Cross-Discipline Team Leader Review

Date	10/13/2016
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	021606/ S-016 and S-017
Applicant	AbbVie
Date of Submission	12/18/2015
PDUFA Goal Date	10/18/2016
Proprietary Name / Established (USAN) names	Zemplar/ paricalcitol
Dosage forms / Strength	Capsule/ 1 mcg and 2 mcg
Proposed Indication(s)	Prevention and treatment of secondary hyperparathyroidism (SHPT) in adults and pediatric patients 10 years and older with CKD stages 3 and 4 and with CKD stage 5 on hemodialysis or peritoneal dialysis
Recommended:	Approval

1. Introduction

On December 18, 2015 AbbVie submitted two supplemental New Drug Applications (sNDA) for Zemplar to:
- fulfil the two the Postmarketing Requirements (PMR) established under Pediatric Research Equity Act (PREA) that were issued at the time of approval of the original NDA (021606) for Zemplar Capsules in adults with chronic kidney disease stages 3 and 4 and sNDA (021606/S-004) for Zemplar Capsules in adults with CKD stage 5 on dialysis. These PMRs required to evaluate efficacy and safety of Zemplar capsules (refer to as Zemplar in this review) in pediatric patients 10-16 years old with secondary hyperparathyroidism (SHPT) and with CKD stage 3-4 and CKD stage 5 on dialysis, respectively.
- update the appropriate sections of Zemplar label with the pediatric information obtained from these two pediatric trials

Zemplar (paricalcitol) is a synthetic, biologically active vitamin D2 analog of calcitriol (1,25-OH vitamin D3) was approved for the prevention and treatment of secondary SHPT in adults with CKD stages 3 and 4 (May 26, 2005) and in patients with CKD stage 5 receiving peritoneal or hemodialysis (June 29, 2009).

The proposed indication for Zemplar is:

> *Prevention and treatment of secondary hyperparathyroidism (SHPT) in adults and pediatric patients 10 years and older with chronic kidney disease (CKD) stages 3 and 4 and with CKD Stage 5 on hemodialysis or peritoneal dialysis*

2. Background

Secondary hyperparathyroidism (SHPT) and mineral metabolism abnormalities (e.g., calcium and phosphorus) may lead to bone disease (abnormalities in bone turnover, mineralization, and strength) and extra-osseous calcifications (deposition of calcium in the kidney, cardiovascular system). Poor bone health could lead to increased fracture risk and calcification of cardiovascular tissues such as the myocardium, conduction system, valves, arterioles and arteries that could result in cardiovascular pathology such as arrhythmia, coronary artery disease or other events. The pathophysiology and consequences of SHPT that occur in the setting of chronic kidney disease (CKD) are similar in adults and children.
However, in children, secondary hyperparathyroidism may also lead to skeletal deformities and growth retardation.

Advanced stage kidney disease (end stage renal disease in particular) is a rare condition in childhood with an estimated worldwide median incidence of 9 per million of the age-related population[1]. Children are priority candidates for kidney transplantation; the majority of pediatric patients undergo kidney transplantation at earlier stages of renal disease and before progression to end-stage renal disease and before SHPT develops. Thus, the number of pediatric patients with SHPT due to CKD is much smaller that the adult kidney chronic disease population. However, similar to adult population with CKD and SHPT, those pediatric patients who develop SHPT require medical treatment to control iPTH and mineral abnormalities. The recommendations for the treatment of SHPT associated with CKD are similar in adults and children. To prevent skeletal and cardiovascular complications in patients with SHPT and CKD, the 2005 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines in children[2] and 2009 Kidney Disease Improving Global Outcomes (KDIGO) therapeutic guidelines in adults[3] recommend that subjects with CKD and iPTH levels above the target range be treated with Vitamin D or its analog alongside treatment of other prevalent mineral abnormalities (hyperphosphatemia, hypocalcemia) associated with chronic kidney disease.

Active vitamin D and vitamin D analogs are first line agents used for the treatment of SHPT in patients with CKD. Multiple therapeutic forms of vitamin D are available on the US market for treatment of SHPT in adults with CKD including oral and injectable formulations of active vitamin D (calcitriol) or partially active vitamin D analogs (doxercalciferol, paricalcitol).

The only vitamin D formulations that have pediatric dosing information in their labels for the treatment of SHPT are injectable formulation of Zemplar (NDA 020819)- in children with CKD stage 5 on dialysis and Rocaltrol Capsules (calcitriol; NDA 021068) – in predialysis children with creatinine clearance 15 to 55 mL/min (i.e with CKD stages 3 and 4)

Regulatory Background

[1] Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. Pediatr Nephrol. 2012 Mar;27(3):363-73.
[2] KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children With Chronic Kidney Disease. http://www2 kidney.org/professionals/KDOQI/guidelines_pedbone/
[3] KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009 Aug;(113):S1-130.

Calcitriol capsules has pediatric information for SHPT in patients with CKD stages 3 and 4. in children with CKD stages 3 and 4. As per Rocaltrol label, the evidence of safety and efficacy of Rocaltrol capsules in predialysis children > 3 years old with SHPT was extrapolated from adults: "the safety and effectiveness of Rocaltrol in pediatric predialysis patients is based on evidence from adequate and well-controlled studies of Rocaltrol in adults with predialysis chronic renal failure …"

Zemplar Injection has pediatric information for SHPT in patients with CKD stage 5 on hemodialysis (sNDA 020819/S-014, approved in 2004).
The efficacy of Zemplar Injection in pediatric patients was established using PTH reduction as a surrogate measure of benefit. A single multicenter, placebo-controlled, randomized, study conducted in 29 pediatric patients 5-19 years old with SHPT and CKD stage 5 on dialysis (15 patients received active drug and 14 patients received placebo) was used to characterize the safety and efficacy of the product. The mean baseline levels of iPTH were 841 pg/mL for the active drug-treated patients and 740 pg/mL for the placebo-treated subjects.

Data from this study demonstrated that 60% of patients who received Zemplar injection and 21% of patients who received placebo achieved two consecutive 30% decreases from baseline iPTH concentrations (primary endpoint; the same primary endpoint is used in the Zemplar Capsules sNDAs).

Zemplar regulatory history

This section summarizes the major regulatory interactions for the Zemplar pediatric development program for the SHPT indication.

Study M10-149 (in pediatric patients 10-16 years old with CKD stages 3 and 4) fulfills the PMR 1814-1 established under the PREA and issued when original NDA for Zemplar Capsules (NDA 021606) was approved on May 26, 2005.
Study M11-612 (in pediatric patients 10-16 years old with CKD stage 5 on dialysis) fulfills the PMR 2094-1 established under PREA and issued with the Zemplar Capsules sNDA 021606/S-004 approved on June 29, 2009.

A partial waiver for Zemplar Capsules for pediatric studies in children age 0-11 years with CKD stage 3-4 and CKD stage 5 was granted by the Agency on February 8, 2002 and on August 21, 2006, respectively.

Pediatric studies M10-149 and M11-612 were conducted under IND (b) (4) using the approved Zemplar soft gelatin capsules for oral administration.

On January 27, 2006, the Sponsor submitted a proposed pediatric study request (PPSR) for the pediatric population with CKD stages 3 and 4.
On June 15, 2006, the Agency denied this request based on multiple deficiencies identified during the review of the submitted program (study M10-149) and recommended to conduct, first, a clinical pharmacology study in pediatric patients to support the dose selection. In this

letter, the Agency also commented on the selection of the primary endpoint for the pediatric studies and recommended to use primary endpoint based on the prespecified iPTH target levels.

On December 15, 2008, the Sponsor submitted a revised protocol for Study M10-149 evaluating safety and efficacy of Zemplar in children with CKD stages 3-4. The Agency reviewed this protocol and recommended to revise primary endpoint and time of primary endpoint evaluation: "the percentage of patients having achieved a pre-specified goal (iPTH levels) according to K/DOQI guidelines at two consecutive time points or at the end of the study should be included as a single primary endpoint". The Sponsor accepted the Agency recommendations and submitted an amendment to the protocol on March 13, 2009: the revised primary endpoint was two consecutive iPTH values within the KDOQI target range.

(b) (4)

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(b) (4)

On March 31, 2011 the Sponsor requested a change of the PMR deadline for Study M11-612 to (b) (4). The Agency indicated that the study status will be changed to "delayed" until the study is completed but the due date will not be changed (December 29, 2011).

The pediatric development program and strategies how to improve the recruitment in study M10-149, in particular, were further discussed during tele-conference between the Agency and the Sponsor on May 1, 2012.
The Sponsor proposed 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 $\geq$ 30% reductions in iPTH compared to baseline" as such revision would permit to decrease the number of subjects required for the

study based on their power calculations (from 72 to 36). The Agency indicated that the new primary endpoint would be acceptable.

Statistical Analysis Plan for study M10-149 was submitted by the Sponsor on June 6, 2012. The biometric reviewer overall agreed with the proposed statistical plan, including the definition of the primary efficacy endpoint as 2 consecutive >30% reductions in iPTH compared to baseline. The biostatistician (Dr. Lee Ping Pian) also recommended to include all randomized patients who take at least one dose of study drug in the primary analysis and to consider those patients who do not have at least two iPTH values during treatment as treatment failures, but not to exclude them from the primary analysis.

Sponsorship of NDA 021606 for Zemplar Capsules was transferred to AbbVie from Abbott in 2013.

The Sponsor continued to experience difficulties with the recruitment of pediatric patients with SHPT due to CKD in both studies. Thus, the Sponsor requested multiple Deferral Extensions for PMR 1814-1 (Study M10-149) and for PMR 1067-2 (Study M11-612) during the development program:
- Deferral Extension for PMR 1814-1 (Study M10-149) was requested on January 3, 2013 and was granted by the Agency; Final Report to be submitted for the study on December 31, 2014
- Deferral Extension for PMR 1067-2 (Study M11-612) was requested on February 1, 2013 and was granted by the Agency; Final Report to be submitted for the study on December 31, 2014
- Deferral Extension request for PMR 1067-2 (Study M11-612) was requested again on August 29, 2013 and granted by the Agency on October 09, 2013; Final Report Submission date in May 2016.
In this submission, the Sponsor also proposed to include hemodialysis pediatric patients in Study M11-612 to increase patient enrollment. Thus, 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 (October 30, 2013).
- Deferral Extensions for PMR 1814-1 (Study M10-149) was requested on October 10, 2014 and was granted by the Agency on November 24, 2014 with the Final Report Submission date of June 20, 2015.

On February 11, 2015, the Agency agreed that the final clinical study reports (but without dataset) for the study M10-149 to fulfil PMR 1814-1 and for the study M11-612 to fulfil PMR 2094-1 will be submitted in in June 2015 and in May, 2016, respectively. The Agency also agreed that sNDAs containing the results of the studies will be submitted by October 30, 2015.

The Sponsor and the Agency discussed and agreed on sNDA content and format and the completeness of the different sNDA modules during Type C meeting on August 3, 2015.

Zemplar capsule was granted Orphan Drug designation for “treatment of pediatric hyperparathyroidism” on October 27, 2015 by the Office of Orphan Products Development.

sNDAs submission: December 18, 2015.

3. CMC/Device

No new information submitted

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were conducted. All required studies (including single dose toxicology studies, in vitro mutagenicity studies, reproductive and developmental toxicity studies) were conducted and reviewed previously under NDA 21606 and 020819 (Zemplar Capsules and Zemplar injections, respectively).

The Agency also agreed that juvenile animal studies were not required to support clinical studies in pediatric population with oral paricalcitol since the clinical monitoring for hypercalcemia was considered adequate based on the results from the earlier nonclinical studies in adult animals.

The Sponsor resubmitted a full ICH S5 battery of reproductive studies with Zemplar previously conducted under NDA 020819 (Zemplar injections) to support labeling changes for Section 8, in accordance with the Pregnancy and Lactation Labeling Rule (PLLR). Pharmacology/toxicology reviewers found the results of the studies to be acceptable to support the labeling changes in Section 8, since the disposition and metabolism of paricalcitol after single oral and intravenous doses are similar in fasted humans and nonclinical studies. Dr. Parvaneh Espandiari concluded that reproduction studies demonstrated slightly increased embryofetal loss and maternal toxicity at high exposures. Thus, the reviewer recommends use of the drug during pregnancy only if the potential benefit justifies the potential risk to the fetus. Of note, patients with advanced renal disease, in general, have low fertility rates because of the effects of hormonal imbalance associated with renal insufficiency, dialysis, other comorbidities and use of concomitant medications.

Lastly, studies in rats have shown that low concentrations of paricalcitol were present in milk of lactating animals; however, the data is not predictable of drug levels in human milk due to the differences in lactation physiology. However, the reviewer does not recommend breast feeding until the human data is available.

Please see Dr. Parvaneh Espandiari review dated September 7, 2016, for the details of the nonclinical program supporting approval of the pediatric doses of Zemplar for the treatment of SHPT in children with CKD Stage 3-5 and labeling changes according to PLLR. She and pharmacology/toxicology supervisor, Dr. C. Lee Elmore, deem the nonclinical data acceptable in support of approval of pediatric doses of Zemplar Capsules for the treatment of secondary hyperparathyroidism in children 10-16 years old with stage 3 -5 CKD and labeling changes provided labeling accurately reflects the nonclinical findings and their recommendations on use of the product.

I concur with Drs. Espandiari's and Elmore's assessment. There does not appear to be any nonclinical issue that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was completed by Dr. S.W. Johnny Lau and Pharmacometrics review was completed by Dr. Lian Ma. Both reviewers recommended approval of pediatric doses of Zemplar for both proposed indications: treatment of SHPT in pediatric patients 10-16 years old with CKD stages 3-4 and treatment of SHPT in pediatric patients 10-16 years old with CKD stage 5 on dialysis. For detailed discussion, please refer to their Clinical Pharmacology review in DARRTS (9/19/2016).

The reviewers concluded that pharmacokinetic (PK) data from the M10-149 single (Part 1) and multiple dose (Part 2) studies in children 10-16 years old with CKD stage 3 and 4; and, population pharmacokinetic analysis (PopPK) using combined data from studies M10-149 and M11-612 (study in children with CKD stage 5) support the efficacy and safety of the proposed Zemplar doses in children with CKD stage 3-4 and stage 5 on dialysis. They also determined that the PK data are acceptable for labeling purposes.

CKD stage 3-4

The results of M10-149, Part 1 show that the estimated PK characteristics (via noncompartment analysis; NCA) were similar between Stage 3 and Stage 4 in children and were consistent with PK characteristics observed in adults (Tables 1 and 2).

Table 1. PK parameters of paricalcitol in pediatric patients 10-16 years old with CKD stage 3-4 (Study M10-149; NCA)

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

Source: Clin.Pharm review, Table 2, p. 7.

Table 2. PK parameters of paricalcitol in adult patients with CKD Stages 3- 4 (NCA)

Pharmacokinetic Parameters	CKD Stage 3 n = 15* 4 µg dose	CKD Stage 4 n = 14* 3 µg dose
C_{max} (ng/mL)	0.11 ± 0.04	0.06 ± 0.01
$AUC_{0-\infty}$ (ng•h/mL)	2.42 ± 0.61	2.13 ± 0.73
CL/F (L/h)	1.77 ± 0.50	1.52 ± 0.36
V/F (L)	43.7 ± 14.4	46.4 ± 12.4
$t_{1/2}$ (h)	16.8 ± 2.65	19.7 ± 7.2

Source: Clin.Pharm review, Table 3, p. 8.

Based on the above PK characteristics, the Clin. Pharm reviewer concluded that starting dose of Zemplar in Part 2 of study M10-149 (i.e. 1 mcg tree times weekly) was appropriately selected: as per prespecified criteria, the starting dose in Part 2 should be 1 mcg if the average pediatric AUC was > AUC in adults (> 2.4 mcg.hr/ml) (refer to Clin. Pharm review).

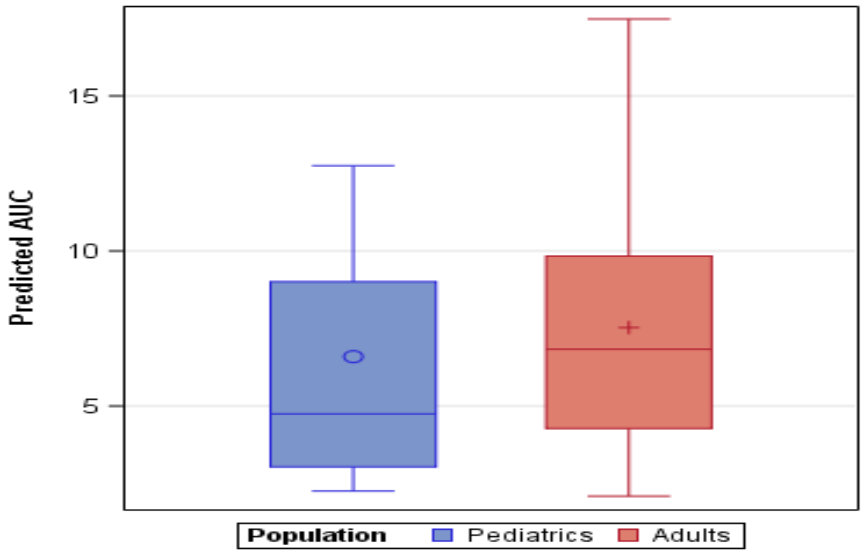
CKD stage 5

The Sponsor submitted PK data obtained from study M10-149 and the results of population pharmacokinetic analysis using combined data from studies M10-149 and M11-162 to support the efficacy of Zemplar Capsules in children with SHPT and CKD stage 5. Clin.Pharm reviewers reviewed the submitted data and concluded that the exposure-response analyses and comparable PK to adults provide supportive evidence of effectiveness of Zemplar at the proposed doses in in children 10-16 years old with SHPT and CKD stage 5 on dialysis. Drs. Lau and Ma review evaluating the efficacy of Zemplar in children with SHPT and CKD stage 5 is briefly summarized below.

NCA was not performed for pediatric patients with CKD stage 5 due to sparse sampling. Thus, PK characteristics in patients with CKD stage 5 were obtained from PopPK analysis based on combined data from M10-149 and M11-612.

As per Dr. Lau, the Sponsor adapted the adult CKD stage 5 model used in the original NDA (for adult indications) to build the clinical response models evaluating the exposure-response relationship of paricalcitol exposure and clinical response variables (iPTH, serum calcium serum phosphorus obtained from Study M11-612) in pediatric patients with CKD Stage 5 on dialysis. Drs. Lau and Ma reviewed the results of these analyses and concluded that the proposed starting dose for children with CKD stage 5 (i.e. iPTH/120) are appropriate and are supported by similar PK to adults (Figure 1) and by exposure-response analyses using efficacy and safety data from study M11-612. Based on this data, they concluded that the proposed dose is predicted to be associated with low rate of hypercalcemia (5%) while demonstrating reasonable rate of efficacy in lowering iPTH levels compared to adult population using iPTH doses of iPTH/80.

Figure 1. Predicted AUC (ng•h/mL) following the proposed starting dose (baseline iPTH/120) in pediatric patients with CKD stage 5, compared to those following the approved starting dose (baseline iPTH/80) in adult patients with CKD stage 5.



Source: Clin.Pharm review, Figure 5, p. 8.

Lastly, Drs. Lau and Ma also confirmed that the results of the exposure-response modeling (performed to obtain the iPTH, calcium, and phosphorus response in the pediatric population based on the adult CKD Stage 5 model structure using the PK characteristics estimated for the pediatric population at the given doses and adjusted parameter estimates) reasonably predict the observed iPTH, calcium and phosphorus response in pediatric patients with SHPT and CKD stage 5, thus, pediatric patients respond similarly to adult patients.

Dr. Ma also evaluated intrinsic factors (weight, sex and renal dysfunction) that could influence exposure and activity of Zemplar in pediatric patients and conducted an additional subgroup analysis. The results of this analysis demonstrated that even though body weight and sex were identified as a significant covariate for CL/F and/or V2/F, body weight and sex do not impact efficacy and safety of drug in intended population. Dr. Ma concluded that since dose titration is based on specific target iPTH, calcium and phosphorus levels, a fixed starting dose is reasonable for pediatric patients regardless of body weight and sex.
Dr. Ma also concluded that extent of renal dysfunction had no clinically relevant effect on the PK of Zemplar in pediatric patients.

6. Clinical Microbiology

Not applicable. No Clinical Microbiology information is included in this NDA.

7. Clinical/Statistical- Efficacy

The Zemplar Capsule pediatric clinical development program included two PMR Phase 3 studies: M10-149 and M11-612.

Study M10-149 was designed to evaluate the efficacy and safety of Zemplar in children 10-16 years old with CKD stage 3-4; thus I will discuss the design and the efficacy results of this study in this section.
I will also briefly discuss the design of study M11-612 in this section; however, the results of this study will be discussed in the next section, since the study was designed to evaluate safety only (the efficacy of Zemplar in children with stage 5 CKD on dialysis was extrapolated from the adult data using PopPK analyses and the results of this extrapolation are discussed in the Clin.Pharm section). However, I will discuss briefly in this section whether this study provides any evidence of the efficacy of Zemplar in children with CKD stage 5.
All other studies will be referenced as needed.

Study M10-149

Study M10-149 was a 2 part study in children 10-16 years old with CKD stages 3-4. Part 1 was an open-label, single dose, multicenter (5 sites in US) study evaluating the PK of Zemplar in a pediatric population. Part 2 was a multicenter (22 sites in US, Europe, and Singapore), 24-week study evaluating safety and efficacy of Zemplar in children with CKD stage 3-4 and consisted of 2 treatment periods: a 12-week randomized, double-blind, placebo-control period followed by 12-week open label period.

The objective of Part 1 of the study was to evaluate the safety, tolerability and PK of a single dose of 3 mcg paricalcitol capsules in pediatric patients ages 10 to 16 years with CKD stages 3-4. The results of Part 1 were summarized in the Clinical Pharmacology section of this memorandum. I will briefly summarize the design of Part 1 within this section.

The objective of Part 2 of the study was to evaluate safety and efficacy of Zemplar versus placebo in reducing plasma iPTH levels from pre-treatment baseline in pediatric patients ages 10 to 16 years with CKD stages 3-4 treated with Zemplar for 12 weeks during double-blind treatment period followed by a minimum of 12 weeks of open-label treatment period. I will focus on the design and the results of Part 2 of this study (referred to as "the study") in this section of memorandum that included the evaluation of efficacy and safety of Zemplar in children with CKD stage 3-4.

Patient population
The eligibility criteria were the same for both parts of the study.
Patients 10-16 years old with CKD stages 3 (defined as eGFR ≥30 and <60 mL/min/1.73m^2) or 4 (defined as eGFR ≥15 and <30 mL/min/1.73m^2) who were diagnosed with secondary hyperparathyroidism (defined as elevated iPTH levels of ≥ 75 pg/ml (stage 3) or ≥ 110 pg/ml (stage 4) during the screening period) and who were vitamin D-treatment naïve or who had completed 2- 4 weeks washout were eligible to participate in the study.

The selected lower inclusion criterion for iPTH levels of > 75 pg/ml (stage 3) or > 110 pg/ml (stage 4) is consistent with KDOQI[4] guidelines for children with CKD (KDOQI guideline 1) which recommend to maintain iPTH levels within normal reference range in children with

[4] KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children with Chronic Kidney Disease. http://www2 kidney.org/professionals/KDOQI/guidelines_pedbone/

CKD stage 3 or slightly above normal reference range (70-110 pg/ml) in children with CKD stage 4 in order to reduce the risk of renal osteodystrophy. It should be noted that the diagnosis of renal osteodystrophy is a histological diagnosis made by bone biopsy. None of the patients in this study had bone biopsies performed.

In order to participate in the study patients were also required to have normal 25-OH D levels (> 30 ng/ml), serum calcium (≥8.4 mg/dl and <10.2 mg/dl) and phosphorus ≥ 2.5 mg/dl and < 5.8 mg/dl levels. Subjects were allowed to continue taking phosphate binders and growth hormone (if the subjects were receiving growth hormone for > 3 months prior to enrollment). Use of cinacalcet, bisphosphonates and glucocorticoids was prohibited during the study.

Study design

Part 1

Part 1 was as an open-label, single-dose, multicenter study in 12 patients 10 -16 years old (6 patients with CKD Stage 3 and 6 patients with CKD Stage 4). Each patient received a single dose of 3 mcg (3 pills x 1 mcg) paricalcitol capsules 30 minutes after breakfast on Day 1.
A single 3 mcg dose was chosen for direct comparison to adults (data is available for single dose 3 µg in adult patients)
PK samples were collected pre-dose and 48 hours post-dose. The applicant estimated the PK parameters of paricalcitol via the noncompartmental method for the observed data.

Part 2

The study included screening period, a 12-week double-blind treatment period followed by 12-week open-label treatment period and a follow up period. All patients were randomized to receive Zemplar or placebo in a 1:1 ratio.

The starting dose was 1 mcg three times weekly (3 mcg/week). Every 4 weeks, each administered dose was allowed to be increased in 1 mcg increments (e.g., increase from 1 mcg three times per week to 2 mcg three times per week) if all of the following criteria had been met: plasma iPTH >70 pg/ml, serum calcium <10.2 mg/dl and serum phosphorus < 5.8 mg/dl. Each administered dose was required to be decreased by 1 mcg (e.g., decrease from 2 mcg three times per week to 1 mcg three times per week) at any time during the study if <u>any</u> of the following criteria were met: 1) iPTH <35 pg/ml (for stage 3) or < 70 pg/ml (for stage 4) and serum calcium > 9.5 mg/dl, or 2) serum calcium >10.2 mg/dl or 3) serum phosphorus >5.8 mg/dl. Any subject who was taking 1 mcg three times weekly (TIW) and required further dose reduction for safety reasons was to be discontinued from the study.

As described above, the titration schedule was based on the absolute prespecified iPTH levels and not on the decrease in iPTH levels by > 30% (primary endpoint). Thus, patients with lower iPTH levels at baseline required < 30% decrease in iPTH levels in order to achieve pre-specified target levels of iPTH. For the same reason, the dose of the drug was not increased further in patients with lower iPTH levels at baseline who achieved target iPTH levels during the treatment even though these patients did not achieve primary endpoint (> 30% decrease in iPTH levels).

Primary efficacy analysis
The primary efficacy endpoint was the proportion of patients who achieved 2 consecutive ≥ 30% reductions in plasma iPTH from baseline at any time during the 12-week double blind portion of the study.

The selection of iPTH as surrogate endpoint to establish clinical benefit in SHPT is briefly discussed below.

- As summarized in Dr. Lubas's review, all currently marketed vitamin D analogs (including Zemplar Capsules, Zemplar Injections in adults and children) were approved for the treatment of SHPT in patients with CKD stage 3-5 based on their iPTH lowering effects (mean decrease in iPTH levels or decrease > 30%).
- Elevated PTH levels in patients with CKD are associated with metabolic bone disease and risk for soft tissue calcifications and, vitamin D analogs improve biochemical endpoints associated with SHPT and metabolic bone disease (PTH, calcium, phosphorus, alkaline phosphatase, bone turnover markers, etc.). These changes would be expected to improve clinical outcomes related to these complications (i.e. bone fractures, pain and decreased end-organ damage). Although there are no data from prospective clinical trials directly demonstrating that reduction in PTH levels with cinacalcet 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 (KDOQI 2005- in children and KDIGO 2009-in adults, respectively) 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 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 continues to accept PTH reduction as a surrogate to determine the efficacy of calcimimetics and vitamin D analogs.
- Thus, as noted above, in multiple communications with the Division the Sponsor was advised to select a single primary endpoint based on two consecutive, pre-specified, iPTH responses at any time during the study including the end of the treatment period. The Sponsor selected to use two consecutive reductions of >30% in iPTH levels compared to baseline as primary endpoint and the Division indicated that this new primary endpoint would be acceptable (tele-conference on May 1, 2012).
- Lastly, a decrease of > 30% has been used in the past to define a robust, unequivocal, response to Vitamin D analog therapy. However, this threshold is not known to have an inherent therapeutic value other than that it is relatively large and unlikely to be affected by adjustment of background medications (i.e., calcium supplements, phosphate binders).

Baseline Demographics and Disposition
A total of 37 patients with CKD stage 3 or 4 were enrolled and randomized in the study; of these, 36 subjects received at least one dose of Zemplar (18 patients) or placebo (18 patients) and were included in the Intent-To-Treat (ITT) dataset. One of 37 subjects withdrew consent

prior to the first dose of the study drug. Of these 36 subjects, 21 subjects had CKD stage 3 and 15 subjects had CKD stage 4. Twenty-nine of 36 subjects completed double-blind treatment period (13 subjects in Zemplar group and 16 subjects in placebo group) and 24/36 subjects completed both parts of the study- double blind and open label phases (12 subjects in Zemplar group and 12 subjects in placebo group). Seven subjects discontinued the double-blind part of the study: 2 subjects in placebo group due to AEs and 5 subjects in Zemplar group (4 subjects who needed dose reduction below 1 mcg TIW due to prespecified laboratory criteria (calcium levels > 10.2 or low PTH; not reported as AEs) and one due to AE)).
The two randomized groups were relatively well balanced at baseline with respect to main demographic and disease characteristics. The mean age of patients was 13.3-14 years (median 14 years). Mean iPTH level was 155.4 pg/ml (median 131 pg/ml) in Zemplar group, and 144 pg/ml (median 103) in placebo group. All patients had baseline 25-OH vitamin D level > 30 ng/ml.

Efficacy results
Dr. Roberto Crackel reviewed the primary statistical analysis methods used to support the establishment of efficacy of Zemplar in pediatric population. Efficacy findings are also reviewed and discussed in Dr. William Lubas's review. For detailed discussions of the efficacy findings see both of these reviews. My memorandum provides a summary of the main efficacy findings.

Dr. Crackel verified the Sponsor's results for the primary analysis and concluded that the study established superiority of Zemplar over placebo at the proposed doses in terms of significant (i.e. > 30%) reduction of iPTH from baseline in pediatric patients 10-16 years old with CKD stages 3 or 4 (Table 1). The study demonstrated that approximately one third of patients with CKD stages 3 or 4 (27.8%) achieved 2 consecutive reductions of at least 30% from baseline in iPTH during 12-week treatment compared to 0 patients in placebo group (Table 3). The between group difference was 27.8 (95% CI for the difference between groups 7.5, 52.8; p=0.045).

Table 3. Primary efficacy results (2 consequitve iPTH reduction > 30% during 12 week of treatment) for Zemplar in patients with SHPT and CKD stages 3 or 4; ITT population.

	Zemplar, n (%)		**Placebo, n(%)**		**p value[a]**
	Responders, n (%)	Non-responders, n (%)	Responders, n (%)	Non-responders, n (%)	
Total	n=18		n=18		
	5 (27.8)	13 (72.2)	0 (0)	18 (100)	0.045
CKD Stage 3	n=10		n=11		
	3 (30)	7 (70)	0 (0)	11 (100)	0.09
CKD Stage 4	n=8		n=7		
	2 (25)	6 (75)	0 (0)	7 (100)	0.467

[a]Fisher's exact test, Statistical significance tested 0.050 level
Proportion of responder in Zemplar group is highlighted in yellow, proportion of responders in placebo group is highlighted in green. Patients with less than 2 consecutive iPTH reduction of >30% were imputed as nonresponders

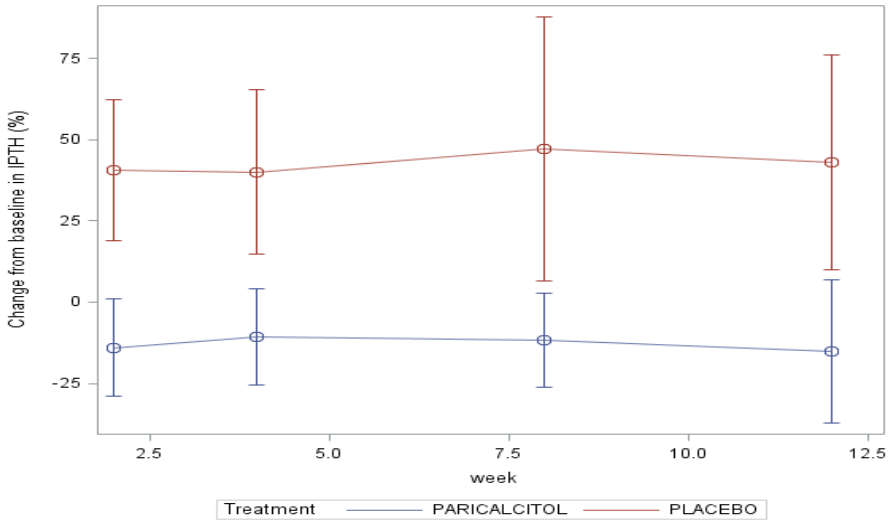
The only subgroup analysis performed was across CKD stratum, which did not yield statistically significant results.

Dr. Crackel repeated the primary efficacy analysis under different scenarios and imputations addressing missing data. Three patients on the trial (2 in Zemplar group and one in placebo group) were unconfirmed responders (i.e. had missing visit adjacent to the visit where there was a > 30% decrease in iPTH from baseline) and were imputed as non-respoonders by the Sponsor. Thus, biostatistician performed two sensitivity analyses to address this missing data - Bayesian approach and AGresti-Caffo method (both methods are less conservative methods and not assuming missing data as non-responders): the difference between treatment arms remained statistically significant (refer to Dr. Crackel's review).

Dr. Lubas also reviewed concomitant medications used during the study (in particular, use of vitamin D analogs that may confound the efficacy results) and confirmed that none of patients in Zemplar group received vitamin D analogs during the study.

Lastly, Dr. Lau reviewed iPTH data obtained from Part 2 study and confirmed that Zemplar was effective in reduction of iPTH concentrations in children with CKD stage 3-4 (Figure 2) (refer to Clin.Pharm review for detailes).

Figure 2. Percent change from baseline in Serum iPTH (pg/mL) during double-blinded phase in Study M10-149



Source: Clin.Pharm review, Figure 6, p. 10.

It should be also noted that the efficacy of Zemplar in lowering iPTH levels in the pediatric population is lower compared to the efficacy in adults observed in pivotal trial on which approval of Zemplar Capsules for treatment of SHPT in adults with CKD stages 3 and 4 is based. In the current Zemplar Capsules label 91% of adults with CKD stages 3 and 4 treated with Zemplar in the 24 week pivotal trial achieved > 30% decrease in iPTH from baseline to the end of the study.
There is also evidence that Zemplar is effective in children with SHPT due to CKD. It was demonstrated that the injectable formulation of Zemplar was efficacious in approximately 60%

of pediatric patients with SHPT and CKD stage 5 in lowering iPTH levels by > 30% from baseline (refer to Zemplar Injection label).
Lastly, vitamin D has the same mechanism of action in children and adults, i.e. regulates calcium and phosphate homeostasis via binding of active 1,25-OH vitamin D to the vitamin D receptors in parathyroid gland and inhibition of the synthesis and secretion of PTH); this constitutes the physiologic rationale for vitamin D analog use in the treatment of SHPT in both patient populations with chronic kidney disease.

Thus, the lower efficacy of Zemplar observed in study M10-149 was most likely due to inadequate design of this study, i.e. enrollment of children with lower baseline iPTH compared to adults in pivotal study and to children with CKD stage 5 treated with injectable formulation of Zemplar (150 pg/ml vs.800 pg/ml and 274 pg/ml, respectively), titration schedule implemented in study M10-149 that was based on prespecified iPTH target ranges (refer to the discussion of titration schedule above), small sample size, short duration of the study, etc. and not to the drug itself. Overall, I agree that *a priori* experience with use of Zemplar capsules and/or injections in adults and in children with SHPT due to CKD and similar mechanism of action of Zemplar support the conclusion that Zemplar can effectively decrease iPTH levels in pediatric patients 10-16 years old with CKD stages 3-4 and SHPT.

Secondary analyses

The trial also included several secondary endpoints (proportion of patients with iPTH levels within KDOQI target range, i.e. 35-69 pg/ml for stage 3 and 70-110 for stage 4; mean change in iPTH from baseline to each post baseline visit; serum calcium and phosphorus within KDOQI targets, etc.). Although secondary analyses of changes in these endpoints demonstrated some between-group difference (Zemplar vs. placebo), the clinical meaningfulness of these comparisons are difficult to interpret since no correction for multiplicity was made for testing of secondary endpoints and the results of all but one secondary analysis did not achieve statistical significance (refer to Dr. Crackel's and Dr. Lubas's review). The only statistically significant between-group difference was observed in mean decrease iPTH levels (-11 to -17 pg/ml decrease in Zemplar group and +50 - +71 increase in the placebo group), which is consistent with the natural progression of the untreated disease (placebo group) and effect of paricalcitol on iPTH (active drug group). Thus, I agree with Dr. Lubas's conclusion (b) (4)

Of 36 subjects enrolled in double-blind part of the study, 29 (80%) continued into open-label extension study. During an open-label single-arm period, the treatment effect observed with Zemplar in double-blind period was observed to be maintained up to 24 weeks. Although data from extension trial provide some evidence of persistence of Zemplar effect for up to 6 months, the quantitative efficacy data obtained from such an open-label, uncontrolled trial should not be used for labeling because, by the very nature of its design, the trial selected a patient population likely to have benefited from the drug, a control group is lacking and the data is confounded by concomitant therapy with other vitamin D analogs.

In conclusion, the efficacy analyses conducted in the M10-149-Part 2 study demonstrate that Zemplar can decrease iPTH level in children 10-16 years old with CKD stages 3 and 4 and

SHPT. I agree with Dr. Crackel's and Dr. Lubas's conclusion that the efficacy results from this study support claim of using Zemplar in proposed doses for treatment of SHPT in children 10-16 years old with CKD stages 3 and 4.

Study M11-612

Study M11-1612 was a Phase 3, 12-week, open-label, single-arm, multicenter (7 sites in US and 2 sites in Europe) study to evaluate the safety of Zemplar in children 10-16 years old with CKD stage 5 on dialysis.

The population of children with advanced kidney disease is overall small and the majority of pediatric patients receive kidney transplant prior to the progression to end stage renal disease requiring dialysis. Thus, because of the difficulties of recruiting a sufficient number of pediatric patients on hemodialysis to perform an adequately powered double-blind, placebo controlled study evaluating efficacy of the drug in intended population, the efficacy was extrapolated using population PK and available adult data.

I will discuss the design of this study in this section and whether this study provided some evidence of efficacy. The safety findings from this study will be discussed in the next section of this memo.

The primary objective of the study was to evaluate the safety of Zemplar with focus on the primary safety concern of hypercalcemia. Two consecutive serum calcium values > 10.2 mg/dl (upper normal limit in the assay) were used to estimate the risk of hypercalcemia.

Patient population

Patients 10-16 years old who were on dialysis for at least 3 months and who were diagnosed with secondary hyperparathyroidism (defined as elevated iPTH levels of ≥ 300 pg/ml but <2000 pg/ml) and who were vitamin D-treatment naïve or who had completed 2- 12 weeks washout were eligible to participate in the study.

The selected lower inclusion criterion for iPTH levels of > 300 pg/ml is consistent with KDOQI[5] guidelines for children with CKD (KDOQI guideline 1) which recommend maintaining iPTH levels within 200-300 pg/ml in order to reduce the risk of renal osteodystrophy.

In order to participate in the study patients were also required to have normal serum calcium (≥8.2 mg/dl and <10.5 mg/dl) and phosphorus < 6.5 mg/dl levels. Subjects were allowed to continue taking phosphate binders and growth hormone (if the subjects were receiving growth hormone for > 3 months prior to enrollment). Use of cinacalcet, bisphosphonates and glucocorticoids was prohibited during the study.

Study design

The study was comprised of screening period and a 12-week treatment period. All patients received Zemplar capsules orally.

The starting dose was calculated using the equation iPTH/120 (last iPTH value in pg/ml) and

[5] KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children With Chronic Kidney Disease. http://www2 kidney.org/professionals/KDOQI/guidelines_pedbone/

was administered three times weekly. Every 4 weeks, each administered dose was allowed to be increased in 1 mcg increments (e.g., increase from 1 mcg three times per week to 2 mcg three times per week) if all of the following criteria had been met: plasma iPTH was >300 pg/ml, serum calcium was <10.2 mg/dl and serum phosphorus < 6.5 mg/dl. Each administered dose was required to be decreased by 2 mcg (e.g., decrease from 3 mcg three times per week to 1 mcg three times per week) at any time during the study if the following criteria were met: iPTH <150 pg/ml and serum calcium < 10.2 mg/dl and phosphorus level < 6.5 mg/dl, or serum calcium >10.2 mg/dl or serum phosphorus >6.5 mg/dl. Any subject who was taking 1 or 2 mcg TIW and required further dose reduction for the safety reasons or the dose had to be withheld for 2 consecutive weeks was to be discontinued from the study.

Baseline Demographics and Disposition

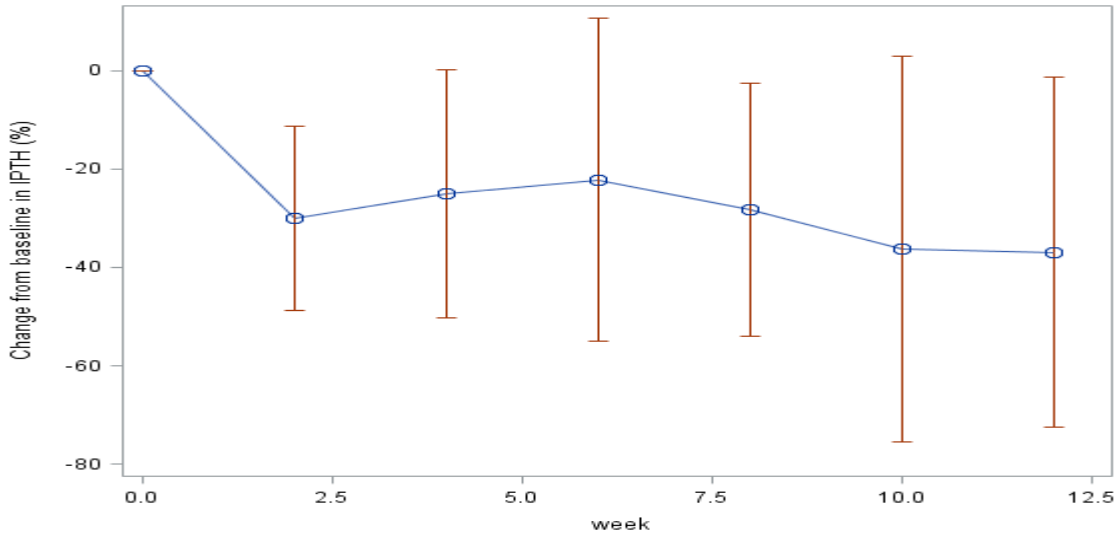
A total of 13 patients with CKD stage 5 on peritoneal dialysis or hemodialysis were enrolled and received treatment with Zemplar. The 12-week completion rate was approximately 85% (11 subjects); two subjects discontinued study (one subject withdrew informed consent and one subject received kidney transplant).

The mean age of patients was 14.5 years (median 15 years); 7 patients were on peritoneal dialysis and 8 were on hemodialysis. Mean iPTH level was 883.6 pg/ml (median 833 pg/ml), mean serum calcium 9.2 mg/dl (median 9.3 mg/dl), mean serum phosphorus was 4.66 mg/dl (median 4.7 mg/dl).

Evidence of efficacy

As stated above, the primary efficacy of Zemplar in children with CKD stage 5 on dialysis was extrapolated from adult data using PopPK (refer to Clin.Pharm section above). However, Dr. Lau conducted the additional analysis and demonstrated that Zemplar at the proposed dose decreases iPTH levels during 12-week treatment (Figure 3).

Figure 3. Mean Serum iPTH (pg/mL) in Study M11-612



Source: Clin.Pharm review, Figure 7, p.11

Approximately 61% of pediatric patients (8/13 patients) achieved 2 consecutive > 30% reductions from baseline in serum iPTH during the trial. Compared to the CKD stage 5 adult data for Zemplar capsules (88% of patients achieved 2 consecutive > 30% decreases in iPTH[6]), the efficacy in pediatric patients with CKD stage 5 is lower . However, these findings are consistent with the results from the previous trial evaluating injectable formulation of Zemplar in pediatric population on hemodialysis[7] (9/15 (60%) subjects achieved > 30% iPTH reduction).
In conclusion, even though the study provides some evidence of efficacy of the oral formulation of Zemplar in this patient population, (b) (4)

8. Safety

Data from study M10-149 and study M11-612 were used to evaluate the safety of Zemplar capsules in pediatric patients with CKD stages 3-5. In the double-blind treatment part of Study M10-149, 11 children with stage 3-4 CKD were treated with Zemplar for > 8 weeks, and 6 children for > 12 weeks. In study M11-612, 8 children with CKD stage 5 were treated with Zemplar for > 8 weeks, and 3 patients were treated for > 12 weeks.

There were no deaths in both studies.

Serious Adverse Events (SAE)

A total of 4 subjects treated with Zemplar experienced SAEs in pediatric clinical program. These SAEs were: abdominal pain and renal failure/hypertensive crisis (CKD stage 3-4; open-label part of study M10-149) and peritoneal dialysis complications and fluid overload (CKD stage 5; study M11-162).

No subjects treated with Zemplar in Part 1 and in double-blind phase of Part 2 of study M10-149 reported SAEs; 2 subjects in placebo group had SAEs (viral infection, blood creatinine increase and suicidal ideation).

Dr. Lubas reviewed narratives of these cases and concluded that these complications are not unusual in this population due to disease progression, concomitant diseases and/or presence of precipitating factors (e.g., infection, dehydration).
I agree with Dr. Lubas that, even though it is not possible to draw a definite conclusion as to whether these events are drug-related, the observed events are not consistent with drug-related safety signals and most likely reflect other causes.

Three of 36 subjects enrolled in study M10-149 Part 2 discontinued double-blind 12-week treatment period prematurely due to the AEs: 2 subjects (11%) in the placebo group and 1 subject (5.6%) in Zemplar group discontinued study due to hypercalcemia (prespecified discontinuation criteria).

[6] Label for Zemplar Capsules
[7] Label for Zemplar Injection

No subjects in Study M11-612 discontinued the study preliminary due to the AEs.

Common Adverse Reactions

In study M10-149, a total of 38.9% (7/18) of Zemplar-treated subjects and 88.9 % (16/18) of the placebo-treated subjects reported at least one AE in double-blind phase of the trial; 62% (18/29) of Zemplar-treated subjects in open-label part of the study reported at least one treatment-emergent adverse event. The only AE that occurred in > 1 patient treated with Zemplar was rhinitis (3 patients); all other AEs occurred in one patient each (nausea, hypercalcemia, urinary urgency, asthma).

In study M11-612, 84.6% (11/13) treated with Zemplar developed at least one treatment-emergent adverse event. The only AEs that were reported in > 1 patients were nausea (2), pyrexia (2), and cough (2); all other AEs occurred in one patient each.

Laboratory Parameters

Hypercalcemia and hyperphosphatemia

There is a known and labeled risk of hypercalcemia and hyperphosphatemia during the treatment with all vitamin D analogs. Thus, the Dr. Lubas paid special attention to the occurrence of out-of-range calcium and phosphorus values and related adverse events, and conducted several additional analyses in order to characterize the frequency and severity of such findings.

Serum Calcium

In the double-blind part of study M10-149 (Part 2), the mean levels of serum calcium increased from baseline to final visit by a 0.05 mg/dl in Zemplar group and decreased by 0.05 mg/dl in placebo group. Visual comparison of scatterplots in Dr. Lubas's review (Dr. Lubas's review Figure 7) indicate multiple values in the abnormal range in both treatment groups, but no obvious outliers at the end of the study.
In study M11-612, the mean serum calcium levels also slightly increased from 9.41 mg/dl at baseline by 0.31 mg/dl. Visual inspection of scatterplot in Dr. Lubas's review (Dr. Lubas's review, Figure 8) demonstrated one outlier during the treatment with Zemplar (one patient had a single value of > 10.8 mg/dl) that might have affected the observed mean changes. Overall, the increase in calcium levels in both studies was small and most likely not clinically meaningful.

In double-blind part of study M10-149, 5 subjects (28%) in Zemplar group and 4 (22%) subjects in placebo group had at least one calcium level above 10.2 mg/dl (predefined calcium level). The majority of patients had only single elevation of calcium that returned to the normal values without dose adjustment. Only one subject treated with Zemplar had 2 consecutive serum calcium values > 10.2 mg/dl (maximum level of 10.5 mg/dl) (defined as hypercalcemia by the Sponsor), the levels normalized at the next visit. In addition, one subject in the open-label part of the study had 2 consecutive levels above the upper normal limit (the maximum calcium value was 10.6 mg/dl); the levels normalized during the follow-up visit. The majority

of patients were asymptomatic. There were a total of three non-serious adverse events of hypercalcemia (1-in Zemplar group and 2 in placebo group) in double-blind part of the study and 4 non-serious adverse events of hypercalcemia in 3 subjects in open-label part of the study. Three subjects discontinued double-blind part of the study preliminary due to hypercalcemia (2 in placebo group and 1 in Zemplar group).

In study M11-612, 5 subjects (5/13; 38%) had at least one elevated calcium level ranging from 10.3 mg/dl to 10.9 mg/dl. Three subjects had 2 consecutive calcium values > 10.2 mg/dl (maximum level 10.9 mg/dl); of these, 2 subjects had normalized levels at the follow up visit. None of the cases of hypercalcemia were reported as AEs.

Overall, I agree with Dr. Lubas's conclusion that the risk of hypercalcemia is low in the intended patient population during the treatment with Zemplar with proper monitoring of calcium levels.

Serum phosphorus

In the double-blind part of study M10-149 (Part 2), mean serum phosphorus levels increased from baseline (4.4 mg/dl) by 0.2 mg/dl in placebo group and by 0.06 mg/dl in Zemplar group (from 4.5 mg/dl at baseline). Overall, mean changes from baseline were small and most likely not clinically meaningful. Visual comparison of scatterplots in Dr. Lubas's review (Dr. Lubas's review, Figure 9) indicate multiple values in the abnormal range in both treatment groups, but no obvious outliers during the study. Three subjects in Zemplar group (17%) and 1 subject in placebo group (5.6%) in double blind part and 6 subjects treated with Zemplar in open-label part of the study had at least one elevated phosphorus level above 5.8 mg/dl (the predefined threshold); the maximum level was 7 mg/dl. Elevated phosphorus levels normalized without the dose adjustment in the majority of subjects. No SAEs of hyperphosphatemia were reported during the treatment with Zemplar and no subjects were withdrawn from the study due to hyperphosphatemia.
In study M11-612, mean serum phosphorus levels increased greater (by 0.64 mg/dl) from baseline compared to the changes in study M10-149. However, these changes remain small and most likely are not clinically meaningful; the greater increase in phosphorus is most likely due to the presence of more advanced disease in pediatric patients with CKD 5 compared to patients with CKD stages 3-4 (in study M10-149). One subject with history of hyperphosphatemia prior to the start of the trial had nonserious AE of hyperphosphatemia with a single peak serum phosphorus level of 15.3 mg/dl; patient was asymptomatic and phosphorus decreased to 7.1 mg/dl at final visit.

I agree with Dr. Lubas's conclusion that the risk of hyperphosphatemia did not increase with Zemplar treatment in pediatric patients with CKD stage 3 -5.

Oversuppression of iPTH levels and risk of adynamic bone disease

There is a concern with all vitamin D analogs that oversuppression of iPTH levels may lead to adynamic bone disease, fractures and bone pain in patients with SHPT and CKD. However, the specific levels of iPTH that is associated with this complication are unknown.

No subjects in both studies had a shift in iPTH value to low (defined as lower limit of normal for assay used; 12 pg/ml) at the final measurement and none of patients enrolled in both trials had bone pain or fractures or had bone biopsy. It should be also noted that while the "normal" iPTH levels in patients with CKD stages 3-5 are higher than low normal levels for assay[8], low iPTH levels are not uniformly predictive of bone histologic states, especially when considered alone (i.e. without concomitant abnormalities in calcium, phosphorus levels or use of medications affecting bone structure such as bisphosphonates).

In conclusion, I agree that the treatment with Zemplar should avoid oversuppression of iPTH levels. However, I do not agree with the recommendations that the dose titration should be based on specific iPTH levels. The optimal iPTH levels are unknown and levels associated with bone adverse events have not been established to date. Thus, I favor the language that recommends the dose titration in order to maintain iPTH levels within target range rather than based on pre-specified iPTH levels.

Other laboratory parameters

There were no clinically meaningful differences between treatment groups in the change from baseline to final visit in any other laboratory parameters (hematology, clinical chemistry, urinalysis, urinary calcium, phosphate, etc.).

Vital signs
There were also no significant changes in vital signs between the treatment groups.

ECG
There were no unexpected or unusual ECG findings in both studies

In conclusion, the safety observations made during the Zemplar clinical program in pediatric patients with CKD stage 3 - 5 are consistent with the known safety profile established for Zemplar in adults and for injectable formulation of Zemplar in children with CKD stage 5 and for the whole class of vitamin D analogs. No new, population-specific safety signals were identified in the Zemplar pediatric program.

9. Advisory Committee Meeting

No AC meeting was held.

10. Pediatrics

Data from study M10-149 (to fulfil the PMR 1814-1 established under the PREA in May, 2005) and from the study M11-612 (to fulfill PMR 2094-1 established under PREA in June, 2009 and the label containing the pediatric information submitted by the Sponsor in these sNDAs were discussed by the Pediatric Review Committee on August 3, 2016. The Pediatric Review Committee (PeRC) determined that the results from these two pediatric trials are

[8] KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children With Chronic Kidney Disease. http://www2 kidney.org/professionals/KDOQI/guidelines_pedbone/

acceptable and fulfill PMR 1814-1 and PMR 2094-1. PeRC also agreed with the presentation of the pediatric study results within the proposed label.

(b) (4)

11. Other Relevant Regulatory Issues

OSI inspection

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.
As per Dr. Lubas's review, all studies were conducted in accordance with Good Clinical Practices governing clinical study conduct.

Financial Disclosure

Financial disclosure documentation was reviewed by Dr. Lubas. He identified one Investigator who received compensations. However, as per Dr. Lubas, there was no clear evidence that the data contributed by (b) (6) site could have affected the study results. (b) (6) data increased the observed risk of hypercalcemia and made the study results less favorable).

12. Labeling

Agreement on the final labeling language has not been reached at the time this review was completed.
However, the following should be changed in the label:

- Dose titration should be based on the safety parameters (calcium levels within normal reference range and iPTH levels within target range avoiding oversuppression).
- Clin.Pharm reviewers recommend to present drug-drug interactions in table format. The table should include a description of clinically significant interactions and instructions for preventing or managing these interactions (Section 7).
- Double blind Part 2 of study M10-149 is a placebo-controlled study that provides substantial evidence supporting the efficacy for the proposed indication, i.e. treatment of SHPT in children with CKD stages 3 and 4. Thus, I recommend including the treatment results from 12- week double-blind period of study M10-149 in section 14 of the label. (b) (4) .
- The description of the design and the results of study M11-612 (b) (4) should be described in section 8 (USE IN SPECIFIC POPULATIONS); the safety results from this trial (hypercalcemia, in particular) should be included in section 6 (ADVERSE REACTIONS).

- The biostatistician reviewers also recommend the following revisions to Section 14:
  - The label should include only results from the pre-specified primary analysis from study M10-149 (i.e. proportion of patients with 2 consecutive > 30% reductions from baseline in iPTH levels.
  - The footnote should be added to the Table 7 (describing the efficacy results from study M10-149) detailing the amount of missing data and that each patient was treated as a non-responder.
  - The proportion of patients who achieved a final PTH level within KDOQI target range should be removed from the label.
  - (b) (4)
- The Division of Pediatric and Maternal Health (DPMH) was consulted on February 10, 2016 to assist in the labeling for this sNDA. The DPMH reviewer revised subsections 8.1 and 8.2 in the Zemplar labeling for compliance with the PLLR and found the proposed language in these sections is overall acceptable (refer to review in DARRTS from 9/14/2016). In addition, the reviewer recommended the following:
  - to add a risk of disease-associated maternal and embryo/fetal risk to Section 8.1 (i.e. maternal risk of hypertension, spontaneous abortion, preterm labor, preeclampsia, fetal intrauterine growth restriction, prematurity, etc.).
  - not to recommend against the breast feeding.
    Based on the animal data, the reviewer concluded that the risk of hypercalcemia in breast-feeding infant is low and there is not enough evidence to recommend against breastfeeding with proper monitoring of signs and symptoms of hypercalcemia in infants. However, there are no data in humans regarding the presence of the drug in milk and physicochemical characteristics of the drug suggest that the drug may be transferred into human milk, thus, the risk of the transfer of the drug into human milk and subsequent hypercalcemia in infants cannot be ruled out completely. In conclusion, I disagree with the above recommendations and recommend to indicate that "breastfeeding is not recommended" until additional information is available.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of Zemplar Capsules for the following indication pending agreement on the final labeling language:

Prevention and treatment of secondary hyperparathyroidism (SHPT) in adults and pediatric patients 10 years and older with chronic kidney disease (CKD) stages 3 and 4 and with CKD Stage 5 on hemodialysis or peritoneal dialysis

- Risk Benefit Assessment

The data submitted in support of Zemplar use in pediatric patients with CKD stage 3-5 and SHPT provides sufficient information to conclude that the benefits of Zemplar use in this pediatric population outweigh the risk associated with the drug.

Benefit:
The applicant demonstrated in study M10-149 carried out in children 10-16 years old with SHPT due to CKD stages 3 and 4 that Zemplar significantly reduced baseline iPTH levels compared to placebo during 12- week treatment period. In this trial, a greater proportion of patients randomized to Zemplar experienced two consecutive reductions in iPTH levels >30% from baseline compared to placebo (i.e. 27.8% versus 0%, respectively). iPTH levels decreased, on average, by 11-17 pg/ml from baseline in the Zemplar group and rose by 50-71 pg/ml from baseline in the placebo group. Directional changes in mineral (calcium, phosphorus) biomarkers were consistent with expectations and suggest that Zemplar use is associated with a net decrease in bone resorption.

The efficacy of Zemplar Capsules in children with SHPT and CKD stage 5 is supported by pharmacokinetic data obtained from study M10-149 and by the results of population pharmacokinetic analysis using combined data from studies M10-149 and M11-162. The exposure-response analyses and comparable PK to adults provide supportive evidence of effectiveness of Zemplar at the proposed doses in in children 10-16 years old with SHPT and CKD stage 5 on dialysis while demonstrating low rates of hypercalcemia associated with Zemplar use in the intended population.

In conclusion, the overall data submitted by the Applicant in these sNDAs establish the benefit of Zemplar Capsules in children 10-16 years old with SHPT and CKD stages 3 and 4 (?) or 5 or CKD stage 5 on dialysis. Zemplar has demonstrated an ability to control SHPT as measured by decreases in iPTH level, similar to other vitamin D analogs approved for the treatment of secondary hyperparathyroidism in patients with CKD. The Division treats a vitamin D induced decrease in serum iPTH levels in patients with low vitamin D levels and SHPT as an acceptable surrogate of efficacy in patients with CKD and secondary hyperparathyroidism.
Thus, notwithstanding the uncertainty noted above (i.e the validity of the assumption that a >30% reduction of iPTH from baseline correlates with a reduction in adverse skeletal outcomes in an absence of prospective, controlled, data establishing such benefit), it is expected that Zemplar will have salutary effects on bone disease associated with CKD and will reduce the risk of skeletal complications (i.e., fracture, bone pain) in these patients.

Risk:
Overall, the benefits of using Zemplar for the treatment of SHPT in pediatric patients with CKD stages 3 and 4 and CKD stage 5 on dialysis outweigh the identified risks.
No new safety signals emerged.

Hypercalcemia, hyperphosphatemia and oversuppression of PTH (that increase the risk for adynamic bone disease) are adverse reactions associated with this class and Zemplar.
In study M10-149, 28% of subjects on Zemplar had at least one elevated calcium level, 17% of patients treated with Zemplar had at least one elevated serum phosphorus level above 5.8

mg/dl. In study M11-612, 38% of subjects treated with Zemplar had at least one elevated calcium level and 1 subject had hyperphosphatemia (defined as phosphorus level > 6.5 mg/dl). These mineral abnormalities improved in the majority of patients without dose adjustment or with dose reduction; the majority of these patients were asymptomatic. Overall, the incidence of hypercalcemia and hyperphosphatemia observed with Zemplar Capsules was low in the pediatric clinical program and did not exceed the incidence of these AEs observed with all approved vitamin D analogs (including Zemplar).
No subjects in both studies had iPTH levels less than lower limit of normal for assay used (12 pg/ml) However, the "normal" iPTH levels should be interpreted with caution, since the "normal" iPTH levels in patients with CKD stages 3-5 are higher than low normal levels for assay and low iPTH levels are not uniformly predictive of bone histologic states. However, none of patients enrolled in both trials had bone pain or fractures.

In conclusion, the safety profile of Zemplar in children with CKD stages 3-5 was found to be generally consistent with the safety profile of the other approved vitamin D analogs in adults and children. All safety concerns can be mitigated through product labeling, appropriate patient selection, monitoring and timely introduction of treatment and/or discontinuation of the drug.

I have discussed the details of my review and recommendation at length with Dr. James P. Smith, Deputy Division Director for the Division of Metabolism and Endocrinology products, and he concurs with my assessment of the benefits and risks for Zemplar Capsules and with my decision to recommend Approval of this product for the prevention and treatment of secondary hyperparathyroidism (SHPT) in children with chronic kidney disease stages 3 and 4 and in children with chronic kidney disease on hemodialysis.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

- Recommended Comments to Applicant

None

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

/s/

MARINA ZEMSKOVA
10/13/2016