Office of Clinical Pharmacology Review

NDA	21-606 (b) (4)
Link to EDR	\\cdsesub1\evsprod\nda021606\ (b) (4)
Submission Dates	June 18, 2015; December 18, 2015; February 3, 2016; March 17, 2016: May 20, 2016
Submission Type	*Efficacy Supplement (Standard review)*
Brand Name	ZEMPLAR®
Generic Name	Paricalcitol
Dosage Form and Strength	Soft gelatin capsule; 1 and 2 µg
Route of Administration	Oral
Proposed Indication	To prevent and treat secondary hyperparathyroidism in patients with chronic kidney disease Stages 3, 4 and 5 (Note: approved in adults; In this application, the applicant is seeking approval in pediatric patients 10 years and older.)
Applicant	*Abbott Laboratories*
Associated IND	INDs associated with EOP2, Pre-NDA, and/or Pediatric Study Plan
OCP Review Team	*S.W. Johnny Lau, RPh, PhD, Lian Ma, PhD,* *Nitin Mehrotra, PhD, Jayabharathi Vaidyanathan, PhD*

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1. EXECUTIVE SUMMARY

Paricalcitol is a synthetic, vitamin D receptor (VDR) activator (VDRA) in the pharmacological class of hormone. Paricalcitol reduces parathyroid hormone (PTH) concentrations by inhibiting parathyroid proliferation and decreasing PTH synthesis and secretion, and can act directly on bone cells to maintain bone volume and improve mineralization surfaces.[1]

Zemplar® (paricalcitol) capsules were first approved on May 26, 2005 in the US for the prevention and treatment of secondary hyperparathyroidism in chronic kidney disease (CKD) Stages 3 and 4. On June 29, 2009, Zemplar capsules were approved in CKD Stage 5 for patients receiving hemodialysis or peritoneal dialysis in the US.

Two pediatric PMRs 1814-1 and 2094-1 were issued at the time of approval requiring the applicant to study paricalcitol capsules in patients 10 – 16 years of age with chronic kidney disease (CKD) Stages 3 and 4, and patients who receiving peritoneal dialysis (CKD Stage 5). The applicant conducted and submitted studies M10-149 (in CKD Stages 3 and 4) and M11-612 (in CKD Stage 5) in the current application seeking to fulfill the PMRs. The applicant also submitted an observational study (P12-053) to assess the safety of paricalcitol use in pediatric patients treated for secondary hyperparathyroidism.

Details on the Clinical pharmacology of paricalcitol capsules in adults are available in the Clinical Pharmacology reviews by Dr. Wei Qiu for the original NDA 21-606 for CKD Stages 3 and 4 dated May 24, 2005, as well as by Dr. S.W. Johnny Lau and others for the paricalcitol capsules for CKD Stage 5 dated June 8, 2009 in DARRTS.

The approved paricalcitol regimen for adults and proposed regimen for pediatric patients 10 years and older are shown in **Table 1**.

Table 1. Approved Dosing Regimen in Adults and Proposed Dosing Regimen in Pediatric Patients

Initial Dosage: CKD Stages 3 and 4	
Adult: Baseline iPTH ≤ 500 pg/mL	1 mcg daily or 2 mcg three times a week*
Adult: Baseline iPTH > 500 pg/mL	2 mcg daily or 4 mcg three times a week*
Pediatric: Ages 10 to 16 years	1 mcg three times a week*
Dose Titration: CKD Stages 3 and 4	
Adult: iPTH The same, increased or decreased by < 30%	Increase dose by 1 mcg daily or 2 mcg three times a week*
Adult: iPTH decreased by ≥ 30% and ≤ 60% relative to baseline	Maintain dose
Adult: iPTH decreased by > 60% or iPTH < 60 pg/mL relative to baseline	Decrease dose by 1 mcg daily or 2 mcg three times a week*
Pediatric: Ages 10 to 16 years	individualized and based on iPTH, serum calcium and phosphorus levels to maintain levels (b) (4)

* Not more frequently than every other day when dosing three times a week.

Initial Dosage: CKD Stage 5	
Adult	Dose in micrograms is based on baseline iPTH (pg/mL)/80. Dose three times a week.*

[1] Robinson DM, Scott LJ. Paricalcitol: a review of its use in the management of secondary hyperparathyroidism. *Drugs* 2005;65(4):559-76.

Pediatric: Ages 10 to 16 years	Dose in micrograms is based on baseline iPTH (pg/mL)/120. Dose three times a week.*
Dose Titration: CKD Stage 5	
Adult	Dose in micrograms is based on most recent iPTH (pg/mL)/80 with adjustments based on serum calcium and phosphorous levels. Dose three times a week.*
Pediatric: Ages 10 to 16 years	Dose in micrograms is based on iPTH, calcium, and phosphorus levels to maintain iPTH [redacted] (b) (4). Dose three times a week.*

* Not more frequently than every other day
Source: Applicant's proposed label for paricalcitol

The pharmacokinetics (PK), efficacy and safety of paricalcitol were evaluated in these 2 studies in patients 10 to 16 year of age who received paricalcitol capsules for CKD Stages 3 and 4 (Study M10-149, N= 43), and CKD Stage 5 receiving peritoneal dialysis or hemodialysis (Study M11-612, N=13). Study M10-149 was a placebo controlled trial while Study M11-612 was a single arm trial.

Population PK analysis were conducted using combined data from both studies. The exposure-response analyses supported that the studied dose regimen of paricalcitol in reductions of iPTH from baseline, with low incidence of hypercalcemia in CKD Stage 5 pediatric patients.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the submissions dated June 18, 2015 and December 18, 2015 for the Pediatric Post-marketing Requirement (PMR) numbers 1814-1 and 2094-1 of NDA 21606. The pediatric studies M10-149 and M11-612 are acceptable and satisfy the Pediatric PMRs 1814-1 and 2094-1, respectively. Specific recommendations are summarized in the table below:

Review Issues	Recommendations and Comments
Evidence of effectiveness in CKD Stages 3 and 4 pediatric patients	A placebo-controlled study M10-149 in 36 pediatric patients with CKD Stages 3 and 4 provides primary evidence of effectiveness.
Evidence of effectiveness in CKD Stage 5 pediatric patients	Comparable PK to adults and significant exposure-response of efficacy in this pediatric patient population provides supportive evidence of effectiveness. A single-arm study M11-612 in 13 pediatric patients with CKD stages 5 with a clinically meaningful response rate of 61.5% also provides evidence of efficacy.
Indication and general dosing instructions	OCP recommends approval of paricalcitol for both proposed indications (CKD Stages 3 and 4 and CKD Stage 5) in pediatric patients. The proposed dosing regimens in pediatric patients 10 years and older with CKD Stages 3, 4 and 5 are acceptable (**Table 1**).
Bridge between the "to-be-marketed" and clinical trial formulations	The formulations used in the PMR studies are same as the proposed commercial formulation.

See recommendations for labeling in the Label Recommendation section (Appendix 3.3) of this review.

2. CLINICAL PHARMACOLOGY QUESTIONS

2.1 What are the design features of the clinical studies used to support the pediatric support dosing or claims?

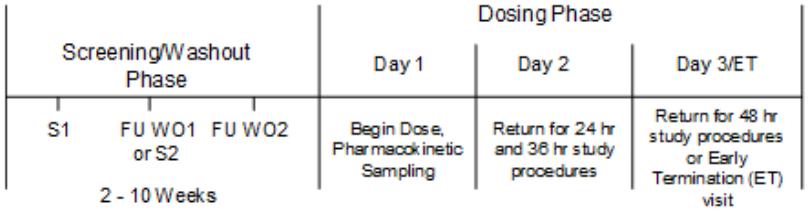
Study M10-149 (CKD Stages 3 or 4)

Study M10-149 has 2 parts with the following objectives:

- Part 1 is to determine the safety, tolerability, and pharmacokinetics (PK) of a single dose of 3 µg paricalcitol capsules in patients age 10 – 16 years with moderate to severe CKD (Stage 3 or 4).
- Part 2 is to determine the safety and efficacy of paricalcitol capsules versus placebo in decreasing serum iPTH in patients age 10 – 16 years with moderate to severe CKD (Stage 3 or 4).

Study M10-149 consists of the PK Part 1 and safety and efficacy Part 2. **Figure 1** and **2** show the schematic of Study M10-149's design.

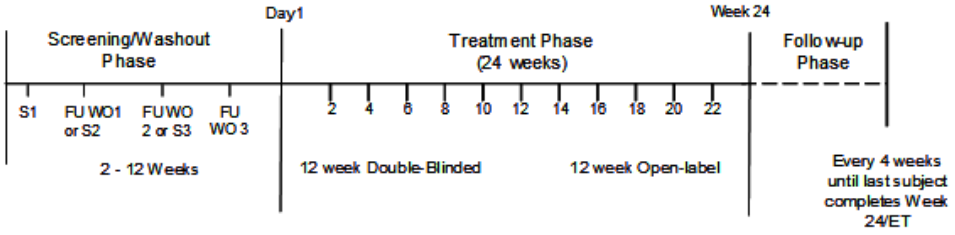
Figure 1. Study M10-149 Schematic – Single-Dose, Open-Label PK (Part 1)



S1, S2 (Screening Visits 1, 2) FUWO1, FUWO2 (Follow-Up Washout Visits 1, 2)
Source: Figure 1 of Section 2.7.2 of NDA 20-616 (b) (4)

Part 1 was as an open-label, single-dose, non-fasting, multicenter study in a total of 12 patients ages 10 – 16 years. Six patients with CKD Stage 3, (Group 1, estimated glomerular filtration rate [eGFR] 30 – 59 mL/min/1.73 m^2) and 6 patients with CKD Stage 4 (Group 2, eGFR 15 – 29 mL/min/1.73 m^2) enrolled in Part 1 of the study. Each patient received a single dose of 3 x 1 µg paricalcitol capsules 30 minutes after breakfast on Study Day 1. The applicant collected serial plasma samples predose and 48 hours postdose to measure plasma paricalcitol concentrations via a validated bioanalytical assay. The applicant then estimated the PK parameters of paricalcitol via noncompartmental method for the observed data.

Figure 2. Study M10-149 Schematic – Safety and Efficacy (Part 2)



S1, S2, S3 (Screening Visits 1, 2, 3)
FUWO1, FUWO2, FUWO3 (Follow-Up Washout Visits 1, 2, 3)
Treatment Group 1 Placebo TIW (3 times weekly)
Treatment Group 2 Paricalcitol 1 mcg capsules TIW (initial dose)
Source: Figure 2 of Section 2.7.2 of NDA 20-616 (b) (4)

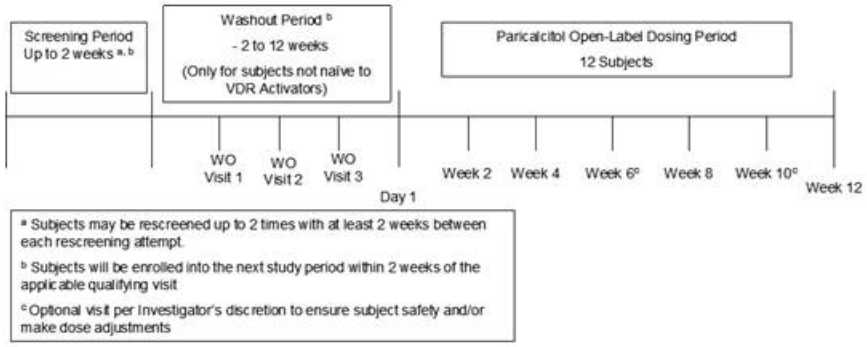
Part 2 studied 36 pediatric patients and was divided into 2 treatment periods: an initial 12 weeks of double-blind treatment period followed by a 12-week open-label treatment period. Twenty-one patients with CKD Stage 3 and 15 patients with CKD Stage 4 enrolled in Part 2 of the study. Patients received paricalcitol capsules 3 times weekly (TIW) for a minimum of 24 weeks. The applicant collected plasma samples at the visit of Weeks 4, 8, 12, 16, 20, and 24 to measure plasma paricalcitol concentrations via a validated bioanalytical assay. The patients took each dose at their regularly scheduled time, irrespective of the timing of the clinic visit. The applicant combined the data of Studies M10-149 and M11-612 to perform a population PK analysis.

Study M11-162 (CKD Stage 5)

The objective of Study M11-162 was to evaluate the safety of paricalcitol capsules for the treatment of secondary hyperparathyroidism in patients age 10 – 16 years with CKD Stage 5, receiving peritoneal dialysis or hemodialysis through the evaluation of the incidence of hypercalcemia.

Study M11-612 was a Phase 3, open-label, single-arm, multicenter study. **Figure 3** shows the schematic Study M11-612's design.

Figure 3. Schematic of Study M11-612



Source: Figure 3 of Section 2.7.2 of NDA 20-616 (b) (4)

All patients received paricalcitol capsules (1 or 2 µg strength). Patients received paricalcitol TIW for a total of 12 weeks. The paricalcitol dose was adjustable in order to maintain an intact parathyroid hormone (iPTH) concentration between 150 pg/mL (15.8 pmol/L) and 300 pg/mL (31.6 pmol/L), without exceeding 16 µg TIW. The applicant collected plasma samples at the visit of Weeks 2, 4, 6, 8, 10, and 12 to measure plasma paricalcitol concentrations via a validated bioanalytical assay. The patients took each dose at their regularly scheduled time, irrespective of the timing of the clinic visit.

The applicant adapted the adult CKD Stage 5 model to build the CKD Stage 5 clinical response models describing the relationships between paricalcitol dose, exposure, and clinical response in CKD Stage 5 pediatric patients. The applicant evaluated the exposure-response relationship of paricalcitol exposure and clinical response variables (including iPTH, serum calcium, and serum phosphorus) through the data from Study M11-612 in CKD Stage 5 pediatric patients ages 10 to 16 years.

2.2 What are the pharmacokinetic characteristics of Paricalcitol in pediatric patients?

For pediatric patients with CKD Stages 3 and 4, the applicant estimated the PK parameters of paricalcitol via noncompartmental analysis (NCA) through the observed data from Part 1 of study M10-149. One

patient (1498202) had an eGFR value of < 15 mL/min/1.73 m^2 at screening even though the 2 prior eGFR values were acceptable at 18 and 16 mL/min/1.73m^2. Thus, this patient is removed from the NCA for CKD Stage 4 group. **Table 2** summarizes the PK parameters of paricalcitol for patients with CKD Stages 3 and 4. These parameters do not show significant differences between the 2 groups. Individual concentration-time profiles of paricalcitol following single dose of 3 µg paricalcitol capsules Part 1 are shown in **Figure 4**.

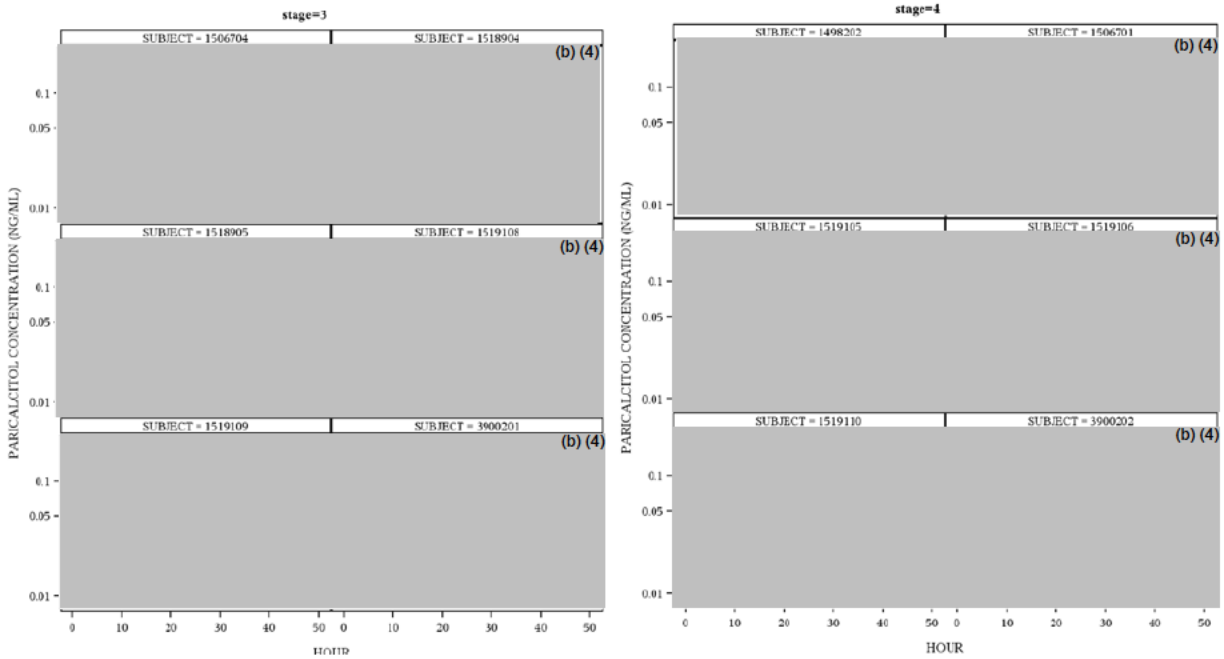
For pediatric patients with CKD stages 5, NCA was not performed due to sparse sampling in study M11-612. The applicant conducted population PK analysis based on combined data from M10-149 and M11-612. Details for the population PK analysis are provided in **Appendix 3.2**.

Table 2. PK parameters of paricalcitol for pediatric patients (10-16 years old) with CKD Stages 3 and 4 (NCA)

Pharmacokinetic Parameters	CKD Stage 3 n = 6 3 µg dose	CKD Stage 4 n = 5 3 µg dose	Combined CKD Stages 3 and 4 n = 11 3 µg dose
C_{max} (ng/mL)	0.12 ± 0.06	0.13 ± 0.05	0.14 ± 0.05
AUC_{∞} (ng·h/mL)	2.63 ± 0.76	3.2 ± 0.99	3.12 ± 0.91
CL/F (L/h)	1.23 ± 0.38	1.02 ± 0.35	1.04 ± 0.31
V/F (L)	27.78 ± 18.60	24.36 ± 5.92	23.36 ± 5.84
$T_{1/2}$ (h)	14.95 ± 6.07	17.54 ± 5.93	16.54 ± 5.85

Source: Reviewer's table.

Figure 4. Individual concentration-time profiles of Paricalcitol following single dose of 3 µg paricalcitol capsules in study 10-149 Part 1 to patients with CKD (left: stage 3; right: stage 4)



Source: Applicant's Study Report of Study 10149, Figure 14.4_1.1

2.3 Are exposures observed in adults comparable to those in pediatric patients with the proposed regimens?

Yes, the observed PK parameters appear to be comparable in adult and pediatric patients at the studied/proposed dose levels.

A summary of paricalcitol PK parameters in adults' studies is provided in **Table 3**. Comparing to **Table 2**, the PK parameters are reasonably comparable in pediatric patients and adults with CKD stages 3 and 4.

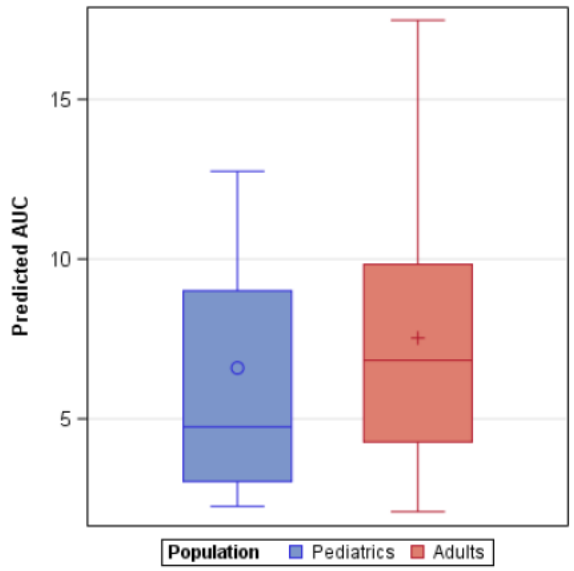
Table 3. PK parameters of paricalcitol for adult patients with CKD Stages 3, 4 and 5 (NCA)

Pharmacokinetic Parameters	CKD Stage 3 n = 15* 4 µg dose	CKD Stage 4 n = 14* 3 µg dose	CKD Stage 5 HD n = 14 0.24 µg/kg dose	CKD Stage 5 PD n = 8 0.24 µg/kg dose
C_{max} (ng/mL)	0.11 ± 0.04	0.06 ± 0.01	0.575 ± 0.17	0.413 ± 0.06
$AUC_{0-\infty}$ (ng•h/mL)	2.42 ± 0.61	2.13 ± 0.73	11.67 ± 3.23	13.41 ± 5.48
CL/F (L/h)	1.77 ± 0.50	1.52 ± 0.36	1.82 ± 0.75	1.76 ± 0.77
V/F (L)	43.7 ± 14.4	46.4 ± 12.4	38 ± 16.4	48.7 ± 15.6
$t_{1/2}$ (h)	16.8 ± 2.65	19.7 ± 7.2	13.9 ± 5.1	17.7 ± 9.6

Source: Applicant's proposed label for paricalcitol

The proposed starting dose (baseline iPTH/120) for CKD stage 5 pediatrics is also expected to produce similar AUC to the approved starting dose in adult patients with CKD stage 5 (**Figure 5**).

Figure 5. Predicted AUC (ng•h/mL) following the proposed starting dose (baseline iPTH/120) in pediatric patients with CKD stage 5, compared to those following the approved starting dose (baseline iPTH/80) in adult patients with CKD stage 5.



Source: Reviewer's analysis

2.4 Is the proposed dosing regimen appropriate for pediatric patients with chronic kidney disease (CKD) Stages 3 and 4?

Yes. The proposed dosing regimen in pediatrics is supported by similar PK to adults, and overall efficacy and safety findings in studies M10-149.

Applicant's Dose Selection Rationale

In Part 1 of study M10-149 (CKD 3 and 4), a single 3 µg dose was chosen for direct comparison to adults (data available for single dose 3 µg in adult patients) and to inform the initial dosing for pediatric subjects in Part 2.

In Part 2 (double-blinded), the protocol-specified criteria for selecting the starting dose were based on PK findings in Part 1 were:

- If the average AUC was similar to adults (1.1 to 2.4 µg*hr/mL), the initial dose of 2 µg TIW was to be used in pediatric subjects.
- If AUC was < 1.1 µg*hr/mL, the initial dose was to be increased to 3 µg TIW to maximize the likelihood of meeting KDOQI criteria for iPTH while limiting hypercalcemia.
- If AUC was significantly higher than that observed in adult (> 2.4 µg*hr/mL) the initial dose for Part 2 was to be decreased from 2 to 1 µg TIW to minimize hypercalcemia.

Results of the PK analysis in Part 1 demonstrated an AUC > 2.4 µg•hr/mL and thus, the paricalcitol capsules dose selected for Part 2 of the study was 1 µg TIW (3 µg per week).

Efficacy and Safety

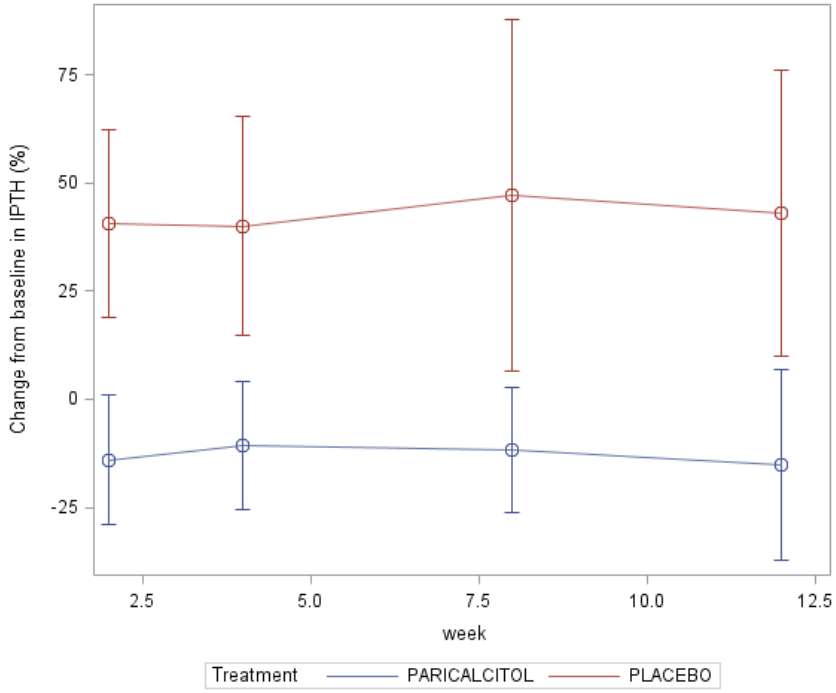
In study M10-149 (CKD Stage 3 and 4 patients), a statistically significant (p-value=0.045) greater proportion of patients in the paricalcitol treatment group (27.8%, 5/18) achieved 2 consecutive decreases ≥ 30% in iPTH levels compared with subjects in the placebo treatment group (0%, 0/18) during the double-blind period (**Figure 6**).

Even though the p-value was marginally significant, the fact that none of the patients in the placebo group responded as opposed to a responder rate of 27.8% in the treatment arm provides evidence that the paricalcitol is effective in the CKD stage 3/ 4 pediatric patient population. Furthermore, visual inspection of individual level time courses of iPTH (not shown) also supported that paricaltitol lowered iPTH levels in CKD stage 3/4 patients.

In terms of safety, deaths, serious adverse events, and premature discontinuation due to adverse events in the double-blind, placebo-controlled part of study M10-149 was similar between the paricalcitol capsules and placebo treated groups. Moreover, the incidence of AEs of blood calcium increased and hypercalcemia, which are potential concerns with the use of paricalcitol, were similar in the two groups during the double-blind period of study M10-149. No subjects had incidence of clinically meaningful hypercalcemia as defined by at least 2 consecutive corrected calcium values > 10.2 mg/dL (the primary safety variable), during the double-blind period of Study M10-149.

Overall, the initial dosing, monitoring, and dose titration strategy in the CKD stage 3&4 study allowed for management of potential safety issues while reduction in iPTH was achieved.

Figure 6. Percent change from baseline in Serum iPTH (pg/mL) during double-blinded phase in Study M10-149



Source: Reviewer's plot

2.4 Is the proposed dosing regimen appropriate for pediatric patients with chronic kidney disease (CKD) Stage 5?

- ***Does clinical pharmacology data provide supportive evidence of effectiveness of paricalcitol in the treatment of pediatric patients with CKD stage 5?***

Yes. The proposed dosing regimen in pediatric patients is supported by similar PK to adults, and exposure-response analyses in efficacy and safety in Study M11-1612. Furthermore, in absence of a control arm, the significant exposure-response for efficacy in pediatric patients with CKD stage 5 provides supportive evidence of effectiveness in this patient population.

Applicant's Dose Selection Rationale

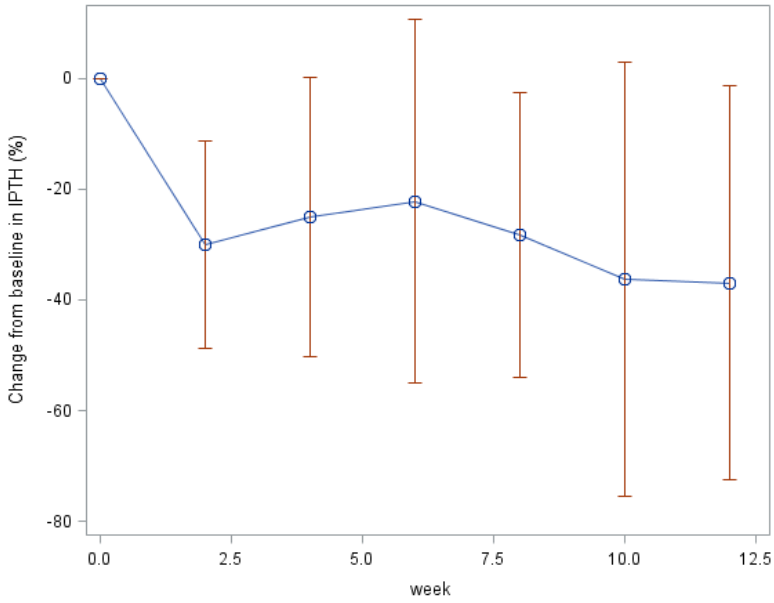
The dose selection for study M11-612 (CKD5) was based on clinical trial simulations, a starting dose based on iPTH/120 is predicted to demonstrate hypercalcemia (Ca >10.2 mg/dL) in only a small proportion of subjects (5%) while demonstrating reasonable rates of efficacy compared to the iPTH/80 dosing regimen.

Efficacy and Safety

In Study M11-612 (CKD Stage 5 receiving dialysis), 8/13 patients (61.5%) had 2 consecutive iPTH reductions of at least 30% from baseline (**Figure 7**). As indicated earlier, although this was a single arm

study, the response rate of 61.5% was considered clinically relevant. As a comparison, the response rate for adults with CKD stage 5 was 88%.

Figure 7. Mean Serum iPTH (pg/mL) in Study M11-612



Source: Reviewer's plot

In terms of safety, there were no clinically significant changes in vital signs, ECG, or laboratory measurements during the study. There were few adverse events but none of the AEs were assessed to be severe or led to discontinuation of study drug. There were 2 subjects with at least 2 consecutive calcium values > 10.2 mg/dL during the study.

Overall, 12-weeks of treatment with paricalcitol in pediatric subjects 12 to 16 years of age with CKD Stage 5 was observed to reduce iPTH without a significant number of hypercalcemia events or new clinically concerning safety observations.

Exposure-Response Analyses

In addition, significant exposure-response for efficacy observed in the CKD stage 5 pediatric patients provides supportive evidence of effectiveness of paricalcitol in this pediatric patient population. The exposure-response relationship of paricalcitol exposure and clinical response variables (including iPTH, serum calcium, and serum phosphorus) was evaluated using clinical data obtained from study M11-612, based on the structure model developed for adult subjects with CKD Stage 5. The results from those analysis indicated that the pediatric patients have similar sensitivity to paricalcitol effects compared to adult patients. The results supported that the studied dosing regimen of paricalcitol caused reduction of iPTH from baseline, with low incidence of hypercalcemia in CKD Stage 5 pediatric patients. Details on applicant's exposure-response analyses are provided in **Appendix 3.2**.

Overall, the initial dosing, monitoring, and dose titration strategy in the CKD stage 5 study allowed for management of potential safety issues while reduction in iPTH was achieved.

2.5 Are the clinically-tested paricalcitol capsules in Studies M10-149 and M11-612 identical to the marketed paricalcitol capsules?

Yes. Study M10-149 used the 1 µg paricalcitol capsules. Study M11-612 used the 1 and 2 µg paricalcitol capsules. All of these capsules are the US-approved and marketed formulations. Also, the applicant discontinued marketing the approved 4 µg paricalcitol capsule for business reasons and not for safety concerns.

3. APPENDICES

3.1 Bioanalytical Method Report

The applicant used a liquid chromatography method with tandem mass spectrometric detection (LC MS/MS) to quantitate paricalcitol in plasma samples for Studies M10-149 and M11-612. **Table 4** details the validation of the paricalcitol LC MS/MS assay.

Table 4. Validation of the bioanalytical assay to measure paricalcitol in plasma samples of Studies M10-149 and M11-612

	2004 Validation	2010 Validation
Analyte	Paricalcitol	Paricalcitol
Matrix	Plasma	Plasma
Anticoagulant	K_2EDTA	K_2EDTA
Sample volume, µL	600	300
Lower limit of quantitation, ng/mL	0.01022	0.0103
Validated assay range, ng/mL	0.01022 – 2.03734	0.0104 – 2.00
Average recovery (%)	122.9	Not assessed
Assay precision (%CV of QC samples)		
Inter-run	4.6 – 6.6	1.4 – 11.9
Intra-run	-6.2 – 4.1	2.3 – 14.0
Assay accuracy (% bias of QC samples)		
Inter-run	-4.3 – 1.0	-3.1 – 13.3*
Intra-run	1.6 – 10.3	-4.9 – 13.5
Storage stability (-20°C for 468 days), % from the nominal concentration	-8.3 – -2.8	Not assessed
Freeze-thaw stability (4 cycles and at least 27 hours 40 minutes at room temperature), % difference from controls	-2.7 – 2.1	Not assessed

*Only has inter-run assay precision and accuracy for the 0.025 ng/mL QC sample for the 2010 validation. All other 2010 validations have QC samples with nominal concentrations of 0.0256, 0.16, and 1.60 ng/mL for both intra-run and inter-run precision and accuracy. For the 2004 validation, the nominal QC concentrations were 0.02937, 0.05873, 0.31324, and 1.56619 ng/mL for both intra-run and inter-run precision and accuracy.

Source: This reviewer's compilation of the applicant's Bioanalytical and Validation Reports for Studies M10-149 and M11-612.

The sponsor used both 2004 and 2010 versions of the bioanalytical methods to measure plasma paricalcitol concentrations for Studies M10-149 and M11-612. The 2010 bioanalytical method is the updated version of the 2004 bioanalytical method for:

- decreased assay sample volume (600 to 300 µL)
- change to stable label internal standard
- reconstitution solution change
- increased HPLC injection volume

Reviewer's Comments:

The validation of the bioanalytical method for paricalcitol appears acceptable with reasonable precision and accuracy.

3.2 Pharmacometrics Review

3.2.1 Applicant's Population PK Analysis

The applicant conducted population PK analysis using data from the two studies in 10 to 16 year old pediatric subjects who received paricalcitol capsules for CKD Stage 3 and 4 (study M10-149, N= 43), and CKD Stage 5 receiving peritoneal dialysis or hemodialysis (study M11-612, N=13). The same model that was developed for the original approval for adults patients was used. The demographic information is summarized in **Table 5**.

Table 5. Demographic Data Summary for Subjects Included in the Population Pharmacokinetic and Exposure-Response Analyses

	Study M10-149[a] (Stage 3 or 4 CKD)	Study M11-612 (Stage 5 CKD)	Study M10-149 and Study M11-612 Total
	Population Pharmacokinetic Analysis	Population Pharmacokinetic/ Exposure-Response Analysis	Population Pharmacokinetic Analysis
Demographic Characteristic		Mean ± SD Median (Min – Max)	
Number of Subject (N)	43	13	56
Age (years)	13.6 ± 1.9 14 (10 – 17)	14.5 ± 1.8 15 (12 – 17)	13.8 ± 1.9 14 (10 – 17)
Weight (kg)	48.5 ± 14.5 46.0 (30.0 – 108.0)	49.0 ± 19.7 48.0 (27.0 – 97.0)	48.6 ± 15.6 46.0 (27.0 – 108.0)
Baseline Calcium (mg/dL)	9.7 ± 0.5 9.7 (8.2 – 10.5)	9.3 ± 0.6 9.4 (8.0 – 10.2)	9.6 ± 0.5 9.7 (8.0 – 10.5)
Baseline iPTH (pg/mL)	156.8 ± 92.4 132.0 (41.0 – 463.0)	883.3 ± 373.6 833.0 (249.0 – 1610.0)	325.4 ± 364.4 159.5 (41.0 – 1610.0)
Baseline Phosphorus (mg/dL)	4.6 ± 0.7 4.5 (3.3 – 6.5)	4.7 ± 1.1 4.7 (2.7 – 6.6)	4.6 ± 0.8 4.6 (2.7 – 6.6)
Race		Number (%)	
White	36 (83.7%)	8 (61.5%)	44 (78.6%)
Black	1 (2.3%)	2 (15.4%)	3 (5.4%)
Asian	3 (7.0%)	1 (7.7%)	4 (7.1%)
American Indian/Alaska Native	1 (2.3%)	1 (7.7%)	2 (3.6%)
Other	2 (4.7%)	1 (7.7%)	3 (5.4%)
Sex			
Male	30 (69.8%)	5 (38.5%)	35 (62.5%)
Female	13 (30.2%)	8 (61.5%)	21 (37.5%)

SD = standard deviation; Min = minimum; Max = maximum

a. One subject turned 17 years of age during the conduct of the study, and 2 subjects were CKD Stage 5 at Screening or baseline, respectively. Both subjects were at CKD Stage 4 during the study.

Source: Applicant's PKPD Report of Study 11612, Table 1

In the population pharmacokinetic model, paricalcitol disposition was best described by a two-compartment model with linear elimination and absorption, which is consistent with the pharmacokinetic model that described the adult data. The covariate relationships investigated for influence on pharmacokinetic parameters included the following:

- Demographics: age (years), weight (kg), sex (male or female), and race (white or other race)

- Disease State: CKD stage, baseline values of albumin, creatinine, iPTH, calcium, and phosphorus
- Liver Function: baseline value of glutamate-oxacetat-transaminase (GOT/AST), baseline value of glutamate-pyruvat-transaminase (GPT/ALT)

Among all the clinical covariates tested, weight was determined to be the significant covariate on pharmacokinetics of paricalcitol in pediatric patients. The median body weight observed in Study M11-612 was 46 kg, and an increase of 10 kg body weight resulted in a 15.9% increase in apparent clearance for males and females. An increase of 10 kg body weight resulted in a 21.7% increase in apparent volume of distribution. The estimated parameters included: linear clearance constant from the central compartment (CL/F), apparent volume of distribution of the central and peripheral compartment (V2/F and V3/F, respectively), and inter-compartmental clearance (Q/F; for the two-compartment model only).

The estimated central value of the apparent volume of distribution was 22.9 L for males and 34.8 L for females, and the apparent clearance was 19.1 L/day for both. The difference in the apparent volume of distribution between males and females is likely due to the difference of intense versus sparse pharmacokinetic sampling between studies and unequal distribution of male and female subjects between Studies M10-149 and M11-612. Although sex was a statistically significant covariate, sensitivity analysis showed that sex had a limited impact on the apparent volume of distribution and clinical outcomes.

The pharmacokinetic parameter estimates, the effects of covariates on these parameters, and their associated variabilities for the final model are presented in **Table 6**.

Table 6. Pharmacokinetic Parameter (Final Model)

Pharmacokinetic Parameter (Unit)	Population Estimate (SEE)	%RSE[a]	95% Confidence Interval
CL/F (L/day)	19.1 (1.43)	7.49	16.3 – 21.9
V_2/F (L)	22.9 (1.29)	5.63	20.4 – 25.4
K_a (1/day)	14.7 (fixed)[b]	-	-
Q/F (L/day)	11.1 (1.87)	16.8	7.44 – 14.8
V_3/F	182 (63.0)	34.6	58.5 – 305
Covariate			
SEX on V_2/F	1.52 (0.161)	10.6	1.20 – 1.84
WTKG on CL/F	0.750 (fixed)	-	-
WTKG on V_2/F	1.00 (fixed)	-	-
Inter-Individual Variability	**Population Estimate (%CV[c])**	**%RSE[a]**	**95% Confidence Interval**
IIV on CL	0.115 (34.9)	28.3	0.051 – 0.179
Residual Variability	**Population Estimate (SEE)**	**%RSE[a]**	**95% Confidence Interval**
Proportional Error Term M10-149	0.204 (0.025)	12.1	0.156 – 0.252
Proportional Error Term M11-612	0.533 (0.118)	22.1	0.302 – 0.764

SEE = standard error of estimate; RSE = relative standard error; IIV = inter-individual variability; CV = coefficient of inter individual variation

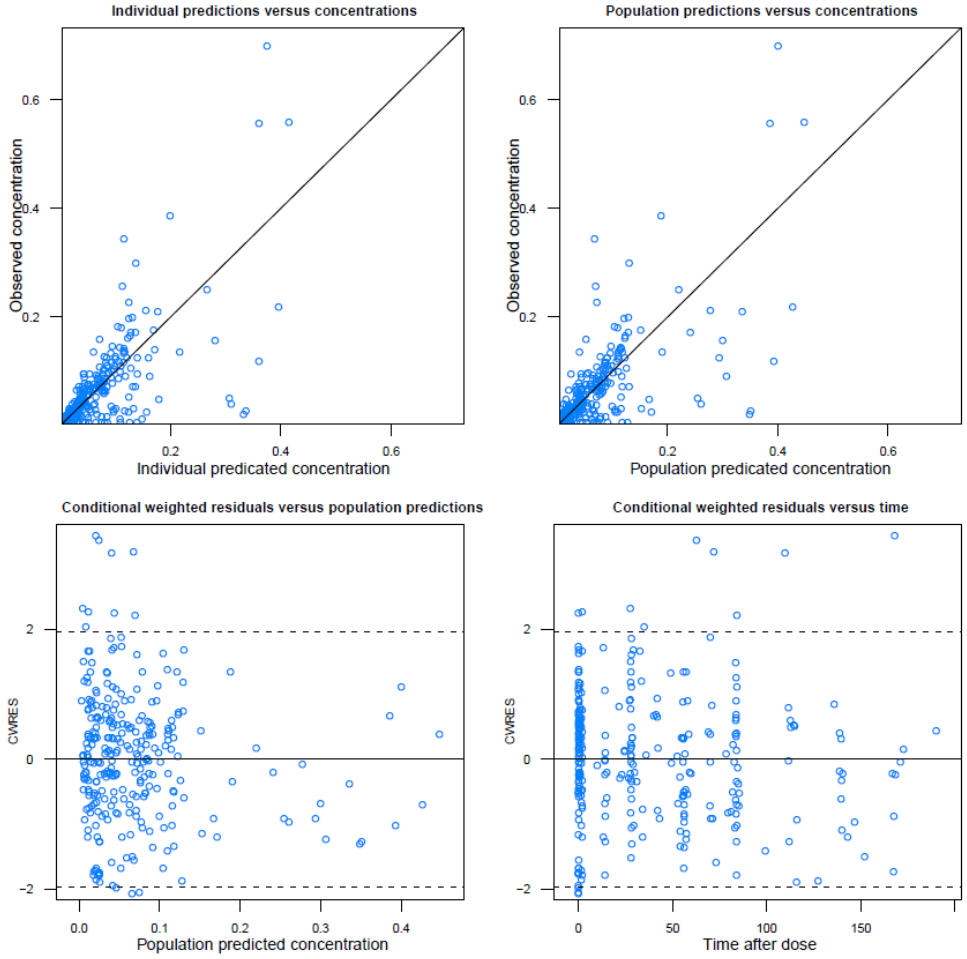
a. % RSE was estimated as the SEE divided by the population estimate multiplied by 100.

b. A fixed K_a value was determined from Study M10-149 data.

c. % CV computed $(e^{IIV} - 1)^{1/2}$ as when the variability was exponential.

Source: Applicant's PKPD Report of Study 11612, Table 2

Figure 8. Goodness-of-fit plots



Reviewer's Comments:

*The reviewer was able to confirm the applicant's analysis and generated similar GOF plots (**Figure 8**).*

- *Body weight (BW) was identified as a significant covariate for CL/F and V2/F while sex was identified as significant covariate for V2/F. However, neither weight, nor sex was found to be a significant covariate on PK parameters in adult CKD stage 5 patients and there is no physiological explanation for sex to have an effect on V2/F. The applicant hypothesized that the difference in V2/F between males and females is likely due to the difference of intense versus sparse PK sampling between studies and unequal distribution of male and female subjects between studies M10-149 and M11-612. Furthermore, the reviewer conducted subgroup analyses (not shown) indicating that BW and sex do not impact efficacy or safety. Since dose titration is allowed for each patient to maintain iPTH, calcium and phosphorus concentrations within specific physiologic thresholds, a fixed starting dose is reasonable for pediatric patients regardless of body weight and sex.*
- *CKD stage was not a significant covariate in the studied patients 10 to 16 years of age, Therefore, the extent of renal dysfunction does not seem to impact paricalcitol exposure, which is consistent with the findings in adults.*

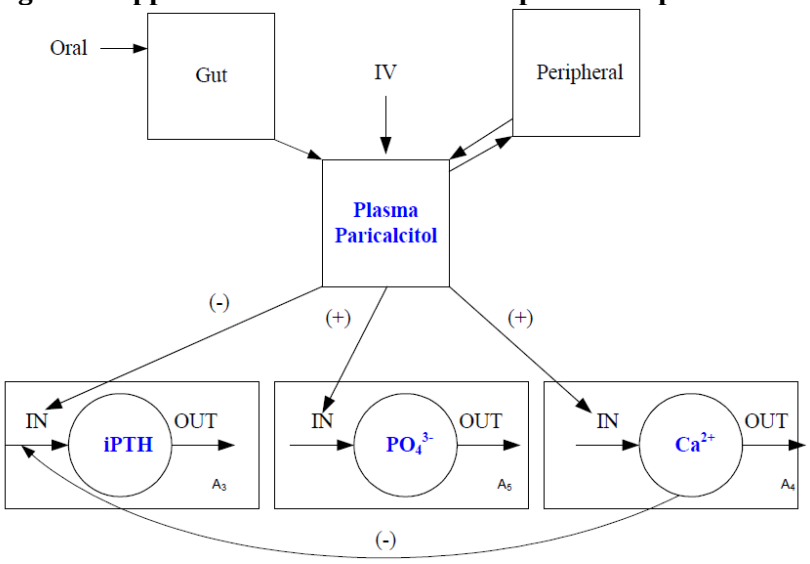
- *The individual PK parameter estimates were utilized as the input to perform exposure-response analysis described in section 3.2.2. The shrinkage for IIV clearance was only 14% supporting the use of individual post-hoc estimates of clearance for subsequent exposure-response analysis.*

3.2.2 Applicant's Exposure-Response Analysis

The exposure-response relationship of paricalcitol exposure and clinical response variables (including iPTH, serum calcium, and serum phosphorus) was evaluated using data from study M11-612 in CKD Stage 5 pediatric patients ages 10 to 16 years.

The individual pharmacokinetic parameter values from the final PK model were used to explore the relationships between paricalcitol exposure and serum iPTH, calcium, and phosphorus levels in CKD Stage 5 pediatric subjects. The base model structure and population estimates were previously determined for adult CKD Stage 5 subjects and adapted for parameter estimation in pediatric patients ages 10 to 16 years with CKD Stage 5. The base exposure- response structural model is shown in **Figure 9**. Further model complexities, including feedback interactions between iPTH, calcium, and phosphorus, were explored.[2]

Figure 9. Applicant's base structural of exposure- response model



Source: Applicant's PKPD Report of Study 11612, Figure 4

The goodness-of-fit for the final model was evaluated graphically and the individual predicted versus observed concentrations for iPTH, calcium, and phosphorus, are shown in **Figure 10**. A comparison of parameter estimates for adult and pediatric populations is shown in **Table 7**.

[2]Noertersheuser PA et al. Exposure-clinical response analysis of paricalcitol in patients with chronic kidney disease (stage 5) on hemodialysis or peritoneal dialysis. *J Clin Pharmacol* 2012;52:1162-73 (adult data but the applicant used Noertersheuser's model to assess the pediatric data)

Table 7. Comparison of PKPD parameter estimates for adult (upper) and pediatric patients (lower)

Estimated parameter	Unit of estimate	Estimate (%RSE)
Structural model parameters		
CRIT = THETA(1)	µg/L	2.25 (16.1)
K_{IN3} = THETA(2) * EXP(-THETA(8)*(LN(iPTH) - 6))	1/day	0.108 (10.1) 0.562 (8.8)
K_{IN4} = THETA(3) * EXP(-THETA(9)*(BLCA – 9.5))	1/day	0.067 (13.3) 0.080 (14.7)
CC = THETA(4)	no dimension	4.04 (19.6)
K_{IN5} = THETA(5) * EXP(-THETA(10)*(BPHO – 5.35))	1/day	0.060 (38.5) 0.112 (14.9)
CRIP = THETA(6)	µg/L	1.20 (22.5)
EC_{50} = THETA(7) - THETA(11)*(AGE-54))	µg/L	0.187 (29.9) 0.0043 (35.2)
K_{OU3} = THETA(12)	1/day	0.079 (10.7)
Inter-individual variability parameters		
CRIT	%CV[a] (%RSE[b])	102.9 (23.9)
CRIP	%CV (%RSE)	136.0 (24.4)
EC_{50}	%CV (%RSE)	193.4 (22.5)
K_{IN3}	%CV (%RSE)	32.4 (16.0)
K_{IN4}	%CV (%RSE)	5.7 (19.1)
K_{IN5}	%CV (%RSE)	18.4 (23.6)
Residual error parameters		
Proportional component (iPTH)	%CV (%RSE)	28.4 (8.4)
Additive component (Calcium)	STD (%RSE)	0.39 (7.9)
Additive component (Phosphorus)	STD (%RSE)	0.91 (5.5)

(Source: Applicant's PKPD Report for adults CKD 5 studies (R&D/05/789), Table 8)

Pharmacodynamic Parameter (Unit)	Pediatric Population		
	Population Estimate (SEE)	%RSE[a]	95% Confidence Interval
CRIT (ng/mL)	5.140 (fixed)	-	-
K_{IN3} (1/day)	0.077 (fixed)	-	-
K_{IN4} (1/day)	0.061 (fixed)	-	-
CC	1.120 (0.705)	62.95	–0.262 – 2.502
K_{IN5} (1/day)	0.119 (fixed)	-	-
CRIP (ng/mL)	1.150 (fixed)	-	-
EC_{50} (ng/mL)	0.106 (0.043)	40.28	0.022 – 0.190
Screening iPTH in K_{IN3} (pg/mL)	0.573 (fixed)	-	-
Screening Calcium in K_{IN4} (mg/dL)	0.082 (fixed)	-	-
Screening Phosphorus in K_{IN5} (mg/dL)	0.091 (fixed)	-	-
K_{OU3} (1/day)	0.049 (0.0066)	13.51	0.0360 – 0.0620
Inter-Individual Variability	**Population Estimate (%CV[b])**	**%RSE[a]**	**95% Confidence Interval**
IIV on CRIT	0.353 (72.361)	-	-
IIV on CRIP	1.280 (115.027)	-	-
IIV on EC_{50}	0.781 (89.628)	70.29	–0.295 – 1.857
IIV on K_{IN3}	0.185 (66.531)	-	-
IIV on K_{IN4}	0.003 (60.757)	-	-
IIV on K_{IN5}	0.027 (61.465)	-	-
Residual Variability	**Population Estimate (SEE)**	**%RSE[a]**	**95% Confidence Interval**
Proportional Error (PTH)	0.091 (0.015)	16.00	0.062 – 0.119
Additive Error (CALC)	0.144 (0.021)	14.86	0.102 – 0.186
Additive Error (PHOS)	1.120 (0.162)	14.46	0.802 – 1.438

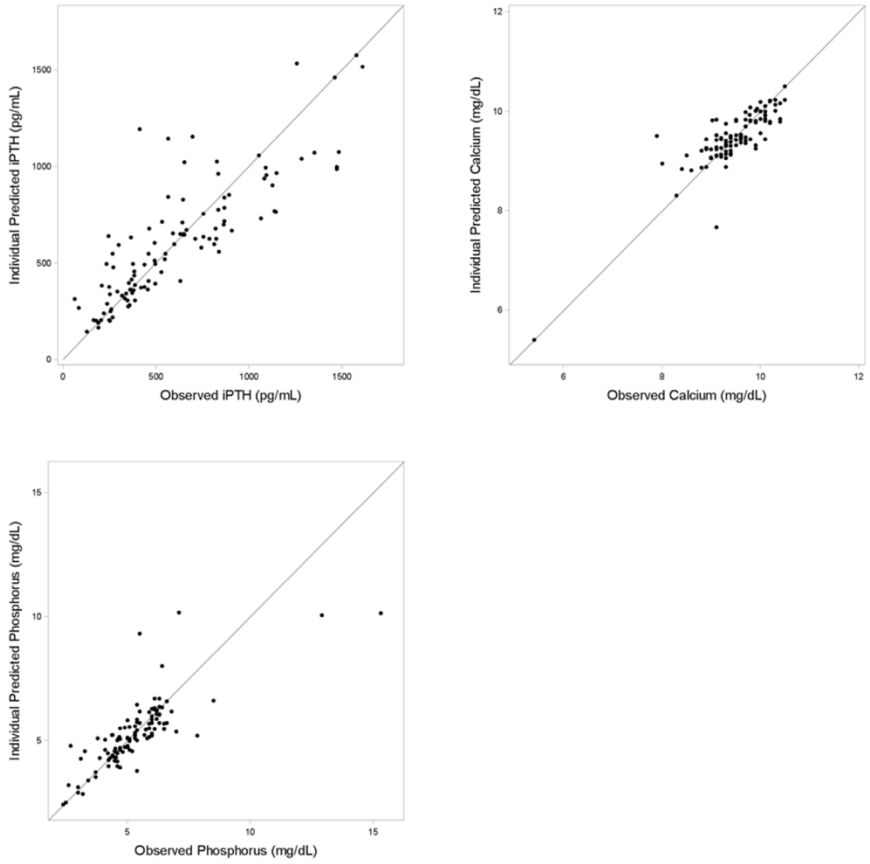
SEE = standard error of estimate; RSE = relative standard error; IIV = inter-individual variability; CV = coefficient of inter-individual variation

a. % RSE was estimated as the SEE divided by the population estimate multiplied by 100.

b. % CV computed as $(e^{IIV} - 1)^{1/2}$ when the variability was exponential.

(Source: Applicant's PKPD Report of Study 11612, Table 7)

Figure 10. Applicant's Goodness-of-fit plots



Source: Applicant's PKPD Report of Study 11612, Figure 8

The pharmacokinetic model parameters included absorption rate constant (Ka), elimination rate constant (Kel), V2/F, and transfer rate constants (K26 and K62). Parameters KIN3, KIN4, and KIN5 represented the production rates of serum iPTH, calcium, and phosphorus, respectively. Paricalcitol concentrations affected the production rates according to maximum effect (Emax) functions, with EC50, CRIT, and CRIP representing the paricalcitol concentrations that produced apparent half-maximal effects on serum iPTH, calcium, and phosphorus production rates, respectively. As part of a negative feedback mechanism, the production rate of serum iPTH was negatively correlated with the calcium concentration, with the parameter "CC" controlling the steepness of that relationship. The parameters KOU3, KOU4, and KOU5 represented the rates of loss of the serum iPTH, calcium, and phosphorus amounts, respectively. The amounts in the compartments for serum iPTH, calcium, and phosphorus were normalized and set to "1," at time zero. The actual iPTH, calcium, and phosphorus concentrations were derived from the normalized amounts by multiplying the compartment values by the corresponding screening concentration values.

Reviewer's Comments:

Applicant's indirect-response models developed for adults and the corresponding parameter estimates appear reasonable to describe the observed iPTH, calcium, phosphorus response in the pediatric population. Although most of parameters were fixed in applicant's model, the reviewer got similar results when the model was rerun without fixing the parameters. The majority of parameter estimates appear to be similar between the population, indicating similar sensitivity to paricalcitol effects in pediatric

subjects to that observed in adults. The exceptions were CRIT and CC, representing potency of paricalcitol on calcium and negative feedback of calcium on iPTH production. Given the conservative trial design with low starting dose and smaller escalation steps for pediatric trials, this difference is not considered meaningful. The population mean estimate of CRIT (paricalcitol concentrations that produced apparent half-maximal effects on serum calcium) was two-fold higher in pediatric patients compared to the adults indicating that pediatrics are likely to have a greater effect on calcium increase at similar exposures compared to adults. The mean estimate for CC is lower in pediatrics, suggesting similar calcium increase would have less effect on suppressing iPTH production in pediatric population than that in adults.

3.3 Review Labeling Comments (Preliminary)

The following are the labeling recommendations relevant to clinical pharmacology for NDA 21-606. The ~~red strikeout~~ font is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the applicant.

2.3 Pediatric Patients

CKD Stages 3 and 4 (Ages 10 to 16 years old)

Initial Dose

(b) (4) 1 mcg (b) (4) three times a week (b) (4), no more frequently than every other day.

Dose Titration

(b) (4) based on iPTH, serum calcium and phosphorus levels to maintain an iPTH level (b) (4)

(b) (4) dose may be increased in 1 mcg increments (b) (4). At any time, (b) (4) dose may be decreased by 1 mcg (b) (4) may be (b) (4) if the patient (b) (4) receiving (b) (4) 1 mcg (b) (4) .

CKD Stage 5 (Ages 10 to 16 years old)

Initial Dose

(b) (4)

Dose Titration

Subsequent dosing should be individualized and based on iPTH, serum calcium and phosphorus levels to maintain an iPTH level (b) (4).

(b) (4)

7 DRUG INTERACTIONS

(b) (4)

(b) (4)

Table (b) (4) shows the clinically significant drug interactions with (b) (4) capsule.

Table (b) (4) Clinically Significant Drug Interactions with Paricalcitol (b) (4)

CYP3A Inhibitors	
Clinical Impact	Paricalcitol is partially metabolized by CYP3A. Hence, exposure of paricalcitol will increase upon coadministration with strong CYP3A inhibitors such as but not limited to: boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole.
Intervention	Dose adjustment of Zemplar Capsules may be necessary. Monitor closely for iPTH and serum calcium concentrations, if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor.
Cholestyramine	
Clinical Impact	Drugs that impair intestinal absorption of fat-soluble vitamins, such as cholestyramine, may interfere with the absorption of Zemplar Capsules.
Intervention	(b) (4) at least 1 hour before or 4 to 6 hours after taking cholestyramine (or at as great an interval as possible) to avoid impeding (b) (4).
Mineral Oil	
Clinical Impact	(b) (4) mineral oil or other substances that may affect absorption of fat which may influence the absorption of (b) (4).
Intervention	Take (b) (4) at least 1 hour before or 4 to 6 hours after taking mineral oil (or at as great an interval as possible) to avoid affecting (b) (4).

8.4 Pediatric Use

(b) (4)

Safety and efficacy of Zemplar Capsules in pediatric patients under the age of 10 years have not been established.

12 CLINICAL PHARMACOLOGY

Secondary hyperparathyroidism is characterized by an elevation in parathyroid hormone (PTH) associated with inadequate levels of active vitamin D hormone. The source of vitamin D in the body is from synthesis in the skin as vitamin D_3 and from dietary intake as either vitamin D_2 or D_3. Both vitamin D_2 and D_3 require two sequential hydroxylations in the liver and the kidney to bind to and to activate the vitamin D receptor (VDR). The endogenous VDR activator, calcitriol [$1,25(OH)_2D_3$], is a hormone that binds to VDRs that are present in the parathyroid gland, intestine, kidney, and bone to maintain parathyroid function and calcium and phosphorus homeostasis, and to VDRs found in many other tissues, including prostate, endothelium and immune cells. VDR activation is essential for the proper formation and maintenance of normal bone. In the diseased kidney, the activation of vitamin D is diminished, resulting in a rise of PTH, subsequently leading to secondary hyperparathyroidism and disturbances in the calcium and phosphorus homeostasis. Decreased levels of $1,25(OH)_2D_3$ have been observed in early stages of chronic kidney disease. The decreased levels of $1,25(OH)_2D_3$ and resultant elevated PTH levels, both of which often precede abnormalities in serum calcium and phosphorus, affect bone turnover rate and may result in renal osteodystrophy.

12.1 Mechanism of Action

Paricalcitol is a synthetic, biologically active vitamin D_2 analog of calcitriol. Preclinical and *in vitro* studies have demonstrated that paricalcitol's biological actions are mediated through binding of the VDR, which results in the selective activation of vitamin D responsive pathways. Vitamin D and paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion.

12.2 Pharmacodynamics

Paricalcitol decreases serum intact parathyroid hormone (iPTH) and increases serum calcium and serum phosphorous in both HD and PD patients. This observed relationship was quantified using a mathematical model for HD and PD patient populations separately. Computer-based simulations of 100 trials in HD or PD patients (N = 100) using these relationships predict slightly lower efficacy (at least two consecutive $\geq$ 30% reductions from baseline iPTH) with lower hypercalcemia rates (at least two consecutive serum calcium $\geq$ 10.5 mg/dL) for lower iPTH-based dosing regimens. Further lowering of hypercalcemia rates was predicted if the treatment with paricalcitol is initiated in patients with lower serum calcium levels at screening.

Based on these simulations, a dosing regimen of iPTH/80 with a screening serum calcium $\leq$ 9.5 mg/dL, approximately 76.5% (95% CI: 75.6% – 77.3%) of HD patients are predicted to achieve at least two consecutive weekly $\geq$ 30% reductions from baseline iPTH over a duration of 12 weeks. The predicted incidence of hypercalcemia is 0.8% (95% CI: 0.7% – 1.0%). In PD patients, with this dosing regimen, approximately 83.3% (95% CI: 82.6% – 84.0%) of patients

are predicted to achieve at least two consecutive weekly ≥ 30% reductions from baseline iPTH. The predicted incidence of hypercalcemia is 12.4% (95% CI: 11.7% - 13.0%) [*see Clinical Studies (14.2) and Dosage and Administration (2.2)*].

12.3 Pharmacokinetics

Absorption

The mean absolute bioavailability of Zemplar Capsules under low-fat fed condition ranged from 72% to 86% in healthy adult (b) (4) volunteers, CKD Stage 5 patients on HD, and CKD Stage 5 patients on PD. A food effect study in healthy adult (b) (4) volunteers indicated that the C_{max} and $AUC_{0-\infty}$ were unchanged when paricalcitol was administered with a high fat meal compared to fasting. Food delayed T_{max} by about 2 hours. The $AUC_{0-\infty}$ of paricalcitol increased proportionally over the dose range of 0.06 to 0.48 mcg/kg in healthy adult (b) (4) volunteers.

Distribution

Paricalcitol is extensively bound to plasma proteins (≥ 99.8%). The mean apparent volume of distribution following a 0.24 mcg/kg dose of paricalcitol in healthy adult (b) (4) volunteers was 34 L. The mean apparent volume of distribution following a 4 mcg dose of paricalcitol in CKD Stage 3 and a 3 mcg dose in CKD Stage 4 patients is between 44 and 46 L.

Metabolism

After oral administration of a 0.48 mcg/kg dose of ^{3}H-paricalcitol, parent drug was extensively metabolized, with only about 2% of the dose eliminated unchanged in the feces, and no parent drug was found in the urine. Several metabolites were detected in both the urine and feces. Most of the systemic exposure was from the parent drug. Two minor metabolites, relative to paricalcitol, were detected in human plasma. One metabolite was identified as 24(R)-hydroxy paricalcitol, while the other metabolite was unidentified. The 24(R)-hydroxy paricalcitol is less active than paricalcitol in an *in vivo* rat model of PTH suppression.

In vitro data suggest that paricalcitol is metabolized by multiple hepatic and non-hepatic enzymes, including mitochondrial CYP24, as well as CYP3A4 and UGT1A4. The identified metabolites include the product of 24(R)-hydroxylation, 24,26- and 24,28-dihydroxylation and direct glucuronidation.

Elimination

Paricalcitol is eliminated primarily via hepatobiliary excretion; approximately 70% of the radiolabeled dose is recovered in the feces and 18% is recovered in the urine. While the mean elimination half-life of paricalcitol is 4 to 6 hours in healthy adult (b) (4) volunteers, the mean elimination half-life of paricalcitol in CKD Stages 3, 4, and 5 (on HD and PD) patients ranged from 14 to 20 hours.

Table (b) (4) Paricalcitol Capsule Pharmacokinetic (b) (4) Parameters (mean ± SD) in CKD Stages 3, 4, and 5 Adult Patients

Pharmacokinetic Parameters (units)	**CKD Stage 3 n = 15***	**CKD Stage 4 n = 14***	**CKD Stage 5 HD** n = 14**	**CKD Stage 5 PD** n = 8**

C_{max} (ng/mL)	0.11 ± 0.04	0.06 ± 0.01	0.575 ± 0.17	0.413 ± 0.06
$AUC_{0-\infty}$ (ng•h/mL)	2.42 ± 0.61	2.13 ± 0.73	11.67 ± 3.23	13.41 ± 5.48
CL/F (L/h)	1.77 ± 0.50	1.52 ± 0.36	1.82 ± 0.75	1.76 ± 0.77
V/F (L)	43.7 ± 14.4	46.4 ± 12.4	38 ± 16.4	48.7 ± 15.6
$t_{1/2}$	16.8 ± 2.65	19.7 ± 7.2	13.9 ± 5.1	17.7 ± 9.6
* Four mcg paricalcitol capsules were given to CKD Stage 3 patients; three mcg paricalcitol capsules were given to CKD Stage 4 patients. ** CKD Stage 5 HD and PD patients received a 0.24 mcg/kg dose of paricalcitol as capsules.				

Specific Populations

Geriatric

The pharmacokinetics of paricalcitol has not been investigated in geriatric patients greater than 65 years [*see Use in Specific Populations (8.5)*].

Pediatric

Paricalcitol C_{max}, AUC, and $t_{1/2}$ values were similar between Stage 3 and Stage 4 CKD pediatric subjects 10-16 years of age. Population pharmacokinetic analysis shows that the pharmacokinetics of paricalcitol in Stage 5 CKD pediatric subjects appear to be similar to those observed in Stage 3 and 4 pediatric subjects. (b) (4)

(b) (4)

Table (b) (4) Paricalcitol Capsules Pharmacokinetic Parameters (mean ± SD) in CKD Stages 3 and 4 (b) (4)

Pharmacokinetic Parameter (units)	**CKD Stage 3 n = 6**	**CKD Stage 4 N = 5**
C_{max} (ng/mL)	0.12 ± 0.06	0.13 ± 0.05
AUC_{∞} (ng•h/mL)	2.63 ± 0.76	3.2 ± 0.99
CL/F (L/h)	1.23 ± 0.38	1.02 ± 0.35
V/F (L)	27.78 ± 18.60	24.36 ± 5.92
$t_{1/2}$ (h)	14.95 ± 6.07	17.54 ± 5.93
* Three 1 mcg paricalcitol capsules were given to CKD Stage 3 or 4 patients.		

Gender

The pharmacokinetics of paricalcitol following single doses over the 0.06 to 0.48 mcg/kg dose range was gender independent.

Hepatic Impairment

The disposition of paricalcitol (0.24 mcg/kg) was compared in patients with mild (n = 5) and moderate (n = 5) hepatic impairment (as indicated by the Child-Pugh method) and subjects with normal hepatic function (n = 10). The pharmacokinetics of unbound paricalcitol was similar across the range of hepatic function evaluated in this study. No dose adjustment is required in patients with mild and moderate hepatic impairment. The influence of severe hepatic impairment on the pharmacokinetics of paricalcitol has not been evaluated.

Renal Impairment

Following administration of Zemplar Capsules, the pharmacokinetic profile of paricalcitol for CKD Stage 5 on HD or PD was comparable to that in CKD 3 or 4 patients. Therefore, no special dose adjustments are required other than those recommended in the Dosage and Administration section [*see Dosage and Administration (2)*].

Drug Interactions

An *in vitro* study indicates that paricalcitol is neither an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A nor an inducer of CYP2B6, CYP2C9 or CYP3A. Hence, paricalcitol is neither expected to inhibit nor induce the clearance of drugs metabolized by these enzymes.

Omeprazole

The effect of omeprazole (40 mg capsule), a strong inhibitor of CYP2C19, on paricalcitol (four 4 mcg capsules) pharmacokinetics was investigated in a single dose, crossover study in healthy subjects. The pharmacokinetics of paricalcitol was not affected when omeprazole was administered approximately 2 hours prior to the paricalcitol dose.

Ketoconazole

The effect of multiple doses of ketoconazole, a strong inhibitor of CYP3A, administered as 200 mg BID for 5 days on the pharmacokinetics of paricalcitol (4 mcg capsule) has been studied in healthy subjects. The C_{max} of paricalcitol was minimally affected, but $AUC_{0-\infty}$ approximately doubled in the presence of ketoconazole. The mean half-life of paricalcitol was 17.0 hours in the presence of ketoconazole as compared to 9.8 hours, when paricalcitol was administered alone [*see Drug Interactions (7)*].

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/s/

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