U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	(b) (4)/21688 S-023
Drug Name:	Cinacalcet
Indication(s):	Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease on Dialysis
Applicant:	Amgen
Date(s):	Stamp: November 23, 2016
	Mid-cycle meeting: February 22, 2017
	Priority Review due date: April 29, 2017
	PDUFA: May 23, 2017
Review Priority:	Priority
Biometrics Division:	Division II
Statistical Reviewer:	Shuxian Sinks, PhD, Statistical Reviewer
Concurring Reviewers:	Yun Wang, PhD, Acting Team Leader
	Thomas Permutt, PhD, Director
Medical Division:	Department of Metabolism and Endocrinology Products
Clinical Team:	William (Bill) Lubas, MD, Clinical Reviewer
	Marina Zemskova, MD, Team Leader
Project Manager:	Meghna Jairath

Keywords: Missing data, Multiple imputation, Tipping point analysis

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Amgen has submitted a new drug application for cinacalcet (Sensipar) on November 23, 2016. The applicant is seeking (b) (4)

Cinacalcet (Sensipar) was currently approved for the treatment of secondary HPT in adult patients with CKD on dialysis, the treatment of hypercalcemia in patients with parathyroid carcinoma, and the treatment of hypercalcemia in patients with primary HPT who are unable to undergo parathyroidectomy.

1.1 Brief Overview of Clinical Studies

Two pediatric studies (studies 2007028 and 20130356) were submitted to evaluate the efficacy and safety of cinacalcet for the treatment of secondary HPT in pediatric patients with CKD receiving dialysis in this NDA submission. Both studies 20070208 and 20130356 were phase 3, randomized, controlled studies in subject 6 to <18 years in age. All subjects received standard of care with vitamin D sterols, calcium supplements, and phosphate binders, regardless of treatment assignment. Table 1 listed the details of the two studies included in the submission.

Table 1 List of All Studies included in Analysis

Study Number	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
20070208	Randomized, double-blind, placebo-controlled, SOC add-on	30 weeks	A 30 weeks open-label follow-up	cinacalcet: 22 subjects Placebo: 21 subjects	Children and adolescents with secondary HPT and CKD from 6 to less than 18 years old
20130356	Randomized, open-label, SOC add-on	20 weeks	--	cinacalcet+SOC : 27 subjects SOC: 28 subjects	Children and adolescents with secondary HPT and CKD from 6 to less than 18 years old

SOC: standard of care

The primary endpoint was the response rate of at least 30% reduction from baseline in mean plasma iPTH during the efficacy assessment period (EAP). In study 20070208, the EAP was defined as weeks 24 to 30. In study 20130356, the EAP was defined as weeks 11 to15 for US only.

1.2 Key Efficacy Results

Based on applicant's analyses results, the proportion of subjects achieving at least 30% iPTH reduction in the cinacalcet group is significantly different from that proportion in the placebo group in study 20070208 (odds ratio: 4.26; 95% CI:0.99,18.3; p-value=0.017), where the analysis of primary endpoint included all data collected prior to the suspension of the investigational product. The applicant's primary analysis showed that there was no statistically significant difference between cinacalcet plus standard of care and standard of care alone in primary endpoint in study 20130356 (odds ratio:1.61; 95% CI:0.44,5.83; p-value=0.48).

However, there were about 38% missing data in placebo group and 64% missing data in cinacalcet group during EAP in study 20070208. In study 20130356, there were about 14% missing data in SOC group and 26% missing data in cinacalcet+SOC group during EAP. The early termination of the study and the longer duration of treatment likely resulted in higher percentage of missing data in study 20070208 than study 20130356. According to the statistical reviewer's analyses results, there was no statistically significant evidence to support the benefit of cinacalcet with respect to the primary endpoint (at least 30% iPTH reduction from baseline) in phase 3 studies 20070208 (odds ratio:1.25; 95% CI:0.28,5.59; p-value=0.77) and 20130356 (odds ratio:2.22; 95% CI:0.59,8.24; p-value=0.67).

1.3 Statistical Issues with the Application

There were substantial amount of missing data presented in both studies 20070208 and 20130356. Clinical data were not collected in the cinacalcet pediatric program after subjects withdrew early due to the transplant. In study 20070208, the applicant's analyses relied on the assumption that the treatment benefit for subjects discontinued early remained the same as the last observed measurement. This is likely an implausible assumption, as iPTH achieved while on treatment might not be sustained after stopping treatment after 7 days.

The applicant intended to borrow the efficacy data from adult to younger pediatric group (day 28 to <6 years). This is problematic as it is not clear whether the results from adult studies are exchangeable into the results from pediatric studies. Based on data collected from studies 20070208 and 20130356, the effectiveness of cinacalcet in pediatric population is different from adult population. In addition, the initial agreement was to extrapolate the efficacy data from the two phase 3 pediatric studies in subject 6 to <18 years in age, not studies in adult population, to younger pediatric group (day 28 to <6 years)).

1.4 Conclusions and Recommendations

The clinical data from the two phase III studies examined in pediatric population do not provide convincing and substantial statistical evidence to demonstrate the clinical benefit of cinacalcet for the overall pediatric population. The conduct of the trials did not comply with good clinical practice to assure the quality of data. With large amount of missing data, the efficacy assessment of cinacalcet in pediatric population could be biased. Therefore, efficacy results from two pivotal

studies 20070208 and 20130356 (b) (4)

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Sensipar is designated and approved as an orphan drug for the treatment of hypercalcemia in patients with parathyroid carcinoma and for the treatment of secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) receiving dialysis. The current approved strengths of Sensipar are 30 mg, 60 mg, and 90 mg in tablets.

2.1.2 History of Drug Development

Amgen submitted a proposed pediatric study request (PPSR) to FDA seeking issuance of a written request (WR) for Cinacalcet for the treatment of pediatric patients with SHPT and CKD on dialysis on May 2007. FDA issued a WR on May 5, 2010, which was amended on December 2010 and March 2011 and included 3 interventional clinical studies to evaluate the pharmacokinetics, safety and efficacy of cinacalcet in children. The initial Investigational New Drug (IND) 109361 was submitted on 17 December 2010, the purpose of that IND was to evaluate the use of Cinacalcet in the treatment of SHPT in pediatric patients with CKD receiving dialysis.

On 5 February 2014, division held a Type A meeting to discuss the proposed multiple-dose study 20130356 and the future development plan for the Cinacalcet pediatric program. FDA did not agree with the proposed open-label, single arm study design for study 20130356, as the design was inadequate to obtain useful safety and efficacy data. FDA also stated that a randomized, open-label, clinical trial with separate Cinacalcet and control arms should be conducted to demonstrate efficacy in children.

On 21 September 2016, a Pre-sNDA face-to face meeting was held. Amgen proposed a Bayesian extrapolation analysis to infer the treatment effect of Cinacalcet on PTH from the adult population to the overall pediatric population and to children age 28 days to <6 years with CKD and SHPT receiving dialysis. FDA did not agree with the proposed analysis and stated that borrowing data from the older adult population could overwhelm the pediatric efficacy results, as insufficient subject and data were collected from pediatric studies.

2.1.3 Data Sources

The data and final study reports were submitted electronically as an eCTD submission. The Submission was archived at the following link as an .enx file:
\\CDSESUB1\evsprod\NDA (b) (4) \ (b) (4) .enx

The information needed for this review was obtained from Module 1 FDA regional information, Module 2.5 Clinical Overview, Module 2.7 Clinical Summary, and Module 5 Clinical Study Reports.

All figures, tables, and other analysis results were created by the statistical reviewer unless otherwise noted.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

All required documents necessary for conducting a statistical review were submitted. The submitted datasets for the clinical trials were of acceptable quality and were adequately documented. The analysis datasets included both derived and enriched data (such as formatted variables, derived endpoint, etc.). Across trials the variables for the primary analysis were consistently named. The statistical reviewer was able to reproduce the results of all primary and key secondary analyses presented in the individual Clinical Study Reports.

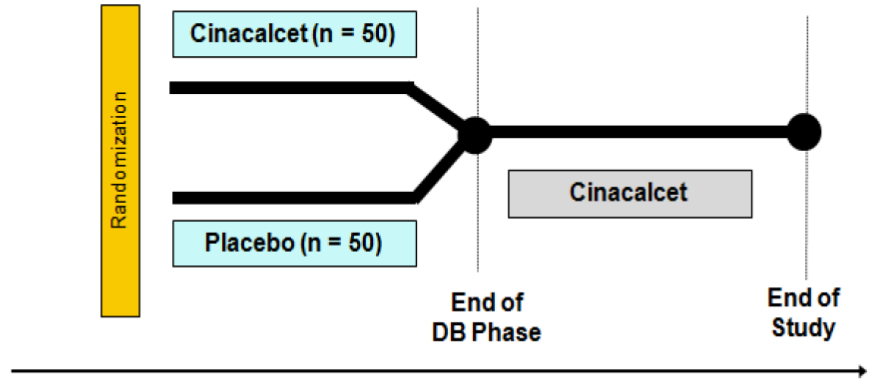
3.2 Evaluation of Efficacy

3.2.1 Study Design

Study 20070208 was a randomized, double-blind, placebo-controlled study which consisted of a 24-week dose-titration phase, and a 6-week efficacy assessment phase (EAP) (see Figure 1). Subjects who complete double-blind phase were eligible to enter a 30-week open-label extension phase. Patients were randomized in a 1:1 ratio to receive either oral cinacalcet or placebo stratified by age group. The starting dose is ≤0.20mg/kg based on dry weight once daily, and the dose could be titrated upward every 4 weeks according to plasma iPTH and serum calcium levels.

Figure 1 Study Design of Study 20070208

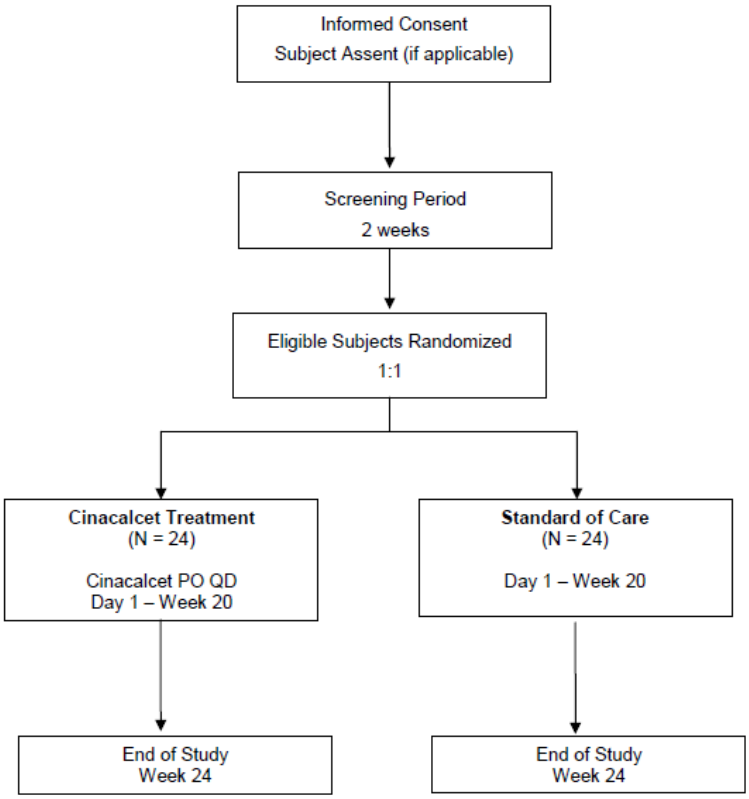
Screening	Double-blind Phase		Open-label Phase	
	Titration	Efficacy Assessment	Titration	Maintenance
Up to 40 Days	24 Weeks	6 Weeks	24 Weeks	6 weeks



DB = double blind.

Study 20130356 was a phase 3, randomized, open-label, multicenter, controlled study in pediatric subjects with secondary HPT and CKD who were receiving dialysis. The study consisted of a 2-week screening period and a 20-week open-label controlled treatment period (see Figure 2). Subjects who completed the study were eligible to enroll in an open-label extension study (20140159) for long-term safety assessment of cinacalcet.

Figure 2 Study Design of Study 20130356



3.2.2 Primary and Secondary Endpoints

The primary endpoint was the response rate of at least 30% reduction from baseline in mean plasma iPTH during the efficacy assessment period (EAP). In study 20070208, the EAP was defined as weeks 24 to 30. In study 20130356, the EAP was defined as weeks 11 to15 for US only.

The key secondary endpoints for study 20070208 were:

- achievement of cinacalcet for lowering the plasma iPTH level to ≤300 pg/ML (31pmol/L)
- percent change in corrected total serum calcium from baseline to the mean value during the EAP
- percent change in serum phosphorus from baseline to the mean value during the EAP
- percent change in Ca*P from baseline to the mean value during EAP
- growth velocity calculated from baseline to week 30 , and from week 30 to week 60
- percent change in ionized calcium from baseline to the mean value during the EAP

The key secondary endpoints for study 20130356:

- proportion of subjects who achieve a mean iPTH value ≤ 300 pg/mL during weeks 17 to 20

- percent change in iPTH from baseline to the mean value during Weeks 17 to 20
- change in corrected total serum calcium from baseline to the mean value during weeks 17 to 20
- change in serum phosphorus from baseline to the mean value during weeks 17 to 20
- proportion of subjects who achieve at least 30% reduction from baseline in mean plasma iPTH during weeks 17 to 20

3.2.3 Statistical Methodologies

3.2.3.1 Primary and Secondary Analyses

In studies 20070208 and 20130356, the primary efficacy analysis was based on Cochran-Mantel-Haenszel (CMH) test stratified by age (6 to <12 years or 12 to 18 years old) to compare treatment groups with respect to mean change from baseline in iPTH at specified EAP.

The analyses of binary secondary endpoints were also based on CMH test as the primary analysis. For continuous secondary endpoints, an analysis of covariance (ANCOVA) was used with baseline age group as the covariate.

3.2.3.2 Approach to Multiplicity

The applicant used Holm's method to control the overall familywise type I error at 0.05 (two-sided) for key secondary endpoints. The secondary endpoints were tested only if the primary endpoint achieved statistically significant at a level of 0.05 (two-sided).

3.2.3.3 Analysis Population

As per the applicant's analysis plan, the full analysis set (FAS) was used for primary and secondary endpoints. The FAS included all randomized subjects with at least one post-baseline assessment. The applicant's analyses used the planned randomized treatment.

The reviewer's analyses were based on an ITT population, where the analysis set was defined as the set that included all randomized subjects regardless of discontinuation.

3.2.3.4 Missing Data

There were substantial amount of missing data due to early termination of the study 20070208, with dropout rates ranging from 42.9% to 77.3%, depending on the treatment group and timing of EAP (see Table 2). The proportion of missingness in that cinacalcet arm was greater than that in the placebo arm. Most non-missing measurements were taken on subjects who were still on treatment. On the other hand, the majority of missing data were from subjects who discontinued treatment due to administrative decision (15 subjects) and kidney transplant (8 subjects).

Table 2 Missingness of iPTH Measurements for Study 20070208

Visit	Placebo (n=21)						Cinacalcet (n=22)					
	Missing		ontrt	Non-Missing		offtrt	Missing		ontrt	Non-Missing		offtrt
	n	%	n	n	%	n	n	%	n	n	%	n
Week 1	2	9.5%	1	19	90.5%	1	0	0.0%	0	22	100.0%	0
Week 3	4	19.0%	2	17	81.0%	1	1	4.5%	0	21	95.5%	0
Week 5	4	19.0%	0	17	81.0%	0	4	18.2%	2	18	81.8%	2
Week 7	3	14.3%	0	18	85.7%	2	3	13.6%	1	19	86.4%	2
Week 9	5	23.8%	1	16	76.2%	1	5	22.7%	1	17	77.3%	3
Week 11	5	23.8%	1	16	76.2%	4	5	22.7%	0	17	77.3%	3
Week 13	8	38.1%	1	13	61.9%	1	7	31.8%	1	15	68.2%	4
Week 15	6	28.6%	0	15	71.4%	2	6	27.3%	0	16	72.7%	4
Week 17	11	52.4%	3	10	47.6%	1	12	54.5%	3	10	45.5%	3
Week 19	7	33.3%	0	14	66.7%	4	10	45.5%	0	12	54.5%	5
Week 21	12	57.1%	2	9	42.9%	2	17	77.3%	2	5	22.7%	1
Week 23	9	42.9%	0	12	57.1%	3	13	59.1%	0	9	40.9%	4
Week 25	9	42.9%	0	12	57.1%	4	16	72.7%	0	6	27.3%	2
Week 27	11	52.4%	0	10	47.6%	3	15	68.2%	0	7	31.8%	3
Week 29	10	47.6%	0	11	52.4%	4	17	77.3%	0	5	22.7%	1

Subjects in study 20130356 had shorter duration of treatment than in study 20070208. There were about 14% missing data in SOC group and 26% missing data in cinacalcet group during week 11 and week 15 (Table 3). The proportion of missing data in cinacalcet arm was greater than that in the Standard of Care arm before week 15. The proportions of missing data were similar between the treatment arms at week 17. The study did not plan to collect data from subjects who discontinued early. Majority of subjects had missing data when they were off-treatment.

Table 3 Missingness of iPTH Measurements for Study 20130356

Visit	Standard of Care (n=28)						Cinacalcet (n=27)					
	Missing		ontrt	Non-Missing		offtrt	Missing		ontrt	Non-Missing		offtrt
	n	%	n	n	%	n	n	%	n	n	%	n
Baseline	0	0.0%	0	28	100.0%	0	2	7.4%	0	25	92.6%	0
Week 3	1	3.6%	0	27	96.4%	0	3	11.1%	1	24	88.9%	0
Week 7	1	3.6%	0	27	96.4%	0	6	22.2%	2	21	77.8%	0
Week 11	4	14.3%	1	24	85.7%	0	7	25.9%	3	20	74.1%	0
Week 15	4	14.3%	1	24	85.7%	0	8	29.6%	1	19	70.4%	0
Week 17	11	39.3%	4	17	60.7%	1	11	40.7%	3	16	59.3%	2
Week 19	10	35.7%	1	18	64.3%	0	13	48.1%	1	14	51.9%	1

3.2.3.5 Applicant's Method of Handling Missing Data

Study 20070208
The applicant claimed that the last two available measurements can be carried forward to handle the measurements for patients who are missing at EAP in study 20070208, due to the reasons for discontinuation unrelated to the treatment. Therefore, missing data were imputed using the last observation carried forward (LOCF) approach for primary and secondary endpoints. For subjects who have missing measurement during the EAP, the mean of last 2 available post measurements in the dose-titration phase were used. If only 1 post-measurement was available, the single value was used.

Study 20130356
Agency had agreed that subjects who withdrew due to renal transplant or parathyroidectomy were considered as completer if they completed at least 12 weeks of treatment before surgery. Missing data were imputed using the non-responder imputation (NRI) method. Subjects who did not have value at week 11 or week 15 were considered as non-responders, regardless of treatment group.

3.2.3.6 Reviewer's Analysis Approach

3.2.3.6.1 Primary analysis
The large amount of missing data would deteriorate the reliability of the results and alter the study conclusion. Given the limitation due to missing data, it is challenging to provide the most clinically meaningful estimate of the treatment effect relevant to real clinical practice. The statistical reviewer thinks the most appropriate analysis should handle the missing data in a fashion that corresponds to the original intended conduct of the study design, but not the actual conduct of the trial.

The analysis was also based on Cochran-Mantel-Haenszel test stratified by Age. Missing data were handled based on the imputation strategy depending on the reasons that the subjects discontinued the study early.

- For subjects in placebo group, all missing data at EAP are assumed to be missing at random.
- For subjects in cinacalcet group, 1) subjects who had discontinued due to clinical hold or study closure (administrative reasons) or kidney transplant are assumed to be missing at random. Subjects who were missing because of study disclosure or kidney transplant are expected to have same behavior of subjects who were not missing, as the reasons for termination are likely unrelated to the treatment. The imputations are based on means and variance-covariance from subjects in cinacalcet who were not missing. 2) Subjects who had discontinued due to treatment related reasons are assumed to have a washout effect, where any potential effect of cinacalcet for those subjects in the cinacalcet group will be washed out. Specifically, missing data at EAP are imputed based on their baseline iPTH and the imputation model fitted using data from subjects in placebo group plus an error.

3.2.3.6.2 Sensitivity Analysis -Tipping Point Analysis

A tipping point analysis was conducted to gauge the extent to which the demonstration of a treatment effect is dependent on the LOCF. The tipping point analysis will provide a range of estimates of treatment effect under varied assumptions about the possible outcomes of the patient dropouts. If "tipping point" from significance to non-significance is unlikely happened in the real clinical setting, one may conclude that the demonstration of efficacy is reliable despite the missing data.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

Study 20070208 randomized 22 patients in the cinacalcet arm and 21 patients in the placebo arm (Table 4). A total of 16 patients completed the efficacy assessment period. Of 27 non-completers, twelve subjects discontinued the study relevant to administrative decision and eight subjects had kidney transplants before completing the EAP. Other reasons included withdrawal of consent from study, noncompliance of study drug and death.

Table 4 Patient Disposition for Study 20070208

	Cinacalcet		Placebo		Total	
	n	%	n	%	n	%
Randomized	**22**	**100.0%**	**21**	**100.0%**	**43**	**100.0%**
Subjects completed study	**5**	**22.7%**	**11**	**52.4%**	**16**	**37.2%**
Subjects discontinued study	**17**	**77.3%**	**10**	**47.6%**	**27**	**62.8%**
Administrative decision	7	31.8%	5	23.8%	12	27.9%
Withdrawal of consent from study	1	4.6%	3	14.3%	4	9.3%
Noncompliance of study drug	1	4.6%	0	0.0%	1	2.3%
Death	1	4.6%	0	0.0%	1	2.3%
Protocol-specified criteria	6	27.3%	2	9.5%	8	18.6%
Kidney Transplant	6	27.3%	2	9.5%	8	18.6%
Other	1	4.6%	0	0.0%	1	2.3%

Study 20130356 randomized 27 patients in the cinacalcet arm and 28 patients in the standard of care arm (Table 5). All subjects received standard of care as background therapy. A total of 36 subjects completed the study. Of 19 non-completers, thirteen subjects terminated the study early due to sponsor decision. The rest of subjects were withdrawal consent of the study.

Table 5 Patient Disposition for Study 20130356

	Cinacalcet		Standard of Care		Total	
	n	%	n	%	n	%
Randomized	**27**	**100.0%**	**28**	**100.0%**	**55**	**100.0%**
Subjects completed study*	**16**	**59.3%**	**20**	**71.4%**	**36**	**65.5%**
Kidney Transplant	0	0.0%	1	3.6%	1	1.8%
Complete 12 weeks of treatment	0	0.0%	0	0.0%	0	0.0%
Subjects discontinued study	**11**	**40.7%**	**8**	**28.6%**	**19**	**34.5%**
Decision by sponsor	6	22.2%	7	25.0%	13	23.6%
Withdrawal of consent from study	5	18.5%	1	3.6%	6	10.9%
Noncompliance of study drug	0	0.0%	0	0.0%	0	0.0%
Death	0	0.0%	0	0.0%	0	0.0%
Protocol-specified criteria	0	0.0%	0	0.0%	0	0.0%
Other	0	0.0%	0	0.0%	0	0.0%

* Subjects completed 12 weeks of treatment prior kidney transplant or parathyroidectomy were considered completers

Across the studies, patient demographics and baseline characteristics were summarized in Table 6 and Table 7. Most subjects enrolled in the studies aged from 12 to 18 years old (67%-76%). The average age across the two studies ranged from 12-13 years. The percentage of females and males enrolled into the studies were around 50% across studies and treatment arms. The number of subjects from US was slightly different. For instance, patients on placebo arm were predominantly (76%) from US in study 20070208.

Table 6 Demographics for Studies

	Study 20070208		**Study 20130356**	
	Placebo (N=21)	**Cinacalcet (N=22)**	**Standard of Care (N=28)**	**Cinacalcet (N=27)**
Age				
Mean (SD)	13 (2.9)	13 (3.6)	12 (3.5)	13 (3.9)
Median (IQR)	14 (12, 15)	15 (10, 16)	12 (10, 16)	14 (9, 16)
6 to <12 years	5 (23.8%)	6 (27.3%)	9 (32.1%)	9 (33.3%)
12 to <18 years	16 (76.2%)	16 (72.7%)	19 (67.9%)	18 (66.7%)
SEX				
Female	10 (47.6%)	12 (54.5%)	15 (53.6%)	12 (44.4%)
Male	11 (52.4%)	10 (45.5%)	13 (46.4%)	15 (55.6%)
GEOREG				
United States	16 (76.2%)	7 (31.8%)	10 (35.7%)	9 (33.3%)
Other	5 (23.8%)	15 (68.2%)	18 (64.3%)	18 (66.7%)
RACE				
White	15 (71.4%)	16 (72.7%)	23 (82.1%)	19 (70.4%)
Black	6 (28.6%)	5 (22.7%)	4 (14.3%)	5 (18.5%)
Other	--	1 (4.6%)	1 (3.6%)	3 (11.1%)

Baseline characteristics were similar across the two studies. Majority subjects were on vitamin D or Phosphate binder before taking study medications. Patients in study 20130356 had higher iPTH baseline measurements than patients in study 20070208. There were no large imbalances in baseline characteristics across treatment arms in the two studies.

Table 7 Baseline Characteristics for Studies

	Study 20070208		Study 20130356	
	Placebo (N=21)	**Cinacalcet (N=22)**	**Standard of Care (N=28)**	**Cinacalcet (N=27)**
Dialysis Mode				
Hemodialysis	12 (57.1%)	15 (68.2%)	17 (60.7%)	21 (84.0%)
Peritoneal	9 (42.9%)	7 (31.8%)	11 (39.3%)	4 (16.0%)
Vitamin D sterol use at baseline				
Y	18 (85.7%)	21 (95.5%)	24 (85.7%)	20 (74.1%)
N	3 (14.3%)	1 (4.55%)	4 (14.3%)	7 (25.9%)
Phosphate binder use at baseline				
Y	19 (90.5%)	20 (90.9%)	18 (64.3%)	15 (55.6%)
N	2 (9.52%)	2 (9.09%)	10 (35.7%)	12 (44.4%)
Weight				
Mean (SD)	46 (21.0)	45 (18.5)	42 (21.7)	41 (17.1)
Median (IQR)	39 (28, 59)	43 (32, 53)	36 (26, 51)	41 (23, 54)
Height				
Mean (SD)	146 (18.9)	149 (19.5)	143 (21.2)	147 (21.9)
Median (IQR)	149 (132, 159)	152 (138, 160)	146 (122, 162)	154 (133, 162)
iPTH				
Mean (SD)	796 (538)	757 (440)	1228 (732)	946 (635)
Median (IQR)	684 (465, 844)	676 (484, 825)	1123 (578,1850)	663 (510,1158)
Corrected total serum calcium				
Mean (SD)	10 (0.6)	10 (0.5)	10 (0.6)	10 (0.6)
Median (IQR)	10 (10, 10)	10 (9, 10)	10 (9, 10)	10 (9, 10)
Serum Phosphorous				
Mean (SD)	6 (1.5)	7 (1.8)	6 (1.1)	6 (1.4)
Median (IQR)	6 (6, 7)	7 (5, 8)	6 (5, 6)	6 (5, 7)

3.2.5 Results and Conclusions

3.2.5.1 Primary Efficacy Results

Results from the primary analyses of study 20070208 and 20130506 are described in Table 8 based on the applicant's approach and reviewer's approach. The findings from applicant's approach were inconsistent across trials and conflicting with the results from reviewer's approach. Based on applicant's primary analysis, treatment with cinacalcet resulted in greater responder rate for at least 30% iPTH reduction than placebo in study 20070208, with odds ratio of 4.26 (95% CI: 0.99, 18.3; p-value=0.017), while the superiority of cinacalcet over standard of care was not declared in study 20130356, with odds ratio of 1.61 (95% CI: 0.44, 5.83; p-value=0.48). Based on reviewer's analysis results, no statistically significant differences were found in response rate for at least 30% iPTH reduction from baseline comparing cinacalcet with control group in both studies 20070208 and 20130506.

Table 8 Primary Analysis Results

	Sponsor's Analysis (Applicant's FAS)				Reviewer's Analysis (ITT)			
	CMH statistic		Odds Ratio		CMH statistic		Odds Ratio	
Studies	Value	P-value	Value	95%CL	Value	P-value	Value	95%CL
20070208 (week 24-30)	5.735	0.017*	4.26	(0.99, 18.3)	0.3	0.77	1.25	(0.28, 5.59)
20130356 (Week 11-15)	0.505	0.48	1.61	(0.44, 5.83)	0.8	0.67	2.22	(0.59, 8.24)

[Source: applicant's clinical study report for study 20070208 page55 and Table 10-1, clinical study report for study 20130506 page 52 and Table 10-2 and statistical reviewer's analysis]

3.2.5.2 Analyses for Secondary Endpoints

According to the applicant's statistical protocol, the secondary endpoints will be analyzed if the test for primary endpoint is successful. The conclusion of superiority is questionable in study 20070208, as the results from the statistical reviewer's primary analysis and sensitivity tipping point analysis do not support the sponsor's result for the primary endpoint. Also, study 20130356 failed to demonstrate the superiority of cinacalcet plus standard of care over standard of care alone. Therefore, the reviewer did not conduct the formal analyses for secondary endpoints for both studies. Applicant's analyses results for secondary endpoints were included as reference (see Table 9 and Table 10).

Table 9 Applicant's Secondary Efficacy Results (Study 20070208, Applicant's FAS)

Binary Variable (CMH)	**Odds ratio (Cinacalcet/Placebo)**	**95% CI**
Proportion of Subjects Mean iPTH ≤ 300 pg/mL during the EAP	1.13	(0.27, 4.75)
Continuous Variable (ANCOVA)	**Difference in LS Mean (Cinacalcet/Placebo)**	**95% CI**
% Change in corrected total serum calcium from baseline to mean value during the EAP	-3.7	(-8.6, 1.3)
% Change in serum phosphorus from baseline to mean value during the EAP	-6.4	(-21, 8.2)
% Change in Ca*P from baseline to mean value during the EAP	-10	(-3.1, 3.6)
% Change in ionized calcium from baseline to the mean value during the EAP	-0.8	(-9.4, 7.9)

Missing data were all imputed using LOCF
Source: applicant's study report for study 20070208 page 57 and Table 10-3

Table 10 Applicant's Secondary Efficacy Results (Study 20130356)

Binary Variable (CMH)	**Odds ratio (Cinacalcet/Placebo)**	**95% CI**
Proportion of Subjects Mean iPTH ≤ 300 pg/mL during the EAP	0.364	(0.062, 2.117)
Continuous Variable (ANCOVA)	**Difference in LS Mean (Cinacalcet/Placebo)**	**95% CI**
% change in iPTH from baseline to the mean value during weeks 17-20	7.7	19.0% (-12.5%, 50.5%)
% Change in corrected total serum calcium from baseline to mean value during weeks 17-20	-0.34	(-0.70,0.01)
% Change in serum phosphorus from baseline to mean value during weeks 17-20	0.76	(0.04, 1.48)

Source: applicant's clinical study report for study 20130356 page 54 and table 10-3

3.2.5.3 The Potential Effect of Missing Data for Study 20070208

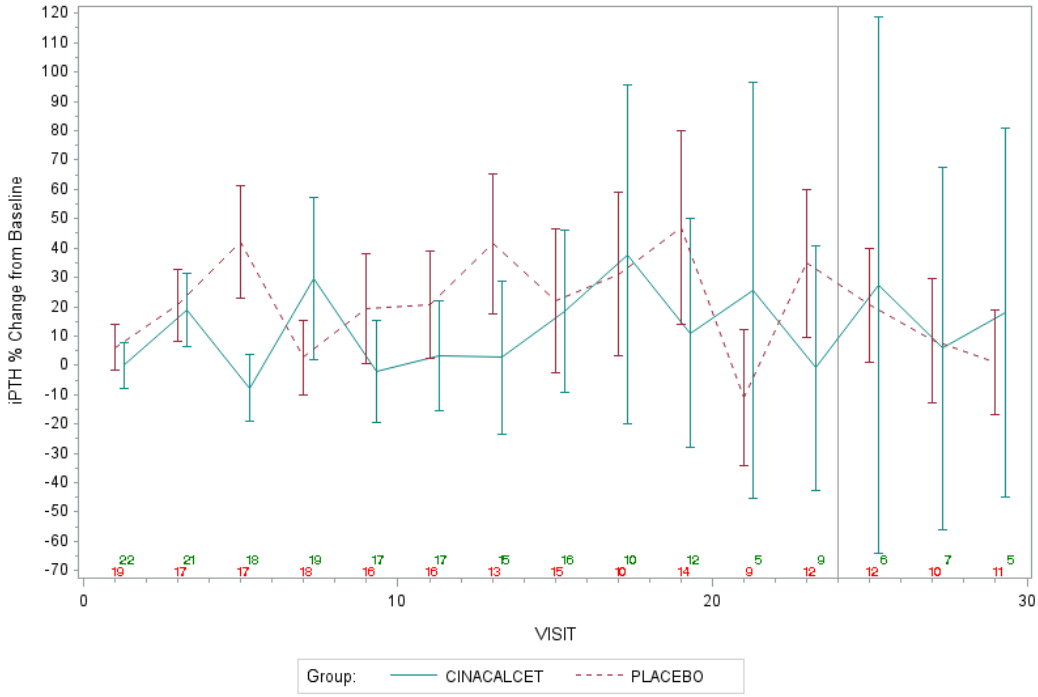
As described in section 3.2.3.4, there were substantial amount of missing data in the controlled studies 20070208. The applicant used LOCF approach to handle the missing data. A tipping point analysis was conducted to study the potential impact of the missing data on the reliability of the efficacy results based on LOCF.

Table 11 Tipping Point Analysis (Study 20070208)

Shift for Cinacalcet		Shift for Placebo					
		-10%	**0%**	**20%**	**30%**	**40%**	**50%**
-50%	Odds Ratio	6.3	7.6	12.6	14.2	17.2	18.1
	95% CI	(1.0 ,39.3)	(1.1 ,51.2)	(1.4 ,112.4)	(1.7 ,115.2)	(1.8 ,159.5)	(2.3 ,145.2)
	P-value	0.048	0.037	0.024	0.013	0.013	0.006
-40%	Odds Ratio	4.9	6.6	9.6	11.9	13.8	15.9
	95% CI	(0.7 ,32.2)	(1.0 ,44.4)	(1.2 ,76.4)	(1.6 ,86.9)	(1.7 ,108.2)	(1.7 ,145.1)
	P-value	0.1	0.052	0.032	0.014	0.013	0.015
-30%	Odds Ratio	4.2	5.6	9.2	9.9	12.3	12.6
	95% CI	(0.7 ,25.9)	(0.9 ,36.4)	(1.1 ,75.8)	(1.3 ,74.4)	(1.3 ,114.2)	(1.4 ,116.6)
	P-value	0.12	0.071	0.039	0.027	0.028	0.026
-20%	Odds Ratio	3.4	4.1	6.7	8.3	9.5	10.4
	95% CI	(0.6 ,19.0)	(0.6 ,26.3)	(0.9 ,49.0)	(1.1 ,60.9)	(1.1 ,81.4)	(1.2 ,86.5)
	P-value	0.16	0.14	0.061	0.038	0.04	0.031
-10%	Odds Ratio	3	3.7	5.7	7	8.3	8.7
	95% CI	(0.6 ,15.5)	(0.6 ,21.8)	(0.8 ,39.0)	(1.0 ,51.0)	(1.0 ,67.8)	(1.2 ,62.0)
	P-value	0.19	0.15	0.077	0.054	0.049	0.031
0	Odds Ratio	2.6	2.9	4.9	5.2	6.6	6.9
	95% CI	(0.5 ,13.8)	(0.5 ,17.9)	(0.7 ,33.1)	(0.6 ,45.0)	(0.9 ,49.2)	(0.9 ,51.3)
	P-value	0.27	0.25	0.11	0.13	0.065	0.059

In order to have the p-value smaller than 0.05, a post withdrawal treatment difference of at least 40% reduction (e.g. -50% in cinacalcet group vs -10% in placebo group) in iPTH has to be assumed between cinacalcet and place groups. Given the treatment effect profile from the observed data (see Figure 3), an assumption of such large treatment difference between the outcomes in dropouts on both arms is likely implausible and unreasonable.

Figure 3 iPTH % Change from Baseline for Study 20070208 (All Observed Data)



As presented in Figure 4, it appears that among subjects who did not complete EAP, patients in cinacalcet arm consistently achieved more iPTH% reduction from baseline over time compared to those in the placebo arm before their discontinuation at early stage. Such trend was not observed among subjects who stayed through the EAP (Figure 5). The applicant's conclusion for superiority of cinacalcet based on LOCF may be driven by the data from non-completers. In addition, large variability among subjects made it even more difficult to determine the effectiveness of cinacalcet in pediatric population. Therefore, the reliability of the efficacy findings based on LOCF is questionable.

Figure 4 iPTH % Change from Baseline for Study 20070208 (Subjects Discontinued Early)

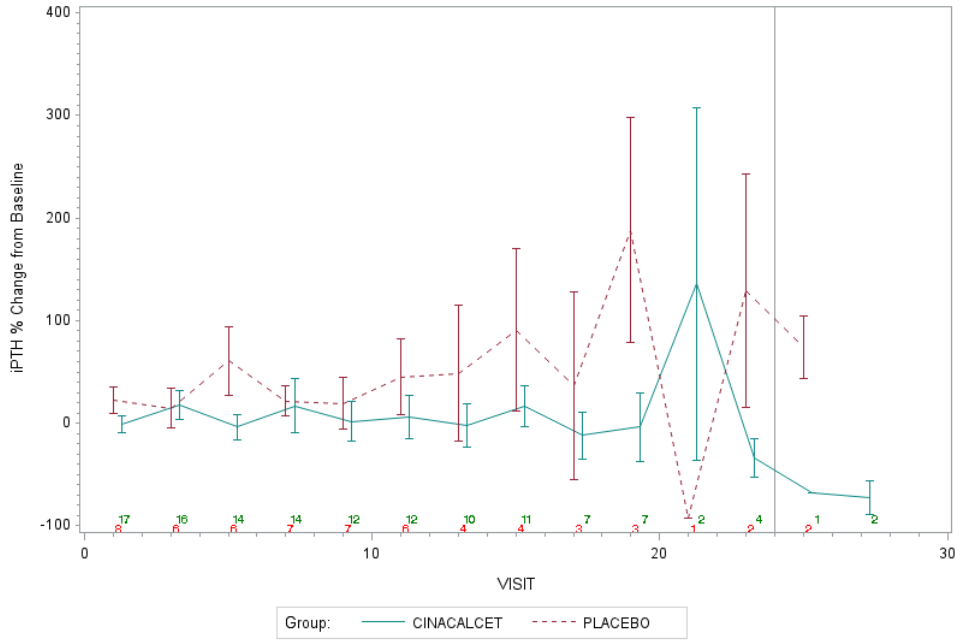
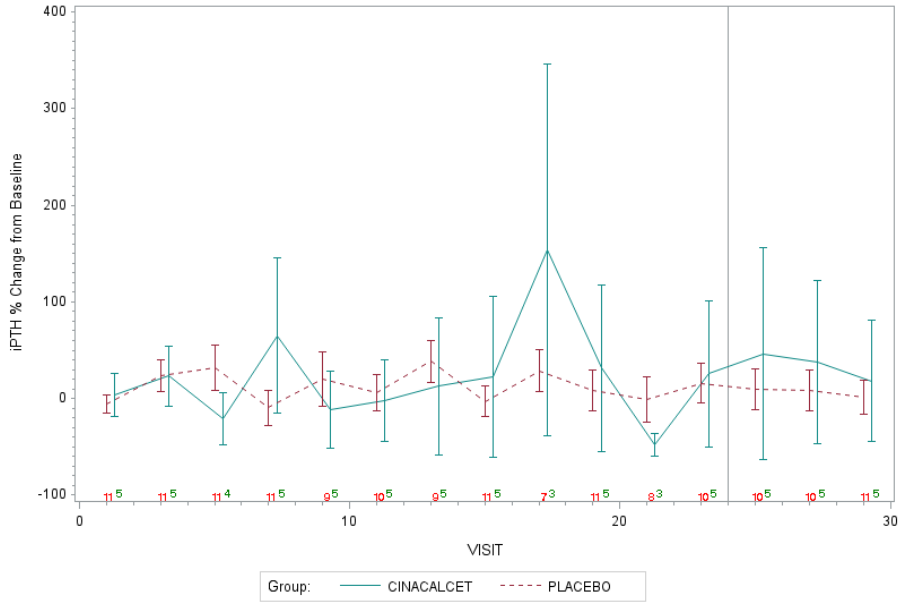


Figure 5 iPTH % Change from Baseline for Study 20070208 (Subjects Completed EAP)



4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, Region

This section included the analysis results of the primary endpoint performed within subgroup levels for the study. Due to the limitations associated with multiplicity and low power, we acknowledge that the subgroup analysis results were considered as supportive and exploratory. Subgroup analyses on the primary efficacy endpoint were performed using a logistic regression in the ITT population with treatment. The analysis was performed within the individual level that defined the subgroup. Multiple imputation was used for handling missing data.

The limited number of subjects in subgroup levels and substantial amount of missing data lead to large variability in the estimated treatment effects in these subgroups. Figure 6 and Figure 7 presented the subgroup analysis results for study 20070208 and 20130356 respectively. Due to large variability, the logarithm of odds ratio were used for graphical presentation. The subgroup findings were consistent with the reviewer's analysis results of overall population.

Table 12 List of Factors and Levels for Subgroup Analyses

Factor	Levels
Sex	Females; Males
Age	6-<12 years; 12- <18 years
Race	White; Other
Region	US; non-US

Figure 6 Subgroup Analysis Results for Study 20070208 (log (odds ratio))

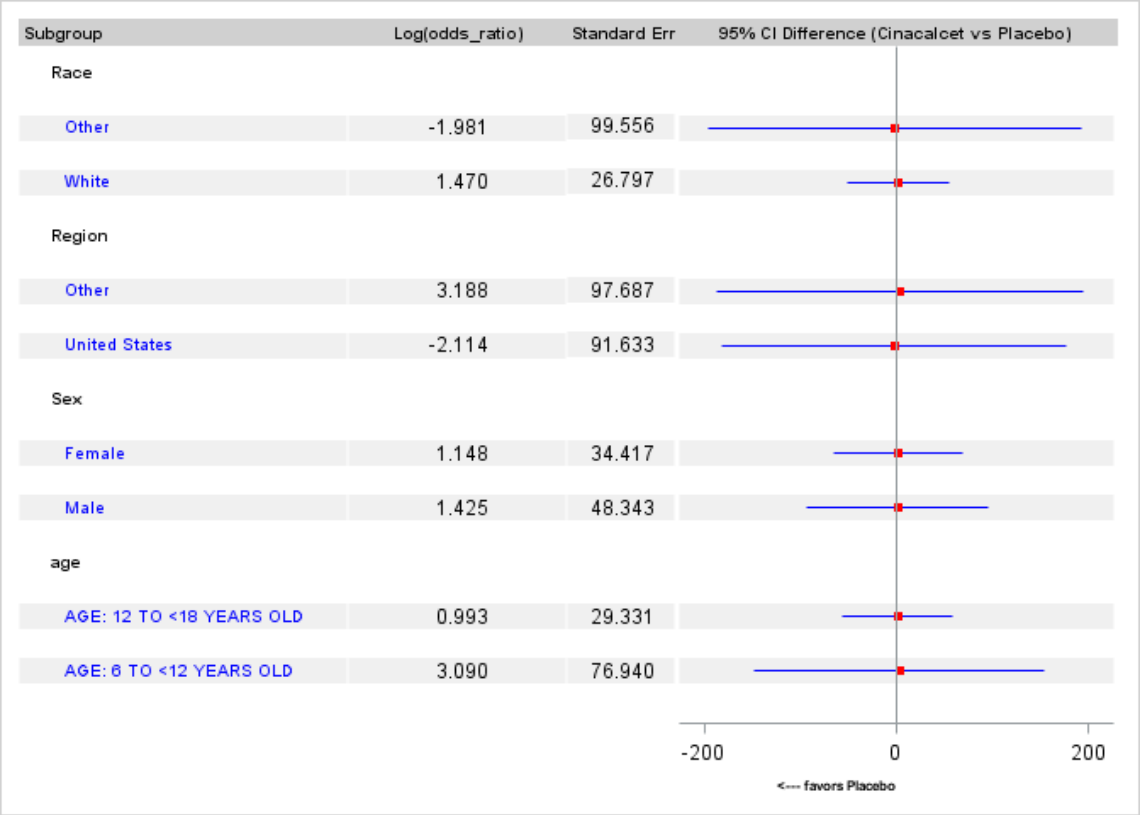
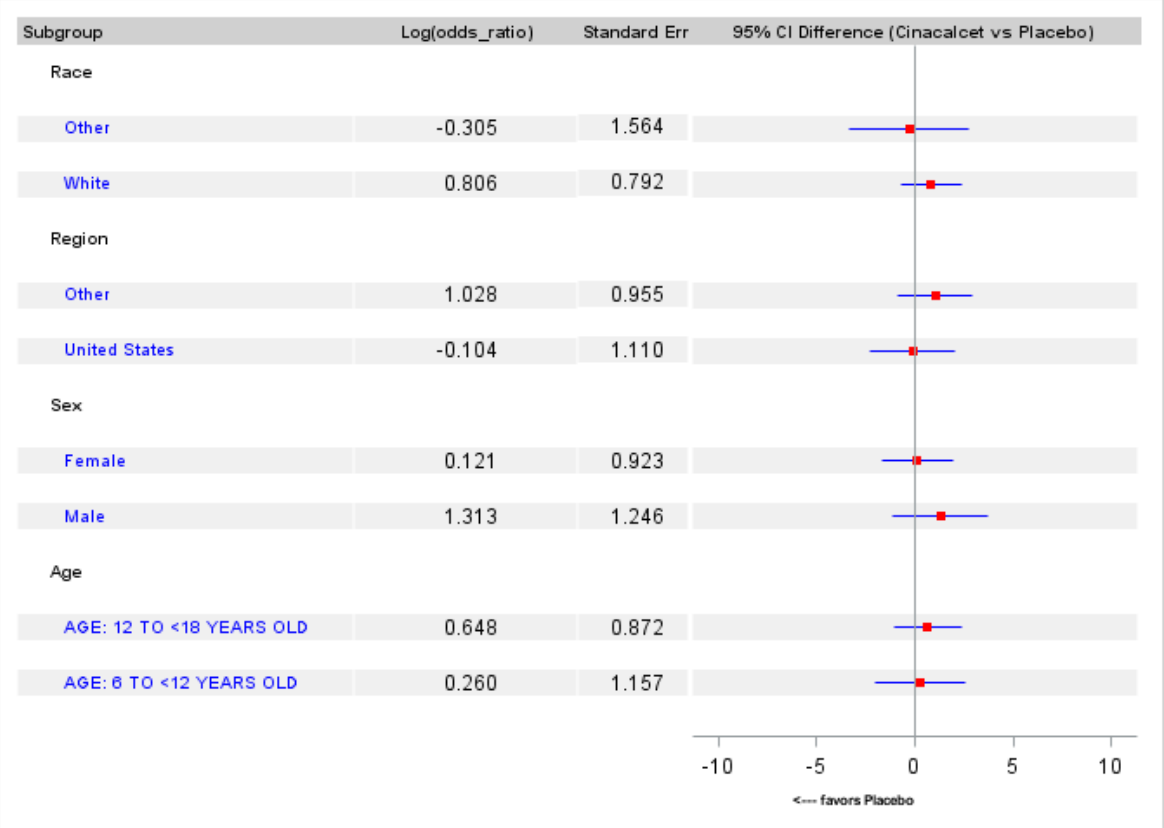


Figure 7 Subgroup Analysis Results for Study 20130356 (log (odds ratio))



5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The potential effect of missing data on the reliability of efficacy results

There were excessive amount of missing data at the end of efficacy assessment period in study 20070208 and 20130356, with dropout rates of 62.8% and 34.5%. Data were not collected after subjects initiated rescue treatment or discontinued the treatment for both studies. There were only a small number of subjects completed the efficacy assessment period. Large variability of iPTH reduction was also observed in both studies.

In study 20070208, the applicant assumed that subjects who discontinued kept the same efficacy assessment as what were last measured on treatment. The missing values at EAP were fulfilled with the mean of the last two observed measurements. However, this last available observation estimand would not be the most appropriate estimand reflecting the real-world clinical settings because subjects could show early improvement in iPTH reduction but suffer deterioration after a period of improvement. The statistical reviewer noticed the iPTH level of subjects who stayed to the end of EAP fluctuated dramatically during the 30 weeks of treatment. Notwithstanding, study 20070208 was terminated early due to partial clinical hold and resulted in large amounts of missing data, the missing data should be addressed in a fashion that corresponds to the original intended conduct of the study design, but not the actual conduct of the trial. The statistical

reviewer performed an analysis using multiple imputation approach described in section 3.2.3.6. The findings showed that there is no evidence to support the superiority of cinacalcet over placebo with add-on standard of care. To explore the potential impact of missing data, a tipping point analysis was conducted. The tipping point analysis suggested that dropouts on cinacalcet have to experience far better outcomes than dropouts on placebo at EAP to support superiority claim. Such an assumption is unreasonable based on collected clinical data in pediatric population. Therefore, the results of the applicant's analysis were not reliable.

The applicant utilized non-responder approach to address missing data in study 20130356. There was no evidence to show the superiority of cinacalcet plus standard care over standard of care along at week 11-15. The statistical reviewer also considered a multiple imputation for handling missing data. The findings were consistent with applicant's results and showed that there was no statistically significant difference between treatment groups in primary endpoint. This could result from the fact that patients were not titrated to effective dose with short duration of treatment.

Evidence to support children under 6

The applicant is also (b) (4) An open label, single-arm study was included to assess the safety and tolerability of cinacalcet in children age 28 days to <6 years. The effectiveness of cinacalcet in children age 28 days to <6 years was agreed to extrapolated from pediatric group age 6 to <18 years upon the written request. As demonstrated in 3.2.5, no sufficient statistical evidence supports the effectiveness of cinacalcet in study 20070208 and 20130356. Therefore, the applicant intended to borrow the efficacy data from adult to younger pediatric group (day 28 to <6 years). Based on data collected from study 20070208 and 20130356, the effectiveness of cinacalcet in pediatric population is different from adult population. It is questionable whether the results from adult studies are exchangeable into the results from pediatric studies.

5.2 Conclusions and Recommendations

The clinical data from the two phase III studies examined in pediatric population do not provide convincing and substantial statistical evidence to demonstrate the clinical benefit for the overall pediatric population. Therefore, efficacy results from two pivotal studies 20070208 and 20130356 (b) (4)

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

/s/

SHUXIAN Z SINKS
04/28/2017

YUN WANG
04/28/2017