# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | (b) (4) (b) (4) |
| Priority or Standard | Priority 2 |
| Application Type | sNDA |
| Application Number(s) | 21688/S-023 |
| Submit Date(s) | November 23, 2016 |
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| PDUFA Goal Date | May 23, 2017 |
| Division / Office | DMEP/ODEII |
| Reviewer Name(s) | William Lubas, M.D., Ph.D. |
| Review Completion Date | May 22, 2017 |
| Established Name | cinacalcet |
| (Proposed) Trade Name | Sensipar |
| Therapeutic Class | Calcimimetic agent |
| Applicant | Amgen |
| Formulation(s) | (b) (4) |
| Dosing Regimen | |

| | |
|---|---|
| Indication(s) | (b) (4) |
| Intended Population(s) | |

Template Version: March 6, 2009

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

(b) (4) because there was inadequate evidence of safety and efficacy in the two inconclusive pivotal trials 20070208 and 20130356.

(b) (4) because there was inadequate safety data in Study 20110100, and because, even when we take into account the totality of the evidence, the current study data do not permit extrapolation of efficacy from the older children or adult data.

It is recommended that pediatric exclusivity be denied because data and information submitted by Amgen do not fairly respond to the Written Request (WR). In addition to Amgen's failure to provide sufficient data to allow pediatric labeling in either population, there were an inadequate number of study completers for Study 20110100 (WR Study 3) to satisfy the terms of the WR.

Approval of labeling supplement S-023 is dependent on final agreement on changes to the Package Insert (PI).

## 1.2 Risk Benefit Assessment

There is inadequate data to support efficacy or safety in pediatric children age 28 days to < 18 years from the clinical studies in this submission due to the large amount of missing data and patient drop outs which occurred in these studies.

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

## 1.4 Recommendations for Postmarket Requirements and Commitments

None

# 2 Introduction and Regulatory Background

## 2.1 Product Information

Sensipar (cinacalcet hydrochloride) is a first-in-class calcimimetic that increases the sensitivity of the calcium-sensing receptor (CaR) on the surface of the parathyroid cell to extracellular calcium. The pharmacologic action of cinacalcet is to reduce serum levels of PTH by increasing the sensitivity of the CaR on the parathyroid gland to extracellular calcium, thus lowering serum calcium levels.

Cinacalcet (Sensipar®) was approved in the United States on 08 March 2004 for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease (CKD) on dialysis, and for the treatment of hypercalcemia in adult patients with parathyroid carcinoma.

Cinacalcet (Sensipar®) was approved in the United States on 25 February 2011 for the treatment of severe hypercalcemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy, where severe hypercalcemia was defined as defined as a screening serum calcium level of > 12.5 mg/dL.

Cinacalcet (Sensipar®) was approved in the United States on 21 November 2014 for the treatment of severe hypercalcemia in patients with primary hyperparathyroidism for whom are parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

| **Treatment of Secondary Hyperparathyroidism in Adult Patients with Stage 5 CKD on Dialysis** | |
|---|---|
| Vitamin D analogs | Calcijex (calcitriol injectable, NDA 18-874) originally indicated for the treatment of hypocalcemia in dialysis patients |
| | Rocaltrol (calcitriol, NDA 18-044 oral capsule, NDA 21068 oral solution) |
| | Hectorol (doxercalciferol, NDA 20-862 oral capsule and NDA 21-027 injectable) |
| | Zemplar (paricalcitol, NDA 20819 injectable, NDA 21606 oral capsule) |
| Calcimimetics | Sensipar (cinacalcet, NDA 21688, oral tablet) |
| | Parsabiv (etelcalcetide, NDA 208325 injectable) |

| | |
|---|---|
| Calcium supplements | OTC products that can be used off label for the treatment of secondary hyperparathyroidism |
| Phosphate Binder | Renagel (sevelamer hydrochloride, NDA 21179 oral tablet) used for the treatment of hyperphosphatemia in Stage 5 CKD on dialysis |

Of these products oral and injectable paricalcitol and oral and injectable calcitriol are the only products with pediatric use information in their PIs for treatment in children.

## 2.3 Availability of Proposed Active Ingredient in the United States

Sensipar (cinacalcet) is currently available as an unscored 30mg, 60mg and 90mg tablets.

## 2.4 Important Safety Issues With Consideration to Related Drugs

The major concern with calcimimetics is hypocalcemia which can result in QT prolongation and cardiac arrhythmias, paresthesia, muscle spasms/tetany, and seizures.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

05 May 2010 FDA issued the initial WR.

04 September 2013 FDA agreed to the early termination of Study 20070208 following a fatality and stated that the cinacalcet pediatric program should continue with enhanced titration and monitoring safeguards.

05 February 2014 FDA agreed that the new titration scheme/regimen incorporated in Study 20130356 was acceptable to allow initiation of a new open-label, randomized, multiple-dose, clinical study of cinacalcet in children.

09 April 2015 FDA issued a revised WR to include definition of completers for Study 20130356.

14 October 2015 FDA issued a revised WR to change the primary and secondary endpoints for Study 20130356 to address Agency concerns about missing data (a US-specific protocol amendment was developed for Study 20130356).

21 September 2016 FDA Type B Pre-supplemental New Drug Application Meeting was held. Agreement was reached regarding the data package that will be submitted to support review of the supplemental New Drug Application and pediatric exclusivity.

### 2.6 Other Relevant Background Information

None

# 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The data quality and completeness were adequate to permit review.

### 3.2 Compliance with Good Clinical Practices

***Rationale for OSI Audits***

- *Site 66010 Dr. Garin had never been inspected, was one of two US sites with the most enrolled pts, and second highest number of AEs reported in Study 20070208.*
- *Sites 66002 & 66009 Dr. Arar had not been previously inspected, one of two US sites with the most enrolled pts, and highest number of AEs reported in Study 20070208.*
- *Site 66011 Sullivan had several enrollment deviations when inspected in 2010/NAI. Was the highest enroller in Study 20110100.*

The clinical sites of Drs. Garin, Sullivan and Arar were inspected and all three inspections received a final classification of NAI (see Dr. Damon Green's review).

### 3.3 Financial Disclosures

Amgen submitted financial disclosure information for the three Studies 20070208, 20110100 and 20130356. They certified that they had not entered into any financial arrangements with 94 investigators at 24 sites in Study 20070208, 45 investigators at 14 sites in Study 20110100 and 125 investigators at 32 sites in Study 20130356 whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), and that these investigators were not the recipients of significant payments of other sorts as defined in 21 CFR 54.2(f).

Amgen was not able to provide financial information from one investigator who enrolled one patient in Study 20070208, one investigator who enrolled three patients in Study 20110100 and three investigators who enrolled 12 patients into Study 20130356. Of these the only investigator that enrolled a substantial number of patients into a given trial was Dr. Borys Sheyman from the Ukraine who enrolled 9 of the 55 patients in Study 20130356 or 16% of the study population. He enrolled 5 subjects in the cinacalcet &

SOC group and 4 subjects in the SOC group. Only 2 of the 5 cinacalcet & SOC subjects (20%) had mean iPTH reductions < 30% while none of the 4 SOC subjects had mean iPTH reductions < 30%. While the efficacy in Dr. Sheyman's cinacalcet & SOC group was slightly less than observed in the total population (20% vs. 26%), the efficacy he observed in the "SOC alone" group was also less than in the total population (0% vs. 18%). Given that Study 20130356 was already a failed trial removing Dr. Sheyman's patient data would not have changed the study results.

There was only one investigator, Dr. Claus Peter Schmitt from Heidelberg Germany that received disclosable financial arrangements corresponding to 21 CFR 54.2. He enrolled 2/18=11% of the subjects in Study 20110100. This small number of patients is unlikely to have affected the results from this open label safety study, and these two patients were not among the 4 completers.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

This application review focused on (b) (4) See the chemistry review signed by Dr. Suon Tran, the application technical leader, for more detailed information on the OPQ recommendation for approval.

## 4.2 Clinical Microbiology

(b) (4)

## 4.3 Preclinical Pharmacology/Toxicology

This submission included a 6-month juvenile dos toxicity study which was reviewed by Dr. Parvaneh Espandiari. The results were consistent with the "exaggerated pharmacologic effects of cinacalcet (e.g., suppressed PTH and decreased serum calcium, with associated effects on bone structure and decreased growth) that are expected to occur in healthy juvenile animals with normal calcium levels at baseline."

Therefore, the Pharm Tox review concluded that the 6-month juvenile dog toxicity study along with previous conducted nonclinical studies, supported the safety of cinacalcet tablets and cinacalcet capsules for sprinkling for administration in the (b) (4) .

## 4.4 Clinical Pharmacology

WR Study 1 (20090005)-An Open-label, Single-dose Study to Evaluate the Safety, Tolerability,
Pharmacokinetics and Pharmacodynamics of Cinacalcet HCl in Pediatric Subjects Aged 28 Days to < 6 Years With Chronic Kidney Disease Receiving Dialysis

Study 20090005 conducted at 7 centers in the United States and the European Union was a phase 1, open-label study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of cinacalcet in subjects aged 28 days to < 6 years with CKD and secondary hyperparathyroidism undergoing hemodialysis or receiving peritoneal dialysis. Fourteen subjects were enrolled but only 12 received cinacalcet and completed the study: 4 subjects (28 days to < 3 years of age, mean age 18.8 months) and 8 subjects (≥ 3 years to < 6 years of age, mean age 4.3 years). Subjects received a single, oral dose of 0.25 mg/kg cinacalcet and were randomized in a 1:1 ratio to one of the following PD (iPTH and measurements of serum calcium) sampling sequences:

1. predose, 2, 8, and 48 hours post dose; or
2. predose, 2, 12, and 48 hours post dose.

Safety monitoring and PK sampling were conducted predose and post dose up to 72 hours.

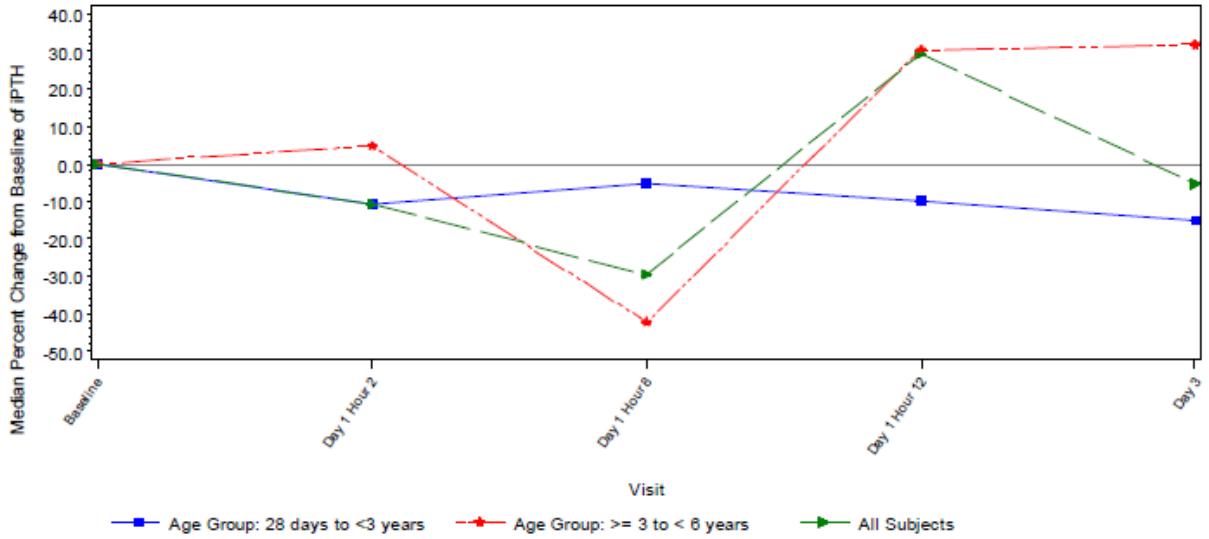
### 4.4.1 Mechanism of Action

Sensipar is a calcimimetic agent that increases the sensitivity of the calcium receptor in the parathyroid to extracellular calcium resulting in a decrease in PTH secretion.

### 4.4.2 Pharmacodynamics

Following a single oral dose of 0.25 mg/kg cinacalcet, reductions in serum iPTH concentrations from baseline were observed at the 2 and 8 hours post dose sampling times (median: -11% and -30%, respectively). Concentrations transiently increased to above baseline at 12 hours post dose (+29%), and returned to near baseline levels by day 3 (-5%). Median percent iPTH reductions were more pronounced at 8 hours post dose in subjects ≥ 3 to < 6 years of age (-42%) than in subjects 28 days to < 3 years of age (-5%).

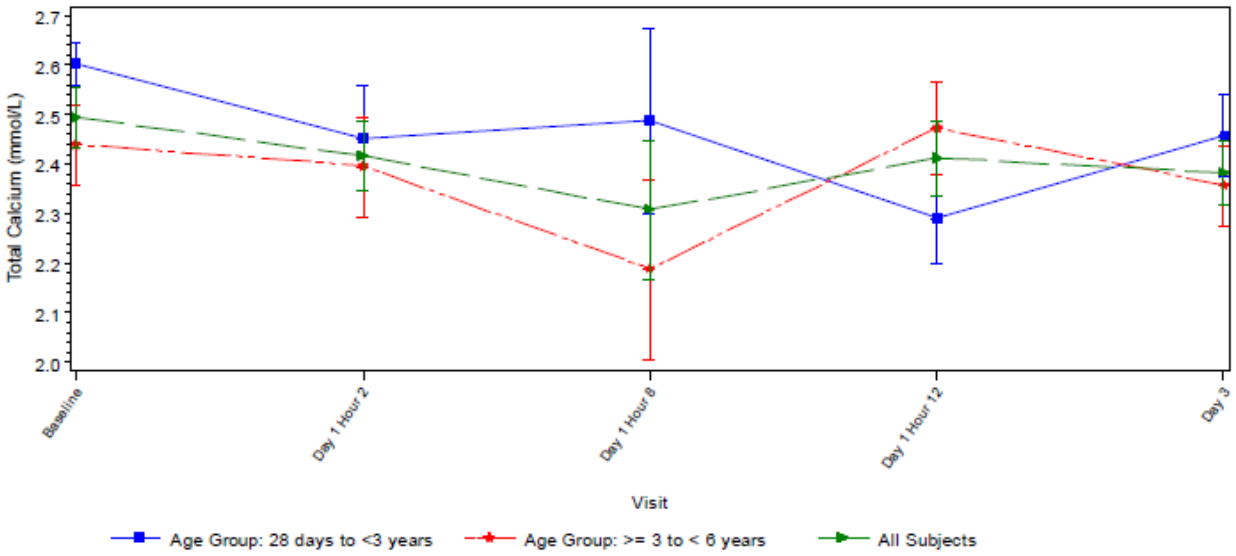
**Figure 1 Median iPTH % Change in Pediatric Patients < 6 years of Age after a Single 0.25mg/kg Oral Dose of Cinacalcet**




Source Fig. 11-3 CSR 20090005

Calcium profiles showed slight decreases from baseline, reached nadirs at 8 hours and subsequently returned to baseline.

**Figure 2 Mean (±SD) Total Serum Calcium in Pediatric Patients < 6 years of Age after a Single 0.25mg/kg Oral Dose of Cinacalcet**




Source Fig. 11-4 CSR 20090005

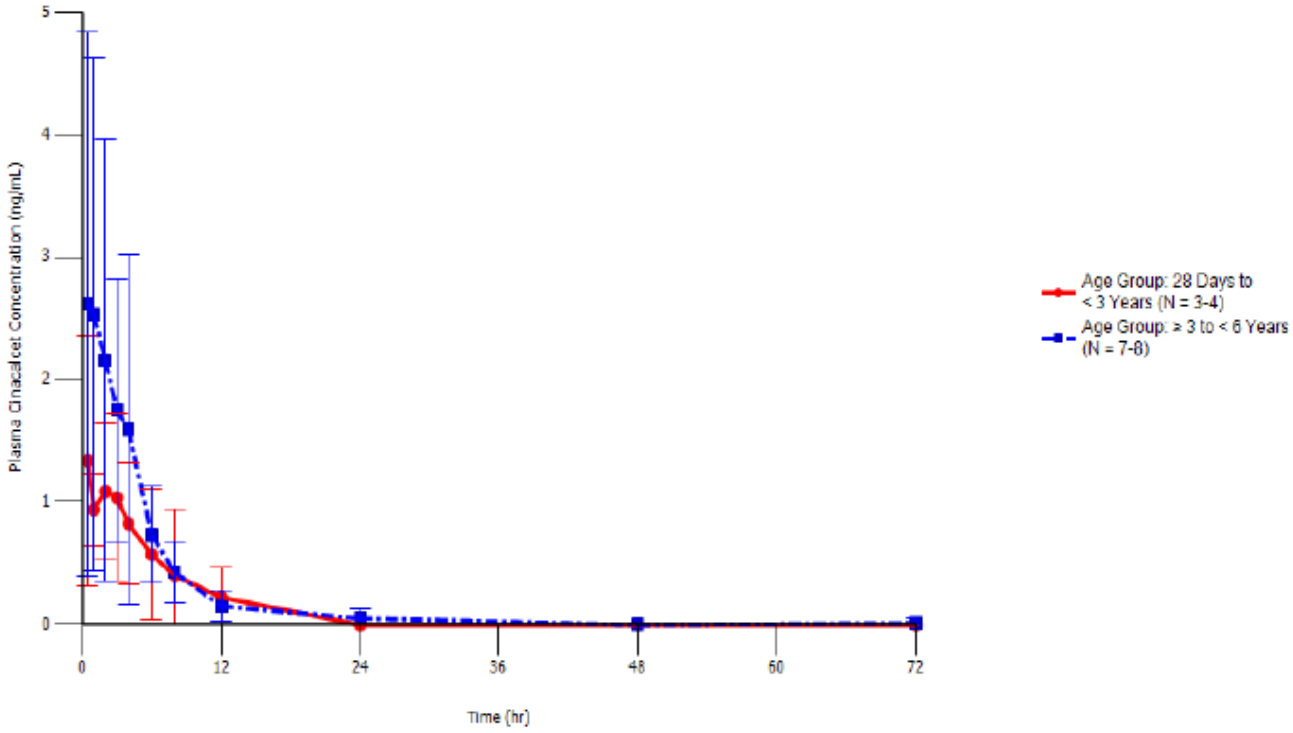
*Medical Officer's comments- Given the small numbers of subjects in each of these groups and the large standard deviations the slightly greater iPTH and*

*serum calcium lowering seen in the older cohort age ≥ 3 to < 6 years may over represent the true difference between the different age cohorts.*

### 4.4.3 Pharmacokinetics

After a single oral dose of 0.25 mg/kg, cinacalcet was rapidly absorbed with a median $t_{max}$ of 1 hour in pediatric subjects 28 days to < 6 years of age.

**Figure 3 Mean (±SD) Plasma Cinacalcet Concentration in Pediatric Patients < 6 years of Age after a Single 0.25mg/kg Oral Dose of Cinacalcet**




Source Fig 11-2 CSR 20090005

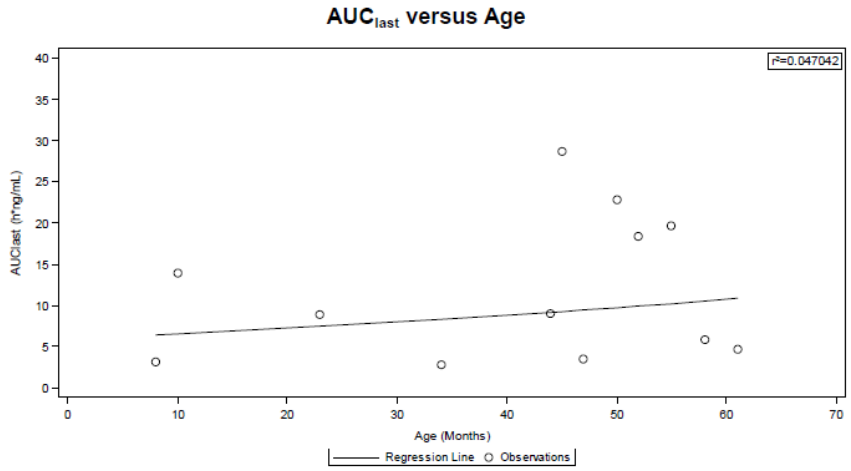
**Table 1 PK Parameters in Pediatric Patients < 6 years of Age after a Single 0.25mg/kg Oral Dose of Cinacalcet**

| 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 |

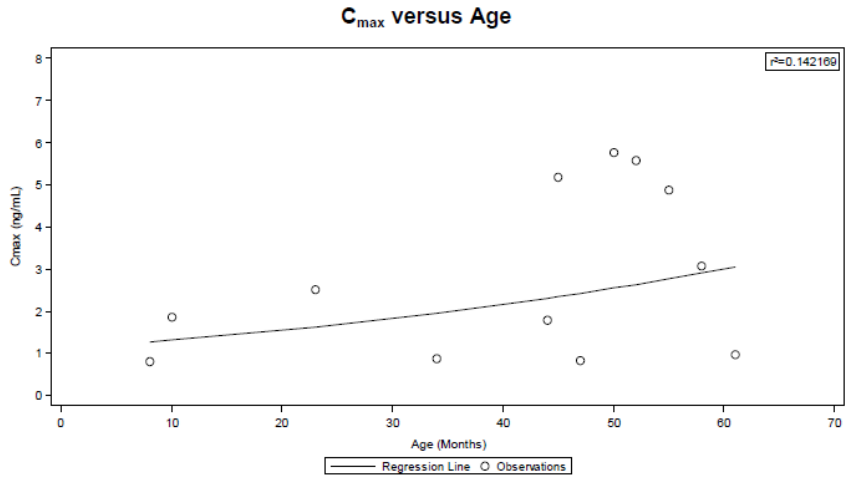
AUC = area under the plasma-concentration-time curve; $AUC_{inf}$ = AUC from time zero to infinity; $AUC_{last}$ = AUC from time zero to time of last quantifiable concentration; CKD = chronic kidney disease; $C_{max}$ = maximum observed plasma concentration; CV% = coefficient of variation; NR = Not reported; SD = standard deviation; $t_{1/2,z}$ = terminal half-life associated with $\lambda_z$; $t_{max}$ = time to reach $C_{max}$
Source Table 11-1 CSR 20090005

The mean pharmacokinetics parameter values for $C_{max}$ and $AUC_{last}$ were approximately twice as high in the older cohort ≥ 3 years to < 6 years of age compared to the younger subjects 28 days to < 3 years of age, but there was a large overlap with respect to the values seen in individual subjects.

**Figure 4 PK Parameters in Pediatric Patients < 6 years of Age after a Single 0.25mg/kg Oral Dose of Cinacalcet with Respect to Age**




Source: Figure 14-9.4.2




Source: Figure 14-9.4.3

*Medical Officer's comments-*
*Given the small numbers of subjects in each of these groups the slightly higher PK values seen in the older cohort age ≥ 3 to < 6 years may over represent the true difference. Plotting the PK data with respect to age demonstrates the large individual variability compared to the small relative increase in $C_{max}$ and $AUC_{last}$ with respect to age in children < 6 years of age. That said, the slightly greater mean oral absorption which was seen in the older cohort is consistent with the greater iPTH lowering seen in this cohort as well.*

**Extrapolation of Pediatric to Adult data**
Cmax and AUC were generally lower after weight based dosing in pediatric patients compared to adult patients, but the difference was not considered significant because of the large individual patient to patient variability that was seen in the data. Since there were no significant covariates that could be identified to explain dose adjustment between pediatric vs. adult data using the PKPD modeling, and given the inconclusive efficacy results due to missing data and the high dropout rate (see Efficacy Review) it is not possible to use the current empiric adult data to extrapolate pediatric efficacy.

**Use with Nasogastric or Gastrostomy tubing**
The Information Response to the FDA 74-Day letter submitted as SDN5 2/17/17 included information about the recovery and compatibility of cinacalcet sprinkled into food and passed through nasogastric or gastrostomy tubes. According to the applicant they had developed a method to adequately assess the recovery of 1 and 5 mg cinacalcet capsules with apple juice, renal infant formula, apple sauce or yogurt. The results showed that the average recoveries of most samples were within the 80-120% acceptance criteria, but some of 1 mg samples were below 80%. PVC was the best tubing with no leachable peaks detected; silicone tubing had some small amount of leachable peaks, while polyurethane tubing exhibited a very large amount of leachable impurities. Therefore, the applicant changed the (b) (4) However, the Clinical Pharmacology review concluded that given the limited data and the large patient to patient variability it is difficult to be sure there is no significant difference in PK when the drug is administered via nasogastric tube or gastrostomy tubing.

**Bioavailability of the Sprinkles Formulation**
Bioavailability of the 5mg cinacalcet capsule swallowed whole vs. sprinkled on food was compared to an equivalent dose swallowed as the tablet in Study 20070293- An Open-label, Randomized, Single-dose, 3-period, 3-treatment Crossover Study to Assess the Comparative Bioavailability of 5 mg Cinacalcet Capsules to the 30 mg Commercial Formulation Cinacalcet Tablets in Healthy Adult Volunteers. Using all available data comparing group A, 6 x 5mg capsule swallowed whole with applesauce, group B, 1 x 30mg tablet swallowed whole with applesauce and group C, 6 x 5mg tablets sprinkled on applesauce showed the 90% confidence interval for $C_{max}$ just barely missed the 80 to 125% limits out to three significant numbers at 0.796 but made it for $AUC_{0-t}$ and $AUC_{0-inf}$ at 0.836 and 0.839, respectively (see Table 2).

Table 2 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 Three Different Cinacalcet Formulations to Healthy Adult Volunteers

| | Geometric Least Squares 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 $C_{max}$ values converted back to the original scale
A = 6 x 5 mg capsule; B = 1 x 30 mg tablet; C = 6 x 5 mg sprinkle
$AUC_{0-t}$ = 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

However, two patients did not have available data for Group C to permit a direct comparison of all 42 pts between Group A and Group C. If these two patients were excluded from the analysis the 90% confidence interval for both $C_{max\ and}$ AUC for the other 40 patients with available data in both Group A and Group C would have resulted in a data within the required 80% to 125% range, suggesting the formulations would be bioequivalent.

Table 3 Geometric Least Squares Means, Point Estimates, and 90% Confidence Intervals for the Ratio for Geometric Least Squares Means for Pharmacokinetic Parameter Estimates Using Balanced Data without 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
Source Clinical Pharm Dr. Sang Chung Review.

*Medical Officer's comments-*
*Whether swallowing the cinacalcet capsule whole is bioequivalent to sprinkling it on food depends on how the given data is interpreted. While we typically require an ITT analysis for safety and efficacy as a conservative approach, given patient to patient variability it does not seem unreasonable to recommend a Per Protocol analysis when comparing different formulations for bioequivalence. In this case that would mean excluding data from the two patients without data available from sprinkled capsules. Such a Per Protocol analysis shows that while absorption is somewhat higher after sprinkling on food it would still be within acceptable 90% confidence intervals.*

*While it may be less clear if swallowing capsules whole would necessarily result in sub-therapeutic dosing, given that the drug needs to be titrated for efficacy, this may be a moot issue as long as the drug is consistently administered in the same manner. However the use of capsules stills represents a potential safety risk as it could represent a choking hazard in younger children. Therefore, it is recommended that the oral powder be repackaged in stick packs or sachet presentations to avoid that possibility.*

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

| Study Type and Protocol Number | Study Objectives | Study Design and Type of Control | Treatment(s) Administered | Number of Subjects Enrolled | Subject Diagnosis and Key Entry Criteria | Study Duration[a] | Study Status, Report Type, and Location |
|---|---|---|---|---|---|---|---|
| Comparative Bioavailability and Bioequivalence Study Report (Module 5.3.1.2) | | | | | | | |
| BA/BE 20070293 | Comparative bioavailability, safety/tolerability, additional PK parameters | Phase 1, randomized, open-label, 3-period, 3-treatment, single-dose, crossover study | Treatment A: 30-mg (6 x 5 mg) cinacalcet capsules with applesauce<br>Treatment B: 30-mg (1 x 30 mg) cinacalcet tablet with applesauce<br>Treatment C: 30-mg (6 x 5 mg) cinacalcet capsule content sprinkled over applesauce | 42 | Healthy subjects 18 to 45 years of age with baseline serum Ca ≥ 9.0 mg/dL (2.25 mmol/L) | 43 days | Complete; Full CSR/ 5.3.1.2 (20070293) |
| Population Pharmacokinetics Study Reports (Module 5.3.3.5) | | | | | | | |
| PK/PD | To describe the relationship between exposure, PTH, and cCa over time | PK/PD modelling study | Per studies included in analyses | 648[b] | Pediatric and adult subjects enrolled in studies included in analyses | N/A | Complete; Population PK/PD Report / 5.3.3.5 (122055) |
| PBPK | To predict cinacalcet PK in children 28 days to < 1 year of age | PBPK modelling study | Per studies included in analyses | 26[b] | Pediatric subjects enrolled in studies included in analyses | N/A | Complete; Population PBPK Report / 5.3.3.5 (122086) |
| Patient Pharmacokinetics/Pharmacodynamics and Initial Tolerability Study Reports (Module 5.3.4.2) | | | | | | | |
| PK/PD and tolerability 20030227 | Safety, tolerability, PK, and PD | Phase 1, open-label, nonrandomized, single-dose study | Single oral dose of 15 mg cinacalcet (one-half of a 30-mg tablet) | 12 | Pediatric subjects 6 to 18 years of age with CKD receiving dialysis | 4 days | Complete; Full CSR/ 5.3.4.2 (20030227) |
| PK/PD and tolerability 20090005 | Safety, tolerability, PK, and PD | Phase 1, open-label, randomized, single-dose study | Single dose of 0.25 mg/kg cinacalcet orally or through a nasogastric/gastric tube as a liquid suspension consisting of the contents from 5-mg cinacalcet capsule(s) mixed in purified water (nasogastric/gastric tube only) or simple (sucrose-based) syrup | 14 | Pediatric subjects 28 days to < 6 years of age with CKD and secondary HPT receiving dialysis | 30 days | Complete; Full CSR/ 5.3.4.2 (20090005) |
| Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Module 5.3.5.1) | | | | | | | |
| Efficacy/ Safety 20070208 | Reduction from baseline of plasma iPTH (by ≥ 30%, to ≤ 300 pg/mL); impact on cCa, phosphorus, Ca x P, growth; safety/ tolerability | Phase 3, multicenter, 30-week, randomized, double-blind, placebo-controlled phase followed by a 30-week open-label phase | Once daily oral dose of cinacalcet or placebo for 60 weeks (starting dose was ≤ 0.20 mg/kg and maximum dose was 4.2 mg/kg not to exceed 180 mg)[c]<br>The dose was uptitrated every 4 weeks upward according to plasma iPTH, serum cCa levels, and subject safety information.<br>Cinacalcet was supplied as 5-mg capsules for sprinkling and as 30-, 60-, and 90-mg film-coated tablets for swallowing. | 43<br>Cinacalcet: 22;<br>Placebo: 21 | Pediatric subjects 6 to < 18 years with CKD and secondary HPT receiving dialysis for ≥ 2 months, iPTH > 300 pg/mL, and cCa ≥ 8.8 mg/dL | 64 weeks | Terminated; Full CSR/ 5.3.5.1 (20070208) |
| Efficacy/ Safety 20130356 | Reduction from baseline of plasma iPTH (by ≥ 30%, to ≤ 300 pg/mL), impact on cCa and phosphorus, safety/ tolerability | Phase 3, multicenter, randomized, open-label, controlled study | Once daily oral dose of cinacalcet for 20 weeks (starting dose was 0.20 mg/kg rounded down to the nearest PSD and maximum dose was 2.5 mg/kg not to exceed 180 mg)[c]<br>Dose was uptitrated every 4 weeks based on plasma iPTH, serum cCa, ionized Ca levels, and subject safety information.<br>Cinacalcet was supplied as 5-mg capsules for sprinkling and as 30-mg film-coated tablets for swallowing. | 55<br>SOC + cinacalcet: 27;<br>SOC: 28 | Pediatric subjects 6 to < 18 years of age with CKD and secondary HPT receiving dialysis for ≥ 30 days, iPTH ≥ 300 pg/mL and cCa ≥ 8.8 mg/dL | 24 weeks | Closed[d]; Full CSR/ 5.3.5.1 (20130356) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Study Reports of Uncontrolled Clinical Studies (Module 5.3.5.2) | | | | | | | |
| Safety 20110100 | Impact on cCa, safety/ tolerability, PK, and PD | Phase 2, multicenter, open-label, single-arm study | Once daily oral dose for 24 weeks (starting dose was ≤ 0.20 mg/kg rounded down to the nearest PSD and maximum dose was 2.5 mg/kg not to exceed 60 mg)[c]<br><br>Dose was uptitrated once every 4 weeks based on plasma iPTH, serum cCa, ionized Ca levels, and subject safety information.<br><br>Cinacalcet was supplied as 5-mg capsules for sprinkling. | 18 | Pediatric subjects 28 days to < 6 years of age with CKD and secondary HPT receiving dialysis, iPTH > 300 pg/mL and cCa ≥ 9.4 mg/dL (28 days to < 2 years) or ≥ 8.8 mg/dL (≥ 2 to < 6 years) | 26 weeks | Closed[d]/ Full CSR 5.3.5.2 (20110100) |
| Safety extension study 20140159 | Long-term safety/ tolerability and effect on laboratory parameters of CKD-MBD | Phase 3, multicenter, single-arm study | Once daily oral dose for 28 weeks (starting and maximum doses dependent on parent study/treatment group)[c]<br><br>Dose was uptitrated once every 4 weeks based on plasma iPTH, serum cCa, ionized Ca levels, and subject safety information.<br><br>Cinacalcet was supplied as 5-mg capsules for sprinkling and as 30-mg film-coated tablets for swallowing. | 18 | Pediatric subjects with CKD and secondary HPT receiving dialysis who completed Study 20130356 (20-week treatment period) or Study 20110100 (week 26 EOS visit) or was onstudy at parent study closure | 32 weeks | Ongoing; Interim Full CSR/ 5.3.5.2 (20140159) |

| Study Type and Protocol Number | Study Objectives | Study Design and Type of Control | Treatment(s) Administered | Number of Subjects Enrolled | Subject Diagnosis and Key Entry Criteria | Study Duration[a] | Study Status, Report Type, and Location |
|---|---|---|---|---|---|---|---|
| Reports of Analyses of Data From More Than One Study | | | | | | | |
| Bayesian extrapolation | To infer a treatment effect of cinacalcet use in children with secondary HPT | Efficacy modelling/extrapolation study | Per studies included in analyses | 1186[b] | Pediatric and adult subjects enrolled in studies included in analyses | N/A | Complete; Extrapolation Report/ 5.3.5.3 (Extrapolation Study Using Bayesian Statistical Methods) |
| Study Reports of Other Clinical Studies (Module 5.3.5.4) | | | | | | | |
| NAPRTCS study 20120116 | Use and safety of cinacalcet | Multicenter, prospective, observational study | Standard medical care with or without cinacalcet treatment | 538 | Patients < 21 years of age who received maintenance dialysis at a NAPRTCS-affiliated center | 3 years | Complete; Final Report/ 5.3.5.4 (20120116) |

| Study Type and Protocol Number | Study Objectives | Study Design and Type of Control | Treatment(s) Administered | Number of Subjects Enrolled | Subject Diagnosis and Key Entry Criteria | Study Duration[a] | Study Status, Report Type, and Location |
|---|---|---|---|---|---|---|---|
| Study Reports of Other Clinical Studies (Module 5.3.5.4) | | | | | | | |
| Observational Study 20090198 | Changes in biochemical markers (iPTH, Ca, phosphorus), safety/ tolerability, cinacalcet and other medication use, bone biomarkers and BMD, if available | Multicenter, retrospective, observational chart review study | At least 1 dose of a commercial tablet formulation of cinacalcet approved for use in adults | 23 | Pediatric subjects 0 to < 6 years of age with CKD and secondary HPT on dialysis who were treated with at least 1 dose of cinacalcet | Data was collected for as long as the subject continued to receive cinacalcet and was ≤ 7 years of age. | Complete; Observational CSR/ 5.3.5.4 (20090198) |

BA = bioavailability; BE = bioequivalence; BMD = bone mineral density; Ca = calcium; Ca x P = calcium phosphorus product; cCa = corrected calcium; CKD = chronic kidney disease; CKD-MBD = chronic kidney disease - mineral and bone disease; CSR = clinical study report; HPT = hyperparathyroidism; iPTH = intact parathyroid hormone; N/A = not applicable; NAPRTCS = North American Pediatric Renal Trials and Collaborative Studies; PBPK = physiologically based pharmacokinetic; PK = pharmacokinetics; PD = pharmacodynamics; PSD = protocol-specified dose; SOC = standard of care

[a] For all except Studies 20090198 and 20120116, study duration includes the first day of dosing through the end-of-study assessments, including the follow-up period, and does not include screening. For Studies 20090198 and 20120116, study duration was as defined in the research plan.

[b] Number of subjects contributing data included in the analysis

[c] Subjects also received SOC at the investigator's discretion and according to clinic practice.

[d] An administrative decision was made to end the study to ensure admission of final CSR to respond to the Written Request by the specified filing deadline.

## 5.2 Review Strategy

Efficacy in children 6 to < 18 years of age from controlled Studies 20070208 and 20130356 was reviewed by both this medical officer in this review and Dr. Susie Sinks in a separate Biometric's review. Study 20110100 in children 28 days to < 6 years was designed as an open label safety study and so was not formally reviewed by the

Biometric's team. Efficacy from Study 20110100 in this review was evaluated using the applicant's data analyses.

Given concern over missing data in Study 20070208, an information request was sent to the applicant to reanalyze the data using a multiple imputation approach. The applicant's response was received in the 3/10/2017 submission. In their reanalysis, placebo subjects with missing data during EAP were assumed to be missing at random (MAR) and the imputations were based on subjects in the placebo group. Cinacalcet subjects who had discontinued due to study closure or kidney transplant were assumed to be MAR and the imputations were based on subjects in the cinacalcet group. Cinacalcet subjects who had discontinued due to other reasons were assumed to be missing not at random and the imputations were based on their baseline intact parathyroid hormone (iPTH) and modelled after subjects in the placebo group.

Given concern over missing data in Study 20130356 due to the fact the subjects were dropping out before the original EAP at weeks 17 through 20, the Division renegotiated the primary endpoint to be reassessed at weeks 11 and 15 as part of amendment #5 to the WR. The sponsor continued to measure the endpoint at the original EAP weeks 17 to 20 as a secondary endpoint and weeks 17 through 20 were still considered the primary endpoint for evaluation by countries outside the US.

Due the clinical hold in the pediatric clinical program there was an interruption during the middle of study 20110100. Patients enrolled in the study prior to the clinical hold, Cohort 1, were assessed separately from subjects enrolled into the study after the clinical hold, Cohort 2, as patients enrolled into Cohort 2 followed a stricter serum calcium monitoring protocol.

## 5.3 Discussion of Individual Studies/Clinical Trials

WR Study 1 (20090005) Single-dose PK/PD study in subjects 28 days to < 6 years of age with secondary HPT and CKD receiving dialysis

WR Study 2 (20070208) 30-week double-blind, placebo- controlled safety and efficacy study in subjects 6 to < 12 years of age (Cohort 1) and 12 to < 18 years of age (Cohort 2) with secondary HPT and CKD receiving dialysis

WR Study 3 (20110100) 26-week (or time-until- transplantation) open-label safety study in subjects 28 days to < 6 years of age with secondary HPT and CKD receiving dialysis

WR Study 4 (20130356) 24-week open-label, controlled safety and efficacy study in subjects 6 to < 12 years of age Cohort 1 and 12 to < 18 years of age Cohort 2 with secondary HPT and CKD receiving dialysis

# 6 Review of Efficacy

## *Efficacy Summary*

**Efficacy in children 6 to < 18 years of age was assessed in WR Study 2 (20070208) & WR Study 4 (20130356).**

WR Study 2 (20070208) was a 30-week double-blind, placebo-controlled, safety and efficacy study in pediatric dialysis subjects age 6 to < 18 years with secondary hyperparathyroidism and CKD. The study was initially designed to enroll 100 total pts (i.e. 50 pts per treatment group) with 99% power based on adult data to detect a difference in the primary endpoint, % of responders with 30% reduction in mean iPTH from baseline during the EAP. However due to a fatality in this study, which was associated with severe hypocalcemia, the pediatric clinical program was placed on hold and this study was eventually closed with efficacy evaluated using the available data. Therefore only 43 subjects were randomized, of which 22 received cinacalcet, and 21 received placebo. This gave only about 80% power for the primary endpoint determination. Because of the early study closure, 63% of subjects discontinued the study during the double-blind phase and 72% discontinued the investigational drug product during the study (82% on cinacalcet and 62% on placebo). This contributed to a large amount of missing data during weeks 25, 27 and 29 of the EAP. The applicant analyzed the data using a Last Observation Carried Forward (LOCF) approach, as they had originally proposed, which is no longer accepted for efficacy by the Biometric's team, and obtained results showing 54.5% response in the cinacalcet arm compared to 19% response in the placebo arm with a p-value of 0.017. The Biometric's team informed the applicant that we no longer consider an LOCF analysis sufficient to support efficacy and asked them to redo their analysis handling the missing data in a fashion that corresponded to the original intended conduct of the study. Therefore, imputation of missing data was to be handled based on whether the reason for a subject's discontinuation from the study early was assumed to be missing at random. The applicant's reanalysis in their 3/10/17 submission showed only a 41.5% response in the cinacalcet arm compared to a 24.2% response in the placebo arm with a p-value of 0.36 so the results were no longer statistically significant. Consistent with the reanalysis, an analysis of all the available data by the Biometric's team reviewer showed no clear difference between treatment groups during the EAP supporting the lack of a significant clinical difference in this study (see Figure 6).

WR Study 4 (20130356) was originally a 24-week open-label, controlled safety and efficacy study in pediatric dialysis subjects age 6 to < 18 years with secondary hyperparathyroidism and CKD comparing treatment with "cinacalcet & Standard of Care (SOC)" vs. "SOC alone". The study was designed during the clinical hold in the pediatric program and therefore included heightened serum calcium monitoring to address the safety concerns associated with the pediatric death in Study 20070208. The primary endpoint was the same as in Study 20070208, % of responders with 30% reduction in mean iPTH from baseline during the EAP, but the EAP occurred earlier at

weeks 17 through 20. Despite the earlier EAP, the applicant still had problems with patient retention and because of the Division's concern over missing data it was agreed to assess the efficacy results sooner at weeks at 11 and 15 as part of amendment #5 to the WR. As it turned out neither the data calculated at week 17 and 20 (p=0.42) nor at weeks 11 and 15 (p=0.48) gave statistically significant results. A plot of median % change in iPTH from baseline by Study Visit confirms there was no greater efficacy with the "cinacalcet & SOC" group vs the "SOC alone" group in this study (see Figure 10). After a review of the study results, it appears that the primary reason for the lower efficacy in this study compared to Study 20070208 is likely sub therapeutic dosing due to the heightened serum calcium monitoring and fewer titration visits. For example, the mean maximum weight-adjusted dose in Study 20130356 was 50% lower than in Study 20070208.

In conclusion, neither of these two Studies (20070208 or 20130356) was able to provide conclusive data to support clinical efficacy for the surrogate primary endpoint of ≥30% response in iPTH lowering from baseline in children age 6 to < 18 years of age with secondary hyperparathyroidism and CKD receiving dialysis.

**Efficacy in children 28 days to < 6 years of age**
Efficacy in this younger population age 28 days to < 6 years was to be derived by extrapolation of data from the older children and adult data. However, since there were no significant covariates observed in the pharmacometric analysis that could be identified to explain dose adjustment between pediatric vs. adult data using the PKPD modeling, and given the inconclusive efficacy results due to missing data and the high dropout rate in children 6 to < 18 years of age, it is not possible to use the current empiric data to extrapolate pediatric efficacy to this lower age group.

While efficacy in children 28 days to < 6 days was estimated by the applicant from the data generated in WR Study 3 (20110100), the study was not designed or powered for statistical significance, and it was planned primarily as a safety study. Efficacy, estimated as the proportion of subjects achieving a ≥30% reduction from baseline in iPTH was calculated as a secondary endpoint at 71% (12/17) which was much higher than was seen in either of the two studies in children 6 to < 18 years of age. Efficacy was greater prior to the clinical hold 100% (7/7) compared to 50% (5/10) after the clinical hold, likely due to the heightened serum calcium monitoring after the clinical hold. Part of the reason for the apparent higher efficacy seen in this study may be related to the fact that the younger children had more severe disease at baseline with median iPTH levels of 1288pg/mL compared to only 680pg/mL in the older children in Study 200702080. Also according to the standard of care policy in the Study 20110100 protocol "Adjustment of active vitamin D sterol doses are permitted during the study to achieve therapeutic goals for PTH levels at the discretion of the investigator." Therefore treating physicians in Study 20110100 may have been more inclined to use additional concomitant therapy with vitamin D analogs in patients with higher baseline iPTH levels, especially given the 89% of subjects were already on baseline vitamin D analog

therapy, and that this was primarily designed as a safety study. The study case report did not address changes in concomitant therapy with vitamin D analogs, calcium supplements and phosphate binders as part of the SOC in this open label study, so it is unclear what impact they may have had on the efficacy results. Therefore, the efficacy results in this study, while potentially significant, cannot be used to support the clinical efficacy of cinacalcet for the treatment of secondary hyperparathyroidism in pediatric dialysis patients 28 days to < 6 years of age.

**General observations about efficacy in the pediatric population**
Similar to the greater iPTH lowering seen in Study 20110100 (e.g. 71%) several published prospective trials using cinacalcet in the pediatric population appear to demonstrate efficacy (see Literature Review Section 9.1). In published clinical studies, mean reduction in iPTH from baseline ranged between 41.7% to 97.6%, while the reduction for individual case reports ranged between 39.4% to 97%. While Study 20110100 and the other studies from the literature were not adequately powered and controlled to constitute substantial evidence of efficacy, this medical reviewer believes that such findings support the conclusion that the negative results from Studies 20070208 or 20130356 in children 6 to < 18 reviewed in this NDA, do not necessarily conclusively represent a lack of efficacy of cinacalcet in pediatric patients but instead represent inconclusive studies.

## 6.1 Indication (WR Study 2, age 6 to < 18 years) Study 20070208

(WR Study 2) Study 20070208-Treatment of Secondary hyperparathyroidism (HPT) in pediatric subjects age 6 to < 18 years with chronic kidney disease (CKD) receiving hemodialysis or peritoneal dialysis

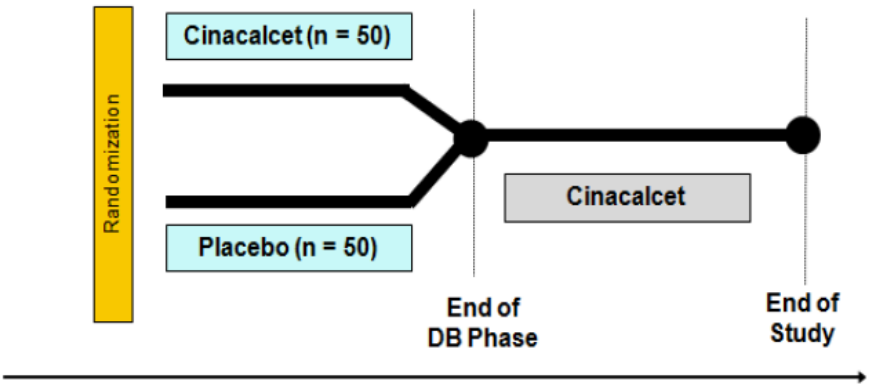
### 6.1.1 Methods

**Trial Design-**
This was a multi-center, randomized, double-blind, placebo-controlled, 30-week trial followed by a 30-week open-label extension in 43 pediatric subjects age 6 to < 18 years with chronic kidney disease (CKD) receiving hemodialysis or peritoneal dialysis. All subjects received standard of care with active vitamin D analogs (e.g. calcitriol, alfacalcidol, paricalcitol etc.), calcium supplements, and phosphate binders at the discretion of the investigator and were randomized 1:1 to receive either cinacalcet or placebo. Randomization was stratified by age group (1) 6 years to < 12 years and (2) 12 years to < 18 years. The double-blind, placebo-controlled phase of the study consisted of a 24-week dose-titration period followed by a 6-week efficacy assessment period (EAP) during which dose escalations were not permitted. Subjects who completed the double-blind phase were eligible to enter the 30-week open-label phase of the study. The investigational drugs issued in the double-blind phase (i.e. cinacalcet or placebo) were discontinued and all subjects were restarted on a 24-week cinacalcet dose-titration

period followed by a 6-week open-label maintenance period. By repeating the dose titration during the open-label extension there was no need to break the study blind during the study.

**Figure 5 Study Design (20070208)**

| Screening | Double-blind Phase | | Open-label Phase | |
|---|---|---|---|---|
| | Titration | Efficacy Assessment | Titration | Maintenance |
| Up to 40 Days | 24 Weeks | 6 Weeks | 24 Weeks | 6 weeks |




DB = double blind.

Dose-titration could occur once every 4 weeks in the dose-titration period of each phase. Blood samples were collected to measure iPTH, total serum calcium, phosphorous, and albumin at baseline (average of screening and day 1 predose) and every two weeks during the double-blind and open-label extensions (e.g. weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29 during the double-blind phase and weeks 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57 and 59 during the open-label extension). Samples drawn 1 week prior to each potential dose titration visit were used to determine if the dose of investigational product (IP) was to be up titrated. Serum calcium was reported as a corrected value by the central laboratory based on calcium and albumin concentrations. Blood samples for pharmacokinetic (PK) analysis were collected pre-dose for all subjects including those receiving peritoneal dialysis or hemodialysis. In addition, in half of the hemodialysis subjects additional measurements were performed early at between 1 and <3 hours post-dose and in the other half of the hemodialysis subjects additional measurements were performed later at >3 to 24 hours post-dose during the double-blind phase. Additional study visits to measure iPTH, total serum calcium, phosphorous, and albumin were scheduled 5 to 7 days after any change in investigational product dose. This included changes due to dose increases, dose decreases or the dose being withheld or restarted.

**Inclusion Criteria (including but not limited to):**

- age 6 to < 18 years old
- diagnosed with chronic kidney disease (CKD) and secondary hyperparathyroidism (HPT) treated with either hemodialysis or peritoneal dialysis for ≥ 2 months.
- screening iPTH level > 300 pg/mL
- screening serum calcium ≥ 8.8 mg/dL
- serum phosphorus ≥ 4.0 mg/dL for children age 6 to less than 12 years and ≥ 3.5 mg/dL for children age 12 to less than 18 years
- patients already receiving active vitamin D analogs had to be on a stable dose within the 2 months preceding randomization
- patients taking growth hormone, had to be on a stable dose defined as no change of > 20% within the 2 months preceding randomization
- dialysate calcium concentration had to be ≥ 2.5 mEq/L for at least 2 months prior to randomization and throughout the duration of the study

**Exclusion Criteria (including but not limited to):**

- anticipated parathyroidectomy within 6 months after randomization
- received therapy with cinacalcet within 1 month prior to randomization
- new onset of seizure or worsening of a pre-existing seizure disorder within 3 months prior to first dose of investigational product
- scheduled date for kidney transplant from a known living donor that makes completion of the study unlikely
- not available for protocol-required study visits, to the best of the subject and investigator's knowledge

**Dose Titration-**

Subjects received investigational product orally once daily at a starting dose of ≤ 0.20 mg/kg based on dry weight. The dose could be up titrated 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 180 mg the maximum recommended adult dose.

**Table 4 Dose Titration Scheme Based on Body Weight**

| 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 |

[a] Starting dose is ≤ 0.2 mg/kg/day for the first dose during double-blind and for the first dose during open-label.
[b] See below for titration instructions

Source Table 1 Study 20070208 protocol

During the double-blind phase, subjects were randomized to receive cinacalcet or placebo. During the open-label phase, all subjects received cinacalcet. 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. Tablets at strengths of 30, 60, or 90 mg were to be swallowed whole with food or shortly after a meal.

At each titration visit dose increases could occur if:

- iPTH ≥ 300 pg/mL and
- corrected serum calcium ≥ 8.4 mg/dL and
- had not reached the highest dry weight based dose of IP, and
- 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 might require a dose decrease or preclude a dose increase.

At each titration visit dose decreases could occur if:

- iPTH < 150 pg/mL and ≥ 100 pg/mL or
- corrected total serum calcium < 8.4 mg/dL and ≥ 8.0 mg/dL or
- 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 required a dose decrease, and did not require withholding the dose, per investigator assessment.

At each titration visit the dose could be withheld if:

- symptoms of hypocalcemia, regardless of the calcium level, or

- corrected total serum calcium < 8.0 mg/dL, or
- iPTH < 100 pg/mL, or
- 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 required a dose withhold, per investigator assessment

If the dose was withheld, corrected total serum calcium was to be measured within 5 to 7 days and drugs could be restarted at the next lower dose once corrected total serum calcium is > 8.4 mg/dL, iPTH ≥ 300 pg/mL, adverse events are resolved, and the subject was stable, per investigator assessment.

### 6.1.2 Demographics

The mean (SD) age of subjects was 13.2 (3.3) years (range, 6 to 18 years): In the cinacalcet group 6 subjects (27%) were between 6 and < 12 years, and 16 subjects (73%) were between 12 and < 18 years. In the placebo group, 5 subjects (24%) were between 6 and < 12 years, and 16 subjects (76%) were between 12 and < 18 years. Twenty-one subjects (49%) were boys, and 22 subjects (51%) were girls. The majority, 72%, were white while 26% were black or African American and 2% were listed as other.

The mean (SD) iPTH concentration at baseline was 757 (440) pg/mL in the cinacalcet group and 796 (538) pg/mL in the placebo group. The mean (SD) corrected total calcium level at baseline was 9.9 (0.5) mg/dL in the cinacalcet group and 9.9 (0.6) mg/dL in the placebo group, and the mean (SD) phosphorous levels were 6.7 (1.8) mg/dL in the cinacalcet group and 6.4 (1.5) mg/dL in the placebo group.

Regarding dialysis mode, 15 subjects (68%) in the cinacalcet group and 12 subjects (57%) in the placebo group were undergoing hemodialysis, and 7 subjects (32%) in the cinacalcet group and 9 subjects (43%) in the placebo group were undergoing peritoneal dialysis.

Twenty-one subjects (96%) in the cinacalcet group and 18 subjects (86%) in the placebo group were using vitamin D sterols at baseline, and the most common vitamin D sterols used at baseline were intravenous paricalcitol/Zemplar (23% in the cinacalcet group and 38% in the placebo group) and oral alfacalcidol (36% in the cinacalcet group and 24% in the placebo group). A total of 8 subjects (36%) in the cinacalcet group and 6 subjects (29%) in the placebo group were using nutritional vitamin D at baseline, and the most common drug was cholecalciferol (32% in the cinacalcet group and 24% in the placebo group).

Twenty subjects (91%) in the cinacalcet group and 19 subjects (91%) in the placebo group were using a phosphate binder at baseline, and the most common phosphate

binders used at baseline were calcium-containing phosphate binders (64% in the cinacalcet group and 62% in the placebo group) and sevelamer HCl (32% in the cinacalcet group and 43% in the placebo group). Five subjects (23%) in the cinacalcet group and 2 subjects (10%) in the placebo group were using a calcium supplement at baseline. A total of 8 subjects (36%) in the cinacalcet group and 3 subjects (14%) in the placebo group were using growth hormone at baseline.

**Table 5 Demographics and Baseline Characteristics**

| | Placebo (N = 21) | Cinacalcet (N = 22) | Total (N = 43) |
|---|---|---|---|
| Sex – n (%) | | | |
| Male | 11 (52.4) | 10 (45.5) | 21 (48.8) |
| Female | 10 (47.6) | 12 (54.5) | 22 (51.2) |
| Age (years) | | | |
| n | 21 | 22 | 43 |
| Mean | 13.2 | 13.3 | 13.2 |
| SD | 2.9 | 3.6 | 3.3 |
| Median | 14.0 | 14.5 | 14.0 |
| Q1, Q3 | 12.0, 15.0 | 10.0, 16.0 | 11.0, 16.0 |
| Min, Max | 7, 17 | 6, 18 | 6, 18 |
| Age group (years) – n (%) | | | |
| 6 - < 12 years | 5 (23.8) | 6 (27.3) | 11 (25.6) |
| 12 - < 18 years | 16 (76.2) | 16 (72.7) | 32 (74.4) |
| Race– n (%) | | | |
| White or Caucasian | 15 (71.4) | 16 (72.7) | 31 (72.1) |
| Black or African American | 6 (28.6) | 5 (22.7) | 11 (25.6) |
| Asian | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| American Indian or Alaska Native | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Native Hawaiian or Other Pacific Islander | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Other | 0 (0.0) | 1 (4.5) | 1 (2.3) |
| Race category – n (%) | | | |
| White | 15 (71.4) | 16 (72.7) | 31 (72.1) |
| Black | 6 (28.6) | 5 (22.7) | 11 (25.6) |
| Other | 0 (0.0) | 1 (4.5) | 1 (2.3) |
| Ethnicity category – n (%) | | | |
| Hispanic or Latino | 5 (23.8) | 3 (13.6) | 8 (18.6) |
| Not Hispanic or Latino | 16 (76.2) | 19 (86.4) | 35 (81.4) |
| Dry weight (kg) | | | |
| n | 21 | 22 | 43 |
| Mean | 46.1 | 45.3 | 45.7 |
| SD | 21.0 | 18.5 | 19.5 |
| Median | 38.5 | 42.6 | 42.3 |
| Q1, Q3 | 27.6, 59.3 | 31.8, 53.3 | 28.9, 54.8 |
| Min, Max | 21, 94 | 18, 83 | 18, 94 |
| Height (cm) | | | |
| n | 21 | 22 | 43 |
| Mean | 146.0 | 148.7 | 147.4 |
| SD | 18.9 | 19.5 | 19.0 |
| Median | 149.0 | 152.3 | 152.0 |
| Q1, Q3 | 132.0, 159.3 | 138.0, 160.0 | 132.7, 160.0 |
| Min, Max | 116, 176 | 112, 180 | 112, 180 |

Source Table 14-2.1, 14-2.2 CSR 20070208

**Table 6 Baseline Laboratory Values**

| | Placebo (N = 21) | Cinacalcet (N = 22) | Total (N = 43) |
|---|---|---|---|
| iPTH (pg/mL) | | | |
| n | 21 | 22 | 43 |
| Mean | 795.8 | 757.1 | 776.0 |
| SD | 537.9 | 440.1 | 484.8 |
| Median | 684.0 | 676.0 | 680.0 |
| Q1, Q3 | 465.0, 844.0 | 484.0, 825.0 | 465.0, 844.0 |
| Min, Max | 300, 2246 | 309, 2407 | 300, 2407 |
| Corrected total serum calcium (mg/dL) | | | |
| n | 21 | 22 | 43 |
| Mean | 9.88 | 9.91 | 9.90 |
| SD | 0.62 | 0.54 | 0.58 |
| Median | 9.80 | 10.05 | 9.90 |
| Q1, Q3 | 9.50, 10.20 | 9.40, 10.30 | 9.40, 10.30 |
| Min, Max | 9.0, 11.3 | 8.9, 10.8 | 8.9, 11.3 |
| Serum phosphorus (mg/dL) | | | |
| n | 21 | 22 | 43 |
| Mean | 6.37 | 6.68 | 6.53 |
| SD | 1.48 | 1.78 | 1.63 |
| Median | 6.00 | 6.70 | 6.00 |
| Q1, Q3 | 5.50, 7.00 | 5.40, 7.60 | 5.50, 7.50 |
| Min, Max | 4.5, 10.6 | 3.7, 12.1 | 3.7, 12.1 |

Source Table 14-2.5 CSR 20070208

*Medical Officer's comments-*
*According to the NAPRTCS 2008 Annual Report, African Americans make up almost 19% of the pediatric CKD population so they are slightly over represented in this study (25.6%). Males on the other hand are slightly under represented in this study (48.8%) as they make up 64% of the pediatric CKD population in the NAPRTCS 2008 Annual Report. Males typically have a higher rate of pediatric renal disease due to a higher prevalence of hypoplasia/dysplasia and obstructive uropathy.*

*The baseline iPTH was slightly higher in the placebo group 796 (538) pg/mL compared to the cinacalcet group 757 (440) pg/mL due to a slightly greater number of high outliers in the placebo group, but this difference is likely not large enough to substantially impact the efficacy results. Baseline corrected serum calcium levels are generally similar between treatment groups while serum phosphorous is slightly higher in the cinacalcet group 6.68 (1.78) mg/dL compared with 6.37 (1.48) mg/dL, but these minor differences are not likely to significantly affect the safety comparison between treatment groups.*

*Treatment with growth hormone was higher in the cinacalcet group 8 (36%) compared to the placebo group 3 (14%) which might favor the cinacalcet group with respect to growth velocity measurements at 30wks and 60wks.*

*In general, the demographics were reasonably distributed between groups, given the small size of the study (n=43).*

**Table 7 Baseline Medication Use**

| | Placebo (N=21) | Cinacalcet (N=22) | Total (N=43) |
|---|---|---|---|
| No vitamin D sterol or nutritional vitamin D use at baseline | 3 (14.3) | 1 (4.5) | 4 (9.3) |
| Vitamin D sterol use at baseline | 18 (85.7) | 21 (95.5) | 39 (90.7) |
| IV Paricalcitol/Zemplar | 8 (38.1) | 5 (22.7) | 13 (30.2) |
| PO Paricalcitol/Zemplar | 1 (4.8) | 1 (4.5) | 2 (4.7) |
| PO Alfacalcidol | 5 (23.8) | 8 (36.4) | 13 (30.2) |
| IV Calcitriol/Calcijex | 2 (9.5) | 1 (4.5) | 3 (7.0) |
| PO Calcitriol/Rocaltrol | 2 (9.5) | 6 (27.3) | 8 (18.6) |
| Nutritional vitamin D use at baseline | 6 (28.6) | 8 (36.4) | 14 (32.6) |
| Cholecalciferol | 5 (23.8) | 7 (31.8) | 12 (27.9) |
| Ergocalciferol | 1 (4.8) | 1 (4.5) | 2 (4.7) |
| No phosphate binder use at baseline | 2 (9.5) | 2 (9.1) | 4 (9.3) |
| Phosphate binder use at baseline | 19 (90.5) | 20 (90.9) | 39 (90.7) |
| Calcium-containing | 13 (61.9) | 14 (63.6) | 27 (62.8) |
| Sevelamer HCl | 9 (42.9) | 7 (31.8) | 16 (37.2) |
| Sevelamer carbonate | 5 (23.8) | 3 (13.6) | 8 (18.6) |
| No calcium supplement use at baseline | 19 (90.5) | 17 (77.3) | 36 (83.7) |
| Calcium supplement use at baseline | 2 (9.5) | 5 (22.7) | 7 (16.3) |
| Calcium | 0 (0.0) | 1 (4.5) | 1 (2.3) |
| Calcium Carbonate | 2 (9.5) | 4 (18.2) | 6 (14.0) |
| No growth hormone use at baseline | 18 (85.7) | 14 (63.6) | 32 (74.4) |
| Growth hormone use at baseline | 3 (14.3) | 8 (36.4) | 11 (25.6) |

Source Table 14-2.4 CSR 20070208

### 6.1.3 Subject Disposition

With a sample size of 100 patients, 50 per treatment group, the study originally had 99% power to detect a difference based on adult data in which 64% of cinacalcet subjects achieved a ≥ 30% reduction in mean iPTH from baseline during the EAP using the last observation carried forward method compared to 13% of placebo subjects. However, due to a fatality in the cinacalcet treatment group, the study was stopped early so less data was collected than originally planned. However, a sample size of 44

(22 per treatment group) would still have been adequate to provide 82% power to detect a difference of 60% in the cinacalcet group compared to 15% in the placebo group using a 2-sided Fisher's exact test at an alpha level of 0.05.

In Study 20070208, a total of 43 subjects were randomized of which 22 subjects received cinacalcet, and 21 subjects received placebo. A total of 16/43=37% of subjects 5/22=23% from the cinacalcet group and 11/21=52% from the placebo group completed the double-blind phase. Of these 5/16=31% were 6 to < 12 years and 11/16=69% were 12 to < 18 years. Thirty-eight subjects overall (88%), 86% in the cinacalcet group and 91% in the placebo group, completed at least 12 weeks of treatment. Only 7 subjects who completed 12 weeks of the study discontinued during the double-blind phase because they went on to kidney transplant. Eventually, 18 subjects (82%) in the cinacalcet group and 13 subjects (62%) in the placebo group discontinued investigational product during the double-blind phase. Only 12 subjects (28%), 7 in the cinacalcet group and 5 in the placebo group, discontinued the study due to the administrative decision to stop the study after the pediatric death.

**Table 8 Patient Disposition for Study 20070208 During the Double-Blind Phase**

| | Placebo (N = 21) n (%) | Cinacalcet (N = 22) n (%) | Total (N = 43) n (%) |
|---|---|---|---|
| Subjects randomized | 21 | 22 | 43 |
| Subjects who received IP | 21 (100.0) | 22 (100.0) | 43 (100.0) |
| Subjects who completed IP | 8 (38.1) | 4 (18.2) | 12 (27.9) |
| Subjects who discontinued IP | 13 (61.9) | 18 (81.8) | 31 (72.1) |
| Total completed 12 weeks - n (%) | 19 (90.5) | 19 (86.4) | 38 (88.4) |
| Subjects who completed the double-blind phase | 11 (52.4) | 5 (22.7) | 16 (37.2) |
| Age group: 6 to < 12 years | 3 (14.3) | 2 (9.1) | 5 (11.6) |
| Age group: 12 to < 18 years | 8 (38.1) | 3 (13.6) | 11 (25.6) |
| Subjects who discontinued the study during the double-blind phase | 10 (47.6) | 17 (77.3) | 27 (62.8) |

IP = investigational product.
Source Table 9-1 CSR 20070208

*Medical Officer's comments-*
*In this study 43 subjects were enrolled, satisfying the WR requirement that at least 40 patients be enrolled in the study.*

*In this study, 5/16=31% of the completers were 6 to < 12 years of age satisfying the WR requirement that >25% of patients completing the double-blind phase were to be 6 to 12 years of age.*

*In this study, 16/43=37% patients completed the double-blind phase of the study and 4/12=33% completed the open-label extension satisfying the WR requirement that at least 14 patients complete the double-blind portion of the study and 2 patients complete the open label extension.*

### 6.1.4 Analysis of Primary Endpoint(s)

Primary Endpoint:
The primary endpoint was the % of subjects with a ≥ 30% reduction from baseline in mean plasma iPTH during the EAP (weeks 25 through 30). 54.5% (12/22) of the subjects in the cinacalcet group achieved the primary endpoint compared to 19.0% (4/21) in the placebo group which was statistically significant using the applicant's analysis (p=0.017, stratified by age).

**Table 9 Primary Endpoint-Proportion of Subjects Achieving a ≥30% reduction in Mean iPTH from Baseline during the EAP (weeks 25 through 30).**

| | 6 - < 12 years | | 12 - < 18 years | | Total | |
|---|---|---|---|---|---|---|
| | Placebo (N = 5) n (%) | Cinacalcet (N = 6) n (%) | Placebo (N = 16) n (%) | Cinacalcet (N = 16) n (%) | Placebo (N = 21) n (%) | Cinacalcet (N = 22) n (%) |
| Efficacy assessment phase | 1 (20.0) | 6 (100.0) | 3 (18.8) | 6 (37.5) | 4 (19.0) | 12 (54.5) |

| | CMH Statistic (Chi-square) | | Odds Ratio (Cinacalcet/Placebo) | | Difference (Cinacalcet - Placebo)[a] | |
|---|---|---|---|---|---|---|
| | Value | p-value | Value | 95% CI | Value | 95% CI |
| Test statistic | 5.735 | 0.017 | 4.26 | (0.99, 18.30) | 35.50% | (8.76%, 62.24%) |

iPTH = intact parathyroid hormone; CMH = Cochran-Mantel-Haenszel; CI = confidence interval.
Full analysis set: all subjects who were randomized and with at least 1 post-baseline assessment
All data collected 7 days after the clinical hold (31 January 2013) were excluded.
[a] Based on the difference in proportions between treatment groups
Source Table 10-1 CSR 20070208

*Medical Officer's comments-*
*The original Biometric's review of the study protocol by Dr. Lee Ping Pian (2/25/2010) as part of a PPSR submission noted that the applicant proposed to perform an LOCF analysis with plans to impute missing data only for patients with no post baseline data. While the exact details of the analysis were not prespecified in the protocol, no comments on the acceptability of an LOCF approach were issued to the sponsor at that time.*

*Since then the Biometric's Division has determined that it no longer recommends using an LOCF approach to deal with missing data, the LOCF analysis which*

*initially gave statistically significant results was no longer considered adequate. Therefore, the Biometric's team asked the sponsor to do an analysis which handled the missing data in a fashion that corresponded to the original intended conduct of the study, but not the actual conduct of the trial. The analysis was to impute, using a multiple imputation approach, iPTH measurements (week 25, 27, 29) during EAP for those without data. Specifically, missing data were to be handled based on whether the reason for a subject's discontinuation from the study early was assumed to be missing at random. Placebo subjects with missing data during EAP were assumed to be missing at random (MAR) and the imputations were based on subjects in the placebo group. Cinacalcet subjects who had discontinued due to study closure or kidney transplant were assumed to be MAR and the imputations were based on subjects in the cinacalcet group. Cinacalcet subjects who had discontinued due to other reasons were assumed to be missing not at random and the imputations were based on their baseline intact parathyroid hormone (iPTH) and modelled after subjects in the placebo group. This strategy made it more likely that cinacalcet subjects who were not discontinued for either study closure or kidney transplant would pay a penalty and have less favorable missing data imputed. This analysis continued to show a greater average efficacy response in the cinacalcet group during the EAP but the results were no longer statistically significant, with a p-value=0.36.*

*An alternative analysis proposed by the applicant allowed 3 additional cinacalcet subjects to be considered missing at random and permitted more favorable imputations, based on subjects in the cinacalcet group, due to the reason behind their discontinuation from the study:*

*(1) one that was relocated to a dialysis center not associated with the study and*

*(2) two that had their iPTH dose withheld and were eventually discontinued from the study due to over response (i.e. low iPTH)*

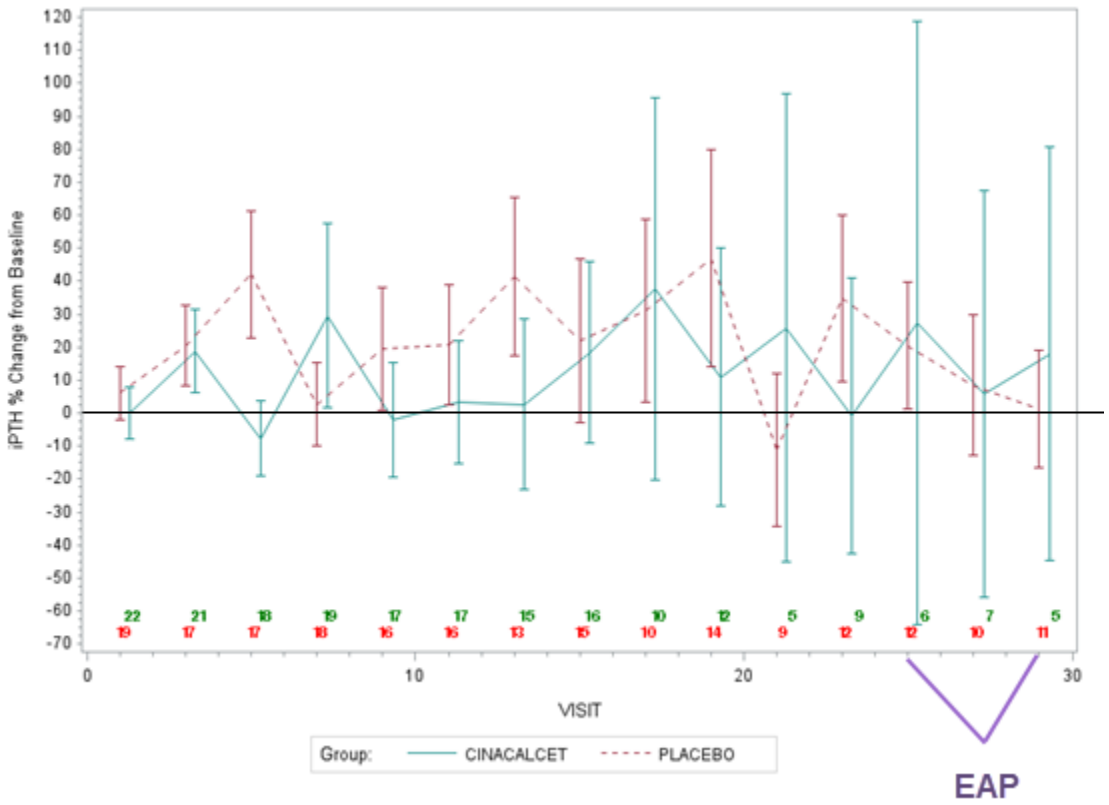
*This analysis continued to show a greater average efficacy response in the cinacalcet group during the EAP but the results were still not statistically significant, with a p-value=0.34.*

*It is likely that both of the analyses which imputed missing data were not statistically significant because of the high variance in the data and the small number of patients in this study.*

*An analysis of all the available data was performed by the statistical reviewer Dr. Susie Sinks and is included in the following figure. The difference between treatment groups appears to be greatest between weeks 9 through 13 and is primarily due to an increase in iPTH levels in the placebo group with no net decrease in iPTH in cinacalcet group from baseline. This difference disappears with longer duration in treatment so that by the EAP, weeks 25 and later, there is no clear difference between treatment groups. The LOCF analysis submitted by*

*the applicant which appeared to give statistically significant results likely overrepresented the earlier results for subjects who later on discontinued from the study.*

**Figure 6 Mean Percent Change in iPTH from Baseline in Study 200070208 during the Double-Blind Phase**




*Source Biometric's Review of Dr. Susie Sinks*

## 6.1.5 Analysis of Secondary Endpoints(s)

*Secondary Endpoints:*

1. achievement of a mean iPTH value ≤ 300 pg/mL during the EAP

The proportion of subjects achieving a mean iPTH value ≤ 300 pg/mL during the EAP was 27.3% in the cinacalcet group and 23.8% in the placebo group; the difference (cinacalcet - placebo) in the proportions was 3.46% (95% CI -22.58%, 29.51%) and not statistically significant (p=0.826).

**Table 10 Secondary Endpoint- Proportion of Subjects with Mean iPTH ≤300pg/mL during EAP**

| | 6 - < 12 years | | 12 - < 18 years | | Total | |
|---|---|---|---|---|---|---|
| | Placebo (N=5) | Cinacalcet (N=6) | Placebo (N=16) | Cinacalcet (N=16) | Placebo (N=21) | Cinacalcet (N=22) |
| Efficacy assessment phase | 1 (20.0) | 3 (50.0) | 4 (25.0) | 3 (18.8) | 5 (23.8) | 6 (27.3) |

| | CMH Statistic (Chi-square) | | Odds Ratio (Cinacalcet/Placebo) | | Difference (Cinacalcet-Placebo)[a] | |
|---|---|---|---|---|---|---|
| | Value | p-value | Value | 95% CI | Value | 95% CI |
| Test statistic | 0.048 | 0.826 | 1.13 | (0.27, 4.75) | 3.46% | (-22.58%, 29.51%) |

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N = Number of subjects in the full analysis set
Full analysis set: all subjects who were randomized and with at least one post-baseline assessment
[a] Based on the difference in proportions between treatment groups
CMH test is stratified by the age group.

Source Table 14-4.2.1. CSR 20070208

A hierarchical testing procedure was prespecified to test the primary and the first four secondary endpoints. Given that the first secondary endpoint was not statistically significant; the statistical analysis plan specified that none of the rest of the secondary endpoints would be tested for statistical significance. In any case, none of the rest of the secondary endpoints provided p-values < 0.05 to make that an issue.

2. percent change in corrected total serum calcium from baseline to the mean value during the EAP
3. percent change in serum phosphorus from baseline to the mean value during the EAP
4. percent change in Ca x P from baseline to the mean value during the EAP
5. growth velocity calculated from baseline to week 30, and from week 30 to week 60
6. percent change in ionized calcium from baseline to the mean value during the EAP

**Table 11 Secondary Endpoint Results for Study 20070208**

| Secondary Endpoint | LS Mean Estimate Placebo | LS Mean Estimate Cinacalcet | Difference in LS Mean (Cinacalcet-Placebo) Estimates | 95% CI |
|---|---|---|---|---|
| Percent change in corrected total serum calcium from baseline to the mean value during the EAP[a] | -1.0 | -4.6 | -3.7 | (-8.6, 1.3) |
| Percent change in serum phosphorus from baseline to the mean value during the EAP[a] | 9.3 | 2.9 | -6.4 | (-21.0, 8.2) |
| Percent change in Ca x P from baseline to the mean value during the EAP[a] | 8.0 | -2.0 | -10.0 | (-22.5, 2.6) |
| Growth velocity calculated from baseline to end of double-blind phase[b] | 3.1 | 3.3 | 0.2 | (-3.1, 3.6) |
| Percent change in ionized calcium from baseline to the mean value during the EAP[a] | -1.5 | -2.3 | -0.8 | (-9.4, 7.9) |

LS = least square; CI = confidence interval; EAP = efficacy assessment phase; Ca x P = calcium phosphorous product.
[a] The analyses included lab values collected prior to the suspension of investigational product.
[b] The end of the double-blind phase was at week 30 by design, but the last assessment in the double-blind phase was used because of the early termination of the study.
Source: *Table 14-4.99.2*, *Table 14-4.99.3*, *Table 14-4.99.4*, *Table 14-4.6.1*, and *Table 14-4.99.5.*
Source Table 10-3 CSR 20070208

The 5th secondary endpoint of growth velocity bears additional mention as it was one of the endpoints specified in the WR. The growth velocity was to be measured at weeks 30 and again at the end of the study at week 60. However, given that the study was terminated early for safety reasons, only the last assessment in the double-blind phase of the study was presented. There was a slight but not significant increase of 0.2cm/year in growth velocity in favor of cinacalcet which may have been due to the fact that more cinacalcet patients were treated with growth hormone (36% vs. 14%), but, as discussed previously, these results were not statistically significant.

**Table 12 Secondary Endpoint- Growth velocity (cm/year) from Baseline to the End of the Double-Blind Treatment Phase**

| | n | Estimate | Standard Error | 95% CI |
|---|---|---|---|---|
| Placebo (N=21) | 19 | 3.1 | 1.20 | (0.7, 5.6) |
| Cinacalcet (N=22) | 17 | 3.3 | 1.22 | (0.8, 5.8) |
| Difference (Cinacalcet-Placebo) | | 0.2 | | (-3.1, 3.6) |

| Source (fixed effect) | DF[a] | Type III SS | Mean Square | F statistic | p-value |
|---|---|---|---|---|---|
| Treatment (Cinacalcet/Placebo) | 1 | 0.419 | 0.419 | 0.017 | 0.896 |
| Age group | 1 | 21.687 | 21.687 | 0.901 | 0.349 |

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N = Number of subjects in the full analysis set
[a] Degrees of freedom
End of DB phase visit is at week 30 by design but the last assessment in the DB phase was used due to the early termination of the study.

Source Table 14-4.6.1. CSR 20070208

*Medical Officer's comments-*
*The WR had required that first (mean iPTH value ≤ 300 pg/mL) and fifth (growth velocity) secondary endpoints listed above were to be included in the final submission. Based on the data submitted by the applicant, neither of these endpoints gave p-values below 0.05, and so could not be used to support efficacy or clinical benefit for the use of cinacalcet in the pediatric dialysis population with secondary hyperparathyroidism.*

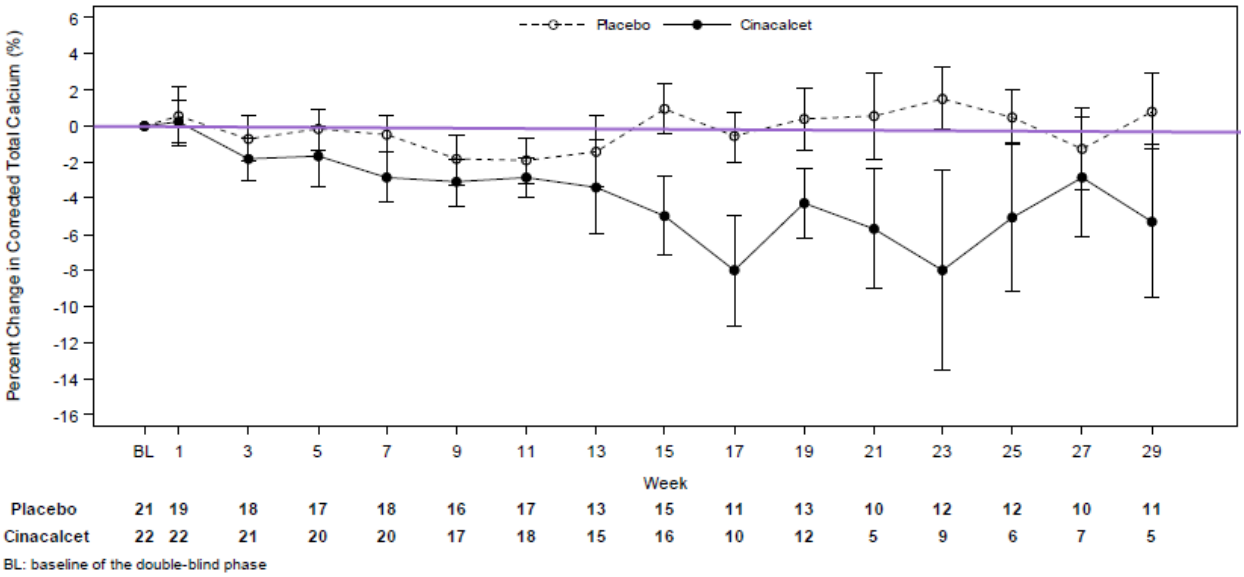
*While the WR Amendment #5 had required that the fifth secondary endpoint of growth velocity be measured both at week 30 (at the end of the double-blind period) and at week 60 (at the end of the open-label extension), the fact that the study was terminated early due to safety concerns limited the value of the later assessment. Only 10 subjects were exposed for a mean of 119 days (4 months) during the open label extension and only 4 subjects completed the 60 weeks. Of these 4 subjects two had been on placebo during the double-blind phase of the study so only two subjects were exposed to cinacalcet for the entire length of the study. From the ADSL dataset it appears that the growth rates for these two subjects (who were both 15 year old boys) decreased from 6.3cm/year for the first 6 months of the study to 2.6 cm/year over the last 6 months of the study in one case, and from 12.1 cm/year for the first 6 months to 1.0 cm/year over the last 6 months in the other case. While these data suggest a loss in growth velocity with prolonged exposure, it is possible that these were teen boys that were just ending their growth spurt so it is not possible to draw clear conclusions about the effect of cinacalcet on growth velocity from the limited data on these two subjects. Therefore this medical reviewer agrees that there was limited value in presenting the growth velocities for the few subjects with data at the week 60*

*visits and as such it was reasonable for the applicant to have presented only the 30 week data in the CSR.*

### 6.1.6 Other Endpoints

There is a small but observable mean decrease in corrected serum calcium of 5 to 6% in the cinacalcet treatment group which seems to reach a trough around week 15, whereas there is no clear change in mean corrected serum calcium in the placebo group. This would support some efficacy in pediatric patients treated with cinacalcet but is clearly not enough to result in significant changes in serum iPTH to be clinically meaningful. This conclusion is supported by the primary endpoint analysis. It is possible that patients with a lower response to cinacalcet may have dropped out and contributed to these results, but for the first 19 weeks or so there seem to be a similar number of drop outs in both treatment groups. During the last 10 weeks, there appears to be a greater drop out in the cinacalcet group (n=5 vs. n= 11 at week 29) possibly suggesting decreased tolerability with long term use.

**Figure 7 Mean (SE) % change in Corrected Total Serum Calcium in the Double-Blind Phase of Study 20070208**

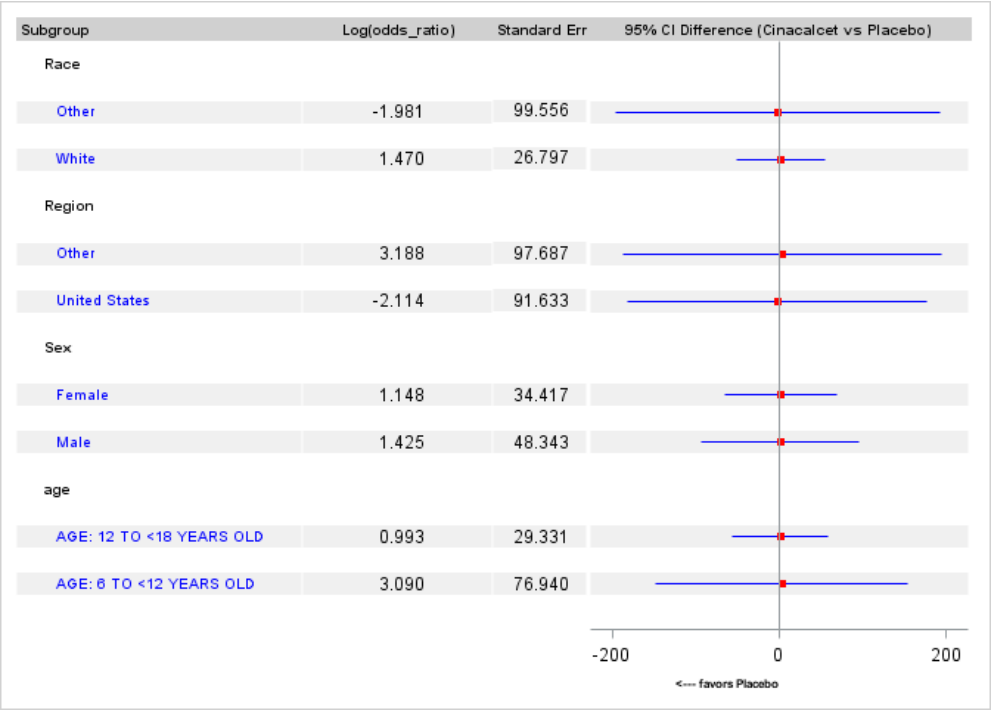



Source Fig 12-2 CSR Study 20070708

### 6.1.7 Subpopulations

There was no difference in efficacy by subgroups of race (White, other), gender, age stratification (6 to <12 years vs. 12 to < 18 years), or Region (USA vs. other).

**Figure 8 Subgroup Analysis for Study 20070208**




Source Stats Review

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The maximum dose level was 120 mg, administered to 1 subject (4.5%) (See table 14-5.2.1.). The mean weight-adjusted daily starting dose was 0.18 mg/kg/day, the mean maximum weight-adjusted daily dose during the study was 0.99 mg/kg/day, and the average weight-adjusted daily dose during the EAP (weeks 25 through 30) was 1.54 mg/kg/day (See table 14a-5.1.1). So the 4 subjects who were able to make it to weeks 25 through 30 of the EAP were able to tolerate daily doses that were 50% higher than the mean.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The large drop out in patients after 12 to 20 weeks of treatment as seen in Figure 6 and Figure 7 above suggests tolerability issues, even with the limited efficacy seen in this study, although no conclusions can be drawn given the limited data.

### 6.1.10 Additional Efficacy Issues/Analyses

None

## 6.2 Indication (WR Study 4, age 6 to < 18 years) Study 20130356

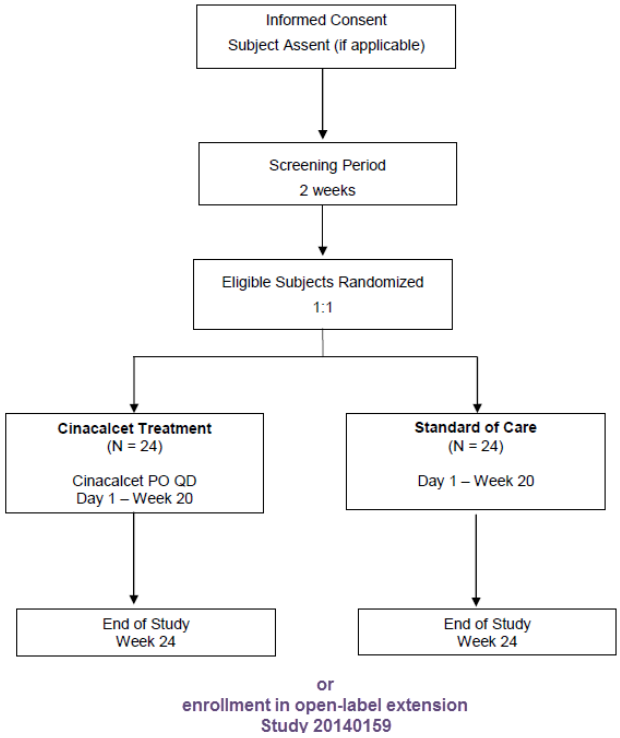
(WR Study 4) Study 20130356-Treatment of secondary hyperparathyroidism in pediatric subjects age 6 to < 18 years with CKD receiving hemodialysis or peritoneal dialysis

### 6.2.1 Methods

**Trial Design**
This was a multicenter, 24-week, open-label, study comparing treatment with "cinacalcet and Standard of Care (SOC)" to "SOC alone" in 48 pediatric subjects age 6 to < 18 years of age with CKD and secondary hyperparathyroidism receiving hemodialysis or peritoneal dialysis. Subjects were randomized 1:1 to treatment for 20 weeks followed by either (1) a 4-week safety follow up period or (2) enrollment into the open-label extension Study 20140159. As SOC, all subjects could receive active vitamin D analogs (e.g. calcitriol, alfacalcidol, paricalcitol and doxercalciferol), calcium supplements, and phosphate binders at the discretion of the clinical investigator. Randomization was stratified by age group (6 to < 12 years and 12 to < 18 years). Subjects who withdrew from the study due a renal transplant were considered to have completed the study if they completed ≥ 12 weeks of treatment before transplant surgery.

> *Medical Officer's comments-*
> *This study was initiated after lifting of the clinical hold in the pediatric program in April 2014, in order to get additional safety and efficacy data in children age 6 to < 18 years given that Study 20070208 was terminated early due to the clinical hold. As a result of the concern that hypocalcemia had contributed to the fatal event in Study 20070208, additional calcium monitoring and cinacalcet dose adjustments, to ensure better management of serum calcium levels and hypocalcemia, were included in Study 20130356. These included real-time weekly ionized calcium measurements, incorporation of local laboratory total calcium values into the dosing schema, subject compliance* measures*, investigational product suspension preparation by pharmacist, dispensing limited quantities of investigational product to limit the potential for overdosing, and addition of exclusionary ECG criteria related to QTc interval, arrhythmias and use of CYP3A4 inhibitors.*

**Figure 9 Study 20130356 Study Design**




Source 20130356 study protocol page 7

**Inclusion Criteria (including but not limited to):**

- age 6 to < 18 years of age at enrollment
- diagnosed with CKD and secondary hyperparathyroidism treated with either hemodialysis or peritoneal dialysis for ≥ 1 month.
- two consecutive screening iPTH levels > 300 pg/mL
- screening serum calcium ≥ 8.8 mg/dL
- dry weight ≥ 12.5kg at screening
- dialysate calcium concentration ≥ 2.5 mEq/L during screening

**Exclusion Criteria (including but not limited to):**

- received therapy with cinacalcet within 1 month prior to randomization
- new onset of seizure or worsening of a pre-existing seizure disorder within 2 months prior to first dose of investigational product
- Initiation or a change of > 20% in the prescribed dose of growth hormone
- scheduled date for kidney transplant within 90 days that makes completion of the study unlikely
- not available for protocol-required study visits, to the best of the subject and investigator's knowledge

- History of clinically significant disorder that in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion
- Corrected QT Interval (QTc) > 500 ms, using Bazett's formula, during screening
- QTc ≥ 450 to ≤ 500 ms, using Bazett's formula, during screening, unless written permission to enroll is provided by the investigator after consultation with a pediatric cardiologist
- History of congenital long QT syndrome, second or third degree heart block, ventricular tachyarrythmias or other conditions associated with prolonged QT interval
- Use of concomitant medications that may prolong the corrected QT interval (e.g., ondansetron, albuterol) during screening
- Use of grapefruit juice, herbal medications or CYP3A4 inhibitors (e.g., erythromycin, clarithromycin, ketoconazole, itraconazole) or, CYP2D6 substrates (e.g., flecainide, propafenone, metoprolol, desipramine, nortriptyline, clomipramine) during screening

**Dose Titration**

Cinacalcet was provided as 5 mg capsules containing an oral powder for sprinkling or as 30 mg film coated tablets for swallowing and was administered once daily with food or shortly after a meal at the same time each day. The protocol specified doses for use in this study were: 2.5, 5, 10, 15, 30, 60, 90, 120, and 180 mg once daily. The capsules were not to be swallowed whole but were to be opened and sprinkled on soft food or suspended into water or sucrose syrup to create a liquid suspension. Dose-titration could occur once every 4 weeks at Weeks 4, 8, 12, and 16. Blood samples were collected to measure iPTH, total serum calcium, phosphorous, and albumin at baseline, every four weeks of treatment (Weeks 3, 7, 11, and 15) one week prior to the proposed dose titration, and weekly from Weeks 17 to 20 during the original EAP. Ionized calcium was measured weekly. The starting dose was 0.20 mg/kg and was titrated upwards according to iPTH, corrected total serum calcium levels, and subject safety information. The maximum dose could not exceed 4.2 mg/kg/day or 180mcg. Dose adjustments were based on

- ionized calcium levels assessed weekly
  - dose reduction at ionized calcium <1.05 mmol/L,
  - dose withheld at ionized calcium <1.0 mmol/L), and
- plasma iPTH assessed monthly (Weeks 3 to 15), and weekly (Weeks 17 to 19)
  - dose reduction at ≥100 to <150 pg/mL,
  - dose withheld at <100 pg/mL and
- corrected calcium assessed monthly (Weeks 3 to 15), and weekly (Weeks 17 to 19)
  - dose reduction at corrected calcium <8.4 mg/dL,
  - dose withheld at corrected calcium < 8.0 mg/dL

Dose decisions were also based on adverse signs and symptoms related to hypocalcemia, investigational product compliance, administration of medications known to prolong the QTc interval, abnormal liver function tests, and unscheduled assessments or laboratory results. The target iPTH range was ≥ 150 to < 300 pg/mL.

### 6.2.2 Demographics

The mean (SD) age of subjects was 12.6 (3.6) years (range, 6 to 17 years): In the "cinacalcet & SOC" group 9 subjects (33%) were between 6 and < 12 years, and 18 subjects (67%) were between 12 and < 18 years. In the "SOC alone" group, 9 subjects (32%) were between 6 and < 12 years, and 19 subjects (68%) were between 12 and < 18 years. Twenty-eight subjects (51%) were boys, and 27 subjects (49%) were girls. The majority, 42 subjects (76%) were white while 9 subjects (16%) were black or African American.

The mean (SD) iPTH concentration at baseline was 946 (635) pg/mL in the "cinacalcet & SOC" group and 1228 (732) pg/mL in the "SOC alone" group. The mean (SD) corrected total calcium level at baseline was 9.8 (0.6) mg/dL in the "cinacalcet & SOC" group and 9.8 (0.6) mg/dL in the "SOC alone" group, and the mean (SD) phosphorous levels were 5.9 (1.4) mg/dL in the "cinacalcet & SOC" group and 5.7 (1.1) mg/dL in the "SOC alone" group.

Regarding dialysis mode, 21 subjects (78%) in the "cinacalcet & SOC" group and 17 subjects (61%) in the "SOC alone" group were undergoing hemodialysis, and 4 subjects (15%) in the "cinacalcet & SOC" group and 11 subjects (39%) in the "SOC alone" group were undergoing peritoneal dialysis.

Eighteen subjects (72%) in the "cinacalcet & SOC" group and 22 subjects (73%) in the "SOC alone" group were using vitamin D sterols at baseline, and the most common vitamin D sterols used at baseline were intravenous paricalcitol/Zemplar (33% in the "cinacalcet & SOC" group and 1% in the "SOC alone" group), oral alfacalcidol (26% in the "cinacalcet & SOC" group and 43% in the "SOC alone" group) and oral calcitriol (15% in the "cinacalcet & SOC" group and 21% in the "SOC alone" group). A total of 7 subjects (26%) in the "cinacalcet & SOC" group and 13 subjects (46%) in the "SOC alone" group were using nutritional vitamin D at baseline, and the most common drug was cholecalciferol (15% in the "cinacalcet & SOC" group and 39% in the "SOC alone" group).

Fifteen subjects (56%) in the "cinacalcet & SOC" group and 18 subjects (64%) in the "SOC alone" group were using a phosphate binder at baseline, and the most common phosphate binders used at baseline were calcium-containing phosphate binders (33% in the "cinacalcet & SOC" group and 29% in the "SOC alone" group) and sevelamer HCl (19% in the "cinacalcet & SOC" group and 32% in the "SOC alone" group). Thirteen subjects (48%) in the "cinacalcet & SOC" group and 11 subjects (39%) in the "SOC

alone" group were using a calcium supplement at baseline. A total of 3 subjects (11%) in the "cinacalcet & SOC" group and 1 subject (4%) in the "SOC alone" group were using growth hormone at baseline.

**Table 13 Demographics and Baseline Characteristics in Study 20130356 (1 of 2)**

| | SOC (N = 28) | SOC + Cinacalcet (N = 27) | Total (N = 55) |
|---|---|---|---|
| Sex - n (%) | | | |
| Male | 13 (46.4) | 15 (55.6) | 28 (50.9) |
| Female | 15 (53.6) | 12 (44.4) | 27 (49.1) |
| Ethnicity - n (%) | | | |
| Hispanic/Latino | 4 (14.3) | 0 (0.0) | 4 (7.3) |
| Not Hispanic/Latino | 24 (85.7) | 27 (100.0) | 51 (92.7) |
| Race - n (%) | | | |
| Black (or African American) | 4 (14.3) | 5 (18.5) | 9 (16.4) |
| White | 23 (82.1) | 19 (70.4) | 42 (76.4) |
| Mixed race | 0 (0.0) | 1 (3.7) | 1 (1.8) |
| White, Native Hawaiian or Other Pacific Islander | 0 (0.0) | 1 (3.7) | 1 (1.8) |
| Other | 1 (3.6) | 2 (7.4) | 3 (5.5) |
| Age (years) | | | |
| n | 28 | 27 | 55 |
| Mean | 12.4 | 12.8 | 12.6 |
| SD | 3.5 | 3.9 | 3.6 |
| Median | 12.0 | 14.0 | 13.0 |
| Q1, Q3 | 10.0, 15.5 | 9.0, 16.0 | 10.0, 16.0 |
| Min, Max | 6, 17 | 6, 17 | 6, 17 |
| Age group - n (%) | | | |
| 6 - < 12 years | 9 (32.1) | 9 (33.3) | 18 (32.7) |
| 12 - < 18 years | 19 (67.9) | 18 (66.7) | 37 (67.3) |

N=Number of subjects enrolled; min = minimum; max = maximum; Q = quartile; SD = standard deviation
Percentages based on N
Source: Table 14-2.2
Source Table 9-3 CSR Study 20130356

**Table 14 Demographics and Baseline Characteristics in Study 20130356 (2 of 2)**

| | SOC (N = 28) | SOC + Cinacalcet (N = 27) | Total (N = 55) |
|---|---|---|---|
| iPTH (pg/mL) | | | |
| n | 28 | 26 | 54 |
| Mean | 1228.43 | 945.72 | 1092.31 |
| SD | 732.08 | 635.35 | 695.53 |
| Median | 1122.87 | 662.72 | 794.51 |
| Q1, Q3 | 577.85, 1850.10 | 510.41, 1158.46 | 516.95, 1464.06 |
| Min, Max | 300.3, 2700.5 | 346.5, 2923.8 | 300.3, 2923.8 |
| Corrected total serum calcium (mg/dL) | | | |
| n | 28 | 26 | 54 |
| Mean | 9.78 | 9.82 | 9.80 |
| SD | 0.57 | 0.64 | 0.60 |
| Median | 9.79 | 9.72 | 9.77 |
| Q1, Q3 | 9.34, 10.19 | 9.30, 10.16 | 9.34, 10.18 |
| Min, Max | 8.9, 11.0 | 8.9, 11.8 | 8.9, 11.8 |
| Ionized calcium (mmol/L) | | | |
| n | 26 | 27 | 53 |
| Mean | 1.200 | 1.195 | 1.197 |
| SD | 0.152 | 0.099 | 0.127 |
| Median | 1.160 | 1.190 | 1.180 |
| Q1, Q3 | 1.110, 1.250 | 1.120, 1.250 | 1.120, 1.250 |
| Min, Max | 0.96, 1.68 | 1.05, 1.44 | 0.96, 1.68 |
| Serum phosphorus (mg/dL) | | | |
| n | 27 | 26 | 53 |
| Mean | 5.65 | 5.90 | 5.77 |
| SD | 1.08 | 1.36 | 1.22 |
| Median | 5.51 | 5.91 | 5.84 |
| Q1, Q3 | 4.96, 6.46 | 5.00, 6.50 | 5.00, 6.46 |
| Min, Max | 3.3, 8.2 | 3.5, 10.0 | 3.3, 10.0 |

Ca = calcium; Ca x P = calcium phosphorus product; N = Number of subjects enrolled; min = minimum; max = maximum; Q = quartile; SD = standard deviation SOC = standard of care
Two subjects randomized to the cinacalcet + SOC group were never dosed. Their baseline lab values are calculated from data collected on or before randomization date.

Source Table 9-5 CSR Study 20130356

*Medical Officer's comments-*
*According to the NAPRTCS 2008 Annual Report, African Americans make up almost 19% of the pediatric CKD population so they are slightly underrepresented in this study (16%). Males typically have a higher rate of pediatric renal disease due to a higher prevalence of hypoplasia/dysplasia and obstructive uropathy as seen by the fact that they make up 64% of the pediatric CKD population in the NAPRTCS 2008 Annual Report. They are somewhat underrepresented in this study at 51% of the population.*

*The mean (SD) iPTH concentration at baseline was higher in this study at 1092 (696) pg/mL compared to 776 (485) pg/mL in Study 20070208, consistent with more severe disease in these patients. Unlike Study 20070208, where iPTH was equally distributed between treatment groups, in this study subjects in the "SOC alone" group had more severe disease than subjects in the "cinacalcet & SOC" group by both mean (1228pg/mL vs. 946 pg/mL) and median values (1123pg/mL vs. 663pg/mL). This was unexpected given that baseline corrected serum calcium and serum phosphorous were well distributed between treatment groups.*

*It is possible that subjects with more severe baseline disease in the "SOC alone" group may have received additional treatment with vitamin D analogs as part of standard of care in this open label study due to their higher baseline iPTH levels. This may have contributed to why there was no statistically significant difference in the primary endpoint (> 30% response in iPTH) in this study, and why unexpectedly efficacy appeared greater in the "SOC alone" group compared to the "cinacalcet & SOC" group at the end of the study during weeks 17 through 20 (see Figure 10). While a similar percentage of patients (72 to 73%) were on vitamin D analogs at baseline in both treatment groups, the data submission did not identify which patients had their vitamin D analog dose increased during the trial, so it was not possible to confirm whether there was a selective increase in use of vitamin D analogs in one group vs the other which would have affected the efficacy results.*

### 6.2.3 Subject Disposition

In Study 20130356 a total of 55 subjects were randomized; 27 subjects to "cinacalcet & SOC", and 28 to subjects "SOC alone". A total of 36/55=65% of subjects completed the study, 16/27=59% in the "cinacalcet & SOC" group compared to 20/28=71% in the "SOC alone" group which was almost double the completion rate for Study 20070208 in which only 16/43=37% of subjects completed the double-blind phase of the study due to the clinical hold. Of the subjects who completed the study 12/36=33% were 6 to < 12 years and 24/36=67% were 12 to < 18 years. A total of 49/55=89% of subjects completed 12 weeks of the study, 23/49=47% in the "cinacalcet & SOC" group compared to 26/49=53% in the "SOC alone" group. All 55 subjects were included in the primary endpoint determination.

*Medical Officer's comments-*
*While the Division initially requested 48 subjects (24 on "cinacalcet & SOC" and 24 on "SOC alone") should complete the study, the WR was later amended as part of WR amendment #4, so that while 48 subjects were to be enrolled, only 40 subjects were required to complete 12 weeks of the 20-week study as long as they were included in the primary endpoint evaluation. In this study, 55 subjects were enrolled, of which 49 completed 12 weeks and data from all 55 were included in the primary endpoint analysis, thus satisfying the final WR requirements with respect to this study.*

**Table 15 Patient Disposition for Study 20130356**

| | SOC (N = 28) n (%) | SOC + Cinacalcet (N = 27) n (%) | Total (N = 55) n (%) |
|---|---|---|---|
| Investigational product accounting | | | |
| Subjects who never received investigational product | 0 (0.0) | 2 (7.4) | 2 (3.6) |
| Subjects who received investigational product | 28 (100.0) | 25 (92.6) | 53 (96.4) |
| Subjects who completed investigational product | 19 (67.9) | 16 (59.3) | 35 (63.6) |
| Subjects who completed 12 weeks of investigational product | 25 (89.3) | 22 (81.5) | 47 (85.5) |
| Age 6 to < 12 years | 9 (32.1) | 8 (29.6) | 17 (30.9) |
| Subjects who discontinued investigational product[a] | 9 (32.1) | 10 (37.0) | 19 (34.5) |
| Protocol deviation | 0 (0.0) | 1 (3.7) | 1 (1.8) |
| Adverse event | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Subject request | 0 (0.0) | 1 (3.7) | 1 (1.8) |
| Decision by sponsor[b] | 6 (21.4) | 4 (14.8) | 10 (18.2) |
| Study closure | 6 (21.4) | 4 (14.8) | 10 (18.2) |
| Protocol-specified criteria | 3 (10.7) | 4 (14.8) | 7 (12.7) |
| Renal Transplant | 3 (10.7) | 2 (7.4) | 5 (9.1) |
| Parathyroidectomy | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Treatment non-compliance | 0 (0.0) | 2 (7.4) | 2 (3.6) |
| Study completion accounting | | | |
| Subjects who completed study | 20 (71.4) | 16 (59.3) | 36 (65.5) |
| Subjects who completed study or 12 weeks of treatment before receiving renal transplant or parathyroidectomy[c] | 20 (71.4) | 16 (59.3) | 36 (65.5) |
| Subjects who discontinued study | 8 (28.6) | 11 (40.7) | 19 (34.5) |
| Subject who completed 12 weeks of study | 26 (92.9) | 23 (85.2) | 49 (89.1) |
| Age 6 to < 12 years | 9 (32.1) | 8 (29.6) | 17 (30.9) |
| Withdrawal of consent from study | 1 (3.6) | 5 (18.5) | 6 (10.9) |
| Decision by sponsor[b] | 7 (25.0) | 6 (22.2) | 13 (23.6) |

N=Number of subjects enrolled; SOC = standard of care
Percentages based on N
All enrolled subjects completed the EOIP and EOS forms except subject 35625004001 who was randomized to SOC + cinacalcet arm and discontinued study the same day as randomization; the subject was unwilling to take syrup-based medications. EOIP form was inactivated and EOS reason was collected as decision by sponsor.
[a] Discontinued study treatment period for SOC subjects
[b] Subjects who discontinued investigational product or study due to study closure in 2016 are summarized under the decision by sponsor category.
[c] Subjects who completed at least 12 weeks of treatment before undergoing kidney transplant or parathyroidectomy are counted as completed study instead of discontinued study according to protocol

### 6.2.4 Analysis of Primary Endpoint(s)

Because of concern over missing data, due to the fact the subjects were dropping out before the original EAP at weeks 17 through 20, the Division renegotiated the primary endpoint to be reassessed at weeks 11 and 15 as part of amendment #5 to the WR. The sponsor continued to measure the endpoint at the original EAP weeks 17 through

20 as a secondary endpoint and weeks 17 through 20 were still considered the primary endpoint for evaluation by countries outside the US. However, neither of these endpoints were statistically significant with p-value=0.48 for Weeks 11 and 15, and with p-value=0.42 for weeks 17 through 20.

**Table 16 Primary Endpoint (US only)-Proportion of Subjects Achieving a ≥30% reduction in Mean iPTH from Baseline during the EAP (weeks 11 and 15) for Study 20130356**

| | 6 - < 12 years | | 12 - < 18 years | | Total | |
|---|---|---|---|---|---|---|
| | SOC (N=9) n (%) | SOC+Cinacalcet (N=9) n (%) | SOC (N=19) n (%) | SOC+Cinacalcet (N=18) n (%) | SOC (N=28) n (%) | SOC+Cinacalcet (N=27) n (%) |
| Week 11 and 15 | 2 (22.2) | 2 (22.2) | 3 (15.8) | 5 (27.8) | 5 (17.9) | 7 (25.9) |
| | CMH Statistic (Chi-square) | | Odds Ratio (SOC+Cinacalcet /SOC) | | Difference (SOC+Cinacalcet - SOC)[a] | |
| | Value | p-value | Value | 95% CI | Value | 95% CI |
| Test statistic | 0.505 | 0.48 | 1.605 | (0.441, 5.837) | 8.1% | (-13.7%, 29.9%) |

N = Number of subjects in the analysis set
[a]Based on the difference in proportions between treatment groups.
CMH test is stratified by the age group

**Table 17 Primary Endpoint (outside US only)-Proportion of Subjects Achieving a ≥30% reduction in Mean iPTH from Baseline during the EAP (weeks 17 through 20, Last Value Carried Forward) for Study 20130356**

| | 6-<12 years | | 12-<18 years | | Total | |
|---|---|---|---|---|---|---|
| | SOC (N=9) n (%) | SOC+Cinacalcet (N=9) n (%) | SOC (N=19) n (%) | SOC+Cinacalcet (N=18) n (%) | SOC (N=28) n (%) | SOC+Cinacalcet (N=27) n (%) |
| Week 17 and 20 | 4 (44.4) | 1 (11.1) | 5 (26.3) | 5 (27.8) | 9 (32.1) | 6 (22.2) |
| | CMH Statistic (Chi-square) | | Odds Ratio (SOC+Cinacalcet /SOC) | | Difference (SOC+Cinacalcet - SOC)[a] | |
| | Value | p-value | Value | 95% CI | Value | 95% CI |
| Test statistic | 0.658 | 0.42 | 0.614 | (0.188, 2.003) | -9.9% | (-33.3%, 13.4%) |

N = Number of subjects in the analysis set
[a]Based on the difference in proportions between treatment groups.
CMH test is stratified by the age group

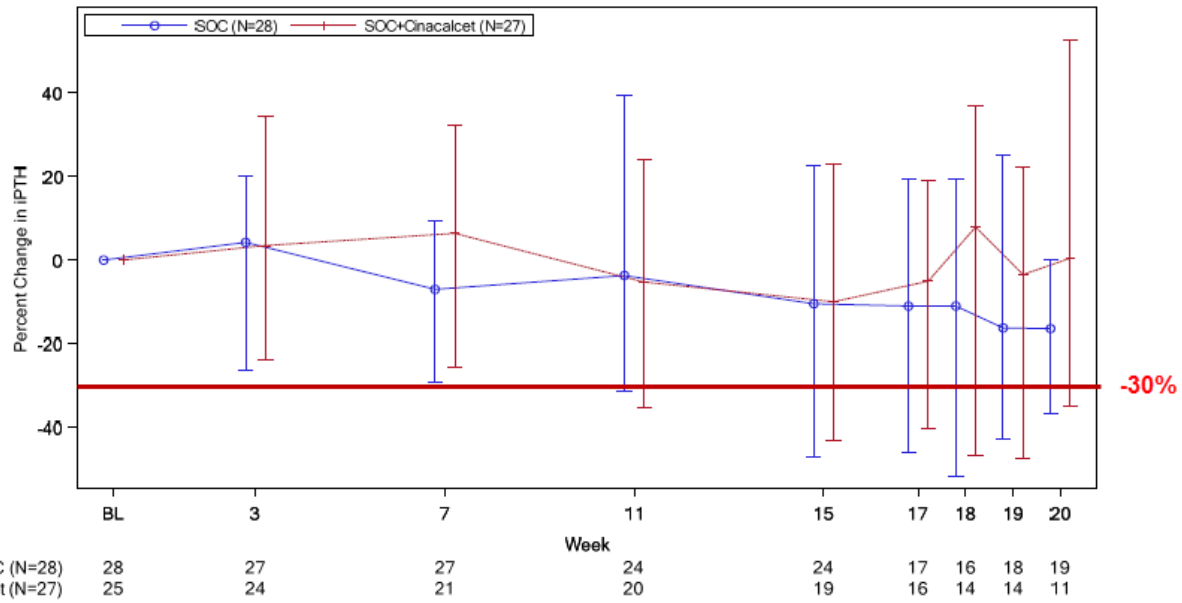
*Medical Officer's comments-*
*The statistical analysis performed by Dr. Sinks gave slightly different values for the CMH statistic at 0.8 and for the p-value at 0.67, but confirmed that there was no statistically significant greater response with respect to the primary endpoint of " >30% reduction in iPTH from baseline". Therefore the Biometric's review found no evidence of efficacy in either Study 20070208 or 20130356 in pediatric dialysis patients age 6 to < 18 years with secondary hyperparathyroidism due to CKD.*

### 6.2.5 Analysis of Secondary Endpoints(s)

The secondary endpoints were not powered for statistical significance and so will not be described in detail.

Efficacy-
There appears to be the beginning of a separation in "% change in iPTH" between the "SOC alone" and "cinacalcet & SOC" curves at about 17 weeks, but it appears unexpectedly that the "SOC alone" group is starting to do better than the "cinacalcet & SOC" group, so the reason for the lack of efficacy in this study does not seem to be insufficient time for dose titration.

**Figure 10 Median (IQR) % change in iPTH from Baseline by Study Visit in Study 20130356**




iPTH = intact parathyroid hormone; IQR = interquartile range; SOC = standard of care
Source CSR 20130356 Fig. 10-1

**Table 18 Secondary Endpoint Results in Study 20130356**

| Primary and Secondary Endpoints[a] | SOC (N=28) | Cinacalcet + SOC (N=27) | Treatment Difference (95% CI) Nominal p-value |
|---|---|---|---|
| Proportion of subjects achieved mean iPTH ≤ 300 pg/mL during weeks 17 to 20 - n (%) | 5 (17.9%) | 2 (7.4%) | -10.4% (-27.7%, 6.8%) 0.25 |
| Percent change in iPTH from baseline to the mean value during Weeks 17 to 20 - % | -11.3% (-33.7%, 11.0%) | 7.7% (-15.9%, 31.3%) | 19.0% (-12.5%, 50.5%) 0.23 |
| Change in corrected serum calcium from baseline to the mean value during Weeks 17 to 20 - mg/dL | 0.06 (-0.19, 0.31) | -0.28 (-0.55, -0.01) | -0.34 (-0.70, 0.01) 0.059 |
| Change in serum phosphorus from baseline to the mean value during Weeks 17 to 20 - mg/dL | -0.09 (-0.60, 0.43) | 0.67 (0.14, 1.21) | 0.76 (0.04, 1.48) 0.039 |

iPTH = intact parathyroid hormone; SOC = standard of care
[a] Last value carried forward (LVCF) imputation was applied
Source: Tables 14-4.3.1, Table 14-4.4.1, Table 14-4.5.1, Table 14-4.6.1

Source Table 10-3 CSR Study 20130356

*Medical Officer's comments-*
*The secondary endpoint results confirm the findings from the primary endpoint that there was a greater reduction in serum iPTH levels in the "SOC alone" group compared to the "cinacalcet & SOC" group. As discussed previously, this medical reviewer speculates that this may have occurred due to an increase in dosing of vitamin D analogs in the "SOC alone" group in this open label study given that they had much higher iPTH values at baseline.*

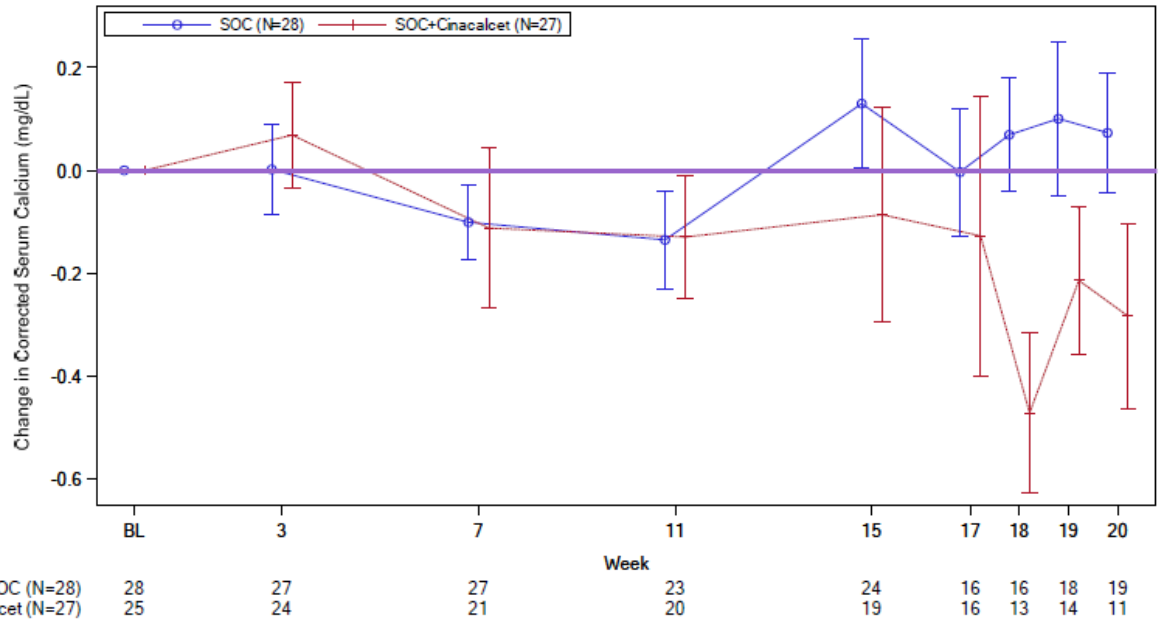
*The greater decrease in corrected serum calcium of -0.34mg/dL in the "cinacalcet & SOC" group compared to the "SOC alone" group (p-value=0.059) is consistent with the known mechanism of action of cinacalcet.*

*There was a greater increase in serum phosphorous seen in the cinacalcet group in this study compared to the control (p-value=0.039) in contrast to the findings seen in Study 20070208 where the increase in serum phosphorous was greater in the placebo control group. The small changes seen here are not likely to be clinical meaningful and more likely represent changes in the use of phosphate binders and dietary changes in this open label study.*

## 6.2.6 Other Endpoints

There is a small but observable mean decrease in corrected serum calcium of 0.2 to 0.4mg/dL in the cinacalcet treatment group at weeks 17 through 20 of treatment. This would support some efficacy in pediatric patients treated with cinacalcet but clearly not enough to result in significant changes in serum iPTH to be clinically meaningful as observed in the primary endpoint analysis.

**Figure 11 Mean (SE) change in Corrected Total Serum Calcium (mg/dL) in Study 20130356**



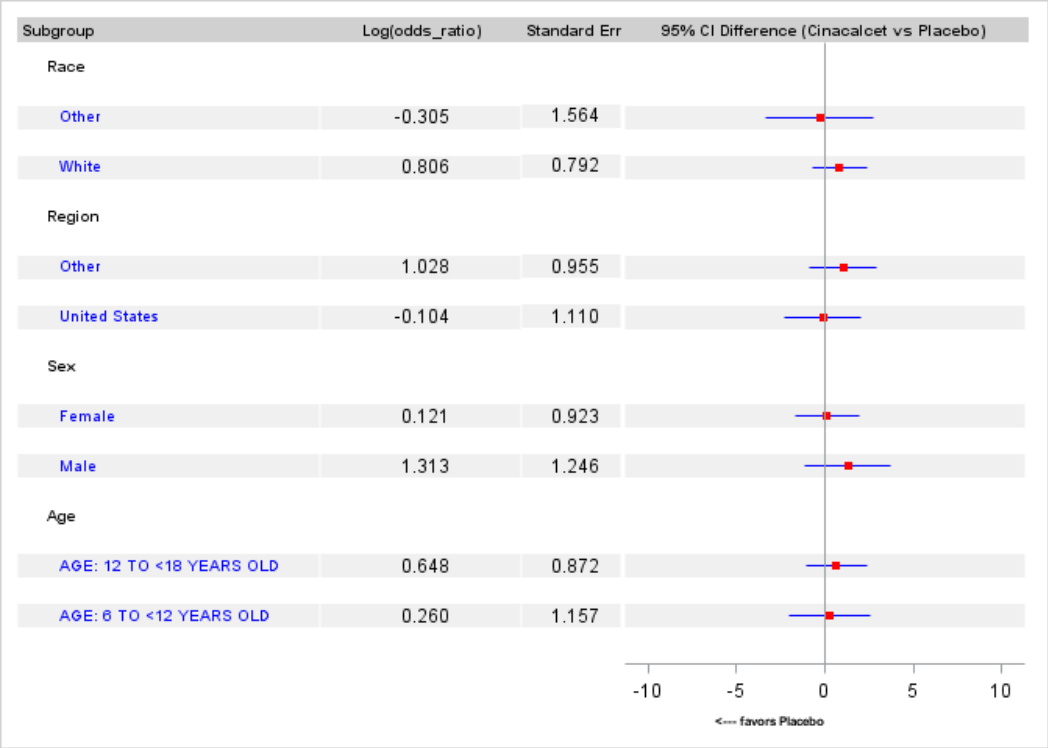

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SOC (N=28) | 28 | 27 | 27 | 23 | 24 | 16 | 16 | 18 | 19 |
| SOC+Cinacalcet (N=27) | 25 | 24 | 21 | 20 | 19 | 16 | 13 | 14 | 11 |

Source Figure 10-2 CSR Study 20130356

## 6.2.7 Subpopulations

There was no difference in efficacy by subgroups of race (White, other), gender, age stratification (6 to 12 years vs. 12 to < 18 years), or Region (USA vs. other).

**Figure 12 Subgroup Analysis for Study 20130356**




Source Stats Review

## 6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The maximum dose level was 60 mg, administered to 2 subjects (8%) (See CSR table 14-5.2.). The mean weight-adjusted daily starting dose was 0.135 mg/kg/day; the mean maximum weight-adjusted dose during the study was 0.55 mg/kg/day (See CSR table 14.5.1). The mean weight-adjusted daily dose during the weeks 11 & 15 EAP was 0.291mg/kg/day and during the weeks 17 through 20 EAP was 0.398mg/kg/day.

These results compare to the higher exposures seen in Study 20070208, completed prior to the clinical hold, where the maximum dose level was 120 mg, administered to 1 subject (4.5%). The mean weight-adjusted daily starting dose was 0.18 mg/kg/day, and the mean maximum weight-adjusted dose during the study was 0.99 mg/kg/day, almost double the maximal dose of 0.55 mg/kg/day in Study 20130356.

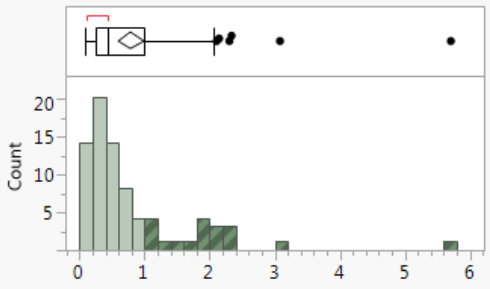
> *Medical Officer's comments-*
> *The applicant believes that the reason for the lower efficacy in Study 20130356, performed after the clinical hold, compared to their results in Study 20070208, performed prior to the clinical hold, was due to lower dosing in the latter study on account of heightened concern over hypocalcemia in these studies in children 6*

*to < 18 years of age. Of note the exposure in Study 20110100 (open label WR Study 3, in the younger children 28 days to < 6 years) also was higher in Cohort 1, prior to the clinical hold, which appeared to show greater iPTH reduction, where the mean start dose was 0.252mg/kg/day and the mean maximum dose was 0.977 mg/kg/day, compared to after the clinical hold, in Cohort 2, where the mean start dose was 0.122mg/kg/day and the mean maximum dose was 0.522mg/kg/day. So both the start dose and mean maximal doses were also decreased by about half after the clinical hold in Study 20110100 in the younger children as well.*

*Therefore, in general it appears from these clinical trials that a mean maximal dose of about 1 mg/kg/day is probably needed to demonstrate efficacy in pediatric patients. From the ISS dataset only 24% or 19 of the 79 subjects with exposure data while on cinacalcet during these pediatric clinical Studies (20070207, 20110100 and 20130356) received maximal weight-adjusted daily doses of > 1mg/kg/day which appear to be necessary to see clinical efficacy. Therefore, it is this medical reviewer's conclusion that there appears to be inadequate cinacalcet exposure in these pediatric clinical trials to properly assess efficacy and thereby the safety of potentially efficacious doses.*

*Distribution of maximal weight-adjusted cinacalcet dose (mg/kg) in Studies 20070207, 20110100 and 20130356*

EXDOSEW




**Quantiles**

| | | |
|---|---|---|
| 100.0% | maximum | 5.7093425606 |
| 99.5% | | 5.7093425606 |
| 97.5% | | 3.0800821355 |
| 90.0% | | 2.0689655172 |
| 75.0% | quartile | 0.9868421053 |
| 50.0% | median | 0.4225352113 |
| 25.0% | quartile | 0.2523364486 |
| 10.0% | | 0.1449275362 |
| 2.5% | | 0.1 |
| 0.5% | | 0.078125 |
| 0.0% | minimum | 0.078125 |

**Summary Statistics**

| | |
|---|---|
| Mean | 0.7846705 |
| Std Dev | 0.8864823 |
| Std Err Mean | 0.0997371 |
| Upper 95% Mean | 0.9832317 |
| Lower 95% Mean | 0.5861093 |
| N | 79 |

*Source ISS ADEX xpt maximal EXDOSEW (mg/kg) weight-adjusted dose per administration for the 79 subjects with exposure data while on cinacalcet, EXTRT=cinacalcet.*

*A 1mg/kg/day dose would be equivalent to a 60mg dose in a 60 kg adult. By comparison according to the Sensipar PI, 90mg was the median dose at the completion of the adult studies in CKD patients with secondary hyperparathyroidism, although patients with milder disease required lower doses. So in comparison to what appear to be efficacious doses in adults most of the pediatric patients seemed to be under dosed.*

### 6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Similar to what was seen in Study 20070208 in Figure 6, there is a large drop out in patients after 15 weeks of treatment as seen here in Figure 10 and Figure 11 suggesting tolerability may be an issue, although no conclusions can be drawn given the limited data.

### 6.2.10 Additional Efficacy Issues/Analyses

None

## 6.3 Indication (WR Study 3, age 28 days to < 6 years) Study 20110100

(WR Study 3) Study 20110100-Treatment of secondary hyperparathyroidism in pediatric subjects age 28 days to < 6 years with CKD receiving hemodialysis or peritoneal dialysis

### 6.3.1 Methods

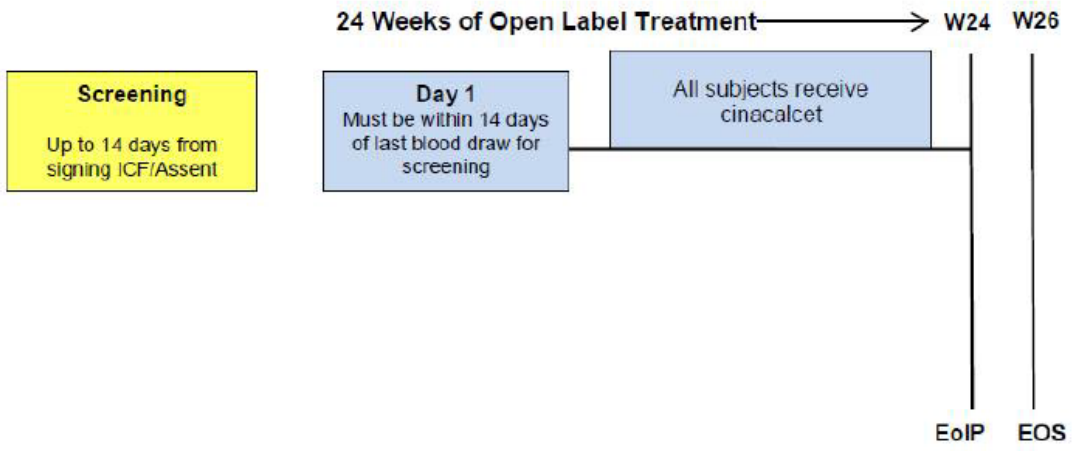
**Trial Design**
This was a multicenter, 26-week, single-arm, open-label, phase 2, safety study in 18 pediatric subjects age 28 days to < 6 years with CKD receiving hemodialysis or peritoneal dialysis. The study included a 24-week treatment period with a 2-week follow-up. Subjects who completed 26 weeks of treatment, or at least 12 weeks of treatment prior to leaving the study to undergo kidney transplantation were considered completers. The WR required 15 subjects to be completers. All subjects, in addition to receiving cinacalcet, received standard of care, which could have included active vitamin D analogs (e.g. calcitriol, alfacalcidol, paricalcitol and doxercalciferol), calcium supplements, and phosphate binders at the discretion of the investigator.

Study enrollment was placed on a partial clinical hold in February 2013 for 14 months due to a fatality in the cinacalcet group in Study 20070208, and was restarted in April 2014 with changes to the protocol to include additional calcium monitoring and cinacalcet dose adjustments to ensure better management of serum calcium levels and hypocalcemia. Therefore, data is presented for all subjects as well as separately for subjects who were on study before (Cohort 1) and after (Cohort 2) the partial clinical hold. Subjects who completed the 26-week study or who ended the study early in June 2016 when the study was closed were deemed eligible to participate in an open-label extension study (Study 20140159).

> *Medical Officer's comments-*
> *Following the pediatric fatality in Study 20070208, this study was revised to ensure better management of serum calcium levels and hypocalcemia. This*

*included real-time weekly ionized calcium measurements, incorporation of local laboratory total calcium values into the dosing schema, subject compliance measures, investigational product suspension preparation by pharmacist, dispensing limited quantities of investigational product to limit the potential for overdosing, addition of exclusionary ECG criteria related to QTc interval, arrhythmias and use of CYP3A4 inhibitors.*

**Figure 13 Study 20110100 Study Design**




EoIP = end of investigational product; EOS = End of Study; ICF = informed consent form; W = Week

Source Fig 8-1 CSR 20110100

**Inclusion Criteria (including but not limited to):**

- age 28 days to < 6 years of age at enrollment
- diagnosed with CKD and secondary hyperparathyroidism treated with either hemodialysis or peritoneal dialysis for ≥ 1 month.
- screening iPTH level > 300 pg/mL
- screening serum calcium
  - ≥ 9.4 mg/dL for age 28 days to < 2 yrs
  - ≥ 8.8 mg/dL for age 2 to < 6 yrs
- serum phosphorus
  - ≥ 5.0 mg/dL for age 28 days to < 1 yr
  - ≥ 4.5 mg/dL for age 1 to < 6 yrs
- dry weight ≥ 7kg at screening
- dialysate calcium concentration had to be ≥ 2.5 mEq/L during screening
- subjects on anti-convulsant medication must be on a stable dose and have a therapeutic blood level of the anti-convulsant at time of screening

**Exclusion Criteria (including but not limited to):**

- received therapy with cinacalcet within 1 month prior to randomization

- new onset of seizure or worsening of a pre-existing seizure disorder within 2 months prior to first dose of investigational product
- scheduled date for kidney transplant from a known living donor that makes completion of the study unlikely
- not available for protocol-required study visits, to the best of the subject and investigator's knowledge
- born prematurely at < 36 weeks gestational age
- unstable chronic heart failure (CHF) defined as worsening pulmonary edema or other signs and symptoms as per investigator assessment during screening
- Hepatic impairment -AST ≥ 1.5 x upper limit of normal (ULN), ALT ≥ 1.5 x ULN or total bilirubin ≥ 1 x during screening
- Corrected QT Interval (QTc) > 500 ms, using Bazett's formula, during screening
- QTc ≥ 450 to ≤ 500 ms, using Bazett's formula, during screening, unless written permission to enroll is provided by the investigator after consultation with a pediatric cardiologist
- Use of concomitant medications that may prolong the corrected QT interval (e.g., ondansetron, albuterol) during screening
- Use of grapefruit juice, herbal medications or CYP3A4 inhibitors (eg, erythromycin, clarithromycin, ketoconazole, itraconazole) or, CYP2D6 substrates (e.g., flecainide, propafenone, metoprolol, desipramine, nortriptyline, clomipramine) within the 14 days prior to enrollment or anticipated requirement of these medications during the study
- Either new or recurrent cardiac ventricular arrhythmias requiring a change in treatment within 10 days prior to screening or enrollment

**Dose Titration**
Dose-titration could occur once every 4 weeks at Weeks 4, 8, 12, 16 and 20. Blood samples were collected to measure iPTH, total serum calcium, phosphorous, and albumin at baseline (within 14 days of treatment) and every four weeks of treatment. Ionized calcium was measured weekly for Cohort 2 only. 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, and 1, 2, 3, 4, 6, 8, 12, and 24 hours).

The starting dose was 0.25 mg/kg and was titrated upwards according to iPTH, corrected total serum calcium levels, and subject safety information. The maximum dose could not exceed 4.2 mg/kg/day.

Dose adjustments and withholding were based on iPTH and corrected serum calcium levels assessed monthly (except weekly during weeks 17 to 19). The target iPTH range was ≥ 150 to < 300 pg/mL. Doses were increased if the iPTH was ≥ 300 pg/mL and corrected serum calcium was ≥ 9.0 mg/dL for subjects < 2 years old or was ≥ 8.4 mg/dL for subjects ≥ 2 years old, provided that none of the criteria for dose maintenance, reduction or withholding were met.

Doses were reduced or withheld under the following criteria:

iPTH:

- dose reduction: < 150 pg/mL and ≥ 100 pg/mL
- dose withheld: < 100 pg/mL

Corrected serum calcium:

- dose reduction: < 9.0 mg/dL and ≥ 8.6 mg/dL in subjects younger than 2 years old, or < 8.4 mg/dL and ≥ 8.0 mg/dL in subjects ≥ 2 years old
- dose withheld: < 8.6 mg/dL if < 2 years, or < 8.0 mg/dL if ≥ 2 years old

The dose could also be withheld if the subject had symptoms of hypocalcemia.

After the partial clinical hold (Cohort 2), changes to the protocol included additional safety measures focused on further minimizing the risk of hypocalcemia and ensuring drug compliance. The starting dose was decreased slightly to 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.

The plasma iPTH and corrected serum calcium levels dosing rules were the same as before the partial clinical hold, but weekly monitoring of ionized calcium levels was added with the following ionized calcium thresholds for dose adjustments:

- dose increase or dose maintenance was permitted if ionized calcium was ≥ 1.13 mmol/L in subjects younger than 2 years old, or ≥ 1.05 mmol/L if ≥ 2 years old
- dose reduction: ≥ 1.08 and < 1.13 mmol/L in subjects younger than 2 years old, or ≥ 1.00 and < 1.05 mmol/L if ≥ 2 years old
- dose withheld: < 1.08 mmol/L in subjects younger than 2 years old, or < 1.00 mmol/L if ≥ 2 years old

The dose could also be withheld if the subject had symptoms of hypocalcemia or another adverse event that warranted investigational product to be withheld. Additional considerations included in the dose decisions were investigational product compliance and administration of medications known to prolong the QTc interval.

### 6.3.2 Demographics

The mean (SD) age of subjects was 35.9 (16.8) months [3 (1.4) yrs], and the youngest subject was 12 months old. Three subjects (17%) were within the age range of 28 days to < 2 years, and 15 subjects (83%) were 2 years to < 6 years. There were 12 boys (67%) and 6 girls (33%). The majority 15 (83%) were white, 2 (11%) were black or African American and 1 (6%) was listed as other.

The mean (SD) iPTH concentration at baseline in this study was 1299 (634) pg/mL. The mean (SD) corrected total calcium level at baseline was 10.2 (0.8) mg/dL, and the mean (SD) phosphorous levels were 6.2 (1.6) mg/dL.

Regarding dialysis mode, an equal number, 9 subjects (50%) were on hemodialysis and 9 subjects (50%) were on peritoneal dialysis. The mean duration on hemodialysis was 17.2 months similar to the mean duration on peritoneal dialysis at 17.9 months.

Sixteen subjects (16/18=89%) were using active vitamin D analogs at baseline, and the most common vitamin D sterols used at baseline were oral (6/18=33%) calcitriol, oral alfacalcidol (5/18=28%) and intravenous paricalcitol/Zemplar (3/18=17%). A total of 10 subjects (56%) were using nutritional vitamin D at baseline, and the most common drugs were cholecalciferol (39%) and ergocalciferol (17%).

Thirteen subjects (13/18=72%) were using a phosphate binder at baseline, and the most common phosphate binders used at baseline were sevelamer carbonate (8/18=44%) and calcium-containing phosphate binders (5/18=28%). Nine subjects (9/18=50%) were using either a calcium supplement or calcium-containing phosphate buffer. A total of 5 subjects (28%) were using growth hormone at baseline.

**Table 19 Demographics and Baseline Characteristics in Study 20110100**

| | Cohort 1 (N = 8) | Cohort 2 (N = 10) | Total (N = 18) |
|---|---|---|---|
| Sex - n (%) | | | |
| Male | 5 (62.5) | 7 (70.0) | 12 (66.7) |
| Female | 3 (37.5) | 3 (30.0) | 6 (33.3) |
| Ethnicity - n (%) | | | |
| Hispanic or Latino | 1 (12.5) | 2 (20.0) | 3 (16.7) |
| Not Hispanic or Latino | 7 (87.5) | 8 (80.0) | 15 (83.3) |
| Race - n (%) | | | |
| American Indian or Alaska Native | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Asian | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Black or African American | 1 (12.5) | 1 (10.0) | 2 (11.1) |
| Native Hawaiian or Other Pacific Islander | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| White | 6 (75.0) | 9 (90.0) | 15 (83.3) |
| Other | 1 (12.5) | 0 (0.0) | 1 (5.6) |
| Age (months) | | | |
| n | 8 | 10 | 18 |
| Mean | 37.1 | 35.0 | 35.9 |
| SD | 18.9 | 15.9 | 16.8 |
| Median | 36.0 | 29.5 | 33.0 |
| Q1, Q3 | 22.0, 51.0 | 26.0, 50.0 | 26.0, 50.0 |
| Minimum, Maximum | 14, 65 | 12, 64 | 12, 65 |
| Age group - n (%) | | | |
| 28 days to < 2 years | 2 (25.0) | 1 (10.0) | 3 (16.7) |
| 2 years to < 6 years | 6 (75.0) | 9 (90.0) | 15 (83.3) |

N = Number of enrolled subjects.
Cohort 1 consists of subjects enrolled before the partial clinical hold. Cohort 2 consists of subjects enrolled after the partial clinical hold.

Source Table 14-2.1

**Table 20 Demographics and Baseline Characteristics in Study 20110100**

| | Cohort 1 (N = 8) | Cohort 2 (N = 10) | Total (N = 18) |
|---|---|---|---|
| iPTH (pg/mL) | | | |
| n | 8 | 10 | 18 |
| Mean | 1414.34 | 1206.92 | 1299.11 |
| SD | 699.90 | 597.85 | 634.18 |
| Median | 1305.55 | | |
| Q1, Q3 | 1086.90, 1553.10 | 860.20, 1390.60 | 890.60, 1390.60 |
| Minimum, Maximum | 520.9, 2902.7 | 396.4, 2346.9 | 396.4, 2902.7 |
| Corrected serum calcium (mg/dL) | | | |
| n | 8 | 10 | 18 |
| Mean | 10.56 | 9.82 | 10.15 |
| SD | 0.75 | 0.61 | 0.76 |
| Median | 10.40 | 9.80 | 10.15 |
| Q1, Q3 | 10.15, 11.30 | 9.50, 10.20 | 9.50, 10.50 |
| Minimum, Maximum | 9.3, 11.5 | 8.9, 10.9 | 8.9, 11.5 |
| Ionized calcium[a] (mmol/L) | | | |
| n | 0 | 7 | 7 |
| Mean | - | 1.174 | 1.174 |
| SD | - | 0.112 | 0.112 |
| Median | - | 1.160 | 1.160 |
| Q1, Q3 | -, - | 1.100, 1.250 | 1.100, 1.250 |
| Minimum, Maximum | -, - | 1.00, 1.34 | 1.00, 1.34 |
| Serum Phosphorus (mg/dL) | | | |
| n | 8 | 10 | 18 |
| Mean | 6.03 | 6.37 | 6.22 |
| SD | 2.02 | 1.34 | 1.63 |
| Median | 5.40 | 5.95 | 5.75 |
| Q1, Q3 | 4.90, 6.10 | 5.50, 7.20 | 5.20, 6.60 |
| Minimum, Maximum | 4.6, 10.8 | 4.5, 9.0 | 4.5, 10.8 |

N = Number of enrolled subjects.
Cohort 1 consisted of subjects enrolled before the partial clinical hold. Cohort 2 consisted of subjects enrolled after the partial clinical hold.
[a] Only subjects in cohort 2 had ionized calcium collected. Three subjects in cohort 2 did not have baseline ionized calcium values because they were enrolled in the study before baseline ionized calcium measurements were a protocol requirement (data on file).

Source Table 14-2.5

*Medical Officer's comments-*
*According to the NAPRTCS 2008 Annual Report African Americans make up almost 19% of the pediatric CKD population so they are underrepresented in this study (11%). Males typically have a higher rate of pediatric renal disease due to a higher prevalence of hypoplasia/dysplasia and obstructive uropathy as seen by the fact that they make up 64% of the pediatric CKD population in the NAPRTCS*

*2008 Annual Report. They are appropriately represented in this study at 67% of the population.*

*The mean (SD) iPTH concentration at baseline was higher in the younger patients in this study at 1299 (634) pg/mL compared to 776 (485) pg/mL in study 20070208 in pediatric patients >6 years of age, consistent with more severe disease in these younger patients.*

*Younger patients, especially those < 2 years of age have higher ULNs for serum calcium and serum phosphorous. Consistent with this the mean serum calcium in this study was 10.15 (0.76) mg/dL; slightly higher than seen in 20070208 in pediatric patients >6 years of age at 9.9 (0.56) mg/dL. In contrast, the mean serum phosphorous in this study was 6.2 (1.6) mg/dL; slightly lower than seen in 20070208 in pediatric patients >6 years of age at 6.5 (1.6) mg/dL. However, in both cases, the variability in the samples is fairly large as measured by the respective standard deviations and as such there is no clear difference in the baseline serum calcium and phosphorous levels between the younger and older patient populations in these trials.*

*Given that the youngest patient enrolled in this study was 12 months of age there is no data for children from 28 Days to <1 year of age, which is the age where CYP enzyme maturation is still taking place in children.*

### 6.3.3 Subject Disposition

A total of 18 subjects were enrolled, 8 prior to the partial clinical hold (Cohort 1), and 10 after the partial clinical hold (Cohort 2). All but one subject in Cohort 1 received cinacalcet during the study. Only 4 subjects (22%, 2 subjects in Cohort 1 and 2 subjects in Cohort 2) were considered study completers. Three completed the full 26 weeks of the study (1 in Cohort 1 and 2 in Cohort 2), and 1 subject in Cohort 1 received a kidney transplant after completing 12 weeks in the study, and as such also satisfied the conditions to be designated a completer. Eleven subjects (61%) completed at least 12 weeks of treatment (3 in Cohort 1, and 8 in Cohort 2). Fourteen subjects (78%) discontinued the study. The most common reason for discontinuation from the study was administrative decision (9/14=64%) due either to the partial clinical hold in the study in Feb. 2013 in Cohort 1 (n=4) or due to study closure in June 2016 in order to be able to submit the study report within the necessary time frame before the cinacalcet patent was set to expire in Cohort 2 (n=5). No subjects discontinued from the study due to an Adverse Event, the need for a parathyroidectomy, or protocol deviation.

*Medical Officer's comments-*
*In a meeting with the Division on 21 Sept. 2016, Amgen had proposed an amendment to the WR to change the number of patients needed in the study from 15 completers identified as*

1. *those who completed the 26 week study or*
2. *those who completed at least 12 weeks in the study and terminated early to undergo a kidney transplant*

*to language that would describe the study population that they had currently amassed namely:*

1. *18 subjects were to have been enrolled and*
2. *12 subjects must have completed at least 12 weeks in the study.*

*The Division did not agree to the proposed changes and left the terms of the WR as they were with the intention to review the data at the time of the submission.* ***At this time, there are only 4 subjects who have satisfied the conditions for being completers, therefore the study did not meet the requirements of the WR.***

**Table 21 Patient Disposition for Study 20110100**

| | Cohort 1 (N = 8) n (%) | Cohort 2 (N = 10) n (%) | Total (N = 18) n (%) |
|---|---|---|---|
| Investigational product (IP) accounting | | | |
| Subjects who never received IP | 1 (12.5) | 0 (0.0) | 1 (5.6) |
| Subjects who completed IP | 0 (0.0) | 2 (20.0) | 2 (11.1) |
| Subjects who completed 12 weeks of IP | 3 (37.5) | 8 (80.0) | 11 (61.1) |
| Subjects who discontinued IP | 7 (87.5) | 8 (80.0) | 15 (83.3) |
| Noncompliance | 0 (0.0) | 1 (10.0) | 1 (5.6) |
| Adverse event | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Full consent withdrawn | 0 (0.0) | 2 (20.0) | 2 (11.1) |
| Administrative decision[a] | 5 (62.5) | 5 (50.0) | 10 (55.6) |
| Protocol-specified criteria | 2 (25.0) | 0 (0.0) | 2 (11.1) |
| Parathyroidectomy | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Kidney Transplant | 2 (25.0) | 0 (0.0) | 2 (11.1) |
| Study completion accounting | | | |
| Subjects who completed study | 2 (25.0) | 2 (20.0) | 4 (22.2) |
| Subjects who completed 26 weeks of study | 1 (12.5) | 2 (20.0) | 3 (16.7) |
| Subjects who completed at least 12 weeks of study before undergoing kidney transplant[b] | 1 (12.5) | 0 (0.0) | 1 (5.6) |
| Subject who completed 12 weeks of study | 5 (62.5) | 8 (80.0) | 13 (72.2) |
| Subjects who discontinued study | 6 (75.0) | 8 (80.0) | 14 (77.8) |
| Noncompliance | 0 (0.0) | 1 (10.0) | 1 (5.6) |
| Adverse event | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Full consent withdrawn | 1 (12.5) | 2 (20.0) | 3 (16.7) |
| Administrative decision[a] | 4 (50.0) | 5 (50.0) | 9 (50.0) |
| Protocol-specified criteria | 1 (12.5) | 0 (0.0) | 1 (5.6) |
| Parathyroidectomy | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Kidney Transplant | 1 (12.5) | 0 (0.0) | 1 (5.6) |

Cohort 1 consists of subjects enrolled before the partial clinical hold. Cohort 2 consists of subjects enrolled after the partial clinical hold.
[a] Administrative decision is due to a partial clinical hold in 2013 for cohort 1 subjects and study closure in 2016 for cohort 2 subjects who were allowed to enroll into open-label extension Study 20140159. One cohort 1 subject discontinued IP due to administrative decision however indicated the completion of study in <End of Study> page.
[b] Subjects who completed at least 12 weeks of study before undergoing kidney transplant are counted as completed study instead of discontinued study according to protocol.
Source: Table 14-1.2.

Source Table 9-1 CSR Study 20110100

## 6.3.4 Analysis of Primary Endpoint(s)

The primary endpoint was a safety endpoint, the proportion of subjects who develop low corrected serum calcium levels < 9.0 mg/dL for ages 28 days to < 2 years, and < 8.4 mg/dL for ages ≥ 2 to < 6 years. No subjects had a corrected low serum calcium < 9.0 mg/dL for ages 28 days to < 2 years, or < 8.4 mg/dL for ages ≥ 2 to < 6 years.

**Table 22 Proportion of Subjects with Hypocalcemia Based on Age Appropriate Corrected Serum Calcium for Study 20110100**

| | Cohort 1 (N = 7) | Cohort 2 (N = 10) | Total (N = 17) |
|---|---|---|---|
| Subjects with cCa < 9.0 mg/dL (2.25 mmol/L) for ages 28 days to < 2 years, or < 8.4 mg/dL (2.1 mmol/L) for ages 2 years to < 6 years – n/N (%) | 0/7 (0.0) | 0/10 (0.0) | 0/17 (0.0) |
| 90% CI | 0.0, 34.8 | 0.0, 25.9 | 0.0, 16.2 |
| Subjects with cCa < 9.0 mg/dL (2.25 mmol/L) for ages 28 days to < 2 years – n/N1 (%) | 0/1 (0.0) | 0/1 (0.0) | 0/2 (0.0) |
| 90% CI | 0.0, 95.0 | 0.0, 95.0 | 0.0, 77.6 |
| Subjects with cCa < 8.4 mg/dL (2.1 mmol/L) for ages 2 years to < 6 years – n/N2 (%) | 0/6 (0.0) | 0/9 (0.0) | 0/15 (0.0) |
| 90% CI | 0.0, 39.3 | 0.0, 28.3 | 0.0, 18.1 |

cCa = corrected serum calcium; CI = confidence interval; N = Number of subjects in the analysis set; N1 = Number of subjects with ages 28 days to < 2 years in the analysis set; N2 = Number of subjects with ages 2 years to < 6 years in the analysis set.
Cohort 1 consists of subjects enrolled before the partial clinical hold. Cohort 2 consists of subjects enrolled after the partial clinical hold.
The confidence interval (CI) was calculated based on exact (Clopper-Pearson) interval.
Source: Table 14-4.1.1.

In addition, no patients had signs and symptoms of hypocalcemia including: numbness, or tingling of fingers, toes, or around mouth, muscle cramps or spasms, muscle aches stiffness of the arms, legs, or jaw; extreme drowsiness and unable to arouse; appearing anxious and out of proportion to the situation, heart rhythm problems, or seizure (See table 12-8 in Study 20110100 CSR)

### 6.3.5 Analysis of Secondary Endpoints(s)

The secondary endpoints were not powered for statistical significance and so will not be described in detail. This review instead will focus on the secondary endpoints dealing with hypocalcemia (safety) and decrease in serum iPTH (efficacy).

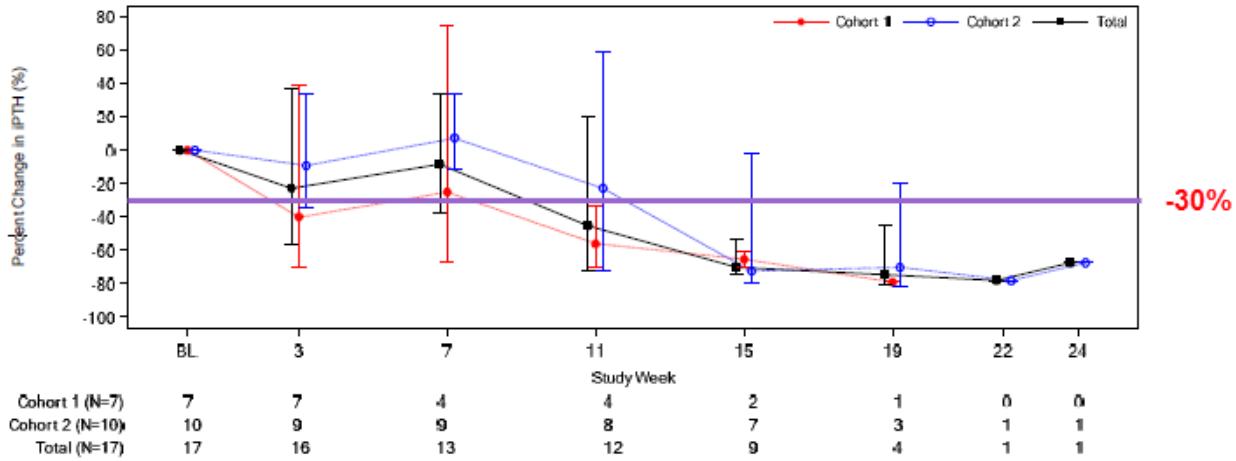
Safety-

- proportion of subjects who develop corrected serum calcium levels < 8.8 mg/dL

Two subjects (2/17=12%, one in each cohort) both within the 2 to < 6-year age range had corrected serum calcium levels that were < 8.8 mg/dL. The values of 8.6mg/dL and 8.5mg/dL were both above the lower limit of normal for this age range of 8.4mg/dL and so did not represent hypocalcemia.

Efficacy-
By study week 15 median percent change in serum iPTH was between -60% and -80% from baseline for treatment Cohorts 1 and 2 and total patients. The percent change in the median iPTH level appeared to level off after week 15 but the later values are not reliable given the large number of patient drop outs.

**Figure 14 Median Percent Change (IQR) in iPTH From Baseline by Study Visit in Study 20110100**




Vertical lines represent the interquartile range (IQR).
Cohort 1 consists of subjects enrolled before the partial clinical hold. Cohort 2 consists of subjects enrolled after the partial clinical hold.
Source CSR Figure 10-1 Study 20110100

- achievement of ≥ 30% reduction from baseline in plasma iPTH

A higher proportion of subjects in Cohort 1 (7/7=100.0%) than in Cohort 2 (5/10=50.0%) achieved ≥ 30% reduction in iPTH. All subjects who completed the study (4 subjects: 2 subjects each per cohort) achieved this threshold of response.

- proportion of subjects who had any decreases in iPTH of > 30% from baseline at two consecutive measurements

8 subjects (4/7=57%, Cohort 1; 4/10=40%, Cohort 2) achieved a > 30% reduction in iPTH from baseline at two consecutive measurements. All 4 subjects who completed the study also met this response threshold for two consecutive measurements.

- achievement of serum iPTH values < 300 pg/mL

53% of subjects achieved serum iPTH < 300 pg/mL during the study, (4/7=57% Cohort 1, 5/10=50% Cohort 2). Three of the 4 subjects who completed the study achieved iPTH values < 300 pg/mL (1/2=50% Cohort 1, 2/2=100% Cohort 2).

- proportion of subjects who have serum iPTH values between 200 and 300 pg/mL at two consecutive measurements

Only one subject (1/17=6%) achieved plasma iPTH values between 200 and 300 pg/mL at any two consecutive measurements.

*Medical Officer's comments-*
*Efficacy appeared greater in this study in the younger age group < 6 years of age than what was observed in children 6 to < 18 years of age in Study 200702080. Part of the reason for this may be that the younger children had more severe disease at baseline with median iPTH levels of 1288pg/mL compared to only 680pg/mL in the older children in Study 200702080. According to the standard of care policy in the Study 20110100 protocol "Adjustment of active vitamin D sterol doses are permitted during the study to achieve therapeutic goals for PTH levels at the discretion of the investigator." Therefore treating physicians would likely be more inclined to use concomitant therapy with vitamin D analogs in patients with higher baseline iPTH levels in this study, especially given the 89% of subjects were already on baseline vitamin D analog therapy, and that this was primarily designed as a safety study. The study report did not identify patients who had their vitamin D analog dose increased during the trial, so it is not possible to confirm whether selective increases in the use of vitamin D analogs may have affected the efficacy results. Therefore the efficacy results in this study, while appearing substantial, cannot be used to support the clinical efficacy of cinacalcet for the treatment of secondary hyperparathyroidism in pediatric dialysis patients 6 to <18 years of age. Efficacy in this age group would need to be extrapolated from efficacy in older children, which was not observed in the two Studies 20070208 and 20130356 included in this submission, or adult patients using PK to bridge across treatment groups. As discussed under Section 4.4.3, there is currently insufficient comparative pediatric and adult data to also permit PKPD modeling to extrapolate pediatric efficacy.*

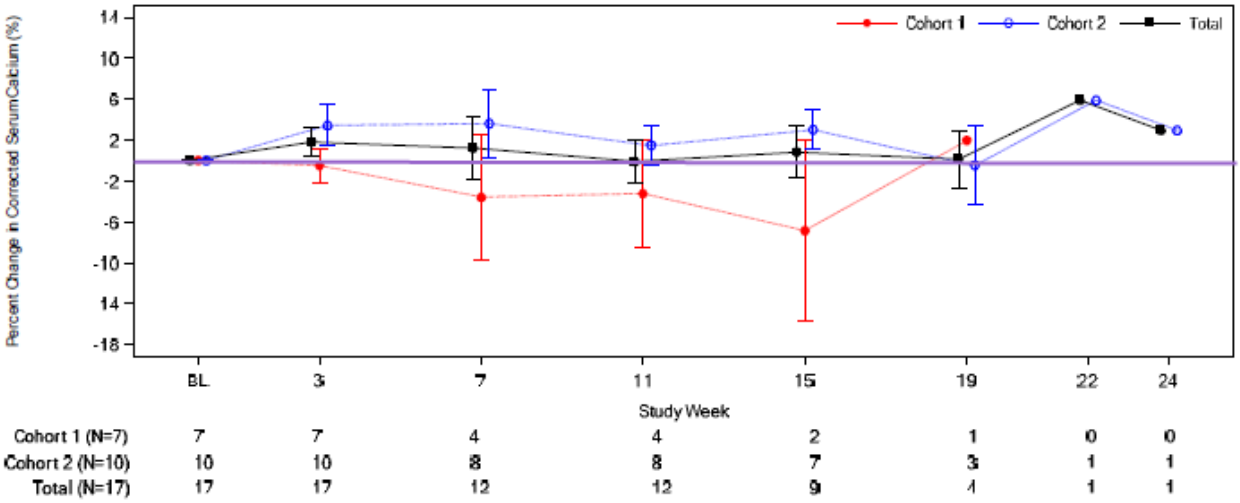
*Efficacy appeared to decrease somewhat during Cohort 2 with the introduction of stricter calcium monitoring. These results were also consistent with what was seen in Study 20130356 in older children 6 to < 18 years of age, which was also performed with stricter calcium monitoring and did not show evidence of clinical efficacy.*

### 6.3.6 Other Endpoints

Similar to results in Study 20070208 there is a 5 to 6% decrease in corrected serum calcium in the cinacalcet treated group in Cohort 1 but that appears to go away with stricter calcium monitoring in Cohort 2.

*Medical Officer's comments-*
*The fact that there appears to be no decrease in serum calcium in Cohort 2 in Figure 15 with the stricter calcium monitoring suggests that the decrease in serum iPTH seen in this group in Figure 14 was likely largely due to increased use of vitamin D analogs or calcium supplements during this study, and not due to cinacalcet.*

**Figure 15 Mean (SE) % change in Corrected Total Serum Calcium in Study 20110100**




### 6.3.7 Subpopulations

There were too few patients in this study to analyze study subgroups for efficacy.

### 6.3.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The maximum dose level was 30 mg, administered to 2 subjects (29%) in Cohort 1. The mean weight-adjusted daily starting dose was 0.252 mg/kg/day, and the mean maximum weight-adjusted dose during the study was 0.977 mg/kg/day for Cohort 1. For Cohort 2, with the introduction of stricter serum calcium monitoring, dosing was lower. The mean weight-adjusted daily starting dose was 0.122 mg/kg/day, and the mean maximum weight-adjusted daily dose during the study was 0.522 mg/kg/day, representing approximately 50% decreases from Cohort 1.

*Medical Officer's comments-*
*The decrease in cinacalcet dosing in Cohort 2 due to the stricter calcium monitoring probably explains why there appears to be no decrease in serum calcium in Cohort 2 in Figure 15 and why this medical reviewer believes that the serum iPTH lowering seen in this cohort is likely largely due to an increase in the use of vitamin D analogs or calcium supplements, and not due to treatment with cinacalcet.*

### 6.3.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The large drop out in patients after 15 weeks of treatment as seen previously in Figure 6, and here in Figure 14 and Figure 15 limit the interpretation of the persistence of efficacy and suggest tolerability may be an issue, although no conclusions can be drawn given the limited data.

### 6.3.10 Additional Efficacy Issues/Analyses

None

# 7 Review of Safety

## ***Safety Summary***

Toxicity associated with the use of calcimimetics is primarily related to the risk of hypocalcemia, which can result in symptoms of paresthesias, muscle spasms, myalgia, bronchospasm, increased risk of seizures, hypotension, prolongation of the QT interval, and cardiac arrhythmias (torsades de pointes & ventricular tachycardia); and gastrointestinal symptoms including nausea, vomiting, abdominal pain, and diarrhea. More recently, concern has been raised about the potential for an increased risk in gastrointestinal bleeding which is more common in adults on chronic dialysis due to comorbid medical conditions, uremic platelet dysfunction, use of anticoagulants during dialysis, and other concomitant medications.

The major safety concern associated with the cinacalcet pediatric clinical program centered around the death of a 14 year old girl in Study 20070208 which resulted in the program being placed on clinical hold for 14 months. In the end, it was decided to continue the clinical program as the drug was the only approved calcimimetic and so provided a treatment option for secondary hyperparathyroidism that was otherwise not available from any other marketed drug product. However, new safety revisions were incorporated into all subsequent pediatric clinical protocols to prevent the recurrence of such an event. The cause of the fatal event was multifactorial and included the fact that this patient developed a concurrent illness with fever, nausea, vomiting and dehydration while anemic (Hct 23%), asplenic and receiving immunosuppressive medications in preparation for a renal transplant. Two weeks prior to the fatal event, she was noted to

be mildly hypocalcemic by an outside lab (7.9mg/dL) so her dose of calcium supplements was increased but a follow up central lab serum calcium value was contaminated and a repeat lab was delayed by several days because of the holidays. In the meantime, her dose of cinacalcet was increased from 60 to 90mcg because of a persistently elevated serum iPTH. On the day of the fatal event, her blood calcium was severely low at 5.3mg/dL, which was unknown to the treating physician at the time who prescribed Zofran for her ongoing nausea. This was a problem as this patient already had a baseline prolonged QTc interval and both Zofran and the low serum calcium can prolong the QTc interval, potentially precipitating a fatal arrhythmia which may have led to the fatal cardiopulmonary event. As a result of this event, it was decided to exclude future patients with prolonged baseline QTc intervals, to exclude concomitant use of drugs that can prolong QTc, to include local lab serum calcium levels in treatment and dosing algorithms, to include weekly serum calcium monitoring instead of the every 2 weeks measurement performed previously, and to include real-time ionized calcium monitoring at the dialysis facilities. As part of the review of the clinical program during the clinical hold, it was also determined that in certain other patients there had been unusual serum iPTH deviations which were potentially attributed to inconsistent administration of cinacalcet, so attempts were made to screen out noncompliant patients and future studies were designed in an open-label fashion, so the treating physician would know which patients were being treated with cinacalcet and make a clear effort to assess drug compliance prior to dose escalation.

Of note, there was one other fatal event in a 2 year old Czech boy during open label extension Study 20140159. This was not associated with an AE of hypocalcemia and was attributed to suppurative bronchopneumonia at autopsy. There was initially some concern about a possible GI bleed in this patient due to the description of coffee sediment emesis noted at the time of the cardiopulmonary resuscitation, but the autopsy found no evidence of gastrointestinal disease. While it is unusual to see fatal events in most pediatric studies, children with end stage renal disease are at much greater risk from infection and morbidity due to their ongoing illness.

In addition to the one serious AE of hypocalcemia which occurred in the 14 year old girl described above, there was also a case of serious hypocalcemia which occurred in a 13 year old black male in an open-label extension. It is not clear why the hypocalcemia was described as serious as he had mild ionized hypocalcemia at 3.9mg/dL, with a normal total serum calcium at 9.6mg/dL. The primary reason behind the severity of the event had to do with serious AEs of hypertension and hypertensive encephalopathy. This patient readily responded to treatment for the hypertension and low serum calcium.

Other than hypocalcemia the other serious AEs seen in multiple patients in this clinical program were typical of this study population and included hypertension, fluid overload, peritonitis, device complications, etc.

Other nonserious AEs of hypocalcemia were also seen in this clinical program: In children 6 to < 18 years in Study 20070208, the rate was slightly higher for cinacalcet 5/22=23% vs. 4/21=19% for placebo during the double-blind phase of the study, and there were an additional 4 cases in the open-label phase. And in children 6 to < 18 years in Study 20130356, the rate of hypocalcemia AEs was higher for "cinacalcet & SOC" 6/25=24% vs. 3/30=10% for "SOC alone". In contrast to the hypocalcemia AEs described above in the older children 6 to < 18 years, there were no AEs of hypocalcemia reported in Study 20110100 in the younger children age 28 days to < 6 years. Similar results were observed in lab abnormalities of hypocalcemia, which were not necessarily described as adverse events. In children 6 to < 18 years in Study 20070208, the rate was higher for cinacalcet 7/22=32% vs. 3/21=14% for placebo, and in children 6 to < 18 years in Study 20130356 the rate was higher for "cinacalcet & SOC" 6/25=24% vs. 2/30=7% for "SOC alone". Again, there were no lab reports of hypocalcemia in Study 20110100 in the younger children 28 days to < 6 years. The low risk of hypocalcemia in Study 20110100 may represent the small number of patients in the younger age group and the short duration of treatment, but it also likely is due to the fact that this study was designed as an open-label safety study and so physicians were extra conscious of the need to monitor and treat for potential hypocalcemia. In fact, the study protocol stated that investigators were free to increase the dose of vitamin D analogs without worrying about whether that might confound the study and limit the ability to detect efficacy in iPTH lowering due to cinacalcet. According to the standard of care policy in the Study 20110100 protocol "Adjustment of active vitamin D sterol doses are permitted during the study to achieve therapeutic goals for PTH levels at the discretion of the investigator." Given that in a real use situation physicians would be more likely to use cinacalcet in subjects with higher baseline serum calcium levels that still need iPTH lowering, but are limited in their ability to increase vitamin D analog or calcium supplement doses, the actual risk of hypocalcemia may be lower than seen in these controlled clinical trials where the use of these agents might have been limited to avoid confounding efficacy due to cinacalcet.

Outside of the risk of hypocalcemia, which appeared to be adequately dealt with by the heightened serum calcium monitoring after the clinical hold was released, there is limited evidence of serious safety risks associated with the use of cinacalcet in this clinical program. The other common AEs seen here in the pediatric population are similar to what was seen in the adult population and are listed in the current PI: muscle spasms, myalgia, dizziness, headache, hypertension, nausea, vomiting, gastroenteritis, abdominal pain, and diarrhea. There was some very limited data in this pediatric program to support an increased risk of GI bleeding with cinacalcet use in the pediatric CKD population. That said, given the problem with missing data due to patients dropping out of studies, suggesting a tolerability issue and the fact the most children were exposed for 16 weeks or less and therefore had limited opportunity for dose titration to demonstrate clear efficacy in this study population, this medical reviewer concludes that there is insufficient long term exposure at efficacious doses from the

clinical studies included in this submission to support any conclusion about the safety of chronic use of cinacalcet in the pediatric population.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

WR Study 2 (20070208) 30-week double-blind, placebo-controlled safety and efficacy study in subjects 6 to < 12 years of age Cohort 1 and 12 to < 18 years of age Cohort 2 with secondary HPT and CKD receiving dialysis

WR Study 3 (20110100) 26-week (or time-until-transplantation) open-label safety study in subjects 28 days to < 6 years of age with secondary HPT and CKD receiving dialysis

WR Study 4 (20130356) 24-week open-label, controlled safety and efficacy study in subjects 6 to < 12 years of age Cohort 1 and 12 to < 18 years of age Cohort 2 with secondary HPT and CKD receiving dialysis

### 7.1.2 Categorization of Adverse Events

The applicant's definitions of AEs and serious adverse events (SAEs) in the protocol(s) were accurate. At each study visit, investigators were to inquire if any serious adverse events of hypocalcemia, seizures, or infections had been experienced, using the worksheets provided. Any laboratory assessments of serum calcium levels associated with the events and assessed through local laboratories (i.e., not a protocol scheduled study laboratory draw) were to be recorded on the applicable eCRF. The adverse event severity grading scale used was the Common Terminology Criteria for Adverse Events (CTCAE V4.0). Adverse event terms included in the data files were appropriately categorized in the AEDECOD (dictionary-derived term) data file.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Given the different study designs it was not appropriate to pool data across studies to compare incidence.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 103 pediatric subjects were exposed to cinacalcet in the combined phase 1, 2, and 3 clinical study pool. There were 5 subjects between 28 days and < 2 years, 24 subjects between 2 and < 6 years, 24 subjects between 6 and < 12 years, and 48 subjects between 12 and < 18 years.

*Medical Officer's comments-*
*About 50% of the data is from adolescents. Of the 5 subjects under 2 years of age only 2 were enrolled in a repeat dose Phase 2 study and received long term exposure to cinacalcet in these studies, and none were under 1 year of age. Therefore, there is insufficient clinical information here to confirm safety in children under 2 years of age, especially as cinacalcet is metabolized by two CYP enzymes CYP3A4 and CYP1A2, which substantially increase in activity over the first year of life (Anderson & Lynn Pharmacotherapy, 2009).*

**Table 23 Total Cinacalcet Exposure in Pediatric Clinical Studies 20070208, 20130356 & 20140159**

| | Exposure to Cinacalcet[a,b] | |
|---|---|---|
| | Randomized Controlled Studies[c] n (subject-years) | All Studies n (subject-years) |
| All phase 1 pediatric studies | 0 (0.00) | 24 (0.07) |
| 28 days to < 2 years | 0 (0.00) | 3 (0.01) |
| 2 to < 12 years | 0 (0.00) | 15 (0.04) |
| 2 to < 6 years | 0 (0.00) | 9 (0.02) |
| 6 to < 12 years | 0 (0.00) | 6 (0.02) |
| 12 to < 18 years | 0 (0.00) | 6 (0.02) |
| All phase 2 and 3 pediatric studies - ESRD | 47 (14.87) | 79 (28.26) |
| 28 days to < 2 years | 0 (0.00) | 2 (0.62) |
| 2 to < 12 years | 14 (5.15) | 33 (11.11) |
| 2 to < 6 years | 0 (0.00) | 15 (3.63) |
| 6 to < 12 years | 14 (5.15) | 18 (7.48) |
| 12 to < 18 years | 32 (9.51) | 42 (16.04) |
| 18 to < 65 years | 1 (0.21) | 2 (0.48) |
| Total | 47 (14.87) | 103 (28.32) |
| 28 days to < 2 years | 0 (0.00) | 5 (0.63) |
| 2 to < 12 years | 14 (5.15) | 48 (11.15) |
| 2 to < 6 years | 0 (0.00) | 24 (3.66) |
| 6 to < 12 years | 14 (5.15) | 24 (7.50) |
| 12 to < 18 years | 32 (9.51) | 48 (16.06) |
| 18 to < 65 years | 1 (0.21) | 2 (0.48) |

n = number of subjects exposed to cinacalcet; ESRD = end-stage renal disease; subject-years = total subject-years of exposure
[a] Data from completed studies and on-going Study 20140159 with cutoff date as 29 April 2016.
[b] Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
[c] Only randomized controlled treatment phases are included.
One subject in pediatric Study 20070208 and 1 subject in pediatric Study 20140159 were 18 years old at enrollment and are classified into "18 to < 65 years" category.
Source ISS Table 4

Out of the 79 patients exposed to multiple doses during the Phase 2 and Phase 3 studies, only about 1/3 or 28 were exposed for 20 weeks or greater (see Table 24) so there is limited information about the longer term safety of cinacalcet from these studies.

**Table 24 Summary of Duration of Exposure in Pediatric Clinical Studies**

| | Before Partial Clinical Hold | | | After Partial Clinical Hold | | | | |
|---|---|---|---|---|---|---|---|---|
| | Study 20070208 (N = 28) | Study 20110100 (N = 7) | Total (N = 35) | Study 20110100 (N = 10) | Study 20130356[a] (N = 25) | Study 20140159[b] (N = 9) | Total (N = 44) | Overall (N = 79) |
| Duration of exposure (days) | | | | | | | | |
| n | 28 | 7 | 35 | 10 | 25 | 9 | 44 | 79 |
| Mean | 128.8 | 66.0 | 116.2 | 101.2 | 164.7 | 149.1 | 147.1 | 133.4 |
| SE | 21.2 | 19.2 | 17.8 | 13.4 | 20.4 | 11.1 | 12.7 | 10.7 |
| SD | 112.1 | 50.9 | 105.3 | 42.4 | 102.2 | 33.3 | 84.2 | 94.8 |
| Median | 100.0 | 83.0 | 89.0 | 106.5 | 140.0 | 143.0 | 131.0 | 121.0 |
| Q1, Q3 | 53.5, 164.5 | 14.0, 123.0 | 37.0, 145.0 | 92.0, 121.0 | 105.0, 255.0 | 130.0, 185.0 | 102.5, 181.0 | 76.0, 166.0 |
| Min, Max | 8, 420 | 10, 125 | 8, 420 | 15, 166 | 6, 337 | 100, 193 | 6, 337 | 6, 420 |
| Duration of exposure by category | | | | | | | | |
| ≥ 4 weeks | 24 (85.7) | 4 (57.1) | 28 (80.0) | 9 (90.0) | 23 (92.0) | 9 (100.0) | 41 (93.2) | 69 (87.3) |
| ≥ 8 weeks | 20 (71.4) | 4 (57.1) | 24 (68.6) | 8 (80.0) | 22 (88.0) | 9 (100.0) | 39 (88.6) | 63 (79.7) |
| ≥ 12 weeks | 17 (60.7) | 3 (42.9) | 20 (57.1) | 8 (80.0) | 21 (84.0) | 9 (100.0) | 38 (86.4) | 58 (73.4) |
| ≥ 16 weeks | 13 (46.4) | 2 (28.6) | 15 (42.9) | 4 (40.0) | 18 (72.0) | 8 (88.9) | 30 (68.2) | 45 (57.0) |
| ≥ 20 weeks | 9 (32.1) | 0 (0.0) | 9 (25.7) | 1 (10.0) | 13 (52.0) | 5 (55.6) | 19 (43.2) | 28 (35.4) |
| ≥ 24 weeks | 7 (25.0) | 0 (0.0) | 7 (20.0) | 0 (0.0) | 9 (36.0) | 3 (33.3) | 12 (27.3) | 19 (24.1) |
| ≥ 36 weeks | 4 (14.3) | 0 (0.0) | 4 (11.4) | 0 (0.0) | 7 (28.0) | 0 (0.0) | 7 (15.9) | 11 (13.9) |
| ≥ 48 weeks | 3 (10.7) | 0 (0.0) | 3 (8.6) | 0 (0.0) | 2 (8.0) | 0 (0.0) | 2 (4.5) | 5 (6.3) |

Source Page 1 of Table 3 ISS

*Medical Officer's comments-*
*Given that the majority of these data were in children exposed for 16 weeks or less and dose titration occurred at 4 week intervals, most patients had at most 3 titrations to try to determine an effective dose. This assumes that it was possible to increase the dose at each of these visits. However, according to the ISS, (Section 1.2.3) 85.7% of subjects in Study 20072008 prior to the clinical hold had the dose withheld or a dose reduction, and the rate slightly increased to 88.6% in Studies 20110100, 20130356 and 20150159 combined after the clinical hold. Therefore, most subjects probably had 2 or less dose titrations from the low starting dose between 0.20mcg/kg/day to 0.25mcg/kg/day, which was chosen to represent about half the adult starting dose, with the hope that starting with a very low dose would be more likely to ensure greater safety in the pediatric trials, and so it is not surprising that efficacy was an issue in the evaluation of these clinical trials.*

**Table 25 Baseline Demographics in Cinacalcet Pediatric Studies**

| | Study 20070208 (N = 28) | Study 20110100 (N = 17) | Study 20130356[a] (N = 25) | Study 20140159[b] (N = 9) | Overall (N = 79) |
|---|---|---|---|---|---|
| Sex - n (%) | | | | | |
| Male | 15 (53.6) | 11 (64.7) | 14 (56.0) | 4 (44.4) | 44 (55.7) |
| Female | 13 (46.4) | 6 (35.3) | 11 (44.0) | 5 (55.6) | 35 (44.3) |
| Ethnicity - n (%) | | | | | |
| Hispanic or Latino | 5 (17.9) | 3 (17.6) | 0 (0.0) | 1 (11.1) | 9 (11.4) |
| Not Hispanic or Latino | 23 (82.1) | 14 (82.4) | 25 (100.0) | 8 (88.9) | 70 (88.6) |
| Race - n (%) | | | | | |
| Black (or African American) | 7 (25.0) | 2 (11.8) | 5 (20.0) | 1 (11.1) | 15 (19.0) |
| Multiple | 0 (0.0) | 0 (0.0) | 1 (4.0) | 0 (0.0) | 1 (1.3) |
| White, Native Hawaiian or Other Pacific Islander | 0 (0.0) | 0 (0.0) | 1 (4.0) | 0 (0.0) | 1 (1.3) |
| White | 20 (71.4) | 15 (88.2) | 17 (68.0) | 8 (88.9) | 60 (75.9) |
| Other | 1 (3.6) | 0 (0.0) | 2 (8.0) | 0 (0.0) | 3 (3.8) |
| Age (years)[c] | | | | | |
| n | 28 | 17 | 25 | 9 | 79 |
| Mean | 13.2 | 2.9 | 13.1 | 14.3 | 11.1 |
| SD | 3.5 | 1.3 | 3.8 | 3.1 | 5.4 |
| Median | 14.5 | 3.0 | 15.0 | 15.0 | 13.0 |
| Q1, Q3 | 10.5, 16.0 | 2.0, 4.0 | 10.0, 16.0 | 12.0, 17.0 | 6.0, 16.0 |
| Min, Max | 6, 18 | 1, 5 | 6, 17 | 9, 18 | 1, 18 |
| Age group - n (%) | | | | | |
| 28 days - < 6 years | 0 (0.0) | 17 (100.0) | 0 (0.0) | 0 (0.0) | 17 (21.5) |
| 6 - < 12 years | 8 (28.6) | 0 (0.0) | 8 (32.0) | 2 (22.2) | 18 (22.8) |
| 12 - < 18 years | 20 (71.4) | 0 (0.0) | 17 (68.0) | 7 (77.8) | 44 (55.7) |

N = Number of subjects in the analysis set
[a] Subjects who received cinacalcet in Study 20130356 are counted in the Study 20130356 column; subjects from this cohort who continued to extension Study 20140159 are also counted in the Study 20130356 column.
[b] Subjects who received standard of care in Study 20130356 and received cinacalcet in Study 20140159 are counted in the Study 20140159 column. The baseline demographics at enrollment of Study 20140159 are used for these subjects.
[c] One subject in Study 20070208 and 1 subject in Study 20140159 were 18 years old at enrollment and are categorized in "12 - < 18 years."

Source Table 8 ISS

*Medical Officer's comments-*
*According to the NAPRTCS 2008 Annual Report, males make up 64% of the pediatric CKD population due to a higher prevalence of hypoplasia/dysplasia and obstructive uropathy. They are slightly underrepresented in this study at 56% of the population. According to the NAPRTCS 2008 Annual Report, African Americans make up almost 19% of the pediatric CKD population so they are adequately represented in this study (19%).*

## 7.3 Major Safety Results

### 7.3.1 Deaths

During the clinical studies in the cinacalcet clinical program there were two deaths in subjects being treated with cinacalcet:

1) In Study 20070208 (6 to < 18 years of age) a 14 year old girl (20866012001) suffered a fatal cardiopulmonary event in the cinacalcet treatment group.

   On (b) (6), during study week 23, the subject had an onset of severe nausea, vomiting, and diarrhea. There was a history of sick contacts with similar symptoms several (2-4) days prior to the onset of events, and the investigator stated that previous episodes of nausea, diarrhea and vomiting were successfully treated at home with 1-2 doses of Zofran under the direction of the pediatric nephrologist on call. The home health nurse performed a week 23 study visit at 10:43 am that day: vital signs showed an oral temperature of 102.4°F, blood pressure of 110/60 mmHg, and heart rate of 120 beats per minute and glucose concentration of 120 mg/dL. The subject was treated with Tylenol 1000 mg and Zofran 4 mg. Later the same day, she went into cardiopulmonary arrest and was pronounced dead at the hospital. The last dose of cinacalcet 90 mg was reported to be taken the day before on (b) (6). At the time of the fatal event, she was treated with immunosuppressive medications in preparation for a renal transplant. Analysis of lab data showed that the subject had substantial increases in iPTH (≥ 300%) despite up titration to 90mg of cinacalcet. A lab report which did not became available until after the fatal event showed a corrected calcium concentration of 5.3 mg/dL on the morning of the subject's death. At baseline, the subject had a prolonged QT interval of 473 ms so both hypocalcemia and Zofran which can prolong the QT interval may have contributed to the fatal event.

The cause of death in this case was determined to be multifactorial and included the following potential causes:

- Concurrent illness resulting in fever, nausea, vomiting, and dehydration, in a patient with anemia (Hct 23%), asplenia, and receiving immunosuppressive medications in preparation for a renal transplant.
- Baseline prolonged QT interval while being treated with a hypocalcemic medication (cinacalcet) and a medication with known QT prolonging effects (Zofran)
- Hypocalcemia (corrected serum calcium of 5.3 mg/dL). During weeks 17 and 19 she continued to have acceptable central lab corrected calcium values of 8.6 and 8.7 and iPTH was 364 and 1071, respectively, so the cinacalcet dose was to be

increased to 90mg on wk 20. A local lab corrected serum calcium from week 20 was low again at 7.9mg/dL so her calcium supplement dose was increased. It was planned to increase the cinacalcet dose to 90mg on wk 20 but mom lost the bottle with the new dose so she continued to give the old dose of 60mg during that wk until she obtained a new bottle of the 90mg dose on wk 21. The blood draw from the clinic on wk 21 (b) (6)) was contaminated with EDTA and so no result was available. The patient was called to arrange a follow up blood draw but there was a delay as this was (b) (6) week. The value of 5.3mg/dL recorded on (b) (6) was obtained on the day of the fatal event but was not available at the time of the cardiopulmonary event.

As a result of this death, the study was placed on a 14 month clinical hold and eventually terminated.

After a complete review of this case and discussion with Amgen, new safety revisions to decrease the risk of hypocalcemia were incorporated in pediatric clinical protocols. These included (but were not limited to):

- Weekly monitoring using ionized calcium to allow for real-time dose adjustment,
- More restrictive limits on serum calcium levels incorporated into dosing algorithms including limiting dosing based on local laboratory calcium values
- Revision to the inclusion/exclusion criteria for subjects with prolonged QTc interval at baseline
- Exclusion of drugs that can prolong the QTc interval,
- Screening out noncompliant patients by the investigator prior to enrollment and further monitoring compliance through the use of compliance diaries,
- Limiting investigational product dispensing to prevent over- and under- dosing.

2) In Study 20140159 (the extension study for subjects who completed Study 20130356 (ages 6 to < 18 years) or Study 20110100 (ages 28 days to < 6 years), a 2 year old Caucasian male from the Czech Republic suffered a sudden fatal event while being treated with cinacalcet.

   The child participated in open-label Study 20110100 for 4 months from (b) (6) unti (b) (6). The child then enrolled into the open-label extension Study 20140159 and continued to receive cinacalcet treatment. One month later, on (b) (6) according to the mother, the child went to sleep normally. When she went to change his diaper, she noticed the child wasn't breathing and was pale with vomit present in his nose and mouth. The subject's mother started resuscitation, and the subject's father called emergency. The rescue team found the subject asystolic, without signs of life, pale, with massive amount of stomach vomit with color like coffee sediment coming out of his nose

and mouth. He was transported to the local hospital where he was declared dead. Blood drawn before HD on (b) (6) (Week 3, 2.5 mg dose), showed ionized calcium (iCa) 1.04mmol/L, total calcium 7.8mg/dL, albumin 3.4g/dL, cCa 2.06mM (8.24mg/dL), phosphorous 9.1mg/dL and iPTH level of 2588.7pg/mL, so the event was likely not due to significant hypocalcemia. There was concern about a potential GI bleed in this patient given the history of coffee like sediment coming from the nose and mouth; however the autopsy did not report any evidence of gastritis, or ulcer disease that could have been the source of a potential bleed making this less likely. Instead the autopsy found dispersive suppurative bronchopneumonia (lobular purulent inflammation of the lungs) and acute exacerbation of chronic pyelonephritis (sudden flaring of chronic inflammation of the kidney collecting system) together with the primary illness - congenital hypoplasia of kidneys. The immediate cause of death of the subject was defined as lobular purulent inflammation of the lungs with sudden flaring of chronic inflammation of the kidney collecting system from congenital insufficiently developed kidneys. It is possible that the patient vomited and aspirated at home and that contributed to the abnormal lung findings seen at autopsy. Nausea and vomiting are among the most common AEs associated with the use of cinacalcet.

### 7.3.2 Nonfatal Serious Adverse Events

**Children 6 to <18 years of age**

Study 20070208
Serious adverse events (AE)s were reported for 9/22=41% of cinacalcet subjects and 19/21=43% of placebo subjects in the double-blind period. Serious AEs seen in 2 or more patients and seen with the use of cinacalcet in either the double-blind phase or open-label extension were hypertension (n=3); hypocalcemia (n=2), peritonitis (n=2); and fluid overload (n=1).

**Serious AEs Occurring in at Least 2 Patients**

| AEDECOD | | Double-Blind | | Open Label |
|---|---|---|---|---|
| | Total | Cinacalcet | Placebo | Cinacalcet |
| Hypertension | 4 | 2 | 1 | 1 |
| Peritonitis | 2 | 1 | 0 | 1 |
| Hypocalcaemia | 2 | 1 | 0 | 1 |
| Fluid overload | 2 | 1 | 1 | 0 |
| Hypertensive encephalopathy | 2 | 0 | 1 | 1 |
| Urinary tract infection | 2 | 0 | 1 | 1 |
| Dehydration | 2 | 0 | 2 | 0 |
| Diarrhoea | 2 | 0 | 2 | 0 |
| Pyrexia | 2 | 0 | 2 | 0 |

Source adae.xpt, AESER=Y; AEPERIOD=DB or OL; AESDY>0; TRT01A, AEDECOD,USUBJID/ AEDECOD by subgrp TRT01A

The single serious AE of hypocalcemia during the double-blind treatment period occurred in subject 20866012001 the 14 year old girl who died from a fatal cardiopulmonary event in the cinacalcet treatment group and was described in detail in section 7.3.1. The other case of hypocalcemia (ionized calcium 3.9 mg/dL was low, but total serum calcium 9.6 was normal) occurred in a 13 year old black male (20866016001) while receiving cinacalcet in the open label extension. The event also was associated with serious AEs of hypertensive encephalopathy, hypertension (Peak BP 153/90) and hemoglobin increased (hemoglobin of 15.1). Approximately 4 months after starting cinacalcet in the open-label extension, during dialysis in which 2.6 liters of fluid were removed about one hour after taking a 30mg dose of cinacalcet he started feeling confused, became combative and complained of moderate continuous pressure-like headache in the front of his head on both sides with no radiation (rated 7/10), cold and some stomach pain. He was taken to a hospital where he vomited once which relieved the abdominal pain and subsequently started having sweats and agitation. Treatment included a dose of intravenous hydralazine, intravenous calcium gluconate, Zofran (ondansetron) for nausea and Tylenol (paracetamol) for headache. The subject was admitted to the hospital due to post dialysis hypertension. Head CT was normal. The following day the ionized calcium had normalized at 4.3 mg/dL. The events of hypertension and hypertensive encephalopathy were considered resolved (BP 89/51). The investigational product was withheld.

Study 20130356
Serious AEs were reported for 4/25=16% of “cinacalcet & SOC” subjects and 2/30=7% of subjects in the “SOC alone” group. No serious AEs were seen in more than one patient in either treatment group. Seven serious AEs (device dislocation, device related infection, dyspnoea, fluid overload, postoperative wound infection, renovascular hypertension, and soft tissue infection) were seen in the same patient (35666014001) all other patients had only one serious AE.

**All Serious AEs in Study 20130356 by Study Treatment**

| AEDECOD | Total | Cinacalcet & SOC | SOC alone |
|---|---|---|---|
| Arteriovenous fistula site haemorrhage | 1 | 1 | 0 |
| Asthma | 1 | 0 | 1 |
| Bacterial infection | 1 | 0 | 1 |
| Device dislocation | 1 | 1 | 0 |
| Device related infection | 1 | 1 | 0 |
| Dyspnoea | 1 | 1 | 0 |
| Fluid overload | 1 | 1 | 0 |
| Ileus | 1 | 1 | 0 |
| Peritonitis | 1 | 1 | 0 |

| | | | |
|---|---|---|---|
| Postoperative wound infection | 1 | 1 | 0 |
| Renovascular hypertension | 1 | 1 | 0 |
| Soft tissue infection | 1 | 1 | 0 |
| Source adae.xpt, AESER=Y, AESDY>0; TRT01A, AEDECOD, USUBJID/ AEDECOD by subgrp TRT01A, | | | |

**Children 28 Days to <6 years of age**

Study 20110100

Serious AEs were reported for 9/18=50% of subjects all who were treated with cinacalcet in this open label study (Source adae.xpt AESER=Y, AESDY>0; USUBJID). Serious AEs of hypertension and device complication were seen in 2 subjects treated with cinacalcet. Six serious AEs (dehydration, device related infection, diarrhoea, hyperglycaemia, hypertension, and upper respiratory tract infection) were seen in the same patient (10066011002).

| All Serious AEs in Study 20110100 | |
|---|---|
| **AEDECOD** | **Cinacalcet** |
| Complication associated with device | 2 |
| Hypertension | 2 |
| Adenovirus infection | 1 |
| Dehydration | 1 |
| Device malfunction | 1 |
| Device related infection | 1 |
| Device related sepsis | 1 |
| Diarrhoea | 1 |
| Failure to thrive | 1 |
| Hyperglycaemia | 1 |
| Ileus | 1 |
| Influenza | 1 |
| Overdose | 1 |
| Peritoneal dialysis complication | 1 |
| Seizure | 1 |
| Upper respiratory tract infection | 1 |
| Source adae.xpt, AESER=Y, AESDY>0; TRT01A, AEDECOD, USUBJID / AEDECOD by subgrp TRT01A | |

*Medical Officer's comments-*

*The two cases of serious hypocalcemia are likely to be cinacalcet related and are a known AE seen with the use of this product. All other serious AEs represent AEs that are common in the dialysis population and so it is not possible to tell from the limited data whether they might be drug related.*

### 7.3.3 Dropouts and/or Discontinuations

**Children 6 to <18 years of age**

Study 20070208
During the double-blind period, outside of the fatal event that may have been partially related to the use of cinacalcet, no subjects in the cinacalcet group had an adverse event that resulted in them being withdraw from the study. In contrast, two subjects (10%) in the placebo group had an adverse event that led to their withdrawal from the study. According to the sponsor no subjects experienced an adverse event that led to withdrawal of cinacalcet during the open-label period of the study.

Study 20130356
According to the sponsor no subjects withdrew from use of the investigational drug product in this study due to an adverse event.

**Children 28 Days to <6 years of age**

Study 20110100
According to the sponsor no subjects withdrew from use of the investigational drug product in this study due to an adverse event.

*Medical Officer's comments-*
*From the limited data in these trials there does not appear to be a signal for adverse events resulting in withdrawal of the investigational drug products, with the caveat that there is very limited exposure especially in the very young children.*

### 7.3.4 Significant Adverse Events

**Children 6 to <18 years of age**

Study 20070208
In the double-blind phase there was a similar percentage of AEs graded ≥2, ≥3 and ≥4 between the cinacalcet and placebo treatment groups.

**Table 26 Summary of Adverse Events in the Double-Blind Phase of Study 20070208**

| | Placebo (N = 21) n (%) | Cinacalcet (N = 22) n (%) |
|---|---|---|
| All treatment-emergent adverse events | 18 (85.7) | 18 (81.8) |
| Grade ≥ 2 | 16 (76.2) | 13 (59.1) |
| Grade ≥ 3 | 10 (47.6) | 7 (31.8) |
| Grade ≥ 4 | 2 (9.5) | 1 (4.5) |
| Serious adverse events | 9 (42.9) | 9 (40.9) |
| Adverse events leading to withdrawal of investigational product | 2 (9.5) | 0 (0.0) |
| Fatal adverse events | 0 (0.0) | 1 (4.5) |

Safety analysis set: enrolled subjects who received at least one dose of investigational product
Percentage based on N.
Source Table 12-1 CSR Study 20070208

Study 20130356
In Study 20130356 there was a slightly higher percentage of AEs graded ≥2, ≥3 and ≥4 in the "cinacalcet & SOC" vs. the "SOC alone" treatment groups.

**Table 27 Summary of Adverse Events in Study 20130356**

| | SOC (N = 30) n (%) | SOC + Cinacalcet (N = 25) n (%) |
|---|---|---|
| All treatment emergent adverse events | 17 (56.7) | 21 (84.0) |
| Grade ≥ 2 | 10 (33.3) | 14 (56.0) |
| Grade ≥ 3 | 3 (10.0) | 4 (16.0) |
| Grade ≥ 4 | 0 (0.0) | 3 (12.0) |
| Serious adverse events | 2 (6.7) | 4 (16.0) |
| Leading to discontinuation of investigational product | 0 (0.0) | 0 (0.0) |
| Life-threatening adverse events[a] | 1 (3.3) | 2 (8.0) |
| Fatal adverse events | 0 (0.0) | 0 (0.0) |

N = number of subjects in the analysis set
Percentage based on N
[a] Immediately life-threatening, as assessed by the investigator. In the cinacalcet+ SOC group, in addition to ileus (grade 4 life threatening event), a subject experienced dyspnea, fluid overload and renovascular hypertension (all grade 3). The SOC subject experienced asthma (grade 3). These events were serious adverse events (Section 16.1.13.1).
Source CSR Study 20130356 Table 12-1

## Children 28 Days to <6 years of age

Study 20110100
There was a similar percentage of AEs graded ≥2, ≥3 and ≥4 in Cohorts 1 and 2, before and after the pediatric clinical hold despite the heightened calcium monitoring after the clinical hold.

**Table 28 Summary of Adverse Events in Study 20110100**

| | Cohort 1 (N = 7) n (%) | Cohort 2 (N = 10) n (%) | Total (N = 17) n (%) |
|---|---|---|---|
| All treatment-emergent adverse events | 7 (100.0) | 9 (90.0) | 16 (94.1) |
| Grade ≥ 2 | 5 (71.4) | 6 (60.0) | 11 (64.7) |
| Grade ≥ 3 | 4 (57.1) | 4 (40.0) | 8 (47.1) |
| Grade ≥ 4 | 1 (14.3) | 2 (20.0) | 3 (17.6) |
| Serious adverse events | 4 (57.1) | 5 (50.0) | 9 (52.9) |
| Leading to discontinuation of investigational product | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Fatal adverse events | 0 (0.0) | 0 (0.0) | 0 (0.0) |

MedDRA = Medical Dictionary for Regulatory Activities; N = Number of subjects in the analysis set.
Cohort 1 consists of subjects enrolled before the partial clinical hold. Cohort 2 consists of subjects enrolled after the partial clinical hold.
Coded using MedDRA version 19.0.

Source Table 12-2 CSR Study 20110100

## 7.3.5 Submission Specific Primary Safety Concerns

Gastrointestinal Bleeding -
In response to the Division's concern about the potential association between cinacalcet use and the occurrence of gastrointestinal bleeding events, Amgen conducted an analysis of data from clinical studies (adult and pediatric studies through August 2016), and postmarketing events. This information was summarized in the Safety Assessment Report under section 5.3.6 of the current submission. Based on the available information, Amgen concluded that there was no current evidence of increased risk of gastrointestinal bleeding disorders coincident with cinacalcet treatment. Amgen plans to list gastrointestinal bleeding as an event of interest and monitor all gastrointestinal bleeding events through routine pharmacovigilance activities.

In the pediatric clinical program, there is limited information to suggest any increased risk of gastrointestinal bleeding events. A fatal event in a 2 year old boy from the Czech Republic in the open label extension Study 20140159 which was associated with coffee colored emesis was eventually attributed to suppurative bronchopneumonia at autopsy.

A review of the ISS dataset for AEs of interest identified 3 patients under the AE higher level terms that may have been related to gastrointestinal bleeding:

| USUBJID | AEHLGT | AETERM | AE Start Day | AE End Day | Age | Gender |
|---|---|---|---|---|---|---|
| 20070208-20851002001 | Gastrointestinal vascular conditions | ESOPHAGEAL VARICES, WORSERING | 429 | 447 | 11 | F |
| 20070208-20866016002 | Gastrointestinal ulceration and perforation | GASTRIC ULCER | 135 | | 16 | F |
| 20130356-35651001002 | Gastrointestinal ulceration and perforation | EROSIVE GASTRODUODENITIS | 9 | 37 | 15 | F |

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

**Children 6 to <18 years of age**

Study 20070208
Adverse events (AE)s were reported for 18/22=82% cinacalcet subjects and 18/21=86% placebo subjects during the double-blind treatment phase.

**Common AEs in Study 20070208 Double-Blind Phase by Treatment Group**

| AEDECOD | Total N=43 | Cinacalcet N=22 | Placebo N=21 |
|---|---|---|---|
| Vomiting | 12 | 7 | 5 |
| Hypocalcaemia | 9 | 5 | 4 |
| Nausea | 7 | 4 | 3 |
| Hypertension | 8 | 3 | 5 |
| Abdominal pain | 6 | 3 | 3 |
| Headache | 5 | 3 | 2 |
| Influenza | 4 | 3 | 1 |
| Muscle spasms | 4 | 3 | 1 |
| Myalgia | 4 | 3 | 1 |
| Tremor | 3 | 3 | 0 |
| Diarrhoea | 6 | 2 | 4 |
| Device related infection | 4 | 2 | 2 |
| Hypotension | 3 | 2 | 1 |
| Nasopharyngitis | 3 | 2 | 1 |
| Anxiety | 2 | 2 | 0 |
| Catheter site infection | 2 | 2 | 0 |
| Dizziness | 2 | 2 | 0 |
| Musculoskeletal stiffness | 2 | 2 | 0 |
| Pyrexia | 5 | 1 | 4 |
| Constipation | 4 | 1 | 3 |
| Cough | 4 | 1 | 3 |
| Hyperkalaemia | 4 | 1 | 3 |
| Chills | 3 | 1 | 2 |

Source adae.xpt, AESDY>0, APERIODC=Double-Blind TRT01A,AEDECOD,USUBJID/ AEDECOD subgrp by TRT01A sorted in order of frequency of Cinacalcet AEs and occurring in at least two subjects in the either treatment group

| Common AEs in Study 20070208 Open-Label Phase | |
|---|---|
| **AEDECOD** | **Cinacalcet** |
| Hypocalcaemia | 4 |
| Nausea | 3 |
| Abdominal pain | 2 |
| Headache | 2 |
| Hypertension | 2 |
| Paraesthesia | 2 |
| Pyrexia | 2 |
| Source adae.xpt, AESDY>0, APERIODC=Open-label occurring in at least two subjects | |

Study 20130356
AEs were reported for 21/25=84% “cinacalcet & SOC” subjects and 19/30=63% subjects in the “SOC alone” group (Source adae.xpt USUBJID,TRT01A/TRT01A).

| Common AEs in Study 20130356 by Treatment Group | | | |
|---|---|---|---|
| **AEDECOD** | **Total N=55** | **Cinacalcet & SOC N=25** | **SOC alone N=30** |
| Hypocalcaemia | 9 | 6 | 3 |
| Muscle spasms | 5 | 3 | 2 |
| Nausea | 4 | 3 | 1 |
| Nasopharyngitis | 4 | 2 | 2 |
| Gastroenteritis | 2 | 2 | 0 |
| Peritonitis | 2 | 2 | 0 |
| Pneumonia | 2 | 2 | 0 |
| Headache | 5 | 1 | 4 |
| Abdominal pain upper | 3 | 1 | 2 |
| Blood calcium decreased | 3 | 1 | 2 |
| Diarrhoea | 3 | 1 | 2 |
| Vomiting | 3 | 0 | 3 |
| Pain in extremity | 2 | 0 | 2 |
| Procedural pain | 2 | 0 | 2 |
| Weight increased | 2 | 0 | 2 |
| Source adae.xpt, AESDY>0, TRT01A,AEDECOD,USUBJID/ AEDECOD subgrp by TRT01A sorted in order of frequency of Cinacalcet AEs and occurring in at least two subjects in either treatment group | | | |

**Children 28 days to <6 years of age**

Study 20110100
AEs were reported for 16/17=94% of subjects all who were treated with cinacalcet in this open label study (Source adae.xpt USUBJID).

| Common AEs in Study 20110100 | |
|---|---|
| **AEDECOD** | **Cinacalcet** |
| Cough | 4 |
| Hypertension | 4 |
| Upper respiratory tract infection | 4 |
| Vomiting | 4 |
| Complication associated with device | 3 |
| Diarrhoea | 3 |
| Pyrexia | 3 |
| Viral infection | 3 |
| Bronchitis | 2 |
| Source adae.xpt, AESDY>0, TRT01A, AEDECOD, USUBJID/ AEDECOD sorted in order of frequency of Cinacalcet AEs and occurring in at least two subjects | |

*Medical Officer's comments-*
*The common AEs seen in the pediatric population are similar to what was seen in the adult population and are listed in the current PI: hypocalcemia, muscle spasms, myalgia, dizziness, headache, hypertension, nausea, vomiting, gastroenteritis, abdominal pain, and diarrhea. While these AEs may be more likely to be drug related, they are also common in the placebo and standard of care groups as seen in these clinical studies.*

## 7.4.2 Laboratory Findings

**Hypocalcemia**

**Children 6 to <18 years of age**

Study 20070208
The number of patients with corrected serum calcium levels < 8.4mg/dL, < 8.0mg/dL and < 7.5mg/dL was higher in the cinacalcet group compared to placebo in Study 20070208 in both age cohorts.

**Table 29 Low Corrected Serum Calcium Levels in the Double-Blind Phase of Study 20070208**

| | 6 - < 12 years | | 12 - < 18 years | | Total | |
|---|---|---|---|---|---|---|
| | Placebo (N=5) $n/N_1$ (%) | Cinacalcet (N=6) $n/N_1$ (%) | Placebo (N=16) $n/N_1$ (%) | Cinacalcet (N=16) $n/N_1$ (%) | Placebo (N=21) $n/N_1$ (%) | Cinacalcet (N=22) $n/N_1$ (%) |
| Subject incidence of cCa < 8.4 mg/dL | 0/5 (0.0) | 2/6 (33.3) | 3/16 (18.8) | 5/16 (31.3) | 3/21 (14.3) | 7/22 (31.8) |
| Subject incidence of cCa < 8.0 mg/dL | 0/5 (0.0) | 2/6 (33.3) | 1/16 (6.3) | 3/16 (18.8) | 1/21 (4.8) | 5/22 (22.7) |
| Subject incidence of cCa < 7.5 mg/dL | 0/5 (0.0) | 1/6 (16.7) | 0/16 (0.0) | 2/16 (12.5) | 0/21 (0.0) | 3/22 (13.6) |



N=Number of subjects in the safety analysis set
Safety analysis set: randomized subjects who received at least one dose of IP
$N_1$ = Number of subjects with at least one post-baseline calcium value
Source Table 14-7.2.1. CSR for Study 20070208

Study 20130356
With increased serum calcium monitoring the rates of hypocalcemia were lower in Study 20130356 compared to Study 20070208. And in fact there was no difference between the rates of more severe hypocalcemia < 8.0mg/dL and < 7.5mg/dL between the "SOC alone" and "cinacalcet & SOC" treatment groups. However the heightened serum calcium monitoring resulted in less efficacy as described above in section 6.2.4.

**Table 30 Low Corrected Serum Calcium Levels in Study 20130356**

| | 6 - < 12 years | | 12 - < 18 years | | Total | |
|---|---|---|---|---|---|---|
| | SOC (N = 10) $n/N_1$ (%) | SOC + Cinacalcet (N = 8) $n/N_1$ (%) | SOC (N = 20) $n/N_1$ (%) | SOC + Cinacalcet (N = 17) $n/N_1$ (%) | SOC (N = 30) $n/N_1$ (%) | SOC + Cinacalcet (N = 25) $n/N_1$ (%) |
| Subject incidence of cCa < 8.4 mg/dL | 1/9 (11.1) | 3/8 (37.5) | 1/20 (5.0) | 3/17 (17.6) | 2/29 (6.9) | 6/25 (24.0) |
| Subject incidence of cCa < 8.0 mg/dL | 0/9 (0.0) | 0/8 (0.0) | 1/20 (5.0) | 1/17 (5.9) | 1/29 (3.4) | 1/25 (4.0) |
| Subject incidence of cCa < 7.5 mg/dL | 0/9 (0.0) | 0/8 (0.0) | 1/20 (5.0) | 1/17 (5.9) | 1/29 (3.4) | 1/25 (4.0) |

N = Number of subjects in the analysis set
cCa = corrected serum calcium
$N_1$ = Number of subjects with at least one post-baseline cCa value
The frequency of cCa measures is lower than the frequency of ionized calcium measures.
Source Table 12-7 CSR for Study 20130356

## Children 28 days to <6 years of age

Study 20110100
Two subjects (2/17=12%, one in each cohort) both within the 2 to < 6-year age range had corrected serum calcium levels that were < 8.8 mg/dL. The values of 8.6mg/dL and 8.5mg/dL were both above the lower limit of normal for this age range of 8.4mg/dL and so did not represent hypocalcemia.

*Medical Officer's comments-*
*From the limited data, it appears that the risk of hypocalcemia was greater in Studies 20070208 and 20130356 in children 6 to < 18 years of age compared to Study 20110100 in children 28 days to < 6 years of age. At first it may seem that the younger patients are at lower risk for hypocalcemia. But this medical reviewer believes that the difference in the risk of hypocalcemia may more likely relate to the difference in study designs and not the age groups of the children. For example the risk of hypocalcemia was lower in Study 20130356 compared to Study 20070208 due to the stricter serum calcium monitoring in the former study. The risk of hypocalcemia may also have been lower in Study 20110100 in children 28 days to < 6 years of age if the use of vitamin D analogs and calcium supplements had been greater in this study. While hypocalcemia is a known adverse event associated with the use of cinacalcet and other calcimimetics in the treatment of secondary hyperphosphatemia, hypercalcemia is a known adverse event with the use of vitamin D analogs for the same condition. While the two Studies 20070208 and 20130356 in children 6 to < 18 were designed as controlled studies looking for efficacy in iPTH lowering, Study 20110100 was designed primarily as a safety study where investigators were free to increase the dose of vitamin D analogs and calcium supplements without worrying about whether that might confound the study and limit the ability to detect efficacy in iPTH lowering due to cinacalcet. Given that the CSRs did not summarize information about change in vitamin D analog and calcium containing supplement dosing during these studies, this hypothesis has yet to be confirmed. However, as treating physicians are likely to use vitamin D analogs and calcium supplements in combination with cinacalcet to help maintain normal serum calcium levels, the risk of hypocalcemia in a clinical study where the use of vitamin D analogs is restricted may overestimate the risk of hypocalcemia with cinacalcet in a real use setting.*

### 7.4.3 Vital Signs

According to the applicant no clinically significant changes have been observed in vital signs results in the pediatric program for cinacalcet to date.

In Study 20070208 hypotension was reported in 1/21=5% of control subjects and in 2/22=9% of cinacalcet subjects. In Study 20110100 hypotension was reported in 1/17=6% of subjects in the cinacalcet group. No events of hypotension were reported in Studies 20130356 or 20140159.

In Study 20070208 hypertension was reported in 1/21=5% of control subjects and in 2/22=9% of cinacalcet subjects. In Study 20110100 hypertension was reported in 2/17=12% of subjects in the cinacalcet group. No events of hypertension were reported in Studies 20130356 or 20140159.

*Medical Officer's comments-*
*There is no clear signal for vital sign abnormalities in the small number of pediatric patients enrolled in this clinical program.*

### 7.4.4 Electrocardiograms (ECGs)

According to the applicant no clinically significant changes have been observed in electrocardiograms results in the pediatric program for cinacalcet to date. There were no AEs reported associated with QT prolongation. For the AE Body System there were two subjects each with Tachycardia and Palpitations, and one subject each with Mitral valve stenosis, Cardiopulmonary failure, and Left ventricular hypertrophy.

*Medical Officer's comments-*
*There is no clear signal for cardiac arrhythmias in the small number of pediatric patients enrolled in this clinical program.*

### 7.4.5 Special Safety Studies/Clinical Trials

None

### 7.4.6 Immunogenicity

Not applicable

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

A review of the AEs of nausea, vomiting, hypertension, hypotension, and hypocalcemia did not identify a dose dependency from the limited data in these clinical trials.

### 7.5.2 Time Dependency for Adverse Events

Most AEs appeared to occur earlier in the course of treatment but the data is limited by the lack of long term exposure.

### 7.5.3 Drug-Demographic Interactions

No drug-demographic interactions were included in this submission.

### 7.5.4 Drug-Disease Interactions

No analyses with respect to medical history were included in this submission.

### 7.5.5 Drug-Drug Interactions

No drug-drug interaction data was included in this submission.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

No human carcinogenicity data was included in this submission.

### 7.6.2 Human Reproduction and Pregnancy Data

Reproductive and developmental toxicology studies were previously submitted under NDA 21688.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Growth velocity was measured as a secondary endpoint in the single Study 20070208. There was no significant difference between growth velocity measured at 6 months in the cinacalcet group compared to placebo, 3.3cm/yr vs. 3.1cm/yr (see Table 12). There appeared to a relative decrease in growth velocity in the cinacalcet group compared to placebo over the next 6 months at 1 year total exposure, but these data were derived from two teenage boys who may have just ending their growth spurt. Therefore there is no clear evidence that cinacalcet affects pediatric growth velocity from the limited data in this clinical program.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information was included in this submission.

## 7.7 Additional Submissions / Safety Issues

The 120 Day Safety Update included limited information on 10 additional patients from Studies 20110100 and 20130356 enrolled into Study 20140159, the open-label safety extension study, since the original interim analysis data cut off. No changes to the limited safety profile occurred as a result of these data.

# 8 Postmarket Experience

Pediatric postmarketing data through June 2016 was summarized by the applicant from literature, solicited, spontaneous, and postmarketing noninterventional study reports. It consisted of 171 adverse events (69 serious) in 81 pediatric subjects. The most frequently reported events were off-label use (n=30), hypocalcemia (n=11), wrong technique in product usage process (n=9), drug ineffective (n=8), and vomiting (n=8). One death was reported in a 14 year old boy receiving cinacalcet not on dialysis for an unspecified indication reported on an unnamed physician's website. Given the limited information on this case, it appears to be different from the fatal event described above which occurred in a 14 year old girl on dialysis (20866012001), but the applicant was not able to identify the website which supposedly was the source of this information to confirm the validity of the MedWatch report. The mean age of the children was 8.9 years (range 0.01 to 17 years), and 57% of the cases, where a gender was described, were in boys which is consistent with renal disease being more common in boys as described previously.

In the 11 cases of hypocalcemia 6 were considered serious. In 5 of these cases there were associated symptoms suggestive of hypocalcemia.

- Serious AEs
  - Seizure in a 14 y/o boy seven days after starting cinacalcet, serum calcium 7mg/dL, treated with calcium gluconate; he recovered and was able to tolerate cinacalcet when reintroduced one month later.
  - Myalgia, increased CPK, edema, pain in extremity and abdominal pain in a 17 y/o girl 11 days after starting therapy with cinacalcet.
  - Muscle spasms, blood calcium abnormal, arthralgia, and blood pressure increased in a 15 y/o boy. Serum calcium prior to cinacalcet treatment reported as 8.8 mg/dL decreased to 7.9 mg/dL 1 week after re-initiation of treatment.
- NonSerious AEs
  - Myalgia in a 14 y/o girl no serum calcium levels reported.
  - Paraesthesia/hypoesthesia in a 17 y/o boy, only normal serum calcium levels were reported.

Cinacalcet was discontinued in 4 of the 5 cases. None of the cases were associated with cardiac arrhythmias. In cases without associated symptoms serum calcium as low as 6.4mg/dL was reported (Normal Range Lower Limit 8.4mg/dL).

Blood calcium decreased was also reported in 3 cases, 2 were serious (accidental ingestion by healthy 1 y/o, headache in 7 y/o), but no low serum calcium levels were included in these reports.

*Medical Officer's comments-*
*There is limited information in these reports but the cases including: the generalized tonic clonic seizure, myalgias, muscle spasms and*

*paraesthesia/hypoesthesia were likely due to the associated hypocalcemia and have been reported previously in adults.*

Nausea (n=8), vomiting (n=4), diarrhea (n=1), and abdominal pain (n=1) are common events associated with the use of cinacalcet in adults. Cinacalcet was discontinued in only one case and temporarily discontinued in another suggesting that in most cases the subjects were still able to tolerate the medication despite these symptoms.

There was one serious case of hepatotoxicity and one of LFT elevations in pediatric subjects, both of which responded to discontinuation of cinacalcet therapy.

There were no reported pediatric cases of gastrointestinal bleeding.

*Medical Officer's comments-*
*Despite the limited information, there is clear evidence of a risk for hypocalcemia/ blood calcium decreased and gastrointestinal events of nausea, vomiting, abdominal pain etc. which are likely to be drug related and have been described previously in adults.*

**WR National Registry Study**-
The WR National Registry Study 20120116 was a prospective, 3-year observational study of subjects < 21 years of age with a diagnosis of CKD receiving maintenance dialysis at affiliated dialysis centers associated with the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry. A diagnosis of secondary hyperparathyroidism was not required for inclusion in this study and baseline laboratory values and the timing of cinacalcet dosing relative to laboratory assessments were not reported, thus, limiting the ability to correlate laboratory values with treatment due to cinacalcet in this study. The study collected demographic and laboratory data on patients using cinacalcet compared to non-users. Cinacalcet users tended to be older mean (SD): 14.0 (5.4) years vs. 10.3 (6.4) years and had been on dialysis for a longer period of time mean (SD): 24.9 (23.0) months vs. 8.9 (18.1) months compared to non-users. They had higher baseline iPTH values mean (SD): 602 (593) pg/mL vs. 378 (445) pg/mL, but there was a large overlap between groups. There was no difference in corrected serum calcium between users and nonusers mean (SD): 9.7 (1.1) mg/dL vs. 9.7 (1.1) mg/dL. Given that the study was not randomized and subject to voluntary reporting it is not possible to directly compare adverse events or treatment outcomes, but from the limited data there did not appear to be clear differences between users and non-users with respect to infections, seizures, or deaths. Interestingly, it appears the most patients were dosed twice daily (BID) with a weekly dose of 210mcg (see Table 31) which would correspond to BID dosing with 15mcg. This would require Sensipar which is currently only available as a 30mcg unscored tablet to be split in half. Of note, a twice daily dosing scheme was not studied in the cinacalcet pediatric clinical program. Due to the long half-life of cinacalcet a twice daily dosing scheme is expected to

increase the mean accumulation ratio from approximately 2 with daily dosing to approximately 2 to 5 fold according the Sensipar PI.

**Table 31 Cinacalcet Dosing in NAPRTCS Registry**

| | Total | |
|---|---|---|
| | N | % |
| **All** | 80 | 100.0 |
| **Cinacalcet Dose (mg)** | | |
| 3 | 1 | 1.3 |
| 6 | 1 | 1.3 |
| 7.5 | 3 | 3.8 |
| 15 | 17 | 21.3 |
| 30 | 46 | 57.5 |
| 45 | 3 | 3.8 |
| 60 | 6 | 7.5 |
| 90 | 2 | 2.5 |
| 120 | 1 | 1.3 |
| Mean (SD) | 30.8 (18.8) | |
| Median (Min,Max) | 30 (3 – 120) | |
| **Cinacalcet Frequency** | | |
| 3× per day | 1 | 1.3 |
| Once per day | 1 | 1.3 |
| Twice per day | 76 | 95.0 |
| 3× per week | 2 | 2.5 |
| **Cinacalcet Dose per week (mg)** | | |
| 21 | 1 | 1.3 |
| 42 | 1 | 1.3 |
| 45 | 1 | 1.3 |
| 52.5 | 3 | 3.8 |
| 90 | 1 | 1.3 |
| 105 | 16 | 20.0 |
| 210 | 43 | 53.8 |
| 315 | 3 | 3.8 |
| 420 | 7 | 8.8 |
| 630 | 3 | 3.8 |
| 840 | 1 | 1.3 |
| Mean (SD) | 221.0 (143.0) | |
| Median (Min,Max) | 210 (21 – 840) | |
| **Cinacalcet Dose per week (mg/kg)** | | |
| 1 to <2 | 4 | 5.0 |
| 2 to <3 | 12 | 15.0 |
| 3 to <4 | 13 | 16.2 |
| 4 to <5 | 12 | 15.0 |
| 5 to <6 | 16 | 20.0 |
| 6 to <7 | 7 | 8.8 |
| ≥7 | 16 | 20.0 |
| Mean (SD) | 5.7 (4.4) | |
| Median (Min,Max) | 4.8 (1.1 – 32.3) | |

# 9 Appendices

## 9.1 Literature Review/References

A total of 34 publications addressing the use of cinacalcet in the pediatric population were identified by the applicant through June 2016, using keywords “cinacalcet” AND “child” or “cinacalcet” AND “pediatric”. These included 5 prospective studies, one retrospective study, 5 case reports on the use of cinacalcet in pediatric dialysis patients with secondary hyperparathyroidism and 17 case reports on the pediatric use of cinacalcet in other conditions. Pediatric ages ranged from 9 months to 19 years (9 were under 6 years of age). The initial dose of cinacalcet, ranged from 0.25 to 1.1 mg/kg/day for weight-based dosing and 10 to 30 mg for fixed dosing. The maximum dose ranged from 0.4 to 2.6 mg/kg/day for weight-based dosing or 30 to 120 mg for fixed dosing. Mean reduction in iPTH from baseline values of 41.7% to 97.6% for clinical studies and 39.4% to 97% for individual case reports were reported. The adverse events which were seen included hypocalcemia, seizure in one patient despite a normal serum calcium, gastrointestinal symptoms (nausea, vomiting, weight loss), paresthesia/ hypoesthesia, over suppression of iPTH and one case in which precocious puberty was triggered in a 5 y/o boy who in retrospect had early hormone abnormalities prior to the initiation of treatment. There were no reports of drug-related hepatic disorders, QT-prolongation or cardiac arrhythmias.

*Medical Officer’s comments-*
*The clinical efficacy observed in these open-label clinical trials from the literature was not confirmed in the blinded placebo-controlled Study 20070208 (WR Study 2) and the open-label active-controlled Study 20130356 (WR Study 4) in this submission. However, these findings mimic the findings in the open label uncontrolled Study 20110100 (WR Study 3) in which adjustment of active vitamin D analog doses was encouraged to achieve therapeutic goals for iPTH. In Study 20110100, 71% of subjects (12/17) achieved ≥30% reduction in iPTH from baseline. It may be that a significant amount of the benefit in the treatment of secondary hyperparathyroidism in pediatric patients with cinacalcet comes from the lowering of serum calcium which permits up titration with vitamin D analogs, which have been shown to be effective in lowering iPTH in this study population. In fact, one of the prospective studies (Alharthi et al 2015) mentions “Changeable doses of active Vit D are mandatory throughout cinacalcet treatment.” Therefore a study design which seeks to minimize titration of vitamin D analogs in order to not confound the efficacy results is likely not relevant to the real use situation, and may underestimate the true benefit of treatment with cinacalcet. Ideally, future studies should enroll patients already on maximally effective doses of vitamin D analogs and permit adjustment of the vitamin D analog dose during the*

*trial which would be more analogous to a real use situation, where add on therapy with cinacalcet is considered. However, as recruitment is a problem in these pediatric studies because of the small number of available patients, there is an incentive to enroll all available patients which could even mean washing out the active vitamin D analog dose in some patients in order to reach baseline iPTH levels that comply with the study inclusion criteria.*

*The adverse event profile seen in the pediatric literature consisting of hypocalcemia, gastrointestinal symptoms, paresthesia/ hypoesthesia, and over suppression of iPTH are representative of what has been seen previously in the adult population. The single case in which onset of precocious puberty was triggered is unique but may have been drug related especially as symptoms abated after cinacalcet was discontinued.*

## 9.2 Labeling Recommendations

This medical reviewer would recommend describing the WR studies in this submission in section 8.4 of the PI, but without the study results. The text should state that the study results were inconclusive due to the large amount of study drop outs and missing data.

An indication for pediatric use should not be given, but safety issues identified in the clinical program could be included in the study descriptions. This should include:

- The need to make sure patients are likely to be compliant with medication prior to initiation of use and to reconfirm dose compliance prior to each dose escalation.
- The need for regular weekly serum calcium monitoring during dose escalation and potentially throughout treatment.
- The need to lower or withhold dosing for low iPTH, or serum calcium.
- The need to avoid use in patients with QTc prolongation at baseline and the need to avoid concomitant treatment with medications that can prolong the QT interval.

## 9.3 Advisory Committee Meeting

None

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/s/

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WILLIAM A LUBAS
05/22/2017

MARINA ZEMSKOVA
05/22/2017

JEAN-MARC P GUETTIER
05/23/2017