CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	21606/S-016, S-017
Priority or Standard	Standard
Submit Date(s)	December 18, 2015
Received Date(s)	December 18, 2015
PDUFA Goal Date	October 18, 2016
Division / Office	ODEII/DMEP
Reviewer Name(s)	William Lubas, M.D., Ph.D.
Review Completion Date	October 11, 2016
Established Name	paricalcitol
(Proposed) Trade Name	Zemplar®
Therapeutic Class	Bone-Vitamin D
Applicant	AbbVie Inc.
Formulation(s)	Oral Capsule
Dosing Regimen	1) start dose-1mcg three times a week and increase by 1mcg three times a week every 4 weeks based on lab data 2) start dose-iPTH (pg/mL)/120 three times a week and

	increase by 1mcg three times a week every 4 weeks based on lab data
Indication(s)	Prevention and Treatment of Secondary Hyperparathyroidism
Intended Population(s)	1) Chronic Kidney Disease Stage 3 and 4-Predialysis pediatric patients 10 years and older (S-016) 2) Chronic Kidney Disease Stage 5-Dialysis pediatric patients 10 years and older (S-017)

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval of Zemplar Capsules for the treatment of secondary hyperparathyroidism in pediatric patients 10 to 16 years of age with CKD Stage 3, 4 and 5.

1.2 Risk Benefit Assessment

Treatment of secondary hyperparathyroidism in pediatric predialysis subjects 10 to 16 years of age with CKD (Stages 3 and Stage 4) was assessed in pivotal study M10-149 using the same endpoint, two consecutive 30% decreases from baseline iPTH between Zemplar and placebo treated patients, previously used to support approval of Zemplar Injection for the treatment of pediatric patients with secondary hyperparathyroidism on hemodialysis. While efficacy was modest at the 12-week endpoint at 5/18=28% in the paricalcitol treatment group vs. 0/18=0% in the placebo group (p-value of 0.045), with longer exposure during the 12-wk open-label extension efficacy improved so that 12/29=41% had two consecutive reductions of at least 30% from baseline by Week 24. While a small increase in hypercalcemia (CTCAE Grade 1) and hyperphosphatemia (>5.8mg/dL) above the background rate was seen the rates of hypercalcemia and hyperphosphatemia were low and were identified prior to the development of any serious adverse events. During the limited exposure in these clinical trials there were no patients who developed consistently low iPTH levels below the lower limit of normal based on pediatric KDOQI recommendations that might increase their risk of adynamic bone disease. That said optimal iPTH levels in patients with Stage 3 and Stage 4 CKD which could prevent renal osteodystrophy are unknown. In general the adverse event profile seen in this pivotal study was consistent with the known safety profile of Zemplar Capsules reported in adult clinical studies and with appropriate monitoring of serum calcium, phosphorous and iPTH the risk benefit assessment supports the use of Zemplar Capsules in this pediatric population.

Efficacy in pediatric dialysis subjects with CKD (Stage 5) 10 to 16 years of age was extrapolated from the adult data using population PK, and study M11-612 was primarily used to support the safety of Zemplar Capsules in this population and to determine the incidence of hypercalcemia using two consecutive measurements of serum calcium > 10.2mg/dL as the primary safety endpoint. The population PK analysis was performed based on combined data from studies M10-149 and M11-612 utilizing the same model used for the approval of the indication in adults with CKD Stage 5 (see Section 3.2 of the Clin Pharm review by Drs. Lau, Ma and Mehrota). The Clin Pharm review was able to confirm the applicant's analysis to support extrapolation of the data to the pediatric population with CKD Stage 5. The proportion of subjects achieving two consecutive ≥30% reductions from baseline in iPTH at 12 weeks was calculated as supportive evidence of efficacy. This endpoint, which was the same as the primary endpoint in study M10-149, was higher in study M11-612 at 62% in the CKD Stage 5 population compared to the rate of 28% seen in study M10-149 in the CKD Stages 3 and 4 population. Part of the reason for the

greater apparent efficacy in this study was likely due to the higher baseline iPTH levels in the dialysis population in study M11-612 (884 ± 374pg/mL) compared to the baseline iPTH levels in the predialysis population in study M10-149 (150 ± 82pg/mL). These data are comparable to the results seen in NDA 20-819 with Zemplar Injection compared to placebo in the pediatric dialysis population 9/15=60% vs. 3/14=21%, respectively, and so are supportive of efficacy in the treatment of secondary hyperparathyroidism in the pediatric dialysis population. Similar to what was seen in study M10-149 there were mild serum calcium elevations above the upper limit of normal but less than 11.5 mg/dL (Grade 1, CTCAE). Serum phosphorous elevations above 6.5mg/dL were higher and more common in the dialysis population in study M11-612 than seen in study M10-149, but none of the cases of hyperphosphatemia were considered serious or associated with other AEs. During the limited exposure in study M11-612 there were no patients who developed consistently low iPTH levels below 2X the upper limit of normal for the assay as recommended by the KDIGO guidelines that might increase the risk of adynamic bone disease. That said optimal iPTH levels in dialysis patients with Stage 5 CKD which could prevent renal osteodystrophy are unknown. In general the adverse event profile seen in study M11-612 was consistent with the known safety profile of Zemplar Capsules reported in adult clinical studies and with appropriate monitoring of serum calcium, phosphorous and iPTH the risk benefit assessment supports the use of Zemplar Capsules in this pediatric population.

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

Paricalcitol, USP, the active ingredient in Zemplar Capsules, is a synthetically manufactured, metabolically active vitamin D analog of calcitriol with modifications to the side chain (D2) and the A (19-nor) ring. Zemplar is indicated for the prevention and treatment of secondary hyperparathyroidism in chronic kidney disease. Zemplar is available as soft gelatin capsules for oral administration containing 1 microgram or 2 micrograms of paricalcitol.

2.2 Tables of Currently Available Treatments for Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease

Secondary hyperparathyroidism associated with CKD Stage 3 and 4*	
Vitamin D analogs	Zemplar (paricalcitol) Capsules
	Rocaltrol (calcitriol) Capsules and Oral Solution
	Hectorol (doxercalciferol) Capsules
	Rayaldee (calcifediol) Capsules
*This table lists indications approved in the adult population. The only oral Vitamin D analog with pediatric dosing information in the label is Rocaltrol.	

Secondary hyperparathyroidism associated with CKD Stage 5 Dialysis Patients*	
Vitamin D analogs	Zemplar (paricalcitol) Capsules and Injection
	Rocaltrol (calcitriol) Capsules and Oral Solution Calcijex (calcitriol) Injection**
	Hectorol (doxercalciferol) Capsules and Injection
Calcimimetics	Sensipar (cinacalcet) Tablets
* This table lists indications approved in the adult population. Only Calcijex Injection and Zemplar Injection have dosing information in their respective labels for the treatment of secondary hyperparathyroidism associated with CKD Stage 5 in pediatric dialysis patients. **Calcijex is officially approved for "the management of hypocalcemia in patients undergoing chronic renal dialysis. It has been shown to significantly reduce elevated parathyroid hormone levels. Reduction of PTH has been shown to result in an improvement in renal osteodystrophy." The pediatric studies were performed with two consecutive decreases from baseline iPTH as the primary endpoint.	

2.3 Availability of Proposed Active Ingredient in the United States

Paricalcitol capsules indicated for the prevention and treatment of secondary hyperparathyroidism associated with CKD Stage 3 and 4 are currently available in the US at dosage strengths of 1 and 2 micrograms.

Paricalcitol injectable indicated for the prevention and treatment of secondary hyperparathyroidism associated with CKD Stage 5 is currently available in the US in 2mcg/mL and 5mcg/mL single dose vials and a 10mcg/2mL multi-use vial.

2.4 Important Safety Issues With Consideration to Related Drugs

Over dosing with Vitamin D related compounds in patients with CKD can be associated with hypercalcemia, hyperphosphatemia, vascular and soft-tissue calcification, and adynamic bone disease.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Zemplar (paricalcitol) pediatric program consists of:

(1) two completed studies M10-149 and M11-612 included and reviewed in this submission and conducted under IND (b) (6) using Zemplar Capsules and

(2) (b) (4)

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Study M10-149 (CKD Stage 3 and 4, ages 10 to 16 years) will fulfill the Postmarketing Requirement (PMR) 1814-1 established under the Pediatric Research Equity Act (PREA) and issued when Zemplar Capsules NDA 021606 were approved on May 26, 2005.

Study M11-612 (CKD Stage 5, ages 10 to 16 years) will fulfill PMR 2094-1 established under PREA and issued with the Zemplar Capsules sNDA 021606/S-004 approved on June 29, 2009.

(b) (4)

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Abbott was the original NDA holder for Zemplar Capsules and in 2013 the NDA was transferred to AbbVie Inc.

CKD Stage 3 and 4 in Patients 10 to 16 Years of Age (Study M10-149):
On January 27, 2006 (Serial No. 093), Abbott submitted a proposed pediatric study request (PPSR) to study Zemplar in the pediatric population with CKD Stages 3 and 4. On June 15, 2006 the Agency sent a PPSR denial letter requesting additional information. On September 27, 2007 (Serial No. 113), Abbott submitted a revised draft protocol for Study M10-149, but was no longer seeking a PPSR. On January 17, 2008, the Agency responded:

- requesting justification for the proposed start dose,
- asking the sponsor to include K/DOQI guidelines for serum iPTH, calcium, phosphorous and 25-OH vitamin D levels in the study design,
- recommending the sponsor to prespecify an endpoint using iPTH values based on KDOQI guidelines that shows efficacy at either two consecutive time points or at the end of the study,
- and expanding the age criteria to include 10 to 11 years old patients in addition to the 12 to 16 years old patients.

On December 15, 2008 (Serial No. 131), Abbott submitted a revised protocol for Study M10-149 in accordance with the Agency's comments. On January 16, 2009, the Agency provided email comments to the revised protocol for Study M10-149 and on March 13, 2009 (Serial No. 136), Abbott responded to the Agency's information requests in an amended protocol:

- redefining the primary endpoint as two consecutive values iPTH values within the KDOQI target range,
- including 25-OH vitamin D > 30ng/ml as an inclusion criteria
- and 5.8 mg/dL as the upper limit of normal for phosphorous

On September 18, 2009 (Serial No. 146), Abbott submitted a final updated Study M10-149 protocol for CKD Stages 3 and 4 prior to the start of enrollment of pediatric patient's ages 10 to 16 years old in the study.

CKD Stage 5 in Patients 0 to 9 and 10 to 16 Years of Age (Studies M11-612 (b) (4)):
On June 30, 2010 (Serial No. 164), (b) (4) On September 03, 2010 the Agency provided the following:

- recommendations on the (b) (4),
- a request for additional dosing simulations using the adult PK data to support a safe starting dose
- and a proposal to design the study as an open label 12-week safety study assessing the risk of hypercalcemia (e.g. two consecutive serum calcium levels > 10.2 mg/dL).

Abbott responded on October 01, 2010 (Serial No. 167) requesting additional advice and revised study designs for the CKD Stage 5 studies:

- Study M11-612 – capsules (ages 10 to 16 years) and
- (b) (4)

On March 31, 2011 (Serial No. 176), Abbott submitted a final updated protocol prior to the start of enrollment in Study M11-612.

PMR 1067-2 due date:
In the July 29, 2011 submission to NDA 021606 (Serial No. 0024) and to IND (b) (4) (Serial No. 124), Abbott requested a change to the PMR due date for Study M11-612 to December 2013. In an email correspondence dated December 29, 2011, the Agency indicated they could not change the due date to December 2013 and the study status would be considered "delayed" until the study was completed. However, the Agency indicated they would use the December

2013 date for tracking purposes for the timing of the study completion and final report submission.

Significant enrollment challenges in Studies M10-149 and M11-612:
On March 02, 2012 (Serial No. 190), Abbott submitted a Type A meeting request to discuss Abbott's pediatric study commitments due to continuing significant enrollment challenges in Studies M10-149 and M11-612. A Type C meeting was granted by the Agency and a May 01, 2012 teleconference was held with comments issued in the Agency's June 01, 2012 Meeting Minutes. Abbott suggested revising the primary endpoint in Study M10-149 from "the proportion of subjects who achieve a final iPTH value in the applicable K/DOQI iPTH target range" to "the proportion of subjects with two consecutive ≥ 30% reductions in iPTH compared to baseline" as this would permit the study to be completed with 36 subjects instead of the 72 subjects initially proposed based on their power calculations. This would also permit the study to be completed up to one year sooner (b) (4). The Agency agreed with the change in the primary endpoint but asked the sponsor to include KDOQI target ranges as a secondary endpoint. The Agency also asked that any future subjects in Study M10-149 be continued past 24 weeks in an open label extension to accumulate additional safety data given that there will now be fewer patients enrolled into the study. To help with study recruitment the Agency also agreed with the following based on the advice from AbbVie's pediatric nephrology experts:

- to reduce the washout period from 4 to 2 weeks,
- to permit investigator discretion for the scheduling of unscheduled visits,
- to limit the fasting requirements prior to blood draws used to screen for iPTH inclusion criteria

(b) (4)

Deferral Extensions due to problems with study recruitment:
A Deferral Extension Request for PMR 1814-1 (Study M10-149) was submitted to the Agency on January 03, 2013 (NDA Serial No. 0206) and for PMR 1067-2 (Study M11-612) on February 01, 2013 (NDA Serial No. 0208). On March 27, 2013, the Agency issued a Deferral Extension Granted letter, which granted the Final Report Submission date of December 31, 2014 for both PMRs 1814-1 and 1067-2. After continued stagnant enrollment, Protocol M11-612 Amendment 4 was submitted to the Agency on June 24, 2013 (Serial No. 213) in order to make Week 6 and Week 10 visits optional per the investigator's discretion in order to align the mandatory study visit schedule with the typical standard of care visit schedule. On August 29, 2013 (NDA Serial No. 0216), AbbVie submitted another Deferral Extension Request and asked to include hemodialysis pediatric patients in Study M11-612 to increase patient enrollment. AbbVie proposed the following revision to the PMR 1067-2: "Deferred pediatric study under PREA for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 5 in patients receiving peritoneal dialysis or hemodialysis in pediatric patients ages 10 to 16 years." On October 09, 2013, the Agency approved the PMR 1067-2 deferral extension request for the Study M11-612 Final Report Submission date until May 2016.

On October 30, 2013, the Agency released PMR 1067-2 and replaced it with PMR 2094-1 for Study M11-612 in response to adding hemodialysis patients to the study. However, the Study M11-612 Final Report Submission date remained May 2016 for PMR 2094-1. (b) (4) [redacted]. On October 10, 2014, AbbVie submitted (NDA Serial No. 0056) a PMR 1814-1 Deferral Extension Request for Study M10-149. On November 24, 2014, the FDA approved the PMR 1814-1 Deferral Extension Request for Study M10-149 with the Final Report Submission date of June 20, 2015.

Timing of CSR submissions to fulfill PMRs and timing of sNDA submissions:
On February 05, 2015, AbbVie proposed to submit the Study M10-149 CSR with no Appendix 16 information or datasets by June 20, 2015 to fulfill PMR 1814-1. The sNDA would be submitted by October 30, 2015 and would include the CSRs, Appendix 16 information, datasets and label revisions from both Studies M10-149 and M11-612. The Study M11-612 CSR would fulfill the PMR 2094-1 Final Report Submission date of May 2016. On February 11, 2015, the Agency agreed via email with AbbVie's February 05, 2015 proposal to submit the sNDA with the Studies M10-149 and M11-612 CSRs by October 30, 2015.

sNDA submission:
On May 18, 2015 (NDA Serial No. 0059), AbbVie submitted a Type C meeting request and briefing package to obtain the Agency's agreement on the overall information for PMR Studies M10-149 and M11-612 that will be submitted by October 30, 2015 to support the sNDA. On August 03, 2015, the FDA provided the Type C Meeting Request-Written Responses with the following requests:

- For Study M10-149, include additional exploratory efficacy and safety analysis that combine data from the double-blind and open-label parts and include additional descriptive summaries of efficacy and safety data over time in all patients in the double-blind or open-label portion of the study.
- For Studies M10-149 and M11-612, include additional presentations (figures/tables) of data during each week (study dose) and over the course (calcium, phosphate and iPTH) of the study.
- Include the datasets for Studies M10-149 and M11-612 in standardized CDISC format.
- List safety data from Studies M10-149 and M11-612 separately.
- Adverse event data from CKD Stages 3 and 4 should not be pooled with Stage 5 data.

- Present the Study M10-149 data in a separate table in addition to pooling the data with the current adverse reaction data in Table 1 in the package insert.
- Include narratives for all deaths, SAEs, all adverse reactions due to hypercalcemia and discontinuations that occurred in the clinical program.
- Summarize references for all published studies using active vitamin D analogs for the treatment of SHPT in the pediatric CKD population.
- Include labeling information to respond to the Pregnancy and Lactation Labeling Rule.

On June 18, 2015 (NDA Serial No. 0060), the final clinical study report (no Appendix 16 information or datasets) for Study M10-149 was submitted to the Agency for PMR 1814-1. On August 21, 2015, in response to Agency's August 03, 2015 additional efficacy and safety analysis requests, AbbVie requested via email to submit the Studies M10-149 and M11-612 datasets in non-CDISC format and to submit the sNDA by December 31, 2015 instead of October 30, 2015.

Orphan drug designation:
On July 31, 2015, an orphan drug designation request for the treatment of pediatric hyperparathyroidism was submitted to the Office of Orphan Products Development (OOPD) for paricalcitol. On October 27, 2015, paricalcitol was granted the orphan designation (#15-4928) for the "treatment of pediatric hyperparathyroidism."

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No inspections of clinical sites were performed in the two pivotal trials, because the studies were too small and had two few patients at each site to make the inspections useful. For example all five patients who were responders in the pivotal study M10-149 were from separate study sites of which only two sites were in the US.

The submission was of adequate quality to perform the review.

3.2 Compliance with Good Clinical Practices

All studies were conducted in accordance with Good Clinical Practices governing clinical study conduct.

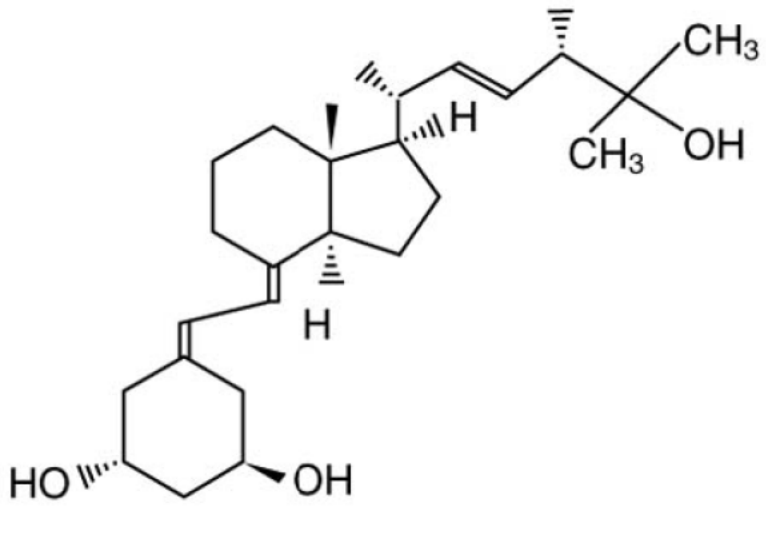
3.3 Financial Disclosures

Financial disclosure information was provided for all 44 investigators in Study M10-149 (12 in Part 1 and 36 in Part 2) and all 16 investigators in study M11-612. Only one investigator, Dr. (b) (6), had disclosable financial arrangements with the applicant. (b) (6) received payments in excess of $25,000 from the applicant. (b) (6) study site enrolled (b) (6). Since Dr. (b) (6) did not (b) (6) there are no concerns about the efficacy assessment in that study. Dr. (b) (6) did enroll (b) (6) study. (b) (6) Excluding this patient from the study data would have little effect on efficacy but would have lowered the rate of hypercalcemia from 3/13=23% to 2/13=15%. Since this patient's data increased the observed rate of hypercalcemia and made the study results less favorable for the applicant it seems unlikely that financial interests impacted on the inclusion of this patient's data into the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Paricalcitol is chemically designated as 19-nor-1α,3β,25-trihydroxy-9,10-secoergosta-5(Z),7(E),22(E)-triene and has the following structural formula:



Zemplar® is available as soft gelatin capsules for oral administration containing 1 or 2 micrograms of paricalcitol. Each capsule also contains medium chain triglycerides, alcohol, and butylated hydroxytoluene. The medium chain triglycerides are fractionated from coconut oil or palm kernel oil. The capsule shell is composed of gelatin, glycerin, titanium dioxide, iron oxide red (2 microgram capsules only), iron oxide yellow (2 microgram capsules only), iron oxide black (1 microgram capsules only) and water.

4.2 Clinical Microbiology

No new microbiology information was included in this submission.

4.3 Preclinical Pharmacology/Toxicology

The Agency had previously agreed that juvenile animal studies were not required to support clinical studies in pediatric patients with oral paricalcitol as clinical monitoring for hypercalcemia was considered adequate given the results from earlier nonclinical studies in adult rats and dogs.

The applicant resubmitted a full ICH S5 battery of reproductive toxicology studies with paricalcitol to support labeling changes for Section 8 of Zemplar capsules, in accordance with the Pregnancy and Lactation Labeling Rule (PLLR). These studies were conducted with the Zemplar Injection formulation and were reviewed previously under NDA 020819. While the labeling update for the current submission is for Zemplar Capsules, the disposition and metabolism of paricalcitol after single oral or intravenous doses are very similar based on submitted data in fasted humans and nonclinical studies. Therefore, results of these studies were considered acceptable by the Pharm Tox review to support the labeling (Section 8) update of Zemplar Capsules. In conclusion, no new data was submitted in this application and no further nonclinical studies were required as a result of the current Pharm Tox review of this submission.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

As kidney function decreases, kidneys are less able to convert enough 25-OH vitamin D to its active form, 1, 25-diOH vitamin D, and to adequately excrete phosphate. When this happens, less calcium is absorbed through the intestines and the higher serum phosphorous concentrations can lead to insoluble calcium phosphate precipitation removing additional calcium from the circulation. The resulting hypocalcemia triggers secondary hyperparathyroidism due to an increase in secretion of PTH from the parathyroid in an attempt to restore normal serum calcium. Chronic increase in serum PTH leads to a high turnover state in the bone with changes to bone architecture and leaching of the mineralized calcium producing renal osteodystrophy and increased fracture risk.

Treatment of this condition involves supplementation with calcium and vitamin D and restriction of phosphorous intake in order to improve total body stores of calcium and limit the secondary hyperparathyroidism.

4.4.2 Pharmacodynamics

No new pharmacodynamic data was included in this submission.

4.4.3 Pharmacokinetics

CKD Stages 3 and 4
The observed exposure seen in Study M10-149 Part 1 following a single 3 mcg paricalcitol dose was similar to what was predicted using the population pharmacokinetic model.

Table 1 Comparison of Observed Versus Predicted Exposures in CKD Stages 3 and 4 Combined

	Observed Values	Predicted Values
Pharmacokinetic Parameter (Units)	**Stages 3 and 4 Combined (N = 12)**	**Stages 3 and 4 Combined (N = 12)**
T_{max} (h)	4.2 ± 1.6	4.2 ± 0.5
C_{max} (ng/mL)	0.13 ± 0.05	0.10 ± 0.03
AUC_{∞} (ng•h/mL)	2.87 ± 0.84	3.26 ± 1.18
$t_{1/2}$[a] (h)	14.2 ± 4.4	20.0 ± 4.9

a. Harmonic mean ± pseudo standard deviation.

Cross reference: PK/PD Report (R&D/15/0489)

Source Table 5 Summary of Clin Pharm peds.pdf

CKD Stage 5
The exposure-clinical response base model structure and population estimates were previously determined for adult CKD Stage 5 subjects and adapted for parameter estimation in pediatric subjects age 10 to 16 years with CKD Stage 5. Exposure-response modeling was performed to obtain the iPTH, calcium, and phosphorus response in the pediatric population based on the adult CKD Stage 5 model structure using the pharmacokinetic characteristics estimated for the pediatric population ages 10 to 16 years at the given doses and adjusted parameter estimates. The validation (see Fig. 5 in the applicant's Summary of Clin Pharm peds.pdf) shows that the model developed for adult subjects and the adjusted pharmacokinetic parameter estimates reasonably predict the observed iPTH, calcium, and phosphorus response in CKD Stage 5 pediatric subjects receiving paricalcitol, confirming that pediatric subjects respond similarly to adult subjects.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	M10-149	5.3.5.1	Part 1: Determine safety, tolerability, pharmacokinetics of a single dose of 3 µg Zemplar capsules in pediatric subjects with moderate to severe CKD (Stages 3 and 4) Part 2: Determine safety and efficacy of Zemplar capsules compared to placebo in decreasing serum iPTH in pediatric subjects with CKD Stages 3 and 4 in 12 weeks of double-blind study drug followed by minimum of 12 weeks open-label Zemplar capsules	Phase 3 Part 1: OL, single-dose, nonfasting, multicenter PK Part 2: Randomized, double-blind, placebo-controlled multicenter safety and efficacy for 12 weeks followed by OL for 12 weeks, all subjects receive Zemplar capsules Follow-Up Phase: Open label, all subjects receive Zemplar capsules	Part 1: paricalcitol 3 µg, single dose; PO Part 2: Double-blind: Zemplar capsules: 1 – 3 µg TIW or placebo TIW; PO OL: Zemplar capsules 1 – 6 µg TIW; PO Follow-Up Phase: Zemplar capsules, 1 – 6 µg TIW; PO	Part 1: 12 Part 2: 37 enrolled; 36 dosed	Pediatric subjects 10 to 16 years old with CKD Stage 3 or 4	Part 1: single dose Part 2: 12 weeks double-blind followed by 12 weeks open-label; then Follow-Up Phase until last subject discontinued or completed the 24-week treatment phase	Completed; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	M11-612	5.3.5.2	Evaluate the safety of paricalcitol capsules for the treatment of SHPT in pediatric subjects ages 10 to 16 years with CKD Stage 5 who are receiving PD or HD, through the evaluation of the incidence of hypercalcemia	Phase 3, open-label, single-arm, multicenter	Zemplar capsules TIW; starting dose: [iPTH in pg/dL]/120 = µg paricalcitol rounded down to the nearest whole number, not to exceed 16 µg TIW	13	Pediatric subjects 10 to 16 years old with CKD Stage 5 and receiving PD or HD	12 weeks	Completed; Full

5.2 Review Strategy

Part 2 of study M10-149, the double-blind, randomized, placebo-controlled, pivotal safety and efficacy study for the approval of Zemplar Capsules in the treatment of secondary hyperparathyroidism in CKD Stage 3 and 4 pediatric patients age 10 to 16 years, was reviewed independently by this medical reviewer and Dr. Crackel from Biometrics. Both the biometrics team and the clinical team collaborated on their independent findings before making their final recommendations.

Efficacy in CKD Stage 5 pediatric patients age 10 to 16 years was extrapolated using adult PK data in the CKD Stage 5 population, pediatric PK data in CKD Stage 3 and 4 patients from Part 1 of study M10-149, pediatric population PK data from Study M11-612 and the applicant's exposure-response modeling. These data were reviewed by the OCP review team of Drs. Lau, Ma, and Mehrotra.
Supportive efficacy data and safety in the CKD Stage 5 pediatric patients age 10 to 16 years in Study M11-612 were reviewed by this medical reviewer.

5.3 Discussion of Individual Studies/Clinical Trials

The pediatric Study M10-149 (CKD Stage 3 and 4) will fulfill the PMR 1814-1 issued under the Zemplar Capsules NDA 021606 approved on May 26, 2005 and Study M11-612 (CKD Stage 5) will fulfill the PMR 2094-1 issued under the Zemplar Capsules sNDA 021606/S-004 approved on June 29, 2009. Both Phase 3 Zemplar Capsule studies were conducted under IND (b) (6).

Study M10-149 was composed of two parts. Part 1 was an open-label, single-dose, non-fasting, multicenter study evaluating the pharmacokinetics of paricalcitol capsules. Part 2 was a 12-wk randomized, double-blind, placebo-controlled multicenter study to evaluate the safety and efficacy of Zemplar in lowering serum intact parathyroid hormone (iPTH) in pediatric predialysis subjects with secondary hyperparathyroidism due to CKD (Stage 3 and Stage 4) followed by a 12-wk open label safety extension study in which all subjects received Zemplar Capsules.

Study M11-612 was an open-label, single-arm, multicenter study designed to evaluate the safety of Zemplar Capsules in pediatric dialysis subjects with secondary hyperparathyroidism due to Stage 5 CKD and to obtain population PK data in these patients. It was agreed to that while the efficacy data in study M11-612 could be used to support the indication in the pediatric CKD Stage 5 population that the primary efficacy evaluation would come from extrapolation of adult CKD Stage 5 PK data and pediatric CKD Stage 3, 4 and 5 data using population PK and the applicant's exposure response model.

6 Review of Efficacy

Efficacy Summary

Supplement-016
Treatment of secondary hyperparathyroidism in predialysis pediatric patients ages 10 to 16 years with CKD (Stages 3 and Stage 4), S-016, was assessed in study M10-149 using the same endpoint, two consecutive 30% decreases from baseline iPTH between Zemplar and placebo treated patients which had been used to approve Zemplar Injection for the treatment of pediatric dialysis patients with end-stage renal disease (3/2004). While iPTH is a surrogate for efficacy in this study population, the Division has accepted that reduction in iPTH levels can result in improved clinical outcomes as discussed in more details under the General Discussion of Endpoint in section 6.1.1. Study M10-149 consisted of two parts. Part 1 was a single dose PK

Supplement-017

Efficacy in pediatric dialysis patients ages 10 to 16 years was extrapolated from adult PK data using a population PK analysis and the applicant's exposure response model, while efficacy from the open-label, single-arm study M11-612 was considered primarily as supportive data. The population PK analysis was performed based on combined pediatric data from studies M10-149 and M11-612 utilizing the same exposure response model used for the approval of the indication in adults with CKD Stage 5 (see Section 3.2 of the Clin Pharm review by Drs. Lau, Ma and Mehrota). The Clin Pharm review was able to confirm the applicant's analysis to support extrapolation of the data to the pediatric population with CKD Stage 5. Study M11-612 was designed as a Phase 3, 12-week, open-label, single-arm, multicenter study to evaluate the safety of paricalcitol capsules in 12 pediatric patients with Stage 5 CKD receiving peritoneal dialysis or hemodialysis. Subjects not naïve to active vitamin D analogs were to complete a 2 to 12 week washout period prior to dosing with paricalcitol. Treatment inclusion criteria included serum iPTH $\geq$ 300 pg/mL and $\leq$ 2000 pg/mL, normal serum calcium levels $\geq$ 8.4 mg/dL to $\leq$ 10.2 mg/dL and phosphorous levels $\leq$ 6.5 mg/dL. The starting three times a week (TIW) dose of paricalcitol was calculated using the last iPTH laboratory value in pg/mL prior to Day 1 and the equation (iPTH/120) which was expected to result in a low risk of hypercalcemia based on data from the applicant's exposure response model. Dose increases in 1mcg TIW increments could occur at 4-week intervals starting with Week 4. Dose decreases at 2mcg TIW could occur at any visit if in the opinion of the investigator, subject safety was at risk. Dose adjustments were made to maintain serum iPTH between 150pg/mL and 300pg/mL, serum calcium levels < 10.2mg/dL, and serum phosphorous levels < 6.5mg/dL. There was no formal primary endpoint analysis in this open-label, single-arm, safety study without a comparator group. However, the proportion of subjects achieving two consecutive $\geq$30% reductions from baseline in iPTH at 12 weeks was calculated as supportive evidence of efficacy. The percentage of responders achieving this endpoint, which was the same as the primary endpoint in Study M10-149, was higher in study M11-612 at 61.5% in the CKD Stage 5 population compared to the rate of 27.8% seen in study M10-149 in the CKD Stages 3 and 4 population. Part of the reason for the greater apparent efficacy in this study was likely due to the higher baseline iPTH levels in the dialysis population in study M11-612 (884 ± 374pg/mL) compared to the baseline iPTH levels in the predialysis population in study M10-149 (150 ± 82pg/mL). These data are comparable to the results seen in NDA 20-819 with Zemplar Injection compared to placebo in the pediatric dialysis population 9/15=60% vs. 3/14=21%, respectively, and so are supportive of the efficacy of Zemplar Capsules in the treatment of secondary hyperparathyroidism in the pediatric dialysis population. Analysis of the data showed that most patients were treated adequately with between 3 and 4 mcg of Zemplar Capsules three times a week, and the highest dose used in the study was 13mcg.

Supplement-16 Pediatric study under PREA for the treatment of pediatric patients aged 10 to 16 years with secondary hyperparathyroidism due to CKD (Stage 3 and Stage 4).

6.1 Indication

Zemplar is a vitamin D analog indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (Stages 3 and 4) in pediatric patients 10 to 16 years of age.

6.1.1 Methods

General Discussion of Endpoints
Elevated serum PTH levels in patients with secondary hyperparathyroidism due to CKD are associated with metabolic bone disease and an increased risk for soft tissue calcifications. It seems reasonable to assume that drugs such as calcimimetics and vitamin D analogs which can improve biochemical markers associated with secondary hyperparathyroidism and metabolic bone disease (i.e. PTH, calcium, phosphorus, alkaline phosphatase, and bone turnover markers) may in the long term result in improved bone health, fewer soft tissue calcifications and improved clinical outcomes. While there are no data from prospective clinical trials directly demonstrating that reduction in PTH levels with calcimimetics or vitamin D improves clinical outcomes (e.g., bone fractures, cardiovascular disease, etc.), the Division has accepted PTH reduction as a surrogate marker of benefit for this indication. The Division's approach is consistent with expert opinions described in past and current treatment guidelines for chronic kidney disease management (KDIGO 2009) which recommend treating elevated PTH and factors that contribute to secondary hyperparathyroidism (hyperphosphatemia, vitamin D insufficiency, hypocalcemia) to prevent mineral and bone complications of CKD. Large trials of long duration would be required to examine the effect of calcimimetics and vitamin D treatment on hard outcome measures and the trials may not be feasible in this population. In the absence of clinical trial data directly informing the question of clinical benefits gained by normalizing PTH, calcium, and phosphorus in the setting of CKD, the Division has accepted substantial PTH reduction as a surrogate to determine the efficacy of calcimimetics and vitamin D analogs.

Zemplar Injection was approved to control secondary hyperparathyroidism in adult patients with chronic renal failure on hemodialysis using a surrogate endpoint based on mean decrease from baseline in serum iPTH in a double-blind, placebo-controlled trial (4/1998). In follow up studies in pediatric patients with end-stage renal disease, Zemplar Injection was approved using two consecutive >30% decreases from baseline in serum iPTH between Zemplar and placebo-treated patients as the primary endpoint (3/2004).

Zemplar Capsules were also approved for the management and treatment of secondary hyperparathyroidism associated with CKD (Stages 3 and Stage 4) in adults using two consecutive >30% decreases from baseline in serum iPTH between Zemplar and placebo treated patients as the primary endpoint (5/2005).

In this submission, treatment of secondary hyperparathyroidism in predialysis pediatric subjects 10 to 16 years of age with CKD (Stages 3 and Stage 4) was assessed in study M10-149 using the same endpoint, two consecutive >30% decreases from baseline in serum iPTH between Zemplar and placebo treated patients.

Study Design
Part 1 of Study M10-149 was a single dose PK study of Zemplar Capsules (3mcg) under nonfasting conditions in 12 pediatric subjects ages 10 to 16 years with CKD, Stage 3 (n=6) or Stage 4 (n=6).

Subjects who were currently taking an active vitamin D agonists had to undergo a 2 to 10 week washout period prior to enrollment in the study.

Inclusion criteria (including but not limited to)-

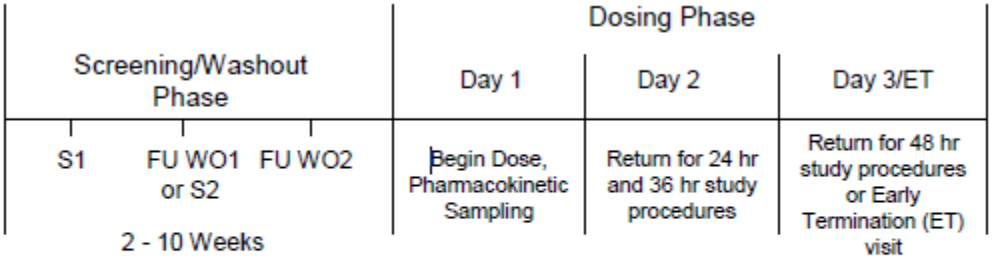
- Male or female subject ≥ 10 years old and ≤ 16 years old
- Subject had CKD Stage 3 or Stage 4 as determined by eGFR (15 to 59 mL/min/1.73 m^2) at screening
- If taking phosphate binders, the subject had to have been on a stable dose (same type and regimen) for at least 4 weeks prior to the Screening Phase
- Female subjects must have had a negative pregnancy test prior to treatment and be following acceptable forms of contraception
- Subjects were not expected to begin dialysis for at least 6 months
- If receiving growth hormone must have been on therapy for > 3 months and expecting to continue to receive it throughout the treatment phase.
- Screening criteria
    - iPTH measurement ≥ 60 pg/mL (Stage 3) or ≥ 90 pg/mL (Stage 4)
    - Adjusted serum calcium value ≥ 8.2 mg/dL to ≤ 10.5 mg/dL
    - Serum phosphorus value ≥ 2.0 mg/dL to ≤ 6.0 mg/dL
- Treatment criteria (active vitamin D analog naïve, or after 2-4 week washout)
    - iPTH measurement ≥ 75 pg/mL (Stage 3) or ≥ 110 pg/mL (Stage 4)
    - Adjusted serum calcium value ≥ 8.4 mg/dL to ≤ 10.2 mg/dL (normal range)
    - Serum phosphorus value ≥ 2.5 mg/dL to ≤ 5.8 mg/dL (4.7mg/dL is ULN)
    - 25-OH Vitamin D level ≥ 30 ng/mL (Part 2 Only)

Exclusion criteria (including but not limited to)-

- Weight < 25 kg (55 lbs)
- Subjects considered by the investigator to be an unsuitable candidate (e.g., unable to swallow capsules, lack of a telephone, evidence of poor compliance, HIV positive or with history of illicit drug or alcohol abuse) to receive paricalcitol capsules or who the investigator felt would be put at risk by the study procedures
- Taking phosphate supplements

- Symptomatic or significant hypocalcemia requiring active Vitamin D therapy (i.e., calcitriol, paricalcitol, doxercalciferol or alfacalcidol) within 6 months prior to the Screening Phase
- Taking maintenance calcitonin, bisphosphonates, cinacalcet, glucocorticoids in an equivalent dose of > 5 mg prednisone daily, or other drugs known to affect calcium or bone metabolism within 4 weeks prior to treatment
- Chronic gastrointestinal disease, which in the investigator's opinion may cause significant gastrointestinal malabsorption or status post small bowel transplant
- History of active kidney stones within 6 months prior to screening
- History of acute kidney failure within 12 weeks of Screening Phase defined as an acute increase in serum creatinine
- History of organ transplant except for bone marrow transplant recipients who were off of immunosuppressant therapy

Figure 1 Study Schematic-Part 1 PK Portion of Study M10-149



S1, S2 (Screening Visits 1, 2)
FUWO1, FUWO2 (Follow-Up Washout Visits 1, 2)

Source Fig.1 Study M10-149 CSR

Subjects in Part 1 were administered 3mcg paricalcitol orally with approximately 100 mL of water at approximately 8:00 am, 30 minutes after breakfast on Study Day 1. Blood samples for the paricalcitol assay were obtained at 0, 1, 2, 4, 6, 8, 12, 24, 36 and 48 hours.

Table 2 Study Activities-Part 1 Single Dose PK Portion of Study M10-149

	Screening/Washout Phase[a]			Dosing Phase		
Activity	S1	FUWO1 or S2[b]	FUWO2	Day 1	Day 2	Day 3/ET[c]
Informed Consent/Assent[d]	X					
Contact IVRS/IWRS[e]	X			X		X
Medical History,[f] Alcohol and Tobacco Use	X	X	X	X		
Weight/Height[g]	X	X	X	X		X
Concomitant Medications	X	X	X	X	X	X
Physical Examination[h]	X	X	X	X		X
12-Lead ECG				X		X
Vital Signs (including pulse rate and temperature)	X	X	X	X	X	X
Pregnancy Test (Females only) – Urine (u), Serum (s)	X (s)	X (s)	X (s)	X (u)		
Limited Chemistry[i] (Ca, P, iPTH, Albumin, and Creatinine)	X	X	X			
Complete Chemistry, Hematology and Urinalysis				X		X
Hepatitis Panel	X					
eGFR Calculation	X	X	X			
Vitamin D Tests[j]	X					
Drug/Alcohol Screen	X	X	X	X		
Study Drug Administration				X		
Blood Samples for Paricalcitol Assay[k]				X	X	X
Adverse Event Monitoring	X[l]	X[l]	X[l]	X	X	X

a. Follow-up reassessment for VDRA washout subjects only.
b. Optional screening visit.
c. Performed at study completion or when a subject is discontinued from the study.
d. Was to be completed prior to performing any study procedures. Screening/Washout Phase procedures were to be performed within approximately 2 weeks before Treatment Day 1.
e. IVRS/IWRS was to be contacted if subject screen failed or at Day 1 for subjects that successfully complete Screening/Washout Phase.
f The medical history was to be updated at each Screening, FU WO and at Day 1 Visit.
g. Weight and height were to be measured with the subject wearing indoor clothing without shoes.
h. Focused PE (HEENT/Lung/heart/abdomen/brief skin survey) was to be performed at Screening visit (S1), optional at S2 and S3 (done if findings were present at S1), complete PE will be performed at Day 1 and Day 3/ET visit.
i Limited Chemistry. Creatinine results used in GFR calculations, using the Schwartz formula.
j. Vitamin D tests: Calcidiol (25-hydroxyvitamin D) and Calcitriol (1,25-dihydroxyvitamin D).
k Samples were collected at 1, 2, 4, 6, 8, 12, 24, 26, and 48 hours after dosing (Section 9.5.1.1.1).
l. Serious adverse events only.

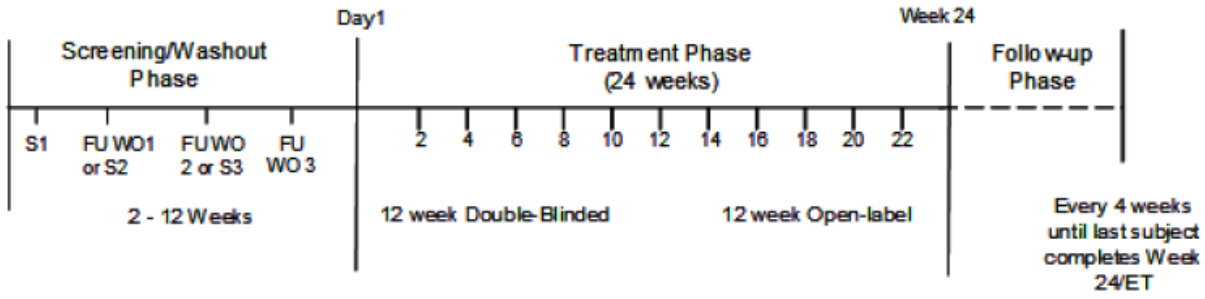
Source Table 5 Study M10-149 CSR

PK parameters measured in Part 1 of the study included: T_{max}, AUC_{∞}, C_{max}, and $t_{1/2}$.

Part 2 of Study M10-149 was a 12-wk double-blind, placebo-controlled, randomized (1:1), safety and efficacy study with a 12-wk open label extension period in 36 pediatric patients 10 to 16 years of age with secondary hyperparathyroidism associated with CKD Stage 3 and Stage 4. Twenty-one subjects with CKD Stage 3 and 15 subjects with CKD Stage 4 were enrolled in Part 2 of the study. Subjects were to take oral paricalcitol capsules three times weekly (TIW) for a minimum of 24 weeks.

Subjects who were currently taking an active vitamin D agonists had to undergo a 2 to 12 week washout period prior to enrollment in the study. There were 13 scheduled visits during the Treatment Phase occurring every other week starting at Treatment Day 1 through Treatment Week 24 (Treatment Day 1, Treatment Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24). Subjects were randomized using an interactive voice response system (IVRS) in a 1:1 ratio to receive either paricalcitol capsules or placebo.

Figure 2 Study Schematic-Part 2 Safety and Efficacy Portion of Study M10-149



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 Fig. 4 Study M10-149 CSR

Table 3 Study Activities-Part 2 Safety and Efficacy Portion of Study M10-149

	Screening/Washout Period[a]				Treatment Phase			Follow-up Phase[b]
Activity	S1	FUWO1 or S2	FUWO2 or S3	FUWO3	Day 1	Weeks 2 to 22[c]	Week 24/ET Visit[d]	Every 4 Weeks Until LSLV
Informed Consent/Assent[e]	X							
PedsQL™ 4.0 Generic Core Scales[f]					X	X	X	X[g]
Medical History, Alcohol and Tobacco Use	X	X	X	X				
Weight and Height	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Physical Examination[h]	X	X	X	X	X		X	
12-lead ECG					X		X	
Vital Signs (including pulse rate and temperature)	X	X	X	X	X	X	X	X
Pregnancy Test[i] (Females Only) – Urine (u), Serum (s)	X (s)	X (s)	X (s)	X (s)	X (u)	X (u)	X (u)	X (u)
Limited Chemistry (Ca P, iPTH, albumin and Creatinine)[j,k]	X	X	X	X		X[j]		X[i]
Complete Chemistry, Hematology and Urinalysis[k]					X	X[l]	X	
Cystatin C					X	X	X	X
Hepatitis Panel	X							
eGFR Calculation	X	X	X	X	X	X	X	X
Vitamin D Tests[m]	X	X	X	X		X[m]	X	X[m]
Drug/Alcohol Screen	X	X	X	X	X			
Bone Markers[n]	X				X		X	
Fibroblast Growth Factor 23 (FGF-23)[o]					X	X	X	X[o]
Blood Samples for Paricalcitol Assay and Dosing Card[p]						X	X	X
First Morning Void[q] (FMV) Urine for UACR					X	X	X	
Contact IVRS/IWRS (Dispense Study Drug)[r]	X				X	X	X	X
Study Drug Compliance						X	X	X
Monitor Adverse Events[s]	X	X	X	X	X	X	X	X

LSLV = Last subject, last visit

a. The Washout Period was for subjects not naïve to VDR Activators. The Washout Period was to last for a minimum of 2 weeks and up to a maximum of 14 weeks.

b. A study follow-up telephone call was to occur for all subjects.

c. Study visits could occur every 2 to 4 weeks depending on the Ca laboratory results which may have triggered unscheduled visits for dose adjustments (increase, decrease, or maintain current dose) as required. Unscheduled visits due to P and iPTH were optional at the investigator's discretion. All subjects were required to complete a Week 2 visit and monthly visits at Weeks 4, 8, 12, 16, 20, and 24/ET for the study. Subjects enrolled under Amendment 5 were eligible to continue to be followed every 4 weeks until the last subject completes their final (Week 24/ET) visit.

d. Was to be performed within 5 days after last dose for all subjects including early termination subjects.

e. Was to be completed prior to the performance of any study procedures.

f. PedsQL™ 4.0 Generic Core Scales were to be given to the subject and parent to complete at their Day 1, Week 12, and Week 24 /ET visits (as applicable by country).

g. PedsQL™ 4.0 Generic Core Scales were to be given to the subject and parent to complete at Follow-Up visit Week 36 and every 12 weeks thereafter (as applicable by country).

h. Focused PE (HEENT/Lung/heart/abdomen/brief skin survey) was to be performed at Screening visit (S1), optional at S2 and S3 (performed if findings were present at S1), complete PE was to be performed at Day 1 and Week 24 /ET visits.

Source Table 6 Study M10-149 CSR

Results of the PK analysis in Part 1 demonstrated a paricalcitol exposure that was higher than seen in adults i.e. AUC > 2.4 µg•hr/mL thus, the starting paricalcitol capsules dose selected for Part 2 of the study was decreased from 2mcg to 1mcg TIW (3mcg per week). Subjects who received placebo during the double-blind treatment phase of Part 2 were to begin taking paricalcitol 1mcg TIW (3mcg per week) at Week 12.

Dosing decisions were based on the results of the limited chemistry evaluation (consisting of serum calcium, phosphorus, iPTH and albumin) measured every 2 weeks. Dose increases were limited to every 4 weeks starting with Treatment Week 4. However, dosing could be adjusted at

any time, if in the opinion of the investigator, subject safety was at risk. Dose adjustments were to be made to maintain serum calcium levels <10.2mg/dL, iPTH levels between 35 and 70pg/mL (Stage 3) or between 70 and 110pg/mL (Stage 4) and serum phosphorous levels <5.8mg/dL:

DOSING DECISIONS BASED ON IPTH
Stage 3 CKD

- If repeat iPTH at two consecutive visits was > 70 pg/mL with corrected calcium ≤ 10.2 mg/dL, and phosphorus ≤ 5.8 mg/dL the dose of study drug could be increased by 1mcg TIW.
- If iPTH was ≥ 35 pg/mL and ≤ 70 pg/mL with corrected calcium ≤ 10.2 mg/dL and phosphorus ≤ 5.8 mg/dL study drug was to be maintained at the current dose;
- If iPTH was < 35 pg/mL return at the next scheduled visit to undergo a limited chemistry evaluation:
    - If the repeated iPTH was < 35 pg/mL, AND:
        - If serum calcium was > 9.5 mg/dL and < 10.2 mg/dL then the dose of study drug was to be reduced by 1mcg TIW and return in 2 weeks for a repeat PTH measurement
          OR
        - If serum calcium was ≤ 9.5 mg/dL then study drug was to be maintained at the current dose.

Stage 4 CKD

- If repeat iPTH at two consecutive visits was > 110 pg/mL with corrected calcium ≤ 10.2 mg/dL and phosphorus ≤ 5.8 mg/dL then the dose of study drug was to be increased by 1mcg TIW.
- If iPTH was ≥ 70 pg/mL and ≤ 110 pg/mL with calcium ≤ 10.2 mg/dL and phosphorus ≤ 5.8 mg/dL study drug was to be maintained at the current dose;
- If iPTH was < 70 pg/mL, then the subject was to return at the next scheduled visit to undergo a limited chemistry evaluation:
    - If the repeated iPTH was < 70 pg/mL, AND:
        - If serum calcium was > 9.5 mg/dL but < 10.2 mg/dL dose of study drug was to be reduced by 1mcg TIW and return in 2 weeks for a repeat PTH measurement
          OR
        - If serum calcium was ≤ 9.5 mg/dL then study drug was to be maintained at the current dose.

DOSING DECISIONS FOR CALCIUM LEVELS (Stage 3 and 4 CKD)

- If at any time adjusted calcium was assessed to be > 10.2 mg/dL the Study Site was to make every effort to contact the subject within 24 hours, and instruct him or her to hold their dose of study drug.
- Starting within 2 weeks (at an unscheduled visit) the site was to check serum calcium value weekly until it was observed to be < 10.0 mg/dL

- Restarting or discontinuing study medication was dependent on the following:
    - For a subject receiving 1mcg TIW of study drug:
        - If calcium was observed to be ≤ 10.2 mg/dL within 2 weeks, the subject may have resumed 1mcg TIW dose of study drug.
        - If the calcium was > 10.2 mg/dL after 2 weeks the subject was to be discontinued from treatment and withdrawn from the study.
    - For a subject receiving ≥ 2mcg TIW:
        - When calcium returned to ≤ 10.2 mg/dL study drug was to be restarted at a dose 1mcg TIW lower than the previous dose.
        - If calcium remained elevated, the study drug was to be discontinued and the subject withdrawn from the study.

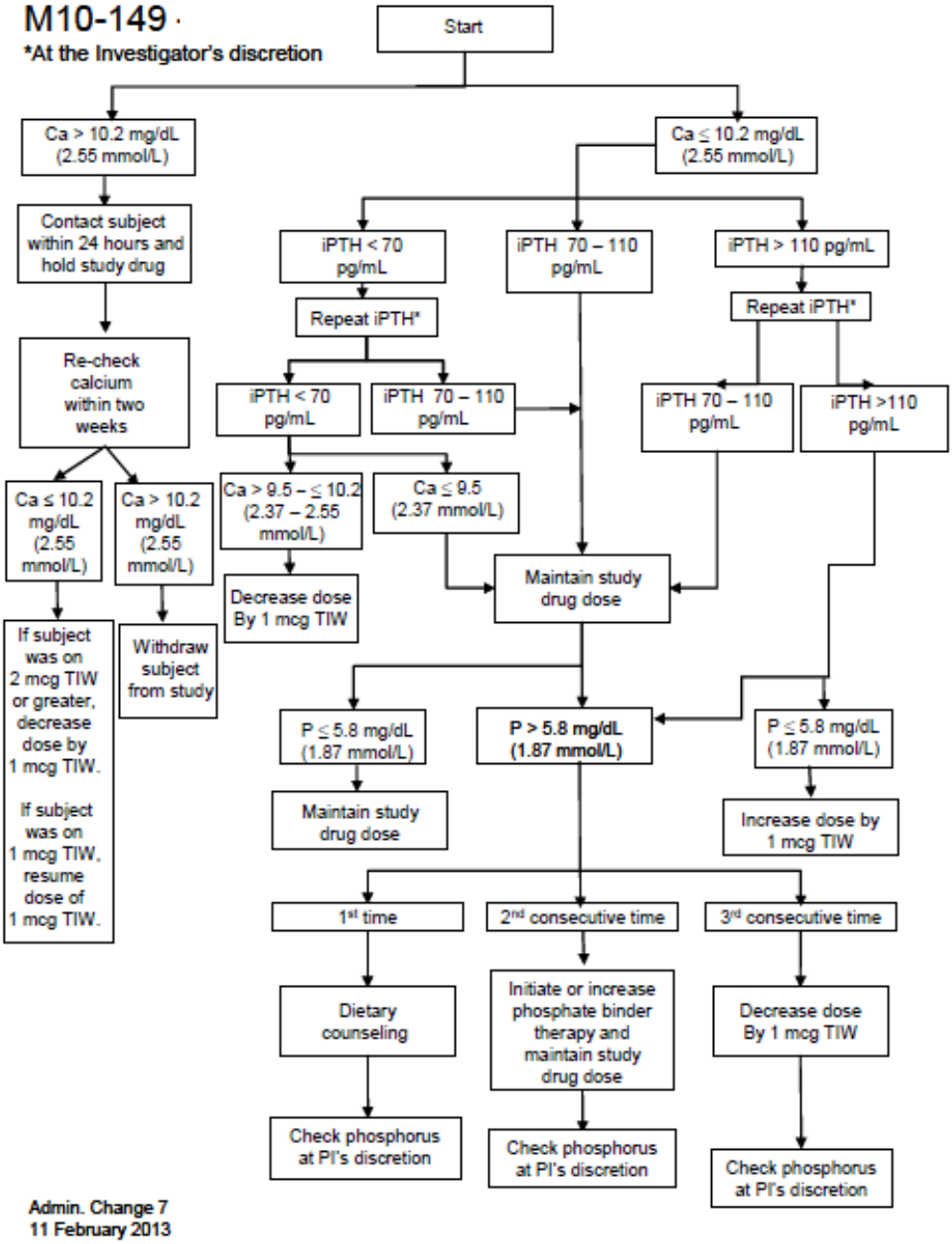
DOSING DECISIONS FOR PHOSPHOROUS LEVELS (Stage 3 and 4 CKD)

- First occurrence of phosphorus > 5.8 mg/dL subject to receive dietary counseling;
- Second consecutive occurrence of phosphorus > 5.8 mg/dL phosphate binder therapy was to be initiated or modified for subjects already having phosphate binder therapy;
- Third consecutive occurrence of phosphorus > 5.8 mg/dL the dose of study drug was to be reduced by 1mcg TIW:
    - If the subject was receiving 2mcg TIW, then the dose was to be decreased to 1mcg TIW;
    - If the subject was receiving 1mcg TIW, then the study drug was to be discontinued and the subject withdrawn from the study.

Throughout the Safety and Efficacy Portion, Part 2 of the study if a subject receiving a 2mcg dose TIW required dose reduction for any reason, then the dose was to be restricted to 1mcg TIW taken no more frequently than every other day. If a subject required a dose reduction below 1mcg TIW, the study drug was to be discontinued and the subject withdrawn from the study.

As part of protocol amendment 7 the dosing decisions were changed as updated in the algorithm in Figure 3. Serum iPTH and phosphorus were to be repeated per the Investigator's discretion.

Figure 3 Dosing Decision Schematic-Part 2 Safety and Efficacy Portion of Study M10-149



Source Fig. 8 Protocol Administrative Change 7 M10-149 25 June 2013, *At investigator's discretion

Primary Endpoint-
The percent of subjects that achieve two consecutive ≥30% reductions in serum iPTH from baseline during the 12-wk double-blind period.

Secondary Endpoints-

- The proportion of subjects who attained a final iPTH value within KDOQI target ranges for each CKD stage (final result-not significant, see M10-149 CSR applicant's Table 26)
- The mean % change in iPTH from baseline to (Weeks 2, 4, 8, and 12) (final result-repeated measures analysis was significant at all weeks, see M10-149 CSR applicant's Table 28)
- The proportion of subjects who attained a final value of KDOQI target for calcium and for phosphorus within age appropriate normal ranges (final result-not significant for both, see M10-149 CSR applicant's Tables 29 and 30)
- The mean change in first morning void urinary albumin to creatinine ratio (FMV UACR) from baseline to (Weeks 4, 8, and 12) (final result-not significant at all weeks, see M10-149 CSR applicant's Table 31)

Tertiary Endpoint-

- PROs Subject & Caregiver Reporting for Wk 12 vs baseline-Pediatric Quality of Life (PedsQL™ 4.0) (not significant, see M10-149 CSR applicant's Tables 32 and 33)

6.1.2 Demographics

In the PK Portion, Part 1 there was a total of 12 subjects, 3 female (25%) and 9 male (75%) with a mean age of 13.5 years. The majority of subjects were Caucasian, composing 10/12 (83%); 1 subject (8%) was Black and 1 subject (8%) was American Indian/Alaska Native. There were 4 subjects (33%) with Hispanic or Latino ethnicity.

In the Efficacy and Safety Portion, Part 2 there was a total of 36 subjects with CKD Stage 3 and 4 in the ITT Dataset in the 12-week, double-blind, treatment phase, 11 female (31%) and 25 male subjects (69%) with a mean age of 13.6 years. The majority of ITT dataset subjects were Caucasian 31 subjects (86%), 3 subjects (8%) were Asian and 2 subjects (6%) were of other races. There were 9 subjects (25%) with Hispanic or Latino ethnicity. Most of the subjects were from US sites (18/36=50%), followed by Spain n=6, Portugal n=5, Germany n=3, Great Britain n=3 and Singapore n=1.

Table 4 Demographic and Baseline Characteristics for Part 2-Safety and Efficacy Portion of Study M10-149

Characteristic		Treatment Group, n (%) Placebo N = 18	Paricalcitol N = 18	Total N = 36	p-value
Sex, n (%)	Female	5 (27.8)	6 (33.3)	11 (30.6)	1.000[a]
	Male	13 (72.2)	12 (66.7)	25 (69.4)	
Race, n (%)	White	17 (94.4)	14 (77.8)	31 (86.1)	0.229[a]
	Black	0	0	0	
	Asian	0	3 (16.7)	3 (8.3)	
	Other	1	1 (5.6)	2 (5.6)	
Ethnicity	Hispanic or Latino	5 (27.8)	4 (22.2)	9 (25.0)	1.000[a]
	No ethnicity	13 (72.2)	14 (77.8)	27 (75.0)	
Age, years	Mean ± SD	13.3 (1.75)	13.9 (1.81)	13.6 (1.78)	0.356[b]
	Median (Min – Max)	14.0 (10 – 16)	14.0 (10 – 17)	14.0 (10 – 17)	
CKD Stage	Stage 3	11 (61.1)	10 (55.6)	21 (58.3)	1.000[a]
	Stage 4	7 (38.9)	8 (44.4)	15 (41.7)	
Weight, kg	Mean ± SD	48.2 (12.25)	46.7 (10.22)	47.4 (11.15)	0.682[b]
	Median (Min – Max)	45.0 (29 – 78)	46.0 (31 – 66)	45.5 (29 – 78)	
Weight, kg (females)	Mean ± SD	42.8 (3.35)	47.7 (14.35)	45.5 (10.67)	0.481[b]
	Median (Min – Max)	44.0 (37 – 45)	40.5 (36 – 66)	43.0 (36 – 66)	
Weight, kg (males)	Mean ± SD	50.3 (13.85)	46.2 (8.19)	48.3 (11.45)	0.378[b]
	Median (Min – Max)	52.0 (29 – 78)	46.0 (31 – 62)	47.0 (29 – 78)	

a. p-value for differences between placebo and paricalcitol from Fisher's exact test.

b. p-value for differences between placebo and paricalcitol are based on one-way ANOVA with treatment as the factor.

Cross reference: Table 14.1__2.1.1.2, Table 14.1__2.1.2.2, Table 14.1__2.1.3.2

Source Table 15 Study M10-149 CSR

Medical officer's comments:
Given that there were only 36 patients in this study there was a reasonable distribution of most demographic characteristics between treatment groups. According to the NAPRTCS 2008 Annual Report African Americans make up almost 19% of the pediatric CKD population so they are clearly underrepresented in this study. Males on the other hand are slightly overrepresented here 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.

Table 5 Baseline Chemistry Lab Values for Part 2-Safety and Efficacy Portion of Study M10-149

Characteristic		Treatment Group: Placebo N = 18	Treatment Group: Paricalcitol N = 18	Total N = 36	p-value[a]
Albumin		n = 18	n = 18	n = 36	
(g/dL)	Mean ± SD	4.66 ± 0.37	4.52 ± 0.42	4.59 ± 0.40	0.280
	Median	4.70	4.65	4.70	
	Min – Max	3.50 – 5.10	3.10 – 4.90	3.10 – 5.10	
Serum Creatinine		n = 18	n = 18	n = 36	
(mg/dL)	Mean ± SD	2.33 ± 0.77	2.36 ± 0.96	2.34 ± 086	0.916
	Median	2.16	2.11	2.16	
	Min – Max	1.28 – 3.86	1.07 – 4.20	1.07 – 4.20	
Corrected		n = 18	n = 18	n = 36	
Calcium	Mean ± SD	9.86 ± 0.42	9.70 ± 0.35	9.78 ± 0.39	0.214
(mg/dL)	Median	9.94	9.68	9.83	
	Min – Max	8.74 – 10.50	9.26 – 10.54	8.74 – 10.54	
Inorganic		n = 18	n = 18	n = 36	
Phosphate	Mean ± SD	4.44 ± 0.83	4.52 ± 0.56	4.48 ± 0.70	0.731
(mg/dL)	Median	4.40	4.65	4.50	
	Min – Max	3.30 – 5.90	3.40 – 5.39	3.30 – 5.90	
iPTH		n = 18	n = 18	n = 36	
(pg/mL)	Mean ± SD	155.44 ± 97.26	144.28 ± 64.86	149.86 ± 81.67	0.688
	Median	103.00	131.50	124.50	
	Min – Max	46.00 – 368.00	57.00 – 306.00	46.00 – 368.00	
25-Hydroxy		n = 18	n = 18	n = 36	
Vitamin D	Mean ± SD	40.78 ± 7.90	52.17 ± 50.26	46.47 ± 35.93	0.349
(mg/dL)	Median	39.50	37.00	37.50	
	Min – Max	31.00 – 57.00	30.00 – 248.00	30.00 – 248.00	

a. p-values for difference between treatment groups are based on one-way ANOVA with treatment as the factor.

Cross reference: Table 14.1__5

Source Table 17 Study M10-149 CSR

Three subjects, two in the placebo group (SUBJID=3990205 Ca=10.4mg/dL; 4034001 Ca=10.5mg/dL) and one in the paricalcitol group (SUBJID=4031405 Ca=10.54mg/dL), had baseline corrected serum calcium levels of >10.2mg/dL, above the exclusion criteria for the study, at baseline on Study Day 1 but were enrolled in the study. The two placebo patients had normal serum calcium levels during the rest of the double-blind period but SUBJID=3990205 had an elevated serum calcium of 10.3mg/dL during the open label extension on paricalcitol. The subject in the paricalcitol group with an elevated serum calcium on Study Day 1 continued to have elevated corrected serum calcium levels > 10.2 mg/dL at the next visit at Week 2 and was discontinued from the study.

Baseline mean 25-OH vitamin D levels were slightly higher in the paricalcitol group compared to the placebo group with values of 52mg/dL vs. 41mg/dL, due to a single outlier in the

paricalcitol group with a value of 248ng/mL, as the median values were closer together at 37mg/dL and 40mg/dL, respectively. All subjects had screening values for 25-OH vitamin D levels above the upper limit of normal of 30ng/dL prior to dosing on Study Day 1.

Medical officer's comments:
The outlier (SUBJID=1519110) with an extremely high pretreatment screening 25-OH vitamin D value of 248mg/dL in the paricalcitol group normalized his 25-OH vitamin D level by Study Day 84 to 63mg/dL. He was considered a nonresponder as his iPTH increased over the course of the 12 week study; so his exclusion from the study would not have affected the study results. Of note his corrected serum calcium was never above the upper limit of normal despite the high 25-OH vitamin D level.

Baseline mean iPTH values were slightly lower in the paricalcitol group compared to the placebo group with respect to mean values of 144pg/mL vs. 155pg/mL while the opposite was true of median values of 132pg/mL vs. 103pg/m/L, respectively, due to a greater number of high outliers in the placebo group. A total of six subjects, three with Stage 3 and three with Stage 4 CKD, had iPTH levels on Study Day 1 prior to dosing the were below the entry inclusion criteria for the study yet were included in the study data because the prior iPTH measurement during the screening period had been elevated. The sponsor included these six patients in the primary endpoint analysis as they met the predefined inclusion criteria at screening, which was how the study protocol was written.

SUBJID	CKD Stage	Baseline iPTH on Study Day 1	Screening Inclusion Criteria
3990205	3	46	≥ 75pg/mL
1519118	3	57	≥ 75pg/mL
3908003	3	71	≥ 75pg/mL
3908001	4	81	≥ 110pg/mL
3883201	4	88	≥ 110pg/mL
3860701	4	100	≥ 110pg/mL

Medical officer's comments:
Of the 6 subjects with decreased iPTH levels on Study Day 1, prior to drug dosing, that would no longer satisfy the screening inclusion criteria, one subject in the paricalcitol treatment group was a responder. It turns out that this subject (SUBJID=1519118) in the paricalcitol group went from an iPTH of 57p/mL at baseline to 27pg/mL and 24pg/mL at Study Weeks 2 and 4, respectively, before being discontinued from the study. As this was one of the five responders in the paricalcitol group, if this subject was excluded from the study the efficacy results would no longer have been statistically significant. It is this medical reviewer's assessment that it is unclear whether these six patients had true secondary hyperparathyroidism given that they seemed to normalize with no specific treatment prior to dosing on Study Day 1. In the past, because there can be a fair amount of variability in iPTH levels, it has been common practice to use an average baseline

value from the last two screening measurements without measuring a value on Study Day 1. If that had been done in this case SUBJID=1519118 would not have had to have been excluded from the study.

Concomitant Medications of Interest-
A total of seven patients (19%) were on the active vitamin D analog, calcitriol, prior to the study (placebo=2, paricalcitol=5). These patients were to be washed out for a period of 2 to 4 weeks prior to entry into the study (see Table 20 M10-149 CSR).

Medical officer's comments:
Assuming that the active vitamin D analog had not been completely washed out prior to entry into the study, these patients likely would have had higher baseline serum iPTH levels and it would have been harder to show a 30% decrease in iPTH from baseline in these subjects. Since more patients in the paricalcitol group were previously on paricalcitol it could have made it harder to show evidence of efficacy in this study, if they were not adequately washed out prior to the study.

Three placebo patients were on the partially activated vitamin D analog calcifediol and were continued on the medication during the study (see Table 21 M10-149 CSR).

Medical officer's comments:
As none of the placebo patients were responders during the study it is unlikely that treatment with calcifediol impacted the study results.

6.1.3 Subject Disposition

In Part 1, the PK Portion of study M10-149, all 12 subjects completed the study.

In Part 2, the Efficacy and Safety Portion of study M10-149, 108 subjects were screened of which 36 patients met the entrance criteria and were randomized into the study. Twelve subjects in each treatment group (67%) completed the 12-week study. Seven subjects discontinued from the double-blind portion of the study, some for multiple reasons:

- 2 on placebo, (one with AE of hypercalcemia and one with AE of chronic renal failure/required dialysis), and
- 5 on Zemplar (4 because they needed dose reduction below 1mcg TIW which was not considered an AE (three due to hypercalcemia, one due to low serum iPTH), and one with AE of hypercalcemia/consent withdrawal).

Most subjects were assigned 1 to 3mcg TIW dosing throughout the study which corresponds to weekly doses of 3 to 9 mcg, which is somewhat lower than the typical adult dose in this population of 9.5mcg/wk, but consistent with the higher paricalcitol exposure seen in the pediatric patients in the PK study.

29/36=80% continued into open-label (OL) extension. Five subjects (17%) discontinued Zemplar during the open label extension:

- four from the original placebo group (two with AEs of hypercalcemia, one with AE of kidney function decreased requiring dialysis, and one vitamin D decreased <7ng/mL; one other subject was discontinued because they needed a dose reduction below 1mcg TIW due to hypercalcemia but it was not considered an AE) and
- one from initial Zemplar group (with AE of hypertensive urgency requiring dialysis).

Treatment Compliance

Table 6 Treatment Compliance for Part 2-Safety and Efficacy Portion of Study M10-149 Double-Blind Phase (ITT dataset)

	PLACEBO			PARICALCITOL		
VISIT	N	MEAN (SD)	MEDIAN (RANGE)	N	MEAN (SD)	MEDIAN (RANGE)
WEEK 4	18	40.6 (5.51)	40.0 (23.3, 50.0)	15	46.0 (15.75)	43.3 (30.0,100.0)
WEEK 8	16	58.5 (20.44)	55.0 (33.3, 90.0)	12	48.1 (9.37)	45.0 (36.7, 63.3)
WEEK 12	18	69.6 (24.89)	73.3 (6.7,100.0)	14	63.3 (26.89)	68.3 (10.0,100.0)
EARLY TERMIATION	1	33.3 (0.00)	33.3 (33.3, 33.3)	5	23.3 (12.83)	26.7 (6.7, 36.4)
OVERALL	18	55.1 (12.40)	56.3 (33.3, 73.3)	18	46.8 (15.18)	47.8 (21.7, 85.6)

NOTE: TREATMENT COMPLIANCE IS CALCULATED AS THE PERCENTAGE OF CAPSULES TAKEN RELATIVE TO THE TOTAL CAPSULES DISPENSED FOR A GIVEN VISIT.

Source Table 14.1_6.2.1

Table 7 Treatment Compliance for Part 2-Safety and Efficacy Portion of Study M10-149 Open-Label Phase (all treated dataset)

	PLACEBO			PARICALCITOL			TOTAL		
VISIT	N	MEAN (SD)	MEDIAN (RANGE)	N	MEAN (SD)	MEDIAN (RANGE)	N	MEAN (SD)	MEDIAN (RANGE)
OVERALL	16	53.6(14.01)	56.1(25.0, 82.2)	13	59.7(17.52)	57.8(37.8,100.0)	29	56.3(15.69)	57.8(25.0,100.0)

NOTE: TREATMENT COMPLIANCE IS CALCULATED AS THE PERCENTAGE OF CAPSULES TAKEN RELATIVE TO THE TOTAL CAPSULES DISPENSED DURING THE OPEN LABEL PART.

Source Table 14.1_6.2.2

Medical officer's comments:

According to the applicant "There was no evidence of a lack of compliance with assigned treatment or dosing." Yet the mean overall values for % of capsules taken relative to those dispensed ranging from 47 to 56% suggesting poor compliance with an oral TIW dosing scheme in this pediatric population in Part 2 of this study.

The applicant was asked to address this concern and performed a reanalysis of their data which was included in the 16 Sept. 2016 submission (SDN73). It turns out the data they submitted was only based on capsules dispensed and capsules taken. Subjects were given a higher number of capsules to allow for flexibility in dose adjustments. The applicant performed a reanalysis of the data taking into account each subjects prescribed dose. There were some assumptions made in this analysis as the exact days the subjects took the medication was not known. For example with TIW dosing there could be slight differences in pill number with respect to whether a subject was taking their medication on a Monday, Wednesday and Friday schedule or a Tuesday, Thursday and Saturday schedule. The revised compliance rate for the double blind portion of M10-149 was 102±

16%, and for the open label portion was 103±26%. Median values for both treatment periods were 100%. Therefore, the revised data support the validity of the study data.

6.1.4 Analysis of Primary Endpoint(s)

Part 1 (PK analysis)

Table 8 PK Parameters Mean (SD)-Part 1 Single 3mcg Paricalcitol Dose PK Portion of Study M10-149

	Pediatric CKD Stage		
Pharmacokinetic Parameter (Units)	**Stage 3 (n = 6)**	**Stage 4 (n = 6)**	**Stages 3 and 4 Combined (N = 12)**
T_{max} (h)	4.0 ± 0.0	4.3 ± 2.3	4.2 ± 1.6
C_{max} (ng/mL)	0.12 ± 0.06	0.14 ± 0.05	0.13 ± 0.05
AUC_{∞} (ng•h/mL)	2.63 ± 0.76	3.12 ± 0.91	2.87 ± 0.84
$t_{1/2}$[a] (h)	13.3 ± 4.3	15.2 ± 4.4	14.2 ± 4.4

T_{max} = time to maximum observed plasma concentration; C_{max} = maximum observed plasma concentration; AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; $t_{1/2}$ = terminal phase elimination half-life

a. Harmonic mean ± pseudo standard deviation.

Source Table 1 Summary of Clin Pharm peds.pdf

Medical officer's comments:
Paricalcitol Cmax, AUC, Tmax, and t½ values were similar between Stage 3 and Stage 4 pediatric subjects. The results were consistent with the findings seen previously in adults and in the current package insert. AUC was slightly higher in the pediatric patients (2.6 to 3.1ng·h/mL vs. 2.1 to 2.4 ng·h/mL) but $t_{1/2}$ was slightly higher in the adult patients 17 to 20 hrs vs. 13 to 15hrs.

Table 9 Paricalcitol PK Parameters Mean (SD)-Adult Patients with CKD Stages 3, 4 and 5

Pharmacokinetic Parameters	**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.				

Source Zemplar Capsules Package Insert

There was a protocol deviation in this study in one subject, SUBJID=1498202, who had an eGFR below the lower limit of 15mL/min/1.73m^2 at screening even though the two prior levels were acceptable at 18 and 16mL/min/1.73m^2. According to the Clin Pharm review the data from this patient with CKD Stage 5 was significantly different from the rest of the patients with CKD Stage 3 and 4 so it was recommended that this patient's data be removed from the study results which are to be included in the final labeling.

Part 2 (Safety and Efficacy Study)
The primary efficacy endpoint during the 12-wk double-blind period was the percent of subjects that achieve two consecutive ≥30% reductions in iPTH from baseline.

Table 10 Primary Endpoint-Proportion of Subjects Achieving Two Consecutive Reductions of ≥30% from Baseline in iPTH (ITT) during the 12-Week Double-Blind Period-Part 2 Safety and Efficacy Portion of Study M10-149

	Paricalcitol	Placebo	Between Group Comparison		
Response	n/N (%)	n/N (%)	Difference	(95% CI)	p-value[a]
Yes	5/18 (27.8)	0/18 (0)	27.8	(7.5, 52.8)	0.045
No	13/18 (72.2)	18/18 (100)			

a. Fisher's exact test was used to calculate p-value. Statistical significance tested 0.050 level.

Cross reference: Table 14.2__1.1

Source Table 24 M10-149 CSR

There were five responders in the paricalcitol treatment group compared to no responders in the placebo group so the primary endpoint was barely statistically significant at 0.045. There were too few pts to show statistical significance by CKD stage but the results were consistent (Stage 3: 3/10 vs. 0/11 and Stage 4: 2/8 vs. 0/7). Of note with longer exposure during the 24-wk open-label extension efficacy improved so that 12/29=41% had two consecutive reductions of at least 30% from baseline. This level of efficacy while substantial was still less than half of what had been seen in adults with CKD Stage 3 and 4 treated for 24 weeks with Zemplar capsules (91% Zemplar capsules vs. 13% Placebo, see Zemplar PI).

Medical officer's comments:
Part of the reason for the lower observed efficacy in the pediatric CKD stage 3 and 4 population maybe related to the fact that the mean baseline iPTH was lower in the pediatric patients at 150 pg/mL compared to the adult studies where it was almost double at 274 pg/mL.

Protocol Violations/Deviations-
There were four protocol deviations identified by the applicant in this study and all were in patients in the placebo group.

- Two subjects 3908003 and 4638601 who received incorrect doses of placebo each on one occasion.

- Subject 4054702 did not satisfy the entry criteria for 25 OH vitamin D of ≥30ng/mL at screening.
- Subject 3990204 required >2000 IU/day of vitamin D therapy during the study which would have been a withdrawal criteria and was not withdrawn.

Medical officer's comments:
It is unlikely that giving a single incorrect dose of placebo as occurred with the first two cases would have affected the study results, as the placebo dose is not likely to affect serum iPTH levels.

While subject 4054702 had a low 25-OH vitamin D value of 19ng/mL at initial screening it increased to normal at 35ng/mL prior to dosing and was 39ng/mL at week 12 so that should not have affected the study results.

While subject 3990204 apparently received > 2000 IU/day of vitamin D therapy which would have made him more likely to become a responder this subject was not identified as a responder during this study so the higher than acceptable vitamin D therapy did not impact the study results. In addition, this subject's 25-OH vitamin D level was 60ng/mL in the normal range at week 12, so a low 25-OH vitamin D level was not the reason why this subject was a nonresponder.

In addition to the protocol violations identified by the applicant this medical reviewer noted that six subjects, three with Stage 3 and three with Stage 4 CKD, had iPTH levels on Study Day 1 prior to dosing the were below the entry inclusion criteria for the study yet were included in the study data because the prior iPTH measurement during the screening period had been elevated. When the applicant was asked about this they said that they included these six patients in the primary endpoint analysis as they met the predefined inclusion criteria at screening, which was how the study protocol was written.

SUBJID	CKD stage	Last screening iPTH	baseline iPTH on Study Day 1	Screening Inclusion criteria	>30% responder
3990205	3	118	46	≥ 75pg/mL	no
1519118	3	77	57	≥ 75pg/mL	yes
3908003	3	96	71	≥ 75pg/mL	no
3908001	4	293	81	≥ 110pg/mL	no
3883201	4	251	88	≥ 110pg/mL	no
3860701	4	146	100	≥ 110pg/mL	no

Of the 6 subjects with iPTH levels on Study Day 1 that would no longer satisfy the screening inclusion criteria, one subject in the paricalcitol treatment group was a responder. It turns out that this subject (SUBJID=1519118) in the paricalcitol group went from an iPTH of 57p/mL at baseline to 27pg/mL and 24pg/mL at study Weeks 2 and 4, respectively, before being

discontinued from the study. If this subject's data was excluded from the study results the study would no longer have been statistically significant.

Medical officer's comments:
It is unclear to this medical reviewer whether these six patients had true secondary hyperparathyroidism given that they seemed to normalize their iPTH level with no specific treatment prior to dosing on Study Day 1. In the past, because there can be a fair amount of variability in iPTH levels, it had been common practice to use an average from the last two screening measurements as the baseline value without measuring a value on Study Day 1. So by not measuring iPTH on Study Day 1 this avoided the possibility of enrolling patients with baseline values below the inclusion criteria and avoided requiring a responder to be someone with a ≥30% reduction in iPTH from what was already a normal iPTH value. If a similar protocol had been done in this case SUBJID=1519118 would not have had to have been excluded from the study. While whether these patients had true secondary hyperparathyroidism may still be an open clinical question, the statistical reviewers agreed that the applicant had performed that prespecified analysis as written in the statistical analysis plan and as such did not have a problem with including these six patients in the final analysis.

Missing Data-
The statistical review noted missing data from one placebo subject and from three paricalcitol subjects at visits adjacent to a visit where there was a ≥30% decrease in iPTH from baseline. Therefore assuming the missing visit had been observed and had a ≥30% decrease in iPTH that subject could have been included as a responder. Adding 1 to 3 additional responders to the paricalcitol group would not have changed the efficacy results but would have resulted in a smaller p-value. However given the current p-value=0.045 adding one responder to the placebo group would have resulted in a p-value of > 0.05 and made the study nonsignificant. The placebo subject 4054701 with the missing data point had a single iPTH value decrease of ≥30% at week 4 and had subsequent values at week 8 and 12 that had increases from baseline suggesting a lack of efficacy, however he was missing the 2 week data point, which if it showed a decrease of ≥30% would have made him a responder.

				iPTH		
SUBJID	**TRT01P**	**Study Day**	**Visit**	**value**	**change**	**% change**
4054701	PLACEBO	1	BASELINE	175		
4054701	PLACEBO	missing	WEEK 2	missing	missing	missing
4054701	PLACEBO	28	WEEK 4	118	-57	-32.5714
4054701	PLACEBO	56	WEEK 8	198	23	13.14286
4054701	PLACEBO	86	WEEK 12	269	94	53.71429

Medical officer's comments:
Given that iPTH increased to values above baseline in the last two visits for subject SUBJID=4054701 this medical reviewer thinks it is highly unlikely that this subject was

a true responder and that concern over the missing data from this subject should not be used to negate the efficacy results.

The statistical reviewer Dr. Crackel performed two sensitivity analyses to control for the missing data in the one placebo patient and the three patients in the paricalcitol group. Both a Bayesian approach and the Agresti-Caffo method/Rubin's rule turned out to be less conservative methods of analysis than the original approach, and resulted in p-values of 0.017 and 0.0335 supporting the statistical significance of the current data.

6.1.5 Analysis of Secondary Endpoints(s)

1) The first secondary endpoint was treatment to serum iPTH KDOQI target by CKD stage:
CKD Stage 3: 35 to 69 pg/mL
CKD Stage 4: 70 to 110 pg/mL

The results were not statistically significant for treating iPTH to KDOQI goal at the final iPTH measurement in the double-blind period for CKD Stage 3 and 4 subgroups individually or for the combined data (Table 11). However, for both CKD Stage 3 and 4 there were more responders in the Zemplar groups compared to their respective placebo groups.

Table 11 Treatment to KDOQI iPTH Goal during Week 12 Double-Blind Period by CKD Stage (ITT)-Part 2 Safety and Efficacy Portion of Study M10-149

Response	Paricalcitol n/N (%)	Placebo n/N (%)	p-value
All			
Yes	6/18 (33.3)	2/18 (11.1)	0.128[a]
No	12/18 (66.7)	16/18 (88.9)	
CKD Stage 3			
Yes	3/10 (30.0)	0/11 (0)	0.090[b]
No	7/10 (70.0)	11/11 (100)	
CKD Stage 4			
Yes	3/8 (37.5)	2/7 (28.6)	1.000[b]
No	5/8 (62.5)	5/7 (71.4)	

a. Cochran-Mantel-Haenszel (CMH) test, adjusting for CKD Stage.

b. Fisher's exact test was used to calculate p-values.

Cross reference: Table 14.2__1.2

Source Table 26 M10-149 CSR

2) The second secondary endpoint was mean change in iPTH from baseline to each post baseline visit at Weeks 2, 4, 8 and 12 using a repeated measures analysis. The results gave p-values < 0.05 for each of the study visits and for the pooled overall data p<0.001. Mean iPTH decreased in all of the Zemplar groups (-11 to -17) while increasing in the Placebo

groups (+50 to +71). This is consistent with the natural progression of the disease if it goes untreated in the placebo group.

Medical officer's comments:
While these data are supportive of efficacy, the statistical significance of these data is not clear as multiplicity was not taken into account in the applicant's analysis. (b) (6)

Table 12 Repeated Measures Analysis of Mean Change from Baseline in iPTH (ITT)- Part 2 Safety and Efficacy Portion of Study M10-149

			Visit		Change from Baseline			Between Group Comparison	
Visit	Treatment Group	N	Mean	(SD)	LS Mean	SE	p-value	Difference (95% CI)	p-value[a]
Overall								−72.40 (−108.05, −36.75)	< 0.001[b]
Baseline	Paricalcitol	18	144.28	(64.86)					
	Placebo	18	155.44	(97.26)					
Week 2	Paricalcitol	16	133.63	(93.80)	−12.16	14.695	0.414	−62.55 (−105.60, −19.49)	0.006[c]
	Placebo	15	183.07	(121.59)	50.39	15.186	0.002[c]		
Week 4	Paricalcitol	16	135.31	(88.24)	−11.27	22.117	0.614	−68.43 (−130.39, −6.47)	0.032[d]
	Placebo	18	214.28	(168.85)	57.16	20.813	0.010[c]		
Week 8	Paricalcitol	13	131.15	(70.38)	−12.79	24.814	0.610	−70.09 (−137.82, −2.37)	0.043[d]
	Placebo	18	213.67	(161.92)	57.31	22.099	0.015[d]		
Week 12	Paricalcitol	12	111.25	(50.84)	−17.05	19.186	0.381	−88.52 (−142.04, −35.01)	0.002[c]
	Placebo	15	230.47	(173.73)	71.47	17.661	< 0.001[b]		

a. p-values are from mixed model: change = trtcd visit trtcd*visit base base*visit/ddfm = kenwardroger var-covar structure = un. (change = change from baseline; trtcd = treatment group code; visit = scheduled visit; ddfm = denominator degrees of freedom for which Kenward Roger was selected; var-covar structure = covariance structure for which unstructured was selected).

b. p = 0.001.

c. p = 0.01.

d. p = 0.05.

Cross reference: Table 14.2__1.6.1

Source Table 27 M10-149 CSR

The third secondary endpoint-[treatment to serum Ca and Phosphate KDOQI targets] and the fourth secondary endpoint-[mean change in first morning void urinary albumin to creatinine ratio (FMV UACR) from baseline to Weeks 4, 8, and 12] gave p-values well above 0.05 and were not considered statistically significant.

6.1.6 Other Endpoints

Self-reported health outcomes were assessed at the baseline and Week 12 using the PedsQL™ 4.0 questionnaire. Separate questionnaires were filled out by the care giver and the subject. No differences with p-values < 0.05 were seen for any of the individual parameters or summary scores.

6.1.7 Subpopulations

Efficacy was evaluated by CKD stage, but was underpowered to look for statistically significant differences. That said, there appeared to be no clear difference in efficacy with respect to the primary endpoint of two consecutive ≥30% reductions in iPTH from baseline for Zemplar vs. placebo with respect to CKD Stage in the pediatric predialysis population (Stage 3 responders: 3/10 vs. 0/11; Stage 4 responders: 2/8 vs. 0/7).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

PK data from Part 1 of Study M10-149 was used to select a safe starting dose for the 12-week double-blind efficacy and safety study in Part 2 of M10-149. The starting dose of 1mcg three times a week was shown to be safe and effective in the majority of pediatric subjects with CKD Stage 3 or 4. However, eventually 4 of the 18 subjects treated with Zemplar during the initial double-blind 12-week phase of the study required a dose reduction below the 1mcg dose and were discontinued from the study. (b) (6) During Study M10-149 dose increases of 1mcg were permitted every four weeks to reach iPTH target levels as long as serum calcium and phosphorous levels where within acceptable guidelines. **Error! Reference source not found.** Table 13Table 13 shows that most patients were treated adequately with between 1 and 3 mcg of Zemplar three times a week. The highest doses used in this study were 5 mcg in one subject with Stage 3 CKD and 7 mcg in one subject with Stage 4 CKD.

Table 13 Number of Patients at Each Assigned Dose by Study Visit-Part 2 Safety and Efficacy Portion of Study M10-149

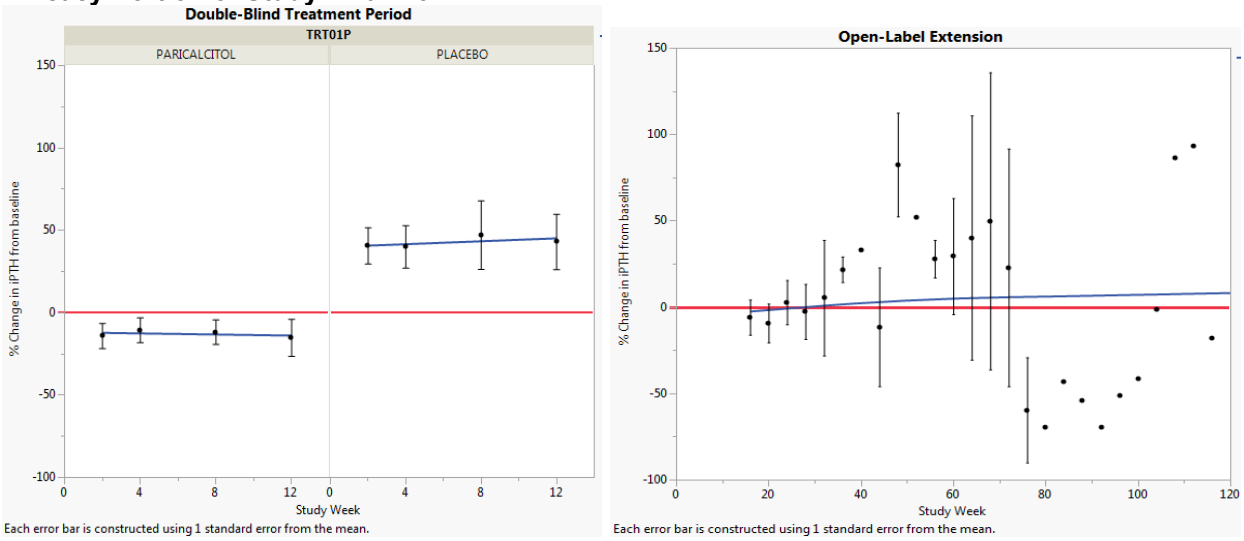
		Number of Subjects (%)							
			Zemplar (TIW)						
Visit	N	Placebo	1 µg	2 µg	3 µg	4 µg	5 µg	6 µg	7 µg
First Dose	36	18 (50.0)	18 (50.0)	0	0	0	0	0	0
Week 4	33	18 (54.5)	14 (42.2)	2 (6.1)	0	0	0	0	0
Week 8	29	16 (55.2)	8 (27.6)	7 (24.1)	1 (3.4)	0	0	0	0
Week 12	30	4 (13.3)[a]	21 (70.0)	7 (23.3)	3 (10.0)	0	0	0	0
Week 16	28	0	18 (64.3)	7 (25.0)	8 (28.6)	1 (3.6)	0	0	0
Week 20	26	0	9 (34.6)	9 (34.6)	7 (26.9)	4 (15.4)	0	0	0
Week 24	11	0	2 (18.2)	3 (27.3)	6 (54.5)	1 (9.1)	1 (9.1)	0	0
Week 28	4	0	1 (25.0)	0	3 (75.0)	1 (25.0)	0	0	0
Week 32	2	0	1 (50.0)	0	1 (50.0)	0	0	0	0
Week 36	2	0	1 (50.0)	0	1 (50.0)	0	0	0	0
Week 40	2	0	1 (50.0)	2 (100)	0	0	0	0	0
Week 44	2	0	0	2 (100)	0	0	0	0	0
Week 48	2	0	0	2 (100)	1 (50.0)	0	0	0	0
Week 52	2	0	0	0	2 (100)	0	0	0	0
Week 56	2	0	0	0	2 (100)	0	0	0	0
Week 60	2	0	0	0	1 (50.0)	1 (50.0)	0	0	0
Week 64	2	0	0	0	1 (50.0)	1 (50.0)	1 (50.0)	0	0
Week 68	2	0	0	0	1 (50.0)	0	1 (50.0)	1 (50.0)	0
Week 72	2	0	0	0	1 (50.0)	0	0	1 (50.0)	0
Week 76	2	0	0	0	1 (50.0)	0	0	1 (50.0)	1 (50.0)
Week 80	1	0	0	0	1 (100)	0	0		0
Week 84	1	0	0	0	1 (100)	0	0		0
Week 88	1	0	0	0	1 (100)	0	0		0
Week 92	1	0	0	1 (100)	1 (100)	0	0		0
Week 96	1	0	0	1 (100)	0	0	0		0
Week 100	1	0	0	1 (100)	0	0	0		0
Week 104	1	0	1 (100)	0	0	0	0		0
Week 108	1	0	1 (100)	0	0	0	0		0
Week 112	1	0	1 (100)	1 (100)	0	0	0		0

Source Table 13 R&D/15/0977-FDA 03AUG2015 Response

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Efficacy is supported for the duration of the 12-week double-blind period of the trial (see left panel in Figure 4).

Figure 4 Percent Change from Baseline in Serum iPTH by Treatment Week- Part 2 Safety and Efficacy Portion of Study M10-149



Source iPTH from DEFFDB (double-blind) and DEFFOL (open-label) efficacy datasets by AVISTN

All patients were treated with Zemplar during the open label extension shown in the right panel above. There are too few subjects followed beyond 24 weeks to support persistence of efficacy or to look for tolerance effects.

6.1.10 Additional Efficacy Issues/Analyses

None

Supplement-17 Pediatric study under PREA for the treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 5 in pediatric patient's ages 10 to 16 years receiving peritoneal dialysis or hemodialysis.

6.2 Indication

Zemplar is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5 in pediatric patients 10 to 16 years of age on hemodialysis or peritoneal dialysis.

6.2.1 Methods

General Discussion of Endpoints-
Zemplar IV had previously been studied and shown to be effective using the endpoint of two consecutive >30% decreases of iPTH from baseline in a double-blind, placebo-controlled 12-week study in pediatric hemodialysis patients age 5 to 19 years (see NDA 20-819). Given the difficulty of recruiting a sufficient number of pediatric dialysis patients to perform an adequately powered double-blind, placebo-controlled efficacy and safety study with the oral capsule formulation, it was determined that efficacy could be extrapolated using population PK and the currently available data. Study M11-612 was therefore designed as an open-label study to demonstrate the safety of Zemplar capsules in the dialysis population, with a focus on the primary safety concern of hypercalcemia. The primary safety endpoint was the number of subjects with at least 2 consecutive elevated serum calcium levels > 10.2mg/dL. The study was initially designed to study the use of Zemplar Capsules in the pediatric peritoneal dialysis population but because of problems with recruiting it was eventually expanded to include both pediatric hemodialysis and peritoneal dialysis patients.

Study Design
Study M11-612 was designed as a Phase 3, 12-week, open-label, single-arm, multicenter study to evaluate the safety of paricalcitol capsules in 12 pediatric subjects with Stage 5 CKD receiving peritoneal dialysis or hemodialysis. Subjects not naïve to active vitamin D analogs were to complete a 2 to 12 week washout period prior to dosing with paricalcitol. The paricalcitol dose was to be adjusted in order to maintain a serum iPTH level between 150pg/mL and 300pg/mL.

Inclusion criteria (including but not limited to)-

- Male or female subject ≥ 10 years old and ≤ 16 years old
- Subject had to be receiving peritoneal dialysis or hemodialysis for at least 3 months prior to screening
- If taking phosphate binders, the subject had to have been on a stable dose (same type and regimen) for at least 2 weeks prior to the Screening Phase
- Female subjects must have had a negative pregnancy test prior to treatment and be following acceptable forms of contraception

- If receiving growth hormone the subject must have been on therapy for > 3 months and expecting to continue to receive it throughout the treatment phase.
- Screening criteria
  - iPTH measurement ≥ 130 pg/mL and ≤ 2000 pg/mL
  - Adjusted serum calcium value ≥ 8.2 mg/dL to ≤ 10.5 mg/dL
  - Serum phosphorus value ≤ 6.5 mg/dL
- Treatment criteria (active vitamin D analog naïve, or after 2-12 week washout)
  - iPTH measurement ≥ 300 pg/mL and ≤ 2000 pg/mL
  - Adjusted serum calcium value ≥ 8.4 mg/dL to ≤ 10.2 mg/dL (normal range)
  - Serum phosphorus value ≤ 6.5 mg/dL (4.7mg/dL is ULN)

Exclusion criteria (including but not limited to)-

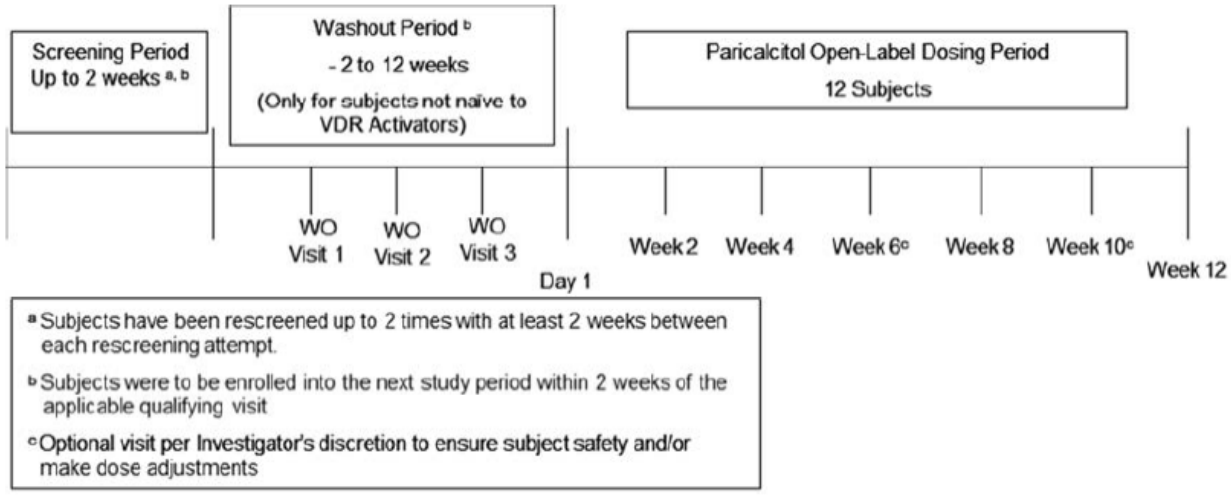
- Weight < 25 kg (55 lbs)
- Scheduled to receive a kidney transplant within 3 months or status post a recent kidney transplant on full immunosuppressant therapy
- Scheduled to stop dialysis within 4 months of screening
- Subjects considered by the investigator to be an unsuitable candidate (e.g., unable to swallow capsules, lack of a telephone, evidence of poor compliance, clinically significant liver disease, HIV positive, malignancy other than basal or squamous cell carcinoma or history of illicit drug or alcohol abuse) to receive paricalcitol capsules or who the investigator felt would be put at risk by the study procedures
- Taking prescription based phosphate supplements
- Receiving cinacalcet at time of screening
- Symptomatic or significant hypocalcemia requiring active Vitamin D therapy (i.e., calcitriol, paricalcitol, or doxercalciferol) within 2 months prior to the Screening Phase
- Taking maintenance calcitonin, bisphosphonates, glucocorticoids in an equivalent dose of > 5 mg prednisone daily, or other drugs known to affect calcium or bone metabolism within 4 weeks prior to treatment
- Chronic gastrointestinal disease, which in the investigator's opinion may have caused significant gastrointestinal malabsorption or status post small bowel transplant
- History of active kidney stones within 4 months prior to screening
- History of parathyroidectomy within 12 weeks prior to the Screening Phase

Medical officer's comments:
While one subject did not meet the inclusion criteria of iPTH ≥300 pg/mL on Study Day 1 her serum iPTH level increased to 387 pg/mL during the study at the Week 4 visit consistent with a diagnosis of secondary hyperparathyroidism.

All subjects had a corrected serum calcium or serum calcium, if albumin value was not available, at baseline (lab day -28 to +1) consistent with the inclusion criteria.

One subject had a serum phosphorous level of 6.6mg/dL at baseline on Study Day 1 but the value decreased to ≤6.3mg/dL for the rest of the 12 week study.

Figure 5 Study Schematic-Study M11-612



WO = Washout
Source Fig. 1 Study M11-612 CSR

Chemistry measurements of serum calcium, albumin, phosphorous and iPTH were scheduled for Weeks 0, 2, 4, 8 and 12/premature discontinuation with visits on Weeks 6 and 10 optional at the investigator's discretion to ensure subject safety or to make dose adjustments.

Dosing Based on Serum iPTH-
The starting dose of paricalcitol was calculated using the last iPTH laboratory value in pg/mL prior to Day 1 and the equation (iPTH/120). Dose increases in 1mcg TIW increments could occur at 4-week intervals starting with Week 4. Dose decreases at 2mcg TIW changes could occur at any visit. The maximal allowable dose was 16mcg TIW. Dosing was not to be given on consecutive days. If a dose was missed it was not to be made up and the subject was not to receive another dose until the next regularly scheduled dosing day. Subjects were to be discontinued from the study for two consecutive missed visits.

Dose Increase-If the iPTH level was > 300 pg/mL and corrected calcium level was ≤ 10.2 mg/dL and phosphorus level was ≤ 6.5 mg/dL then the dose of study drug was to be increased by 1mcg TIW or restarted at a dose of iPTH/120 if it had been previously withheld.

Dose Maintained-If iPTH level was ≥ 150 pg/mL and ≤ 300 pg/mL and corrected calcium level was ≤ 10.2 mg/dL and phosphorus level was ≤ 6.5 mg/dL then the dose was to be maintained or restarted at a dose of iPTH/120 if it had been previously withheld.

Dose Decreased-If iPTH level was < 150 pg/mL and corrected calcium level was ≤ 10.2 mg/dL and phosphorus level was ≤ 6.5 mg/dL then the dose was to be decreased by 2mcg TIW. If the subject was receiving a dose of 1 or 2mcg TIW, then the dose was to be withheld.

If iPTH level was still < 150 pg/mL upon being rechecked, then the dose was to be further decreased. If the subject was receiving a dose of 1 or 2mcg TIW, then the dose was to be withheld. If the dose was withheld for more than 2 consecutive study visits, the subject was to be discontinued from study drug but serum iPTH was to be measured weekly until the iPTH level normalized (≥ 150 pg/mL and ≤ 300 pg/mL).

Dose Adjustment for Hypercalcemia-If at any time the corrected calcium level was > 10.2 mg/dL, then the dose of study drug was to be reduced by 2 mcg TIW. If the subject was receiving 1 or 2 mcg TIW, then the dose was withheld and rechecked weekly until corrected serum calcium reached ≤ 10.2 mg/dL. If at the next visit the corrected calcium level was still > 10.2 mg/dL the dose reduction was to be repeated or dosing withheld if the subject was receiving 1 or 2 mcg TIW. If the dose was withheld for 2 consecutive weeks, the subject was to be discontinued from study drug. However, the investigator was to re-check corrected calcium levels weekly until the corrected calcium normalized to ≤ 10.2 mg/dL.

Dose Adjustment for Hyperphosphatemia- If at any time phosphorus results were > 6.5 mg/dL it was to be checked weekly (per investigator's discretion) until it reached ≤ 6.5 mg/dL and the appropriate action from the following list was to be applied:

1. First occurrence of phosphorus > 6.5 mg/dL
   Subject was to receive dietary counseling (per investigator discretion);
   Study drug dose was to be maintained.
2. Second consecutive occurrence of phosphorus > 6.5 mg/dL
   Phosphate binder therapy was to be initiated, increased, or modified (per investigator discretion);
   Study drug dose was to be maintained.
3. Third consecutive occurrence of phosphorus > 6.5 mg/dL
   Dose of study drug was to be decreased by 2 mcg TIW;
   If subject was receiving 1 or 2 mcg TIW, then the dose was to be withheld.
4. After the third consecutive occurrence of phosphorus level > 6.5 mg/dL phosphorus level was to be rechecked weekly until it returned ≤ 6.5 mg/dL.

If the subject's dose had to be withheld for 2 consecutive weeks, the subject was to be discontinued from study drug. Regardless of dose administration, the investigator was to recheck phosphorus levels weekly until they returned to ≤ 6.5 mg/dL.

Table 14 Study Activities-Study M11-612

Activity	Screening	Washout Period[a]		Dosing Period[b]						
		Washout Visit 1	Optional Washout Visits 2 and 3	Day 1	Week 2	Week 4	Week 6[c]	Week 8	Week 10[c]	Week 12/ Premature Discontinuation[d]
Informed Consent/Assent[e]	X									
Medical History, Alcohol, Drug and Tobacco Use[f]	X			X						
Drug/Alcohol Screen	X			X						X
Physical Exam	X	X[g]	X[g]	X						X
Height and Weight	X			X						X
Concomitant Medications[h]	X	X	X	X	X	X	X	X	X	X
Dialysate – Ca Concentration	X	X	X	X	X	X	X	X	X	X
12-lead ECG[i]				X						X
Vital Signs	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Tests[j]	X	X	X	X	X	X	X	X	X	X
Complete Chemistry and Hematology[k]	X			X			X			X
Limited Chemistry[k,l]		X	X		X	X		X	X	
Vitamin D Test[m]	X	X	X	X			X[n]			X
Hepatitis Screen	X									
Bone Markers	X			X						X
C-Reactive Protein				X			X			X
Fibroblast Growth Factor 23	X			X			X			X
PedsQL™ Questionnaires[o]				X		X		X		X
Adverse Event Monitoring[p]	X	X	X	X	X	X	X	X	X	X
Contact IVRS/Dispense Study Drug[q]	X			X	X	X	X	X	X	X
Blood Collection for Assay of Paricalcitol and Dosing Card[r]					X	X	X	X	X	X
Pharmacogenetic Sample[s]				X						
Study Drug Compliance					X	X	X	X	X	X

a. The Washout Period was for subjects not naïve to VDR Activators. The Washout Period was to last for a minimum of 2 weeks and up to a maximum of 12 weeks. After Washout Visit 1, up to 2 additional washout visits may have been used at discretion of investigator, up to Washout Week 12.

b. Unscheduled visits to collect limited chemistry could have occurred between scheduled study visits during the Dosing Period.

c. Optional visit may have occurred per investigator's discretion to ensure subject safety and/or make dose adjustments.

d. Was to be performed within approximately 5 days after last dose of study drug for subjects who prematurely discontinued from the study.

e. Was to occur prior to performing any screening or study-specific procedures.

f. Complete medical history was to be collected at Screening and updated as needed on Dosing Day 1.

g. Physical exam was to include at a minimum HEENT (Head, Eyes, Ears, Nose, and Throat)/Lung/heart/abdomen/brief skin survey and could have been repeated at subsequent washout visits if significant findings were present at Screening.

h. Concomitant medications that the subject received 4 weeks prior to Screening and throughout the Dosing Period were to be recorded. Information on growth hormones, phosphate binders, and Vitamin 25D repletion was to be collected on separate concomitant medication pages.

i. 12-lead resting Electrocardiogram (ECG) was to be obtained prior to blood collection at or within 1 week prior to the Day 1 Visit and at or within 1 week prior to the Week 12/Premature Discontinuation Visit.

j. For all female subjects. Serum pregnancy test was to be sent to the central laboratory for analysis.

k. Subjects were not required to fast for any blood draws, however, it was preferred that they had fasted for Day 1, if possible.

l. Limited chemistry was to be collected at unscheduled visits and weekly through clinical normalization for subjects that prematurely discontinued study drug.

m. Vitamin D tests: Calcidiol (25-hydroxyvitamin D) and Calcitriol (1,25-dihydroxyvitamin D).

n. Testing for vitamin D was required only at Week 6 for subjects who were being repleted for vitamin D.

o. At sites in the United States and United Kingdom, PedsQL™ Generic Core Scale, Version 4 and End Stage Renal Disease Module, Version 3.0 was to be provided to the subject and parent/legal guardian to complete. Questionnaires were to be administered prior to any blood draws.

p. Monitoring for serious adverse events (SAE) was to begin from the time of consent through 30 days after the last dose of study drug. Adverse events were to be collected from the first dose of study drug through 30 days after the last dose of study drug. A detailed description for procedures involving adverse event/serious adverse event assessments is presented in Section 9.5.1.3.

q. Investigator was to contact the interactive voice response system (IVRS) to assign subject number at Screening. The investigator was to contact IVRS at Dosing Day 1, Weeks 2, 4, 8 (and Weeks 6 and 10, if conducted) for study drug dispensing. Doses of the study drug for scheduled visit days were to be administered to the subject by site personnel at the clinical site. Investigator was to contact IVRS at Week 12/Premature Discontinuation to make a Completion or Premature Discontinuation call.

r. Blood collection for assay of paricalcitol and dosing card was to be collected prior to dosing at the times specified in the table.

s. The pharmacogenetic sample was optional. Consent to collect a pharmacogenetic sample must have been signed by the subject and parent/legal guardian prior to collection.

Source CSR M11-612 Table 3

6.2.2 Demographics

Table 15 Demographic and Baseline Characteristics-Study M11-612

Characteristic		Total N = 13	
Sex, n (%)	Female	8	(61.5)
	Male	5	(38.5)
Race, n (%)	White	8	(61.5)
	Black	2	(15.4)
	Asian	1	(7.7)
	American Indian/Alaska Native	1	(7.7)
	Native Hawaiian or other Pacific Islander	0	
	Other	0	
	Multi Race	1	(7.7)
Ethnicity, n (%)	Hispanic or Latino	6	(46.2)
	No ethnicity	7	(53.8)
Age, years	Mean ± SD	14.5	± 1.76
	Median (Min – Max)	15.0	(12.0 – 17.0)[a]
Weight, kg	Mean ± SD	49.0	± 19.70
	Median (Min – Max)	48.0	(27.0 – 97.0)
Weight, kg (females, n = 8)	Mean ± SD	53.8	± 22.85
	Median (Min – Max)	48.0	(27.0 – 97.0)
Weight, kg (males, n = 5)	Mean ± SD	41.4	± 11.52
	Median (Min – Max)	34.0	(32.0 – 58.0)

Source Table 9 Study M11-612 CSR

More females 8 (62%) than males 5 (38%) were enrolled. The mean age was 14.5 years ± 1.8 years. The majority of subjects were White 8 (61.5%), 2 (15.4%) were Black, 1 (7.7%) was Asian, 1 (7.7%) was American Indian/Alaska Native, and 1 subject (7.7%) was multi-race. Of the 13 subjects enrolled, 6 subjects (46.2%) reported Hispanic or Latino ethnicity.

Relevant medical history- All thirteen subjects had anemia, ten had hypertension, seven had a history of peritoneal dialysis and eight had a history of hemodialysis (see Study M11-612 CSR Table 12).

Concomitant medications of interest (see Study M11-612 CSR Table 13)-Eleven subjects were receiving erythropoietin/darbepoetin and nine were on an iron formulation. Multiple subjects were on antihypertensive medication: amlodipine (6), clonidine (2), carvedilol (1), labetolol (1), lisinopril (2), losartan (1), nifedipine (2). Six subjects were on the phosphate binder Sevelamer, seven were on the phosphate binder calcium carbonate and one was on Lokovit (Ca/VitD). Seven subjects were on medication to replete vitamin D levels including cholecalciferol (4) and

ergocalciferol (3). One patient each had been on the active vitamin D analogs, doxercalciferol and alfacalcidol prior to the study but they were not continued during the study.

Table 16 Baseline Chemistry Lab Values-Study M11-612

Characteristic		Total N = 13	
Albumin	Mean ± SD	4.07	± 0.37
(g/dL)	Median (Min – Max)	4.00	(3.50 – 4.70)
Serum Creatinine	Mean ± SD	7.48	± 3.15
(mg/dL)	Median (Min – Max)	7.72	(2.11 – 13.42)
Corrected Calcium[a]	Mean ± SD	9.24	± 0.68
(mg/dL)	Median (Min – Max)	9.30	(8.00 – 10.14)
Inorganic Phosphate	Mean ± SD	4.66	± 1.13
(mg/dL)	Median (Min – Max)	4.70	(2.70 – 6.60)
iPTH	Mean ± SD	883.62	± 373.81
(pg/mL)	Median (Min – Max)	833	(249 – 1610)
25-Hydroxy Vitamin D	Mean ± SD	18.62	± 10.81
(ng/mL)	Median (Min – Max)	16	(7 – 44)
1, 25-Hydroxy Vitamin D	Mean ± SD	28.62	± 15.99
(pg/mL)	Median (Min – Max)	25.20	(10.00 – 61.50)
BSAP	Mean ± SD	148.79	± 123.80
U/L	Median (Min – Max)	104.60	(40.20 – 486.00)
Osteocalcin	Mean ± SD	605.78	± 433.99
(ng/mL)	Median (Min – Max)	534.10	(19.60 – 1440.00)

BSAP = bone specific alkaline phosphatase

a. Baseline measurement of corrected calcium was collected for 9 subjects.

Source Table 11 Study M11-612 CSR

6.2.3 Subject Disposition

Table 17 Subject Disposition-Study M11-612

	Total
Number of Subjects Planned	12
Number of Subjects Screened	26
Number of Subjects Who Entered the Screening Period	15
Number of Subjects Who Entered the Washout Period	13
Number of Subjects Received at Least Once Dose of Study Drug	13
Number of Subjects Who Completed the Study	11
Number of Subjects Who Prematurely Terminated Study Drug	2

Cross reference: Table 14.1__1.1

Source Table 7 CSR Study M11-612

Thirteen subjects were enrolled and eleven completed the study. One subject discontinued due to parents withdrawal of consent and one withdrew to have a kidney transplant.

Treatment Compliance
According to the applicant there were no findings in the capsule counts, individual subject dosing records, or protocol deviations related to dosing to indicate any irregularities with treatment compliance that affected the analyses. That said compliance was poor in this study with mean values for % of capsules taken relative to those dispensed ranging from 32 to 46% at best.

Table 18 Treatment Compliance-Study M11-612

	PARICALCITOL		
VISIT	N	MEAN (SD)	MEDIAN (RANGE)
WEEK 2	11	44.8 (17.30)	46.7 (20.0, 70.0)
WEEK 4	13	45.3 (21.94)	46.7 (13.3,100.0)
WEEK 6	6	31.7 (19.75)	21.7 (13.3, 60.0)
WEEK 8	12	46.1 (27.44)	40.8 (8.9, 95.6)
WEEK 10	8	37.8 (13.47)	38.3 (10.0, 58.3)
WEEK 12	13	45.2 (23.62)	38.3 (16.7, 86.7)
OVERALL	13	43.7 (13.82)	45.3 (16.7, 63.3)

NOTE: TREATMENT COMPLIANCE IS CALCULATED AS THE PERCENTAGE OF CAPSULES TAKEN RELATIVE TO THE TOTAL CAPSULES DISPENSED FOR A GIVEN VISIT.

Source Table 14.1_6.1 CSR Study M11-612

Medical officer's comments:
The applicant was asked to address this concern and performed a reanalysis of their data which was included in the 16 Sept. 2016 submission (SDN73). It turns out that the original data they submitted was only based on capsules dispensed and capsules taken. Subjects were given a higher number of capsules to allow for flexibility in dose adjustments. The applicant performed a reanalysis of the data taking into account each subjects prescribed dose. There were some assumptions made in this analysis as the exact days the subjects took the medication was not known. For example with TIW dosing there could be slight differences in pill number with respect to whether the subject was taking the medication on a Monday, Wednesday and Friday schedule or a Tuesday, Thursday and Saturday schedule. The revised compliance rate for study M11-612 was 99± 9.3%. The estimated median value was 100%. The revised data support the validity of the study data.

6.2.4 Analysis of Primary Endpoint(s)

There was no formal primary efficacy endpoint analysis in this open-label safety study. However, two consecutive corrected serum calcium values > 10.2mg/dL, the upper limit of normal in this assay, was used to estimate the risk of hypercalcemia as a safety endpoint. The applicant identified two subjects with two consecutive corrected serum calcium values > 10.2mg/dL for a rate of hypercalcemia in this 12-week trial of 15.3% with 95% CIs of 1.9% to 45.4%.

Table 19 Subjects with at Least 2 Consecutive Calcium Values > 10.2mg/dL-Study M11-612

Subject Had at Least 2 Consecutive Calcium Values > 10.2 mg/dL (2.55 mmol/L)	Number (%) of Subjects	95% CI[a]
Yes	2/13 (15.3)	(1.9%, 45.4%)
No	11/13 (84.6)	

a. Exact confidence limits for the proportion.

Cross reference: Table 14.3__4.3
Source Table 35 CSR Study M11-612

Medical officer's comments:
This medical reviewer identified an additional subject with two consecutive serum calcium levels > 10.2mg/dL, for a rate of 3/13=23%, which was later also verified by the applicant. A detailed explanation of the risk of hypercalcemia in this study population was left to the Safety Review (7.3.5 Submission Specific Primary Safety Concerns).

Protocol Deviations-
The protocol deviations included in the clinical study report were reviewed and found to be minor and unlikely to impact the study results.

The clinical study report mentions that 10 plasma samples from two subjects (SUBJID 4031401 and 5047701) for paricalcitol analysis were inadvertently thawed during shipping and exposed to room temperature for 10 days. The applicant states that stability data for paricalcitol in plasma at room temperature demonstrates the integrity of samples for up to 263 hours (11days), which should support the use of these samples in the final results.

Medical officer's comments:
The data from these two patients was reviewed by the Clinical Pharmacology reviewer Dr. Lian Ma and found to be acceptable as it gave results similar to that seen in other patients receiving similar doses.

6.2.5 Analysis of Secondary Endpoints(s)

Efficacy was not formally tested in this open label study without a comparator group, but data was summarized for subjects with two consecutive ≥30% reductions from baseline in serum iPTH during the 12-week treatment period. This was the same endpoint used as the primary endpoint in the efficacy analysis for Study M10-149.

Table 20 Proportion of Subjects Achieving Two Consecutive ≥30% reductions from Baseline in iPTH (All Treated Population)-Study M11-612

Response[a]	n/N	Proportion	(95% CI)[b]
Yes	8/13	61.5	(31.6, 86.1)
No	5/13		

a. The All-Treated dataset is defined as the set of all subjects who took at least one dose of study drug.

b. Exact confidence limits for the proportion.

Cross reference: Table 14.2__1.2
Source Table 17 CSR Study M11-612

Medical officer's comments:
The proportion of subjects achieving two consecutive ≥30% reductions from baseline in iPTH at 12 weeks was higher in study M11-612 at 61.5% in the dialysis population vs. 27.8% in study M10-149 in the predialysis population. One possible explanation for the higher efficacy in the dialysis patients is the higher baseline iPTH levels in the dialysis population in study M11-612 (884 ± 374pg/mL) compared to the baseline iPTH levels in the predialysis population in study M10-149 (150 ± 82pg/mL). These data are comparable to the results seen in NDA 20-819 with paricalcitol injection compared to placebo in the pediatric dialysis population 9/15=60% vs. 3/14=21%, respectively, and so are supportive of efficacy in the treatment of secondary hyperparathyroidism in the dialysis population. Nevertheless, efficacy in this population will still be formally extrapolated from the adult data using population PK.

Efficacy data was also summarized for subjects with two consecutive iPTH values in the treatment goal range of 150 to 300 pg/mL during the 12-week treatment period. These data show that about 39% of pediatric dialysis subjects can consistently reach iPTH treatment goals with Zemplar Capsules during a 12-week treatment period.

Table 21 Proportion of Subjects Achieving Two Consecutive iPTH Values between 150 and 300 pg/mL (All-Treated)-Study M11-612

Response[a]	n/N	Proportion	(95% CI)[b]
Yes	5/13	38.5	(13.9, 68.4)
No	8/13		

a. The All-Treated dataset is defined as the set of all subjects who took at least one dose of study drug. Subject 5079601 had an iPTH value of 249 pg/mL at baseline visit, and was not counted as having 2 consecutive iPTH values between 150 pg/mL and 300 pg/mL.

b. Exact confidence limits for the proportion.

Cross reference: Table 14.2__1.1
Source Table 16 CSR Study M11-612

6.2.6 Other Endpoints

Health Outcome Questionnaires-
Self-reported health outcomes from subjects and their caregivers were assessed separately at baseline and Week 12 using the PedsQL™ 4.0 questionnaire and the PedsQL™ End Stage Renal Module version 3.0 Questionnaire.

The results for the subjects' PedsQL™ 4.0 questionnaire indicated a trend towards improvement from baseline to final assessment in each of 6 functioning parameters (physical, emotional, social, school, physical health, and psycho-social) and the total score. The total score for subjects improved from baseline to the final assessment by a mean score of 5.2 ± 4.3.

In contrast, the results for the caregivers' PedsQL™ 4.0 questionnaire revealed a trend towards worsening from baseline to final assessment in mean scores for 5 of 6 functioning parameters (physical, social, school, physical health, and psycho-social), while they reported a trend towards improvement from baseline to final assessment for 1 of 6 functional parameters, the emotional functioning parameter. In addition, parents reported a mean change in total score from baseline to the final assessment of –5.1 ± 4.9.

The results for the subjects' PedsQL™ 3.0 End Stage Renal Module questionnaire indicated a trend towards improvement from baseline to final assessment in 6 of the 7 parameters (general fatigue, about kidney disease, treatment problems, family and peer interactions, worry, and physical appearance) with no change in 1 parameter (communication). The total score for the subjects' patient reported outcome (PRO) had a mean change from baseline to final assessment of 7.7 ± 4.4.

The results for the caregivers' PedsQL™ 3.0 End Stage Renal Module questionnaire also indicated a trend towards improvement from baseline to final assessment in 4 of the 7 parameters (general fatigue, about kidney disease, treatment problems, and family and peer interactions), with a trend towards worsening in 3 of 7 parameters (worry, physical appearance, and communication). The total score for the caregivers' PRO had a mean change from baseline to final assessment of –1.1 ± 3.4.

> *Medical officer's comments:*
> *The large standard errors in these scores make it difficult to draw any clear conclusions about the mean changes from baseline data and what sort of response might be considered clinically relevant. The mixed results pointing to an improvement on the part of the pediatric patients in contrast to a perception of worsening on the part of their caretakers is probably not that unexpected in an open-label trial. These findings point to the need for better designed PROs that are validated by the Agency and the need for randomization and blinding in order to obtain useful information from PROs used in pediatric clinical studies.*

6.2.7 Subpopulations

The study with only 13 patients was too small to be able to look at data in subpopulations.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Clinical trial simulations of Zemplar Capsules in pediatric CKD Stage 5 patients undergoing peritoneal dialysis were conducted using different iPTH based dosing schemes and a titration scheme similar to the one used in adults with CKD Stage 5 with a serum calcium cut off of 10.2 mg/dL. Based on the clinical trial simulations, the rate of hypercalcemia decreased when the starting dose was reduced from the currently approved adult dose of iPTH/80 to iPTH/120, with only 5% of subjects predicted to experience two consecutive elevations of calcium > 10.2 mg/dL with the iPTH/120 regimen compared to 16% of subjects predicted to have two consecutive elevations of calcium > 10.2 mg/dL with the iPTH/80 regimen. Therefore, the iPTH/120 dosing scheme was used as the starting dose in Study M11-612. Dose increases of 1mcg every 4 weeks were permitted to reach iPTH target levels as long as serum calcium and phosphorous levels where within acceptable guidelines. Table 22 shows that most patients were treated adequately with between 3 and 4 mcg of Zemplar three times a week, and the highest dose used in the study was 13mcg.

Table 22 Number of Patients at Each Assigned Dose by Study Visit-Study M11-612

	N (%) of Subjects at Each Dose Interval					
Dose, TIW	Week 2 N = 13	Week 4 N = 12	Week 6 N = 12	Week 8 N = 10	Week 10 N = 10	Week 12 N = 10
1 µg	0	1 (8.3)	1 (8.3)	0	1 (10.0)	1 (10.0)
2 µg	2 (15.4)	2 (16.7)	3 (25.0)	1 (10.0)	1 (10.0)	0
3 µg	3 (23.1)	3 (25.0)	2 (16.7)	1 (10.0)	1 (10.0)	3 (30.0)
4 µg	3 (23.1)	4 (33.3)	5 (41.7)	3 (30.0)	2 (20.0)	2 (20.0)
5 µg	1 (7.7)	0	1 (8.3)	1 (10.0)	2 (20.0)	0
6 µg	2 (15.4)	2 (16.7)	1 (8.3)	0	1 (10.0)	1 (10.0)
7 µg	1 (7.7)	1 (8.3)	2 (16.7)	2 (20.0)	1 (10.0)	1 (10.0)
8 µg	0	0	0	0	0	0
9 µg	0	0	0	0	0	0
10 µg	1 (7.7)	1 (8.3)	0	0	0	0
11 µg	0	0	1 (8.3)	1 (10.0)	1 (10.0)	1 (10.0)
12 µg	1 (7.7)	1 (8.3)	1 (8.3)	0	0	0
13 µg	0	0	1 (8.3)	1 (10.0)	1 (10.0)	1 (10.0)

TIW = three times weekly

Notes: A subject who reported two or more different paricalcitol doses for a given visit window is counted in each dose.

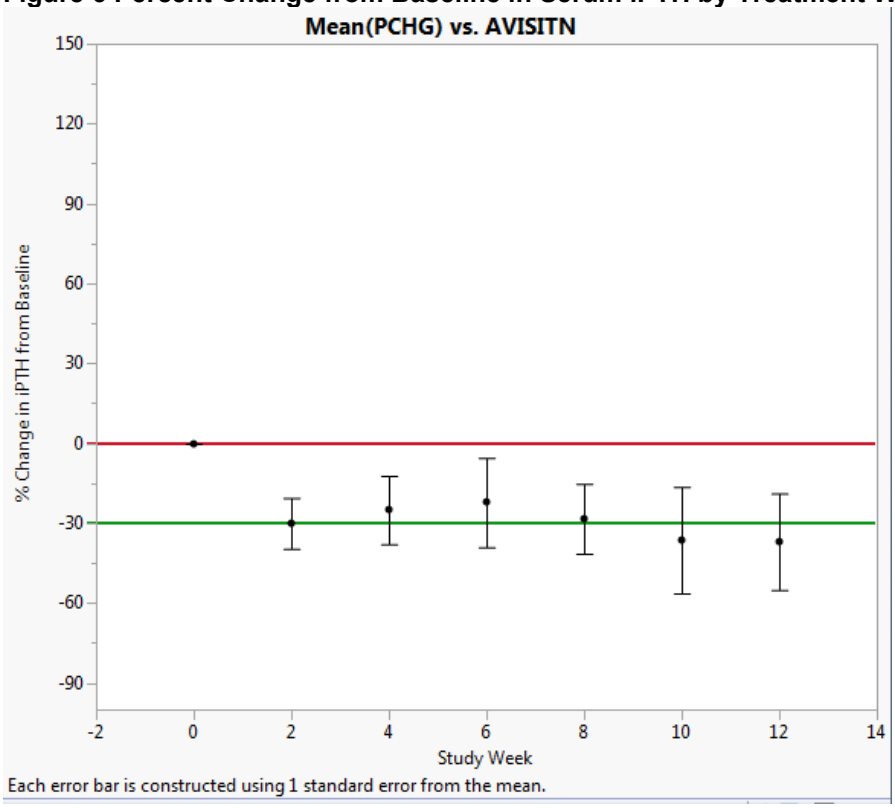
Percentages were calculated on non-missing values.

Source Table 1 R&D/15/0978-FDA 03AUG2015 Response

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

A decrease in mean iPTH from baseline was observed throughout the 12-week study period (see Figure 6). Efficacy seemed to level off between Weeks 10 and 12. There is insufficient data to support persistence of efficacy or to look for tolerance effects beyond Week 12.

Figure 6 Percent Change from Baseline in Serum iPTH by Treatment Week-Study M11-612



The red line refers to the baseline iPTH, the green line refers to a 30% decrease from baseline.
M11-612 DEFF dataset, PARAM=IPTH, PCHG, by AVISITN

Study Week	Number of Pts with Data
0	13
2	13
4	12
6	7
8	12
10	9
12	10

6.2.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

Supplement-016
The safety of Zemplar Capsules in the treatment of secondary hyperparathyroidism in predialysis pediatric patients ages 10 to 16 years with CKD (Stage 3 and Stage 4), S-016, was assessed in study M10-149. Study M10-149 was composed of two parts. Part 1 was a single dose PK study in 12 pediatric subjects, and had limited safety data. Part 2 was a 12-wk double-blind, placebo-controlled, randomized (1:1), safety and efficacy study with a 12-wk open-label extension period in 36 pediatric patients 10 to 16 years of age with secondary hyperparathyroidism associated with CKD Stage 3 or Stage 4. There were no deaths in this study and no AEs that were considered serious or severe were drug related.

During the double-blind period there was one subject on Zemplar (5.6%) and one on placebo (5.6%) that discontinued from the study due to hypercalcemia. Two additional subjects (6.9%) discontinued from the study due to hypercalcemia during the open-label extension. Hypercalcemia was reported as an AE in three patients in the double-blind portion of study M10-149, one in the paricalcitol group (5.6%) and two in the placebo group (11%). Three additional subjects had AEs of hypercalcemia while receiving paricalcitol in the open label extension (10%). Of the four AEs of hypercalcemia in subjects taking paricalcitol three were considered mild and one was of moderate severity. None were considered severe or serious. Three of these subjects ended up being discontinued from the study while one subject had the study drug dose interrupted. The primary safety endpoint in this study was the incidence of "clinically meaningful hypercalcemia" defined as two consecutive corrected serum calcium values > 10.2 mg/dL. One subject in the paricalcitol treatment group (1/18=5.6%) had two consecutive corrected serum calcium measurements > 10.2 mg/dL during the 12-week double-blind phase of the study at the Study Day 1 and Week 1 visits and was terminated early from the study at the Week 4 visit. Since the elevated serum calcium seen on Study Day 1 was drawn prior to starting the study medication AbbVie did not consider this a drug related case of "clinically meaningful hypercalcemia". There was also one other subject who had two consecutive corrected serum calcium measurements > 10.2 mg/dL during treatment with paricalcitol in the open label extension (1/29=3.4%). Peak serum calcium levels in both of these patients were less than 10.6mg/dL. Mild serum calcium elevations above the upper limit of normal but less than 11.5 mg/dL (Grade 1, CTCAE) were seen both during pretreatment screening and during treatment with paricalcitol. Five subjects (5/18=28%) in the paricalcitol treatment group had corrected serum calcium levels > 10.2mg/dL compared to four subjects (4/18=22%) in the placebo group.

No subjects experienced hyperphosphatemia during the double-blind period of Study M10-149, while two subjects (6.9%) experienced nonserious adverse events of mild to moderate severity of

hyperphosphatemia during the open-label extension. During the double-blind treatment period, three subjects (3/18=17%) in the paricalcitol treatment group had 6 serum phosphorous levels > 5.8mg/dL compared to one subject (1/18=5.6%) with 3 serum phosphorous levels > 5.8mg/dL in the placebo group. The peak serum phosphorous levels ranged from 6.2 mg/dL to 6.3 mg/dL. During the open label extension an additional six subjects (21%) had 12 serum phosphorous levels > 5.8mg/dL. The peak serum phosphorous levels ranged from 5.9 mg/dL to 7.0 mg/dL.

Pediatric KDOQI guidelines from 2005 recommended maintaining iPTH levels above 35pg/mL in CKD Stage 3 and above 70pg/mL in CKD Stage 4. KDIGO guidelines from 2009, which did not specifically address the pediatric population, stated that optimal iPTH levels in CKD Stage 3 to 5 predialysis patients are unknown. The lower limit of normal for the iPTH assay used in these trials was 12pg/mL. No pediatric predialysis subjects had iPTH levels of ≤12 pg/mL during the 12-week double-blind portion of study M10-149, although one subject did have a single value of 12pg/mL when treated with paricalcitol during the open label extension. In addition, one subject had two consecutive values < 35pg/mL in the paricalcitol group during the double-blind study period, and one subject had two nonconsecutive values < 35pg/mL while treated with paricalcitol during the open-label extension.

There was no substantial increase in hypercalcemia, hyperphosphatemia or low serum iPTH during the double-blind period in Study M10-149 in pediatric patients treated with paricalcitol compared to placebo. There were a small number of cases of hypercalcemia/blood calcium increased, hyperphosphatemia and low serum iPTH in patients treated with paricalcitol during the open label extension. However without a control group it is not possible to tell how much of an increase these cases represent above the background rate expected in this study population.

The most common AEs observed in studies M10-149 can be grouped into categories typically seen in the pediatric CKD population:

- GI-related symptoms (e.g. nausea, abdominal pain, and diarrhea)
- Pediatric infections (e.g. URI, strep pharyngitis, ear pain, cough, pyrexia etc.)
- CKD related symw2ptoms (e.g. chronic renal failure, hyperkalemia, blood creatinine increased)

The adverse event profile is similar to what has seen in the adult population.

Supplement-017

Study M11-612 was designed as a Phase 3, 12-week, open-label, single-arm, multicenter study to evaluate the safety of paricalcitol capsules in 12 pediatric subjects with Stage 5 CKD receiving peritoneal dialysis or hemodialysis. The primary safety endpoint in this study was the incidence of "clinically meaningful hypercalcemia" defined as two consecutive corrected serum calcium values > 10.2 mg/dL. In study M11-612 there were three subjects who had two consecutive serum calcium measurements > 10.2 mg/dL (3/13=23%), but none of the cases of hypercalcemia was classified as an adverse event. Similar to what was seen in study M10-149 there were mild serum calcium elevations above the upper limit of normal but less than 11.5 mg/dL (Grade 1, CTCAE) both during pretreatment screening and during treatment with paricalcitol. During the

open label treatment with paricalcitol five patients (5/13=38%) had eight calcium measurements ranging from 10.3mg/dL to a maximum of 10.9mg/dL.

During this open label study four subjects had seven serum phosphorous levels > 6.5mg/dL. The peak serum phosphorous levels ranged from 6.6 mg/dL to 15.3 mg/dL. The subject with the peak phosphorous value of 15.3 mg/dL was the only subject with an adverse event of hyperphosphatemia in this study. Besides this patient and another patient with a peak serum phosphorous value of 8.5mg/dL all other patients had peak serum phosphorous levels of ≤7.0mg/dL. None of the high levels of serum phosphorous, even the peak level of 15.3mg/dL in one patient, were associated with AEs other than hyperphosphatemia.

KDIGO recommends maintaining iPTH levels at 2x the upper limit of normal for the assay (2x 65 pg/mL=130pg/mL) in Stage 5 dialysis patients as they are expected to require higher PTH levels due to PTH resistance in bone. No pediatric dialysis subjects had iPTH below the lower limit of normal for the assay levels (12 pg/mL) in study M11-612. Three subjects had single values of 61, 84 and 129 on Study Days 15, 62 and 85, respectively. No subjects had two or more values < 130pg/mL.

The most common AEs observed in study M11-612 can be grouped into categories typically seen in the pediatric CKD population:

- GI-related symptoms (e.g. nausea, vomiting, abdominal pain and diarrhea)
- Pediatric infections (e.g. pyrexia, cough etc.)
- CKD related symptoms (e.g. fluid overload, and hypertension)

The adverse event profile in this study was also similar to what has seen in the adult population.

In summary, while treatment with paricalcitol is likely to result in an increase in hypercalcemia and hyperphosphatemia above the background rate, data from the current studies demonstrate that with appropriate monitoring the rates of hypercalcemia and hyperphosphatemia are low and these events can be identified and properly managed without resulting in serious adverse events. During the limited exposure in these clinical trials there were no patients who developed consistently low iPTH levels that might put them at risk of adynamic bone disease. However, it is still important to recommend regular monitoring of iPTH with chronic long term use, not only to determine that the dose is adequate as children continue to grow but to make sure chronic over suppression of PTH does not interfere with normal bone growth and development. Finally, in general the adverse event profiles seen in these pediatric clinical trials are consistent with the known safety profile of Zemplar reported in adult clinical studies.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study M10-149 in CKD Stage 3 and Stage 4 predialysis pediatric subjects with secondary hyperparathyroidism and study M11-612 in CKD Stage 5 dialysis patients with secondary hyperparathyroidism were used to evaluate safety.

7.1.2 Categorization of Adverse Events

The applicant's definitions of AEs and serious adverse events (SAEs) in the protocol(s) were accurate. Severity categorization (e.g., mild, moderate, severe) of AEs by the Applicant was appropriate.

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

Not applicable.

7.2 Adequacy of Safety Assessments

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

Study M10-149
During the 12-week double-blind period, the median number of days of study drug exposure was 83 for the placebo treatment group and 84 for the Zemplar treatment group.

Table 23 Summary of Drug Exposure-Study M10-149 Part 2 Safety and Efficacy Study

Number of Days of Study Drug Exposure					
Double-Blind Treatment Period[a] (ITT Data Set)					
Placebo N = 18		Zemplar Capsules N = 18		Total N = 36	
Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
81 (9)	83 (54 – 89)	68 (28)	84 (16 – 86)	74 (21)	84 (16 – 89)
Open-Label Treatment Period (All-Treated Data Set)					
Placebo During Double-Blind Period N = 16		Zemplar Capsules During Double-Blind Period N = 13		Total N = 29	
144 (184)	85 (29 – 718)	92 (15)	88 (75 – 123)	121 (138)	85 (29 – 718)

a. There were no statistically significant differences between treatment groups using 2-way ANOVA with terms of treatment and country, p = 0.123.

Source Table 2 summary-clin-safety-peds.pdf

Study M11-612
During the 12-week treatment period for Study M11-612 thirteen subjects received at least 1 dose of study drug. The median treatment duration was 83 days (range: 20 to 85 days). Three subjects were exposed for >12 weeks.

Table 24 Summary of Drug Exposure-Study M11-612

Number of Days Exposed to Study Drug					
N	Mean	(SD)	Median	(Range)	
13	73	(20)	83	(20 – 85)	

Cross reference: Table 14.1__5.1

Source CSR M11-612 Table 23

7.2.2 Explorations for Dose Response

Both studies M10-149 and M11-612 were designed with 12-week dose titration schemes. Most pediatric patients age 10 to 16 years in the CKD Stage 3 and 4 population in study M10-149 responded adequately with between 1 and 3 mcg of Zemplar three times a week. The highest doses used in this study were 5mcg in one subject with CKD Stage 3 and 7mcg in one subject with CKD Stage 4. Most pediatric patients age 10 to 16 years in the CKD Stage 5 population in study M10-149 were treated adequately with between 3 and 4 mcg of Zemplar three times a week, and the highest dose used in the study was 13mcg.

7.2.3 Special Animal and/or In Vitro Testing

According to the Pharmacology/Toxicology review by Dr. Espandiari the Agency had previously agreed that juvenile animal studies were not required to support clinical studies in pediatric patients with oral paricalcitol as nonclinical studies in adult rats and dogs suggested that hypercalcemia-related toxicities can be prevented with clinical monitoring for serum calcium.

To support labeling changes for Section 8 of Zemplar capsules, consistent with the Pregnancy and Lactation Labeling Rule (PLLR), the applicant resubmitted a full ICH S5 battery of reproductive toxicology studies with paricalcitol. These studies conducted with Zemplar Injection were previously reviewed under NDA 020819 and in Dr. Espandiari's current review were found to be acceptable to support the labeling of Zemplar Capsules.

7.2.4 Routine Clinical Testing

See Table 2 and Table 3, and Table 14 for a detailed listing of clinical testing in studies M10-149 (Part 1 and Part 2) and M11-612, respectively. Serum calcium was adequately monitored by measurements at two week intervals during the course of these studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events of concern with this drug class, active vitamin D analogs, relate to the occurrence of hypercalcemia hyperphosphatemia and low serum PTH.

7.3 Major Safety Results

7.3.1 Deaths

No subjects died in Studies M10-149 or M11-612.

7.3.2 Nonfatal Serious Adverse Events

Study M10-149
Part 1 (all patients were treated with a single 3mcg dose of paricalcitol):
No subjects in Part 1 of this study experienced a serious adverse event.

Part 2 (18 patients on paricalcitol, 18 patients on placebo):
No subjects in the paricalcitol group experienced a serious adverse event.

Two predialysis subjects in the placebo group experienced serious adverse events related to viral infection, blood creatinine increased and suicidal/homicidal ideation which were considered unrelated to the study medication.

Open-label Extension (all 29 patients were treated with paricalcitol):
Two predialysis subjects experienced serious adverse events: one subject had abdominal pain/renal impairment, and one subject had chronic renal failure/hypertensive crisis.

Study M11-612 (all 13 patients were treated with paricalcitol):
Two dialysis subjects experienced serious adverse events: one subject had a peritoneal dialysis complication, and one subject had fluid overload.

Medical officer's comments:
The four subjects with serious adverse events during treatment with paricalcitol in these two studies had events which are typical of these study populations. Abdominal pain, blood creatinine increased, chronic renal failure, hypertension and fluid overload have been reported in adults treated with Zemplar. Given the small number of events and the fact that such events are common in the CKD population it is not possible to draw any clear conclusions about whether these events were drug related from the current data.

7.3.3 Dropouts and/or Discontinuations

Study M10-149
Part 1 (all patients were treated with a single 3mcg dose of paricalcitol):
No subjects in Part 1 of M10-149 discontinued from the study due to an AE.

Part 2 (18 patients on paricalcitol, 18 patients on placebo):
Double-blind period:
Three subjects were discontinued for AEs during the double-blind period:

- 2 subjects (11%) in the placebo treatment group (one each with hypercalcemia and chronic renal failure) and
- 1 subject (5.6%) in the Zemplar treatment group with hypercalcemia.

Open-label Extension (all 29 patients were treated with paricalcitol):
Five subjects (17%) were discontinued for AEs during the open-label extension:

- 2 subjects with hypercalcemia and
- one each with vitamin D decreased, renal impairment and hypertensive crisis.

Study M11-612 (all 13 patients were treated with paricalcitol):
No subjects in Study M11-612 discontinued from the study due to an AE.

Medical officer's comments:
Hypercalcemia, chronic renal failure, Vitamin D decreased, renal impairment and hypertension have been reported in adults with CKD treated with Zemplar. In the double-

blind period there was one patient on Zemplar and one on placebo that discontinued due to an AE of hypercalcemia, but there were two other patients in the Zemplar treatment group who discontinued because they could not titrate to a lower dose than 1mcg who also had laboratory evidence of hypercalcemia which was not considered an AE (i.e. serum calcium > 10.2mg/dL). So three patients (3/18=16.7%) discontinued with hypercalcemia in the paricalcitol treatment group compared to only 1 patient (5.6%) in the placebo group. There were no unexpected AEs leading to study discontinuation in pediatric patients treated with paricalcitol from the limited safety information in these two clinical trials.

7.3.4 Significant Adverse Events

Adverse events were characterized as mild, moderate or severe.

Study M10-149
Part 1 (all patients were treated with a single 3mcg dose of paricalcitol):

No AEs in Part 1 of M10-149 were considered severe.

Part 2
Double-blind period (18 patients on paricalcitol, 18 patients on placebo):
Two subjects (11%) both in the placebo group had severe AEs during the double-blind period:

- 1 subjects (5.6%) had worsening of CKD resulting in discontinuation from the study and starting hemodialysis
- 1 subject (5.6%) had suicidal ideation after a recent classmate committed suicide.

Open-label Extension (all 29 patients were treated with paricalcitol):
One subject had two severe AEs of hypertension and worsening CKD resulting in the patient receiving a kidney transplant.

Study M11-612 (all 13 patients were treated with paricalcitol):
No AEs in Study M11-612 were considered severe.

Medical officer's comments:
There was no increased risk of severe AEs in pediatric patients treated with paricalcitol from the limited safety information in these two clinical trials.

7.3.5 Submission Specific Primary Safety Concerns

As mentioned previously, the adverse events of concern with vitamin D analogs relate to the occurrence of hypercalcemia, hyperphosphatemia and low serum PTH.

Hypercalcemia-
There were three adverse events of hypercalcemia reported in the double-blind portion of study M10-149 in predialysis patients, one in the paricalcitol group (5.6%) and two in the placebo group (11%). Three additional subjects (10%) had AEs of hypercalcemia while receiving paricalcitol in the open label extension. Of the four AEs of hypercalcemia in subjects taking paricalcitol three were considered mild and one was of moderate severity. None were considered severe or serious. Three of these subjects ended up being discontinued from the study while one subject had the study drug dose interrupted. In the open label study M11-612, in dialysis patients, none of the cases of hypercalcemia was classified as an adverse event.

The primary safety variable in both studies M10-149 and M11-612 was the incidence of "clinically meaningful hypercalcemia" defined as two consecutive corrected serum calcium values > 10.2 mg/dL even though the upper limit of normal (ULN) varied between 9.8mg/dL to 10.34mg/dL depending on study site.

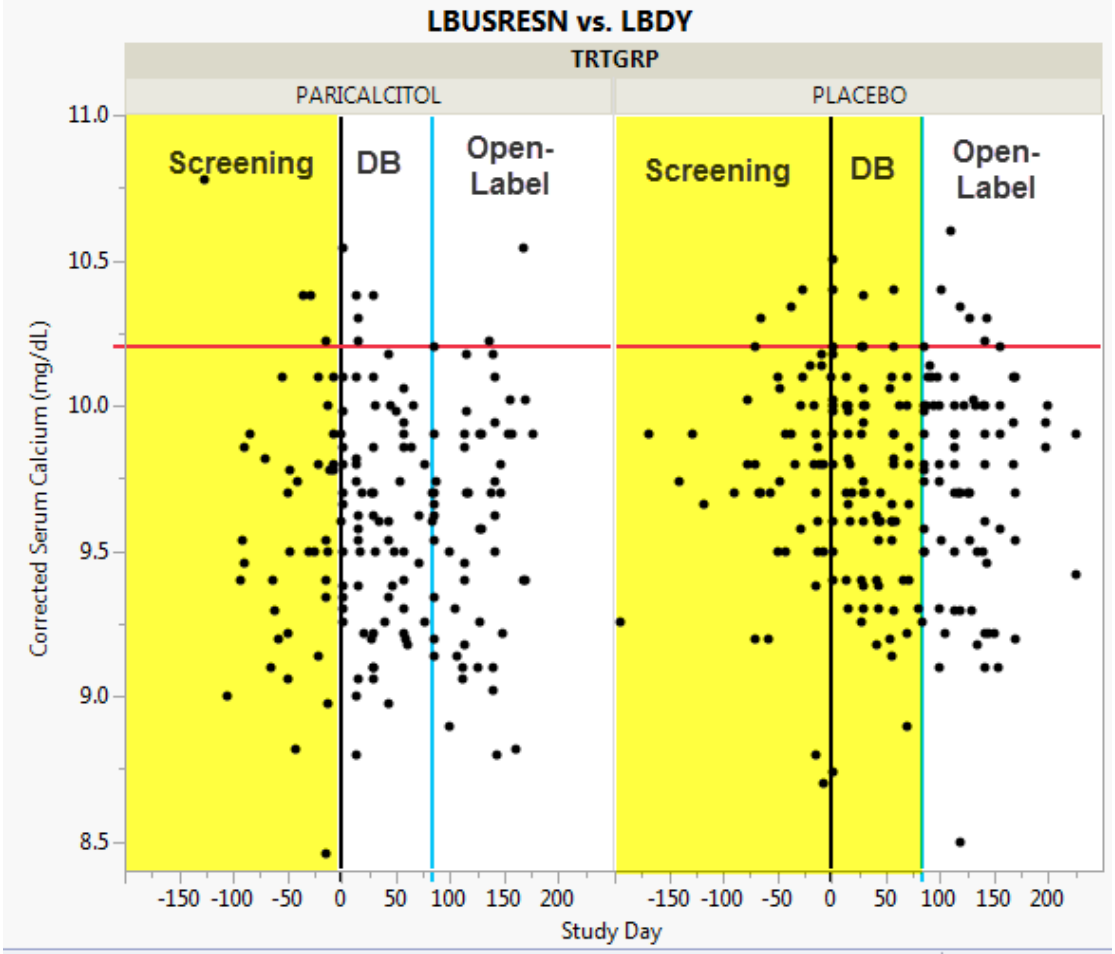
In pediatric predialysis patients in study M10-149 one subject (SUBJID= 4031405) in the paricalcitol treatment group (1/18=5.6%) had two consecutive corrected serum calcium measurements > 10.2 mg/dL during the 12 week double-blind phase of the study at the Study Day 1 and Week 1 visits and was terminated early from the study at the Week 4 visit. This subject had a peak serum calcium level of 10.5 mg/dL and had a normal serum calcium of 10.06mg/dL at the early termination visit. He probably should not have been enrolled in the study as PreStudy serum calcium levels were also elevated at 10.38 mg/dL on Study Day -29 and 10.22 mg/dL on Study Day -14. This subject was not listed in the Abbvie's submission (see M10-149 CSR Table 72) as having had two consecutive serum calcium measurements >10.2mg/dL while on paricalcitol because the measurement on Study Day 1 was taken before paricalcitol administration. There was also one subject (SUBJID=3990201, 1/29=3.4%) who had been on placebo during the double-blind period who had two consecutive corrected serum calcium measurements > 10.2 mg/dL during treatment with paricalcitol in the open label extension. This subject had a peak serum calcium level of 10.6 mg/dL and had a normal serum calcium of 9.7mg/dL at the early termination visit.

In pediatric dialysis patients in study M11-612 there were three subjects who had two consecutive serum calcium measurements > 10.2 mg/dL during the open label study (SUBJID=1498203, 1519101 and 4031401, 3/13=23%). The peak serum calcium levels were 10.9 mg/dL, 10.4mg/dL and 10.54 mg/dL, respectively, and values normalized at follow up visits in two subjects (1498203 and 4031401); subject 1519101 did not have any follow up measurements.

Corrected serum calcium levels by study day are shown in Figure 7 for Study M10-149 from Study Day -200 to +300. Treatment periods without exposure to paricalcitol are highlighted in yellow for easier comparison. Mild serum calcium elevations above the upper limit of normal but less than 11.5 mg/dL (Grade 1, CTCAE) were seen both prior to (highlighted in yellow) and during treatment with paricalcitol. During the double-blind treatment period, five subjects (5/18=28%) in the paricalcitol treatment group had 6 corrected serum calcium levels >

10.2mg/dL compared to four subjects (4/18=22%) with 4 corrected serum calcium levels > 10.2mg/dL in the placebo group.

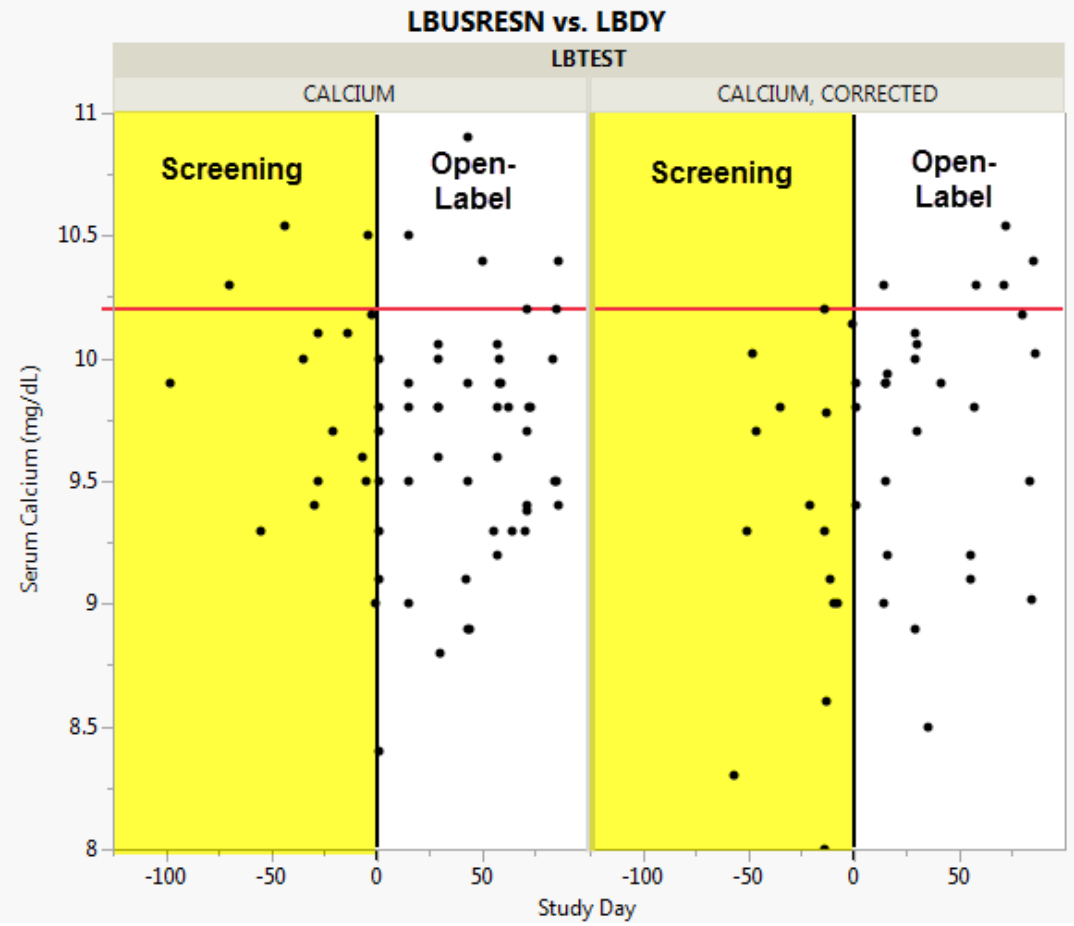
Figure 7 Corrected Serum Calcium by Study Day and Treatment Group-Study M10-149 Part 2 Safety and Efficacy Study



Source M10-149, LB2 dataset, LBUSREN, LBTEST=Calcium, Corrected; LBDY >-200 and < 300, by TRTGRP. The red horizontal line depicts ULN=10.2mg/dL, the blue vertical line represents Study Day=84 (Week 12). Area highlighted in yellow not exposed to paricalcitol.

Both serum calcium and corrected serum calcium from the open-label study M11-149 are listed in Figure 8 as not all patients had serum albumin levels drawn at each visit to permit calculation of corrected serum calcium. There were 93 calcium measurements vs. only 49 corrected serum calcium measurements. Here as well mild serum calcium elevations above the upper limit of normal but less than 11.5 mg/dL (Grade 1, CTCAE) were seen both prior to (highlighted in yellow) and during treatment with paricalcitol. During the open label treatment with paricalcitol five subjects (5/13=38%) had eight calcium measurements ranging from 10.3mg/dL to a maximum of 10.9mg/dL.

Figure 8 Calcium and Corrected Serum Calcium by Study Day-Study M11-612



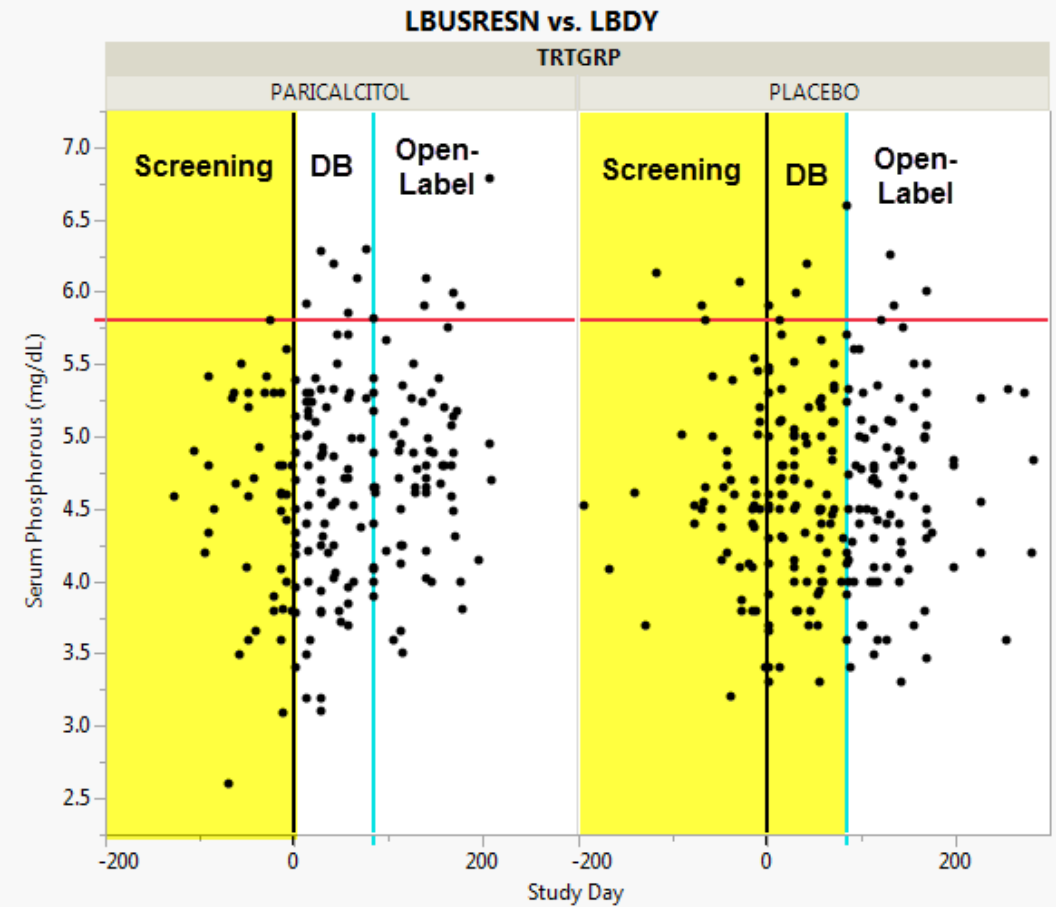
Source M11-612, LB dataset, LBUSREN by LBDY, LBTEST=Calcium or Calcium, Corrected. The red horizontal line depicts ULN=10.2mg/dL. Area highlighted in yellow not exposed to paricalcitol.

Medical officer's comments:
Clearly there is a background rate of mild hypercalcemia in both the predialysis and dialysis populations as shown in Figs. 7 and 8 above during the screening period in both studies and in patients treated with placebo during the double-blind phase of study M10-149. The rate of two consecutive serum calcium levels > 10.2mg/dL in subjects treated with paricalcitol ranged from 3.4 to 5.6% in predialysis patients in study M10-149 to 23% in dialysis subjects in study M11-612, but adverse events of hypercalcemia were only reported in predialysis patients in study M10-149. Given that the designation of an adverse event requires clinical discretion it is likely that investigators assumed the cases of mild hypercalcemia seen in the dialysis patients were consistent with their degree of CKD and did not represent adverse events which needed to be reported. While treatment with paricalcitol is likely to result in an increase in hypercalcemia above the background rate the observed difference seen here appears small from the limited data in these studies. The current study data demonstrate that with appropriate monitoring hypercalcemia can be identified when it is still mild in severity to permit necessary dose adjustments and prevent progression to serious adverse events.

Hyperphosphatemia-
No subjects experienced hyperphosphatemia during the double-blind period of Study M10-149. Two subjects (SUBJID=3895501 and 4638601, 6.9%) experienced nonserious adverse events of mild to moderate severity of hyperphosphatemia during the open label extension. Peak serum phosphorous levels in these patients were 5.7 mg/dL (ULN=4.8mg/dL) and 7.0mg/dL (ULN=5.3mg/dL), respectively. Follow up values in these subjects returned to normal levels. In the open label Study M11-612 one subject (7.7%) had an adverse event of hyperphosphatemia (SUBJID=3990202). The event was described as mild in severity and nonserious despite a peak serum phosphorous level of 15.3mg/dL on Study Day 64. This patient had been taking Sevelamer for hyperphosphatemia prevention prior to starting the trial, and the dose was increased from 800mg with snacks and 1600mg with meals to 1600mg with snacks and 2400mg with meals on Study Day 71. A repeat serum phosphorous level on study day 83 was 7.1mg/dL and the subject was discontinued from the study. According to the applicant no further testing was performed on this subject as part of the study protocol, and no other AEs were associated with the high serum phosphorous levels observed in this patient.

The study design for M10-149 in predialysis patients included exclusion criteria for subjects with phosphorous levels > 5.8mg/dL and included dosing decisions to lower phosphorous levels > 5.8 mg/dL during the study, even though the normal upper limit of normal for serum phosphorous was somewhat lower and ranged from 4.5 to 5.7mg/dL according to the lab dataset. During the double-blind treatment period, three subjects (3/18=17%) in the paricalcitol treatment group had 6 serum phosphorous levels > 5.8mg/dL compared to one subject (1/18=5.6%) with 3 serum phosphorous levels > 5.8mg/dL in the placebo group. The peak serum phosphorous levels ranged from 6.2 mg/dL to 6.3 mg/dL. During the open label extension an additional six subjects (21%) had 12 serum phosphorous levels > 5.8mg/dL. The peak serum phosphorous levels ranged from 5.9 mg/dL to 7.0 mg/dL.

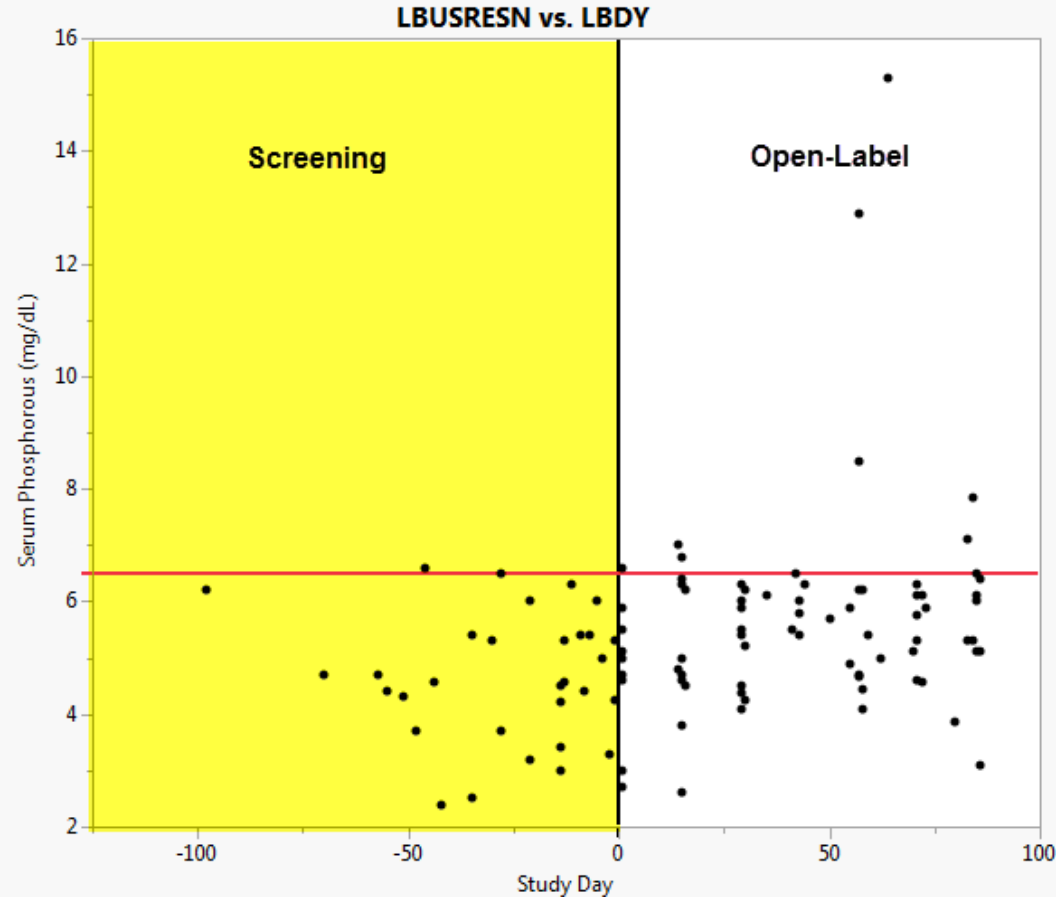
Figure 9 Serum Phosphorous by Study Day and Treatment Group-Study M10-149 Part 2 Safety and Efficacy Study



Source M10-149, LB2 dataset, LBUSREN, LBTEST=Inorganic Phosphate; LBDY >-200 and < +300, by TRTGRP. The red horizontal line depicts 5.8 mg/dL, the blue vertical line represents Study Day=84 (Week 12). Area highlighted in yellow not exposed to paricalcitol.

The study design for the open label study M11-612 in dialysis patients included exclusion criteria for subjects with phosphorous levels > 6.5mg/dL and included dosing decisions to lower phosphorous levels > 6.5 mg/dL during the study, even though the normal upper limit of normal for serum phosphorous was somewhat lower and ranged from 4.8 to 5.7mg/dL according to the lab dataset. During this open label study four subjects had seven serum phosphorous levels > 6.5mg/dL. The peak serum phosphorous levels ranged from 6.6 mg/dL to 15.3 mg/dL. The subject with the peak phosphorous value of 15.3 mg/dL (SUBJID=3990202, described previously in more detail) was the only subject with an adverse event of hyperphosphatemia in this study. Besides this patient and another patient with a peak serum phosphorous value of 8.5mg/dL (SUBJID= 1498204), all other patients had peak serum phosphorous levels ≤7.0.

Figure 10 Serum Phosphorous by Study Day-Study M11-612



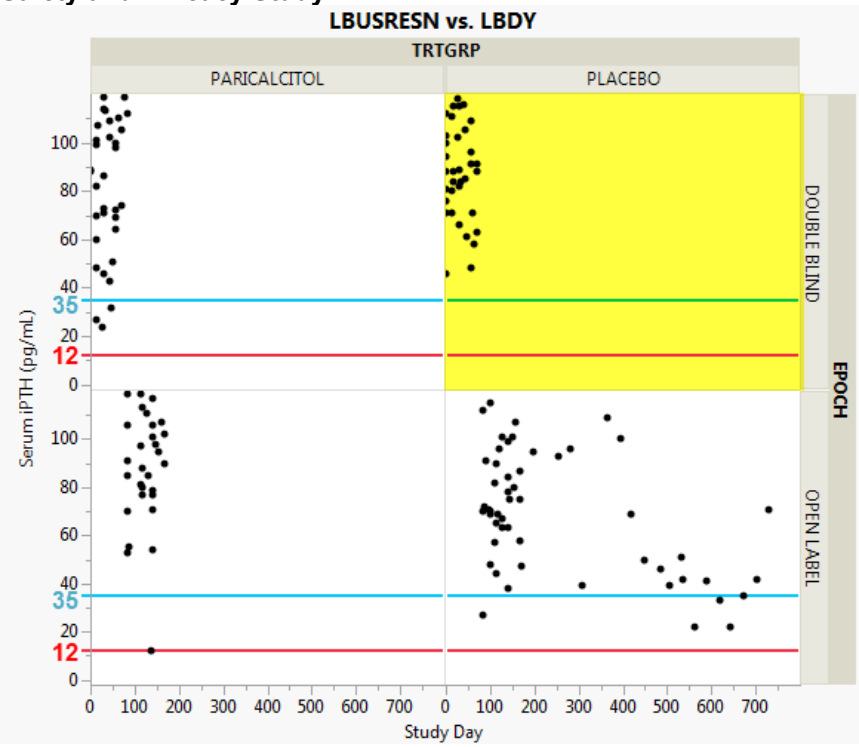
Source M11-612, LB2 dataset, LBUSREN, LBTEST=Inorganic Phosphate, LBDY>-100 and < 100. The red horizontal line depicts 6.5mg/dL, the blue vertical line represents Study Day=84 (Week 12). Area highlighted in yellow not exposed to paricalcitol.

Medical officer's comments:
In total 3 subjects in the two studies had nonserious adverse events of hyperphosphatemia that were mild or moderate in severity. Two were treated by increasing their Renagel dose and one was eventually discontinued from the study due to the hyperphosphatemia. Except for the two dialysis subjects in the Study M11-612 with very high serum phosphorous levels of (SUBJID= 3990202, 12.9, 15.3 and 7.1mg/dL) and (SUBJID= 1498204, 6.8 and 8.5mg/dL) all other subjects had levels of 7.0mg/dL or less. None of the high levels of serum phosphorous were associated with AEs other than hyperphsophatemia. In summary, the risk of serious AEs due to hyperphosphatemia is low and with proper monitoring of serum phosphorous hyperphosphatemia can be adequately controlled in pediatric patients treated with paricalcitol.

Low iPTH
In order to minimize the risk for adynamic bone disease it is important to avoid over suppression of serum PTH which can result from excessive use of vitamin D analogs such as paricalcitol. Pediatric KDOQI recommendations from 2005 recommended maintaining iPTH levels above 35pg/mL in CKD Stage 3 and above 70pg/mL in CKD Stage 4. More recent KDIGO recommendations from 2009, which do not specifically address the pediatric population, stated that optimal iPTH levels in Stage 3 to 5 CKD predialysis patients are unknown. In contrast, KDIGO recommends maintaining iPTH levels at 2x the upper limit of normal for the assay in Stage 5 dialysis patients (2x 65=130pg/mL) as they are expected to require higher PTH levels due to PTH resistance in bone.

The lower limit of normal for the iPTH assay used in these trials was 12pg/mL. No pediatric predialysis subjects had iPTH levels of 12 pg/mL or less during the 12-week double-blind portion of study M10-149, although one subject did have a single value of 12pg/mL when treated with paricalcitol during the open label extension. In addition, one subject had two consecutive values < 35pg/mL in the paricalcitol group during the double-blind study period, and one subject had two nonconsecutive values < 35pg/mL while treated with paricalcitol during the open-label extension.

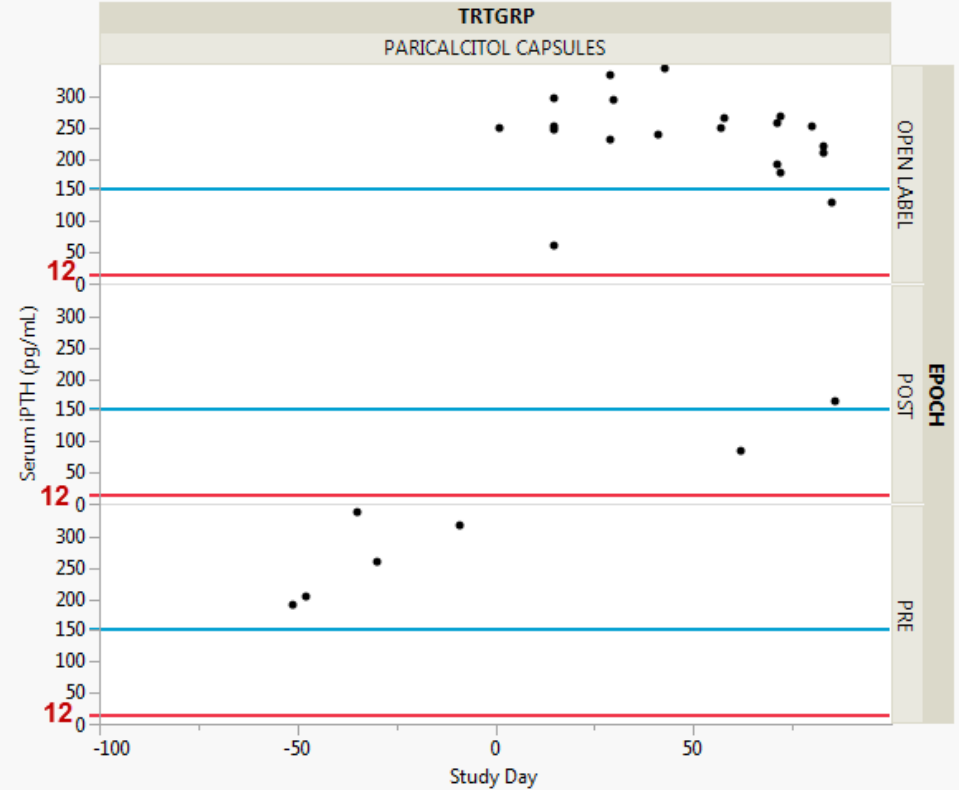
Figure 11 Serum iPTH (0 to 120pg/mL) by Study Day and Treatment Group-Study M10-149 Part 2 Safety and Efficacy Study



Source M10-149, LB2 dataset, LBUSREN < 120pg/mL, LBTEST=iPTH, by TRTGRP, EPOCH= DB or OL. The blue horizontal line depicts 35pg/mL (KDOQI lower limit CKD Stage 3) and the red horizontal line depicts 12pg/mL (LLN). Area highlighted in yellow not exposed to paricalcitol.

No pediatric dialysis subjects had iPTH levels ≤12 pg/mL in study M11-612. Three subjects (3976302, 5079601 and 1519101) had single values of 61, 84 and 129 on Study Days 15, 62 and 85, respectively. No subjects had two or more values < 130pg/mL.

Figure 12 Serum iPTH (0 to 350pg/mL) by Study Day and Treatment Epoch-Study M11-612



Source M11-612, LB2 dataset, LBUSREN < 350pg/mL, LBTEST=iPTH, by TRTGRP, EPOCH= Pre, OL and Post. The blue horizontal line depicts 150pg/mL (KDOQI lower limit for CKD Stage 5). The KDIGO lower limit of 2x ULN would be 130pg/mL not shown here. The red horizontal line depicts 12pg/mL (LLN for this assay).

Medical officer's comments:
During the limited exposure in these clinical trials there were no patients who developed consistently low iPTH levels that might put them at risk of adynamic bone disease. However, it is still important to recommend regular monitoring of iPTH with chronic long term use, not only to determine that the dose is adequate as children continue to grow but to make sure chronic over suppression of PTH does not interfere with normal bone growth and development.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study M10-149
Part 1 (all patients were treated with paricalcitol):
Two subjects in Part 1 of M10-149 had AEs, one with nausea/abdominal pain and one with headache.

Part 2
Double-blind period (18 patients on paricalcitol, 18 patients on placebo, source Table 50 CSR):
Only one AE was more common in the paricalcitol group and occurred in at least two subjects: rhinitis was seen in 3 subjects on paricalcitol (17%) vs. no subjects in the placebo group.
Other AEs of interest that did not meet these criteria were:

- Abdominal pain, diarrhea, gastroenteritis, blood creatinine increased, muscle spasms, and renal failure chronic which were all seen in 1 placebo patient and 0 paricalcitol patients.
- Nausea was seen in 0 placebo patients and 1 paricalcitol patient.
- Hypercalcemia was seen in 2 placebo patients and 1 paricalcitol patient.

Open-label Extension (all patients were treated with paricalcitol, source Table 51 CSR):
No AEs were seen in 4 or more patients.
AEs seen in 3 patients were: hypercalcemia, hyperkalemia, and nasopharyngitis.
AEs seen in 2 patients were: hyperphosphatemia, chronic renal failure, headache, cough, epistaxis, ear pain, strep pharyngitis, and URI.

Study M11-612 (all patients were treated with paricalcitol, source Table 26 CSR):
No AEs were seen in 3 or more patients.
AEs seen in 2 patients were nausea, pyrexia, and cough.
AEs of interest seen in only 1 patient were blood calcium increased, hyperphosphatemia, abdominal pain, abdominal pain upper, diarrhea, vomiting, and headache.

> *Medical officer's comments:*
> *There was no clear increase in hypercalcemia or hyperphosphatemia during the double-blind period in Study M10-149 in subjects treated with paricalcitol compared to placebo. There were a small number of cases of hypercalcemia/blood calcium increased and hyperphosphatemia in subjects treated with paricalcitol during the open label extension part of study M10-149 and the open label study M11-612 but without a control group it is possible that this represents the low background rate in this population.*
>
> *Most of the common AEs observed in studies M10-149 and M11-612 can be grouped into categories typically seen in the pediatric CKD population:*
>
> - *GI-related symptoms (e.g. nausea, vomiting, abdominal pain, and diarrhea)*
> - *Pediatric infections (e.g. URI, strep pharyngitis, ear pain, cough, pyrexia etc.)*

- *CKD related symptoms (e.g. chronic renal failure, blood creatinine increased, hypertension)*

There were no unexpected findings in the common AEs seen in pediatric patients treated with paricalcitol from the limited safety information in these two clinical trials.

7.4.2 Laboratory Findings

M10-149
Clinical Chemistry-
During the double-blind period, Part 2, the only laboratory finding with a statistically significant mean change from baseline to final measurement was serum iPTH (paricalcitol -27pg/mL vs. placebo +63pg/mL, $p< 0.001$ using a one way ANOVA, see CSR M10-149 Table 62), which is consistent with paricalcitol efficacy in the treatment of secondary hyperparathyroidism. For corrected serum calcium the difference was paricalcitol (+0.06 mg/dL vs. placebo -0.05mg/dL, p=0.402). Vitamin D analogs like paricalcitol would be expected to increase serum calcium consistent with the trend seen here for an increase in serum calcium in the paricalcitol group. For inorganic phosphate the difference was paricalcitol (+0.06 mg/dL vs. placebo +0.20mg/dL, p=0.471). Vitamin D analogs like paricalcitol would be expected to increase phosphorous levels as well but the increase seen here was lower in the paricalcitol group compared to placebo. Changes in diet or concomitant medications by the treating physician may have limited the increase in phosphorous levels which were seen in the paricalcitol group. For serum creatinine the difference was paricalcitol (+0.20 mg/dL vs. placebo +0.12mg/dL, p=0.505). This small increase in serum creatinine in both treatment groups may represent the natural progression in the course of CKD.

During the open-label extension treatment period the mean iPTH values for subjects previously on paricalcitol and placebo were lower than at baseline (-23mg/dL and -51mg/dL, respectively see CSR M10-149 Table 63), consistent with continued efficacy during the open-label extension. For corrected serum calcium the mean difference was slightly higher for both the paricalcitol and placebo groups than what was seen at the end of the double blind period (+0.06mg/dL → +0.12mg/dL and -0.05 → +0.01mg/dL), consistent with the expected effect of a vitamin D analog to increase serum calcium levels. For inorganic phosphate the differences was +0.37mg/dL for subjects previously on paricalcitol and -0.09 for subjects previously on placebo. The trend for an increase in inorganic phosphate levels in the paricalcitol group is consistent with the expected effect of a vitamin D analog. Serum creatinine continued to increase in both the paricalcitol and placebo groups from what was seen at the end of the double blind period (+0.20mg/dL → +0.51mg/dL and +0.12mg/dL → +0.35mg/dL), which may represent the natural progression in the course of CKD.

Hematology-
During the double blind period, Part 2, there we no statistically significant differences for mean changes from baseline to the final visit in the complete blood count and differential (see CSR M10-149 Table 60).

During the open-label extension there were no clear trends with respect to mean changes from baseline to the final visit.

Urinalysis-
During the double-blind period, Part 2, there was a non-statistically significant trend for an increase in specific gravity in the paricalcitol group vs. placebo (mean change from baseline of +0.0011 vs. -0.0007, p=0.079). However, no paricalcitol or placebo treated subjects experienced a shift from low or normal specific gravity at baseline to high at the final visit. There were no significant findings in urine pH or first morning void urine albumin/creatinine ratio (FMV UACR).

During the open-label extension there were no clear trends with respect to changes in urinalysis parameters.

M11-612
Clinical Chemistry-
During this open-label, single-arm study there was a -438pg/mL mean change from baseline to final measurement in iPTH consistent with an improvement in secondary hyperparathyroidism in these patients. For corrected serum calcium there was a mean change from baseline to the final measurement of +0.31mg/dL consistent with the expected effect of a vitamin D analog. For inorganic phosphate there was a mean change from baseline to the final measurement of +0.64mg/dL, consistent with the expected effect of a vitamin D analog. For serum creatinine there was a mean change from baseline to the final measurement of +0.48mg/dL, which may represent natural disease progression in the course of CKD.

Hematology-
During this open label single arm study there were no clear trends with respect to mean changes from baseline to the final visit.

Urinalysis-
Urinalysis was not routinely monitored in this study protocol.

7.4.3 Vital Signs

Vital signs assessments of blood pressure, pulse, and weight were performed at every study visit.

M10-149

During the double-blind period, Part 2, there were no statistically significant or clinically meaningful differences between treatment groups in vital sign variables in the change from baseline to the final measurement in: systolic blood pressure, diastolic blood pressure, heart rate, weight, or temperature (see M10-149 CSR Table 74). During the open-label extension there were no clear trends with respect to mean changes from baseline to the final visit. (see M10-149 CSR Table 75).

M11-612
During this open label single arm study there were no clinically meaningful observations in vital signs according to the applicant.

7.4.4 Electrocardiograms (ECGs)

There were no unusual or unexpected ECG findings in either Study M10-149 or Study M11-612.

M10-149
In Study M10-149, 34 ECG's were reported as normal. In the 14 subjects with "abnormal" ECGs, mostly due to sinus bradycardia and left ventricular hypertrophy, none were considered to be clinically significant.

M11-612
In Study M11-612, 8 ECG's were reported as normal. In the 5 subjects who had "abnormal" ECGs noted during the study, these were due to sinus tachycardia/arrhythmia, left ventricular hypertrophy, and left atrial enlargement; none were considered to be clinically significant.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency for AEs was not studied in these trials.

7.5.2 Time Dependency for Adverse Events

Time dependency for AEs was not studied in these trials.

7.5.3 Drug-Demographic Interactions

Drug-demographic interactions were not studied in these trials.

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not studied in these trials.

7.5.5 Drug-Drug Interactions

No specific drug-drug interaction studies were included in this submission.
From previously submitted in vitro studies, Zemplar is not expected to inhibit CYP3A, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C1, CYP2D6, or CYP2E1 nor induce CYP2B6, CYP2C9, or CYP3A. Because of the low sample size in the current studies it was not possible to determine any new clinically significant drug-drug interactions between Zemplar and concomitant medications.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable

7.6.2 Human Reproduction and Pregnancy Data

The Applicant resubmitted a full ICH S5 battery of reproductive toxicology studies with paricalcitol to support labeling changes for Section 8 of Zemplar Capsules, consistent with the Pregnancy and Lactation Labeling Rule (PLLR). These studies were conducted with the Zemplar Injection formulation using intravenous administration and were reviewed previously under NDA 020819 for Zemplar Injection. See the Pharmacology/Toxicology review by Dr. Espandiari for a discussion of these nonclinical findings. According to this review the results of these studies are acceptable to support the labeling (Section 8) update of Zemplar Capsules.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

There is limited off-label use in the pediatric population. IMS health data from 2012 estimated paricalcitol use based on outpatient retail pharmacy data in the US in pediatric patients age 0 to 6 years at 41 patients and age 7 to 17 years at 274 patients. The numbers were too low to be included in the chart submitted by the applicant in their most recent Annual Report.

Table 25 Total US Prescriptions and Drug Occurrences by Age-Zemplar Annual Report July 2016

Drug Name/ List No.	TRx^	Total Drug Occur ** (000s)	Drug Occur** 0-1 Yr. (000s)	Drug Occur** 2-12 Yrs. (000s)	Drug Occur** 13-16 Yrs. (000s)	Drug Occur** 17+ Yrs. (000s)	Drug Occur** Unspecified (000s)
Zemplar® (paricalcitol) Capsules 2 mcg List 4314	(b) (6)						
Zemplar® (paricalcitol) Capsules 4 mcg*** List 4315							
Zemplar® (paricalcitol) Capsules 1 mcg List 4317							

* TRx (total prescriptions) Source: IMS Health Incorporated USA, National Prescription Audit (NPA).

** Source: Physician Drug and Diagnosis Audit (PDDA), SDI.

*** The Zemplar 4 mcg capsules were discontinued due to business reasons.

Source SDN 792 7/21/2016 NDA 21606

9 Appendices

9.1 Literature Review/References

NKF KDOQI GUIDELINES-KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children With Chronic Kidney Disease
http://www2.kidney.org/professionals/KDOQI/guidelines_pedbone/

Interventions for metabolic bone disease in children with chronic kidney disease.
Hahn D, Hodson EM, Craig JC.
Cochrane Database Syst Rev. 2015 Nov 12;(11):CD008327. doi: 10.1002/14651858.CD008327.pub2. Review.

Intravenous **paricalcitol** for treatment of secondary hyperparathyroidism in children on hemodialysis.
Greenbaum LA, Benador N, Goldstein SL, Paredes A, Melnick JZ, Mattingly S, Amdahl M, Williams LA, Salusky IB.
Am J Kidney Dis. 2007 Jun;49(6):814-23.

Paricalcitol versus calcitriol treatment for hyperparathyroidism in **pediatric** hemodialysis patients.
Seeherunvong W, Nwobi O, Abitbol CL, Chandar J, Strauss J, Zilleruelo G.
Pediatr Nephrol. 2006 Oct;21(10):1434-9. Epub 2006 Aug 10.

Are new vitamin D analogues in renal bone disease superior to calcitriol?
Salusky IB.
Pediatr Nephrol. 2005 Mar;20(3):393-8. Epub 2005 Feb 3. Review.

Secondary hyperparathyroidism in children with chronic renal failure: pathogenesis and treatment.
Sanchez CP.
Paediatr Drugs. 2003;5(11):763-76. Review.

Comparative review of the pharmacokinetics of vitamin D analogues.
Bailie GR, Johnson CA.
Semin Dial. 2002 Sep-Oct;15(5):352-7. Review.

Successful treatment of severe secondary hyperparathyroidism with high dose paricalcitol in a three year-old child on dialysis
http://www.elsevier.pt/en/revistas/revista-portuguesa-endocrinologia-diabetes-e-metabolismo-356/artigo-resumo/successful-treatment-severe-secondary-hyperparathyroidism-with-high-dose-S1646343914000649
Rocha, Liliana; Sousa, Ana Catarina; Rezende, Daria; Faria, Maria Sameiro; Costa, Teresa; Mota, Conceição Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo 10.2 (Jul 1, 2015): 152-155.

9.2 Labeling Recommendations

1 INDICATIONS AND USAGE
Revise indications to specify use is approved in adults and children 10 years of age and older.

2 DOSAGE AND ADMINISTRATION
Include separate dosing direction sections for adults and children.
Remove references to (b) (6)

Remove (b) (6)

6 ADVERSE REACTIONS
List AE tables and additional information by CKD Stage 3 and 4, and CKD Stage 5 separately for adults and children.

7 DRUG INTERACTIONS
Information to be put into tabular form by Clin Pharm and to include clinical impact and proposed intervention in separate subsections.

8 USE IN SPECIFIC POPULATIONS
Update with information to comply with the Pregnancy and Lactation Rule (PLLR).

Pregnancy
Poorly controlled CKD in pregnancy is likely to be associated with increased risks to the developing fetus. However, there is limited data as to whether treatment with paricalcitol during pregnancy mitigates the background risk or itself is associated with an increased risk of major birth defects or miscarriage.

Lactation
Given that it is not known how much paricalcitol is present in human breast milk, there is a clear concern over the potential risk of hypercalcemia in newborn infants who are breast fed by mothers receiving paricalcitol. Hypercalcemia can present with vague symptoms which in newborns include anorexia, vomiting, constipation, and lethargy, all which may be misdiagnosed in this age group especially in premature infants. Of greatest concern are the small but potential risk for seizures and cardiac arrhythmias. Currently we don't know what an optimum monitoring scheme would be to look for possible hypercalcemia. Therefore lactation is not recommended during treatment with paricalcitol.

Pediatric Use
Safety and effectiveness have been established in pediatric patients age 10 to 16 years with secondary hyperparathyroidism due to CKD Stages 3, 4 and 5. AEs reported in pediatric studies are consistent with the safety profile of paricalcitol seen in adults.

12 CLINICAL PHARMACOLOGY
Update with PK data from Part 1 of study M10-149 in children age 10 to 16 years with CKD Stages 3 and 4.

14 CLINICAL STUDIES
Update with clinical data from study M10-149 in children age 10 to 16 years with CKD Stages 3 and 4. (b) (6)
.

17 PATIENT COUNSELING INFORMATION
Update with recommendation against lactation during treatment with paricalcitol

9.3 Advisory Committee Meeting

Not applicable

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

/s/

WILLIAM A LUBAS
10/13/2016

MARINA ZEMSKOVA
10/13/2016