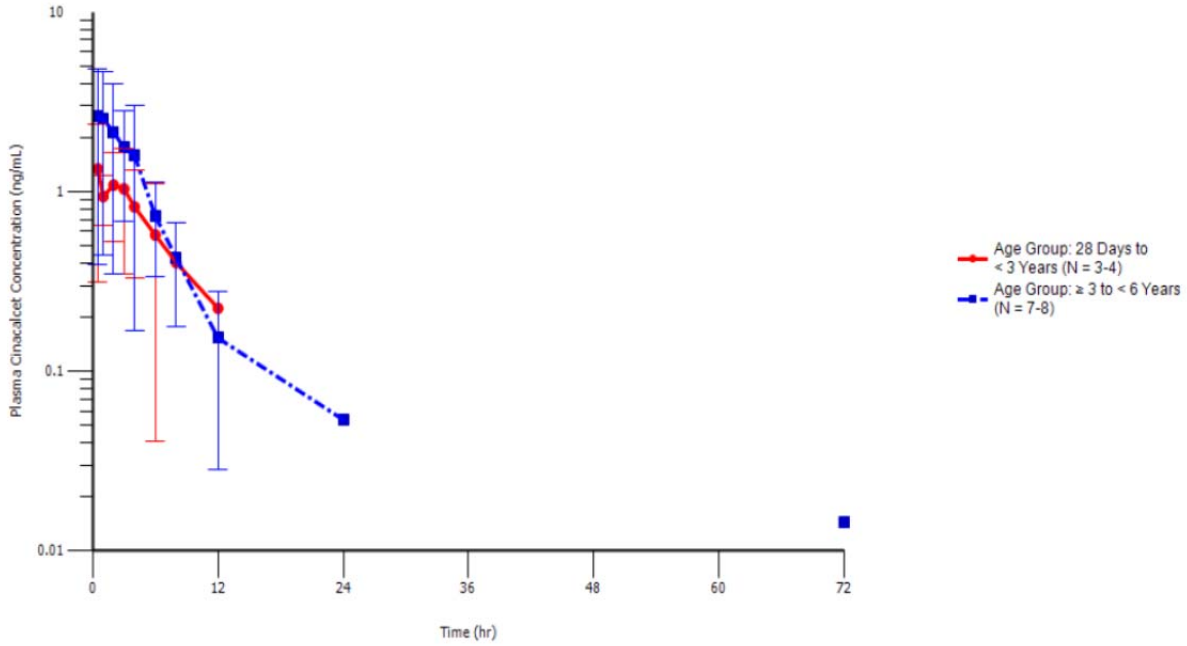


Figure 9 Mean (±SD) Plasma Cinacalcet Concentration-time Profiles by Age Group After Oral Administration of Cinacalcet at 0.25 mg/kg to Pediatric Subjects < 6 Years of Age With CKD Receiving Dialysis (Study 20090005)

Source: Figure 11-2, CSR Study 005

1.1.3 Study 20070208 (WR 2)

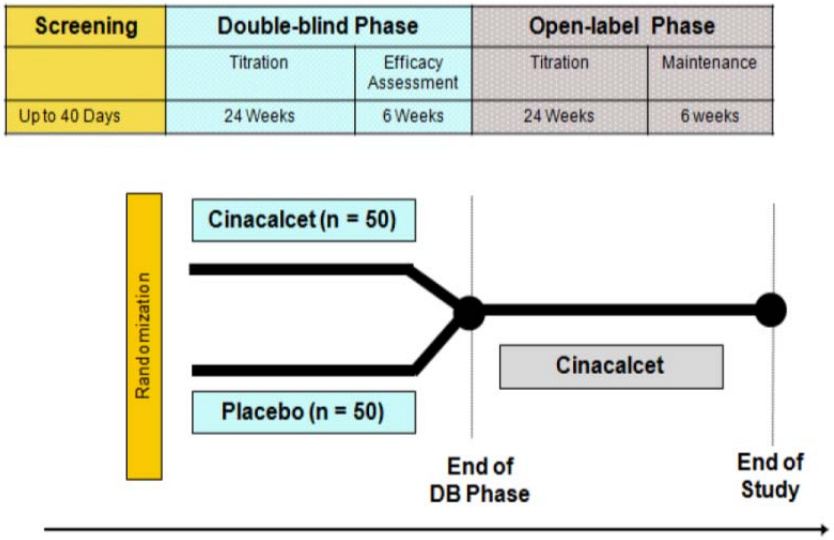


Figure 10 **Study Design (Study 208, WR Study 2)**

Dosing regimen: Once daily at a starting dose of ≤ 0.20 mg/kg based on dry weight, and the dose was titrated upward according to plasma iPTH and serum calcium levels and subject safety information every 4 weeks. The maximum dose was 4.2 mg/kg, not to exceed a total dose of 180 mg for any subject, the labeled recommended adult maximum dose.

The 2.5 mg dose used half of a suspension of a 5 mg capsule in sucrose syrup. The doses of 5, 10, and 15 mg were given as 1, 2, and 3 capsules, respectively. Capsules were to be opened, and the contents were to be sprinkled on food or compounded into sucrose syrup. The capsule shell was not to be consumed and was to be destroyed after use. Tablets at strengths of 30, 60, or 90 mg were to be swallowed whole with food or shortly after a meal.

PK Sampling: Blood samples for pharmacokinetic (PK) analysis were collected pre-dose (trough and baseline) for all subjects (those receiving peritoneal dialysis or hemodialysis, respectively). For hemodialysis subjects only, a second sample was collected between 1 and less than 3 hours post-dose (half of hemodialysis subjects) or 3 to 24 hours post-dose (half of hemodialysis subjects) on day 1 and weeks 3, 7, 11, 15, 19, 23, 27, 33, 37, 41, 45, 49, 53, and 57.

Based on the limited available data, observed cinacalcet concentrations were within the expected range of exposures for this population. The cinacalcet concentration data will be pooled with the results from other pediatric studies, analyzed using population PK, and reported separately.

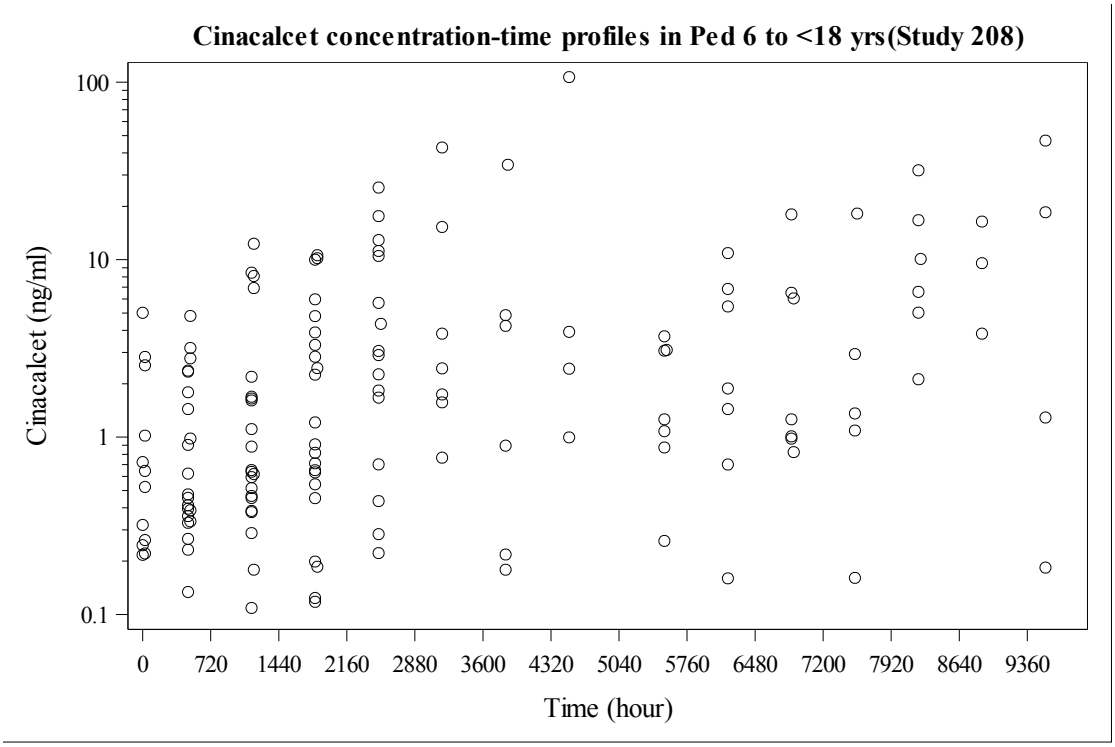


Figure 11 Cinacalcet concentrations (Study 208)

1.1.4 Study 20110100 (WR 3)

Dosing Regimen:

Prior to the partial clinical hold (cohort 1), the starting dose was 0.25 mg/kg (based on dry weight) and was titrated upwards (maximum allowed daily dose of 4.2 mg/kg) according to plasma iPTH, corrected total serum calcium levels, and subject safety information. There were no protocol-specified doses for cohort 1; however, a maximum of 5 dose titration steps from the starting dose were permitted, and example dose titrations based on dry weight is provided in Table 2 of Section 6.1.2 of the original protocol (09 August 2011). The maximum dose could not exceed 2.5 mg/kg/day or 60 mg, whichever was lower.

After the partial clinical hold (cohort 2), changes to the protocol included additional safety measures focused on further minimizing the risk of hypocalcemia and subject's adherence to cinacalcet use. The starting dose (based on dry body weight) was 0.20 mg/kg rounded down to the next lowest protocol specified dose. The protocol specified doses were 1, 2.5, 5, 7.5, 10, 15, 30, and 60 mg. The maximum dose could not exceed 2.5 mg/kg/day or 60 mg, whichever was lower.

Cinacalcet capsules 5 mg were opened, and the contents were either sprinkled on soft food to be eaten by the subject, or suspended into sucrose syrup to create a liquid suspension and administered through the subject's feeding tube. Blood samples were collected for PK characterization at trough, and 10 over 24 hour at Week 12 (Table 11)

Table 11 Schedule of on-treatment study assessments (WR Study 3)

	Week																						EOIP	*Optional Sub study*[f,g]	ET/ EOS[h,i]
Treatments and Procedures	**1**	**2**	**3**	**4**	***5***	**6**	**7**	**8**	***9***	**10**	**11**	**12**[e]	***13***	**14**	**15**	**16**	***17***	**18**	**19**	**20**	***21***[b]	**22**	**23**	**24**	***24***	**W26**
Assent/IC																									X	
Vital signs				X				X				X				X				X				X		X
Height (stadiometry)																										X
Post-dialysis weight				X				X				X				X				X				X		X
ECG																										X
Hematology												X														X
Serum chemistry												X														X
Total and bioavailable testosterone (males)																										X
Ionized calcium[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]	X	X	X	X	X	X	X	X		
Plasma iPTH[a]			X				X				X				X				X			X		X		X
Corr serum calcium			X				X				X				X				X			X		X		X
Serum phosphorus			X				X				X				X				X			X		X		X
Serum albumin			X				X				X				X				X			X		X		X
Alkaline phosphatase												X												X		X
PK[b]				X				X				X				X				X				X	X	
Dialysate calcium [c]																										X
Assessment of dialysis dose (Kt/V)[c]																										X
eDiary Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant meds	Record Continuously																						X			X
Dose titration				X				X				X				X				X						
IP dispensation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[k]	
AE/SAE evaluation[d]	Record Continuously																						X			X

AE = adverse events; ECG = electrocardiogram; eDiary = electronic subject diary; EOIP = end of investigational product; EOS = end of study; ET = early termination; IC = informed consent; IP = investigational product; iPTH = intact parathyroid hormone; PK = pharmacokinetic; PTH = parathyroid hormone; SAE = serious adverse event.

[a] PTH levels were to be measured 18 to 24 hours postdose (ie, from when dose was taken on the previous day).

[b] The date and time of the dose of IP taken immediately prior to the PK blood sample was recorded. As it is likely this dose was taken in the home of the subject, site staff instructed the parent/guardian to bring this information to the site during the clinic visit.

[c] Also was recorded if changed at any time between the required collection times at day 1 and End of Study.

[d] Included collection of adverse events (hypocalcemia, seizures, and infections) using the worksheet (Appendix C in Section 16.1.1).

[e] The week 12 visit required a mandatory PK assessment over a 24 hour period in order to obtain 10 PK samples (predose, and then post-dose at 30 minutes, hours 1, 2, 3, 4, 6, 8, 12, and 24).

[f] The date and time of the dose of cinacalcet taken immediately prior to the first PK blood sample drawn was recorded. As it is likely this dose was taken in the home of the subject, site staff instructed the parent/guardian to bring this information to the site/hospital.

[g] If Informed Consent/Assent was signed for the optional 24-hour PK assessment substudy at week 24, the subject was to complete all of the EOIP assessments required by the protocol in addition to having the additional 10 PK samples collected at the same time points as listed above (footnote e) for week 12.

[h] Assessments at week 26 must have been completed in order for the End of Study visit to be considered complete.

[i] After last dose of cinacalcet (due to either study completion or early study closure); subject must have been assessed for any adverse event 14 days afterwards, and for any serious adverse event 30 days afterwards. It was preferable that this assessment occurred at the investigator's site, but it could have occurred via telephone.

[j] For cohort 2, ionized calcium assessments were determined at each weekly dispensing visit.

[k] A single dose of cinacalcet was administered at week 24 for subjects participating in the optional PK substudy.

Primary PK Results:

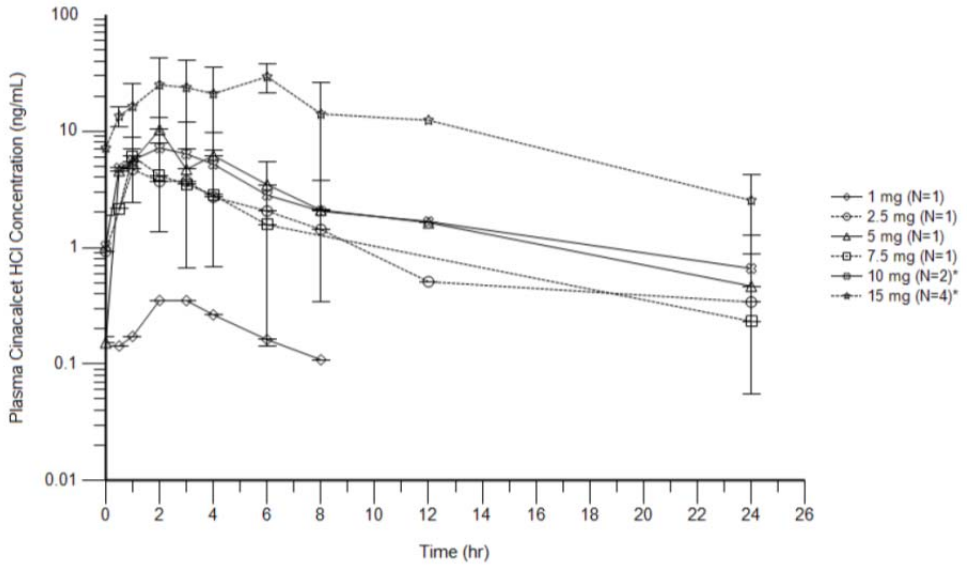


Figure 12 Mean (±SD) Plasma Cinacalcet Concentration-time Profiles at Week 12 After Daily Oral Administration to Pediatric Subjects < 6 Years of Age With CKD and Secondary Hyperparathyroidism Receiving Dialysis (Study 20110100)

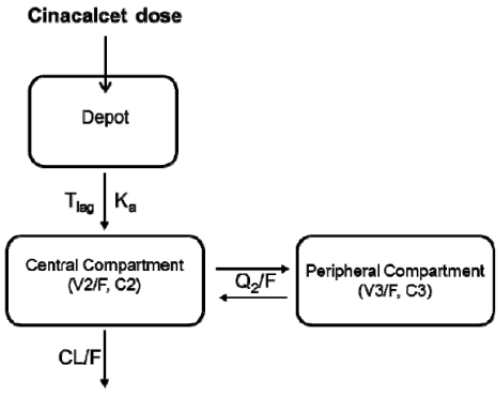
Table 12 Pharmacokinetic Parameter Estimates for Cinacalcet in Plasma at Week 12 after Daily Oral Administration to Pediatric Subjects < 6 Years of Age With CKD and Secondary HPT Receiving Dialysis

Week 12 Dose (mg)	Summary Statistics	t_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)	V_z/F (L)	CL/F (L/hr)
1	N	1	1	NR	NR	NR
	Value	2.0	0.352	NR	NR	NR
2.5	N	1	1	1	1	1
	Value	1.1	4.70	31.7	682	79.1
5	N	1	1	1	1	1
	Value	2.0	10.3	59.8	864	83.6
7.5	N	1	1	1	1	1
	Value	1.0	6.09	35.8	1760	211
10*	N	2	2	2	1	1
	Mean	1.2	8.07	57.9	5710	441
	SD	NR	NR	NR	NR	NR
	Median	1.2	8.07	57.9	5710	441
	CV%	NR	NR	NR	NR	NR
15*	N	4	4	3	2	2
	Mean	3.4	23.2	307	1150	106
	SD	2.2	14.4	226	NR	NR
	Median	3.3	26.1	304	1150	106
	CV%	65.3	62.0	73.7	NR	NR
Summary Statistics for Dose- and Weight-Normalized C_{max} and AUC_{last}						
Cohort 1	N	-	3	2	-	-
	Mean	-	15.1	160	-	-
	SD	-	16.6	195	-	-
	CV%	-	110.3	121.7	-	-
Cohort 2	N	-	7	6	-	-
	Mean	-	17.8	176.8	-	-
	SD	-	10.0	177	-	-
	CV%	-	56.3	100.4	-	-

1.1.5 Population PK/PD analysis (Report 122055)

Table 13 Summary of primary study design included for population PK/PD analysis

Study	Phase	Cinacalcet Dose in mg	PK, iPTH and cCa Sampling Scheme	Number of subjects included in analysis	Population
20070208	1	Titrated dose: 2.5 ~15 mg	PK at predose, post dose on Day 1, week 3, 7, 11, 15, 19 and 23 PD at predose, Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23	43	CKD / sHPT in child aged 6-18 yr
20110100	2	Titrated dose: 1, 2.5, 5, 7.5, 10, 15, 30, and 60 mg	PK at predose, post dose on Week 4, 8, 12, 16, 20 and 24 PD at predose, week 3, 7, 11, 15, 19, 22 and 24	17	CKD / sHPT in child aged 28days-6 yr
20030227	1	single 15 mg	PKPD at predose, on Day 1 at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours postdose.	12	CKD / sHPT in child aged 6-17 yr
20090005	1	single 0.25 mg/kg	PK at 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (Day 2), 48 (Day 3), and 72 (Day 4) hours post dose PD at predose, day 1 and 4	12	CKD / sHPT in child aged 28days-6 yr
20000172	3	dose titration (every 3wks), 30, 60, 90, 120, and 180 mg	PK at predose, 2, 4, and if possible 6 h postdose on wk 24. Trough samples on wks 2, 5, 11, and 16. Weekly trough samples throughout dose-titration and biweekly throughout efficacy stage	403	ESRD with sHPT in adult
20000187	1	Dose titration (weekly dose adjustment) 25, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, and 300 mg	PK trough samples on days 4, 6, and 7 of each dose level. PK/PD at predose, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h postdose on day 7 of each dose level. Additional PK samples at 48, 72, 96, and 120 h after the final dose	22	Adults with CKD
980126	2a	Single dose in Part 1 with a 4 wk wash out then 8 QD doses in Part 2: 5, 10, 25, 50, 75, and 100 mg	Intensive PK/PD over 72 h after single dose in (P1) and over 24 h after QD (P2) dosing on days 1 and 8. At 24 h postdose on days 2 to 7, and at 48 and 72 h postdose on day 8 and 15(P2).	60	sHPT
970241	1	Single and multiple dose of 1, 5, 25, 50 or 100 mg	Intensive PK at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48 and 72 hrs post dose PD at predose, 0.5, 1, 2, 4, 8, 12, 18, 24, 48 and 72 hrs post dose	79	Healthy adult subjects



T_{lag} = lag time; K_a = absorption rate constant; V2/F = apparent volume of distribution for the central compartment; V3/F = apparent volume of distribution for the peripheral compartment; C2 = compartment 2; C3 = compartment 3; CL/F= apparent clearance; Q_2/F = apparent distribution clearance.

Figure 13 Structural Population Pharmacokinetic Model (Source; Figure 13, 2.7.2)

Table 14 Parameter Estimates and Relative Standard Errors for Pharmacokinetic Models

	Base Model with Index Dataset		Final Model with Combined Dataset	
	Estimate	RSE (%)	Estimate	RSE (%)
K_a (1/hr)	0.869	10.90	0.88	7.32
CL/F (L/hr)	261.35	5.30	258.89	4.65
V_2/F (L)	3470.65	7.29	3309.71	6.37
V_3/F (L)	17810.90	10.60	16689.30	9.65
Q/F (L/hr)	280.22	8.27	277.476	6.36
T_{lag} (hr)	0.391	4.98	0.373	4.61
ω_K_a (%)	108	20.90	114	17.30
ω_CL/F (%)	72	11.60	74	8.92
corr_CL/F and V2/F	0.85	13.0	0.86	10.10
ω_V_2/F (%)	77	14.90	82	12.20
ω_V_3/F (%)	79	30.10	80	17.90
ω_Q/F (%)	47	40.20	63	18.10
ω_T_{lag} (%)	25	19.80	33	13.80
σ_ other studies (additive on logDV) (%)	70	0.48	70	0.39
σ_ Ph3 (additive on logDV) (%)	83	1.85	84	1.52

CL/F = apparent clearance; V_2/F and V_3/F = apparent volume of distribution for the central and peripheral compartments, respectively; Q_2/F = apparent distribution clearance; K_a = absorption rate constant; T_{lag} = lag time; RSE = relative standard error; ω_K_a, ω_CL/F, ω_V_2/F, ω_V_3/F, ω_Q/F, and ω_T_{lag} = intersubject variability (expressed in CV%) on K_a, CL/F, V_2/F, V_3/F, Q/F and T_{lag}, respectively;
σ_Ph3 and σ_other studies = residual error expressed as additive on the natural logarithm-transformed cinacalcet concentrations and predictions for phase 3 studies and other studies, respectively.
Source: Table 5 of Report 122055

(Source; Table 6, 2.7.2)

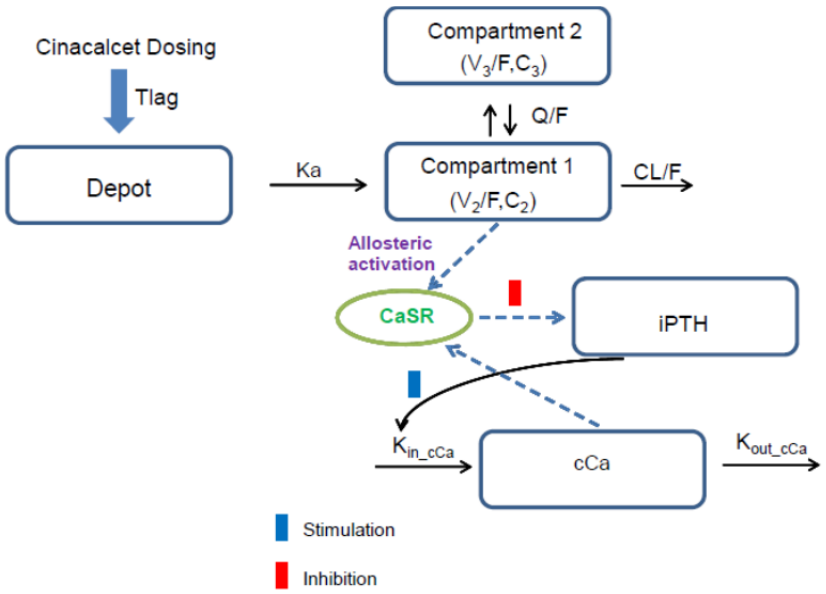


Figure 14 Schematic summary of population PK/PD model (Source: Figure 15, 2.7.2)

Table 15 Parameter estimates and relative SE for PK/PD models

	Base PKPD Model with Index Dataset		Final PKPD Model with Combined Dataset	
	Estimate	RSE	Estimate	RSE
PTH0_Patient (pM)	53.65	3.55	54.43	2.90
Ca0_Patient (mM)	2.45	0.37	2.45	0.30
Ratio _Patient (1/mM)	0.06	9.62	0.075	7.76
$K_{out,ca}$_Patient (1/hr)	0.02	14.6	0.03	13.6
Power on PTH_Patient	0.07	14.1	0.07	10.20
Power on RO_Patient	-3.51	-7.81	-3.18	-6.03
PTH0_HV (pM)	2.43	21.50	2.38	19.60
$K_{out,ca}$ _HV (1/hr)	0.01	25.80	0.01	19.20
Power on RO_HV	-10.21	-18.60	-9.44	-12.40
Ratio _HV (1/mM)	0.02	25.50	0.02	18.40
Power on PTH_HV	1.44	53.5	1.56	35.30
Ca0_HV (mM)	2.30	2.03	2.30	1.56
ω_PTH0 (%)	64.8	4.92	64.00	3.91
ω_Ca0 (%)	6.87	7.65	6.55	6.31
ω_Ratio (%)	79.46	13.70	77.80	12.20
ω_Power on PTH (%)	135.30	15.50	115.99	12.90
ω_Power on RO (%)	80.90	11.30	73.2	9.30
σ_ iPTH_Patient (additive on logDV) (%)	66	0.32	65	0.28
σ_ cCa_Patient (additive on logDV) (%)	26	0.42	26	0.32
σ_ iPTH_HV (additive on logDV) (%)	47	1.86	48	1.41
σ_ cCa_HV (additive on logDV) (%)	19	1.46	19	1.11

PTH0_Patient and PTH0_HV: baseline PTH level for patient and healthy subjects, respectively.
Ca0_Patient and Ca0_HV: baseline calcium level for patient and healthy subjects, respectively.
Ratio_Patient and ratio_HV: for patient and healthy subjects, respectively.
$K_{out,ca}$ _Patient and $K_{out,ca}$ _HV: the first order elimination rate for calcium for patient and healthy subjects, respectively.
Power on PTH_Patient and Power on PTH_HV: the power relating changes in PTH from baseline to calcium production for patient and healthy subjects, respectively.
Power on RO_Patient and Power on PTH_HV: a constant determining the strength of the effect of changes in receptor occupancy on PTH production for patient and healthy subjects, respectively.
ω_PTH0, ω_Ca0, ω_ratio, ω_power on PTH, and ω_power on RO: intersubject variability (expressed in CV%) on PTH0, Ca0, ratio, power on PTH, and power on RO, respectively.
σ_ iPTH_Patient and σ_ iPTH_HV: residual error expressed as additive on log scaled PTH for patients and healthy subjects, respectively.
σ_ cCa_Patient and σ_ cCa_HV: residual error expressed as additive on log scaled calcium for patients and healthy subjects, respectively.

(Source: Table 7, 2.7.2)

1.1.6 Physiologically based pharmacokinetic modeling (Study 122086)

Cinacalcet compound file (Table 13) was developed for adult population and refined it using available sensitivity analysis in Simulator with drug interaction with ketoconazole data. For pediatric PK simulations, SIMCYP pediatric module, which is known to reflect ontogeny of drug metabolizing enzymes in addition to changes in physiologic parameters due to growth and development.

Simulation for adult population overestimated concentrations in the terminal phase as only a minimal PBPK (one-compartment) model was available in SIMCYP while cinacalcet PK is best described by a two-compartment model. Cinacalcet compound file was refined through sensitivity analysis using drug interaction with ketoconazole data focusing on adjustment for the relative contribution ($f_{m,CYP}$) of CYP1A2, 2C9, 2C19, and 3A.

For simulation in pediatric population, in vivo-derived ontogeny data were introduced as advancement to the default in vitro-derived ontogeny in SIMCYP, version 10. The sponsor indicated that the plasma concentration-time profiles across the pediatric age range including ages 28 days to 9 months were reasonably predicted using the cinacalcet compound file and the PBPK model.

The sponsor concluded using the PBPK analysis that the average, weight-normalized oral clearance of cinacalcet varies less than 1.5-fold for pediatric patients aged 28 days to 1 year, as well as for pediatric patients aged 28 days to 17 years. The simulations also projected that the average C_{max}, AUC and weight-normalized oral clearance of cinacalcet varied less than 1.5-fold for patients aged 28 days to 1 year at the lowest dose used in the simulation (0.2 mg/kg), supporting its selection as the weight-based starting dose for this age range. There was apparent concordance between the observed and predicted cinacalcet PK data across the pediatric age range based on the cinacalcet compound file, in vivo-based ontogeny, and the PBPK model.

Table 16 Parameters for the final Cinacalcet compound file (source, Table 1, CSR 122086)

Parameter	Value	Source
Molecular Weight (free base)	357.4	Product monograph
LogD	4.79	Product monograph
pKa	8.72	Product monograph
Fraction unbound (f_u) in plasma	0.05	Amgen Study Report #100158
Red blood cell partitioning	0.80	Amgen Study Report #102739
P_{app} ($x10^{-6}$ cm/s, Caco-2 cell line)	3.27	Amgen Study Report # 100154
K_a (h^{-1})	1.48	Wang, B et al, *Clin Pharmacol Ther*. 2001; 69: P91.
$f_{u,gut}$	0.0059	Estimated using Simcyp
V_{ss} (L/kg)	12.5	Amgen Study Report # 990751 (V_{ss} = 944 L; median weight 75.6 kg)
$f_{u,mic}$	0.36	Estimated using Simcyp
CL_{int} (µL/min/pmol)	CYP1A2: 1.58 CYP2C9: 0.86 CYP2C19: 0.98 CYP3A: 3.62	Estimated from $f_{m,CYP}$ obtained from Amgen Study Report # 102724 and refined using the cinacalcet AUC with KTZ co-administration (Amgen Study Report 20000101)
Renal Clearance (L/h)	0.0	Kumar,GN et al *Drug Metab Dispos*. 2004; 32: 1491-1500

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