

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-606

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER MEMORANDUM

NDA: 21-606

DRUG: Paricalcitol capsules (Zemplar)

INDICATION: Secondary hyperparathyroidism in stage 3 and 4 chronic kidney disease

COMPANY: Abbott

PRIMARY MEDICAL REVIEWER: Julie Golden, MD

PRIMARY REVIEWER'S REGULATORY RECOMMENDATION: Approve

DATE OF MEMO: May 6, 2005

I. BACKGROUND

Active vitamin D and its analogues remain the mainstays in the management of secondary hyperparathyroidism in patients with varying degrees of chronic kidney disease (CKD)¹. Hypercalcemia, elevated Ca X P ion product (both linked to increased risk for cardiovascular disease), and oversuppression of iPTH levels, leading to low-turnover bone disease, are the dose limiting toxicities of the vitamin D compounds.

On the basis of three 12-week, placebo-controlled studies, paricalcitol injection (5 mcg/mL) was approved for the prevention and treatment of secondary hyperparathyroidism in patients with stage 5 CKD.

With this NDA submission, Abbott is seeking approval of 1 mcg, 2 mcg, and 4 mcg paricalcitol capsules for the prevention and treatment of secondary hyperparathyroidism in patients with pre-dialysis, or stage 3 and 4 CKD². This request is based on the results of three randomized, double-blind, placebo-controlled 24-week studies in patients with stage 3 and 4 CKD.

Dr. Golden has done a thorough review of the submitted data and recommends that the NDA be approved.

¹ Sensipar (cinacalcet), an oral calcimimetic, was recently approved for the treatment of secondary hyperparathyroidism in patients with stage 5 CKD. It can be used alone or concomitantly with vitamin D compounds.

² Rocaltrol (oral calcitriol) and Hectorol (oral doxercalciferol) are currently approved for the treatment of secondary hyperparathyroidism in patients with stage 3 and 4 CKD.

IV. FINANCIAL DISCLOSURE

A Form 3454 was submitted by Laura Williams (Global Project Head, Renal) certifying that she did not enter into any financial agreement with any of the listed clinical investigators that could influence the outcome of the study.

A Form 3455 was submitted by Dr. Williams indicating that _____, an investigator on study _____ received unrestricted grant support (\$18,000), equipment (\$6000), compensation for consulting work, and honoraria for speaking engagements. The sponsor did state that Dr. _____ site conducted the study in accordance with the protocol, ICH, GCP guidelines, FDA regulations, and guidelines governing clinical study conduct, ethical principles having their origin in the Declaration of Helsinki (1989 revision) and all applicable local regulations. Dr. _____ did not randomize any subjects in study _____, therefore the outcome of the study was unaffected by his financial arrangements with Abbott.

V. DSI AUDITS

The Division of Scientific Investigation completed an audit of the following three clinical sites:

Dr. Daniel Batlle, Chicago, IL, Dr. Hanna Abboud, San Antonio, TX, and Dr. Barton Levine, Los Angeles, CA. These sites were chosen as they enrolled the largest number of subjects in each respective pivotal study (2001019, 2001020, and 2001021).

An audit report of Dr. Batlle's site inspection revealed two protocol violations: subject 802 had a history of cardiac graft and a cholecystectomy that was not recorded on the CRF, and the study coordinator was not listed on Form FDA 1572 as a sub-investigator (for which a 1-item Form FDA 483 was issued). Data from the site were found to be acceptable.

An audit report of Dr. Abboud's site inspection revealed general adherence to applicable statutory requirements as well as FDA regulations governing the conduct of clinical investigations and the protection of human subjects. Form FDA 483 was not issued. Data from the site were found to be acceptable.

An audit report of Dr. Levine's site inspection revealed several protocol violations: subjects 901, 902, and 905 had dosage changes that were not per protocol, and a 3-item Form FDA 483 was issued. The audit report acknowledged that in general, data in source documents and CRFs matched the data in sponsor provided data listings. Data from the site were found to be acceptable.

II. CLINICAL DATA

The clinical development plan for paricalcitol capsules included 10 phase 1 and three phase 3 studies. I will restrict my discussion to the results of the phase 3 studies (19, 20, and 21).

All three trials were randomized, placebo-controlled, double-blind, multi-center, 24-week studies. Studies 19 and 20 utilized a 2 or 4 mcg TIW dosing schedule, while study 21 incorporated a 1 or 2 mcg daily dosing regimen.

Since the designs and the efficacy and safety results were for the most part similar for the three phase-3 trials, for ease of presentation, I will focus attention on study 19 in this secondary review.

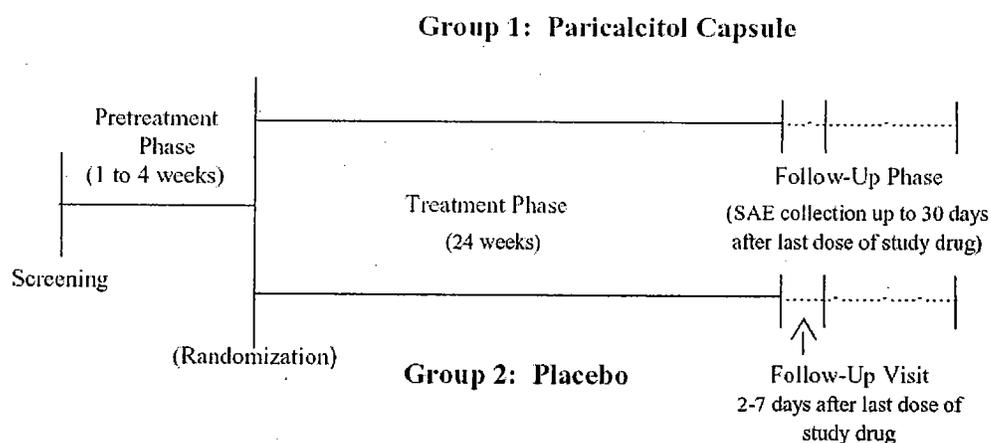
Study 2001019

Study Title: A phase 3, prospective, randomized, placebo-controlled, double-blind, multi-center study to determine the safety and efficacy of zemplar capsules in reducing elevated serum intact parathyroid hormone levels in subjects with chronic kidney disease.

Study Objectives: To determine the safety and efficacy of zemplar capsules as compared with placebo in reducing elevated iPTH levels in patients with stage 3 and 4 CKD.

Study Design: This was a phase-3, randomized, placebo-controlled, double-blind 24-week study of patients with stage 3 and 4 CKD with baseline iPTH levels > 150 pg/mL.

The general study design is depicted in the following figure.



Subjects must not have been on pharmacological vitamin D therapy for at least 4 weeks and must have had an iPTH value of ≥ 120 pg/mL to enter the Pre-Treatment Phase. The serum creatinine, BUN, and albumin values were used to calculate the subject's eGFR.

Subjects with an eGFR of 15 to 60 mL/min were eligible to undergo Pre-Treatment Phase procedures.

Subjects were to have 2 consecutive iPTH measurements (from samples drawn at least 1 day apart) that averaged ≥ 150 pg/mL (all values must have been ≥ 120 pg/mL), 2 consecutive results for serum calcium levels 8.0 to 10.0 mg/dL, and 2 consecutive results for phosphorus levels ≤ 5.2 mg/dL.

During the Treatment Phase, subjects were to self-administer the study drug TIW, on Monday, Wednesday and Friday, for a total of 24 weeks. The initial dose was 2 or 4 mcg (depending on baseline iPTH levels). Clinic visits were scheduled every 2 weeks, starting at Treatment Week 3. All laboratory procedures at Treatment Week 1 were to have occurred prior to the first dose of study drug. Serum iPTH, calcium, phosphorus, and albumin were measured every 2 weeks, beginning with Week 3. Dose adjustments were to be made according to pre-defined criteria for chemistry results for iPTH, calcium, and phosphorus (see Appendix). Doses may have been increased in 2 mcg increments every 4 weeks. Dose reductions were to occur according to a pre-defined algorithm. However, dosing could have been adjusted any time if, in the judgment of the Investigator, a risk to subject safety existed. Multivitamin supplements containing less than or equal to 400 IU of vitamin D were not restricted.

In the two TIW dosing studies, the initial dose was 2 or 4 mcg of paricalcitol TIW according to the baseline iPTH level (table below). The doses of the drug were subsequently titrated by 2-mcg increments based on serum calcium, phosphorus, and iPTH levels. Dose increases could occur only once every 4 weeks and dose decreases, for safety reasons, could occur weekly.

In the single QD dosing study, the initial dose was 1 or 2 mcg of paricalcitol QD based on the baseline iPTH level, as shown in the following table. Titration of the drug was based on serum calcium, phosphorus, and iPTH levels.

Baseline iPTH Level	Initial Dose
Study 2001019 and Study 2001020	
≤ 500 pg/mL	2 mcg
> 500 pg/mL	4 mcg
Study 2001021	
≤ 500 pg/mL	1 mcg
> 500 pg/mL	2 mcg

Patient Population: Male and female subjects 18 years of age or older with eGFR of 15 to 60 mL/min were eligible for inclusion into the study. Specific inclusion criteria included:

- Subject had not been on active vitamin D therapy for at least 4 weeks prior to the

screening visit.

- For those subjects taking phosphate binders, the subject had been on a stable regimen at least 4 weeks prior to the screening visit.
- Subjects had to have 2 consecutive iPTH values > 150 pg/mL taken at least 1 day apart; 2 consecutive serum calcium levels ≥ 8.0 to ≤ 10.0 mg/dL; and 2 consecutive serum phosphate levels < 5.2 mg/dL for enrollment into the treatment phase of the study.

Specific exclusion criteria included:

- Subject had acute renal failure within 12 weeks of the study.
- Subject had a spot urine result demonstrating a urine calcium-to-urine creatinine ratio of > 0.2 or had a history of kidney stones.
- Subject was taking maintenance calcitonin, bisphosphonates, or drugs that could have affected calcium or bone metabolism, other than females on stable estrogen and/or progestin therapy.
- Within the last 12 weeks prior to screening, subject had taken Aluminum-containing phosphate binders, or required such medication > 3 weeks during the course of the study.

Efficacy Endpoints: The primary efficacy endpoint was the proportion of patients in each group who had at least 2 consecutive $> 30\%$ reduction from baseline in iPTH. Secondary efficacy endpoints included mean absolute and percent changes in iPTH and mean absolute and percent changes in biochemical markers of bone turnover.

Safety Endpoints: The primary safety variable was the number of patients in each group who had 2 consecutive serum calcium measurements > 10.5 mg/dL. An analysis of the number of patients who had at least one serum calcium measurement > 10.5 mg/dL was also conducted. Other safety variables included the changes in serum phosphorus and calcium X phosphorus ion product; standard clinical chemistry and hematology parameters; 24-hour urinary levels of calcium, phosphorus, and creatinine clearance; and eGFR.

Subject Disposition: Of the 39 subjects randomized into the study and treated with Zemplar, 30 (77%) completed treatment and 9 (23%) were terminated prematurely from the study. Five of the subjects terminated prematurely due to "other" reasons (*i.e.*, required dose reduction to 0 mcg [2 subjects], history of kidney stones [2 subjects], death [1 subject]), 2 were lost to follow-up, 1 withdrew consent, and 1 terminated prematurely due to adverse events.

Of the 36 subjects randomized into the study and treated with placebo, 27 (75%) completed treatment and 9 (25%) were terminated prematurely from the study. Five of the subjects terminated prematurely due to "other" reasons (*i.e.*, required dose reduction to 0 mcg, study drug not dispensed in error, Investigator decision, study drug dispensed was assigned to another subject, coordinator miscalculation of study drug dose [1 subject each]), 2 terminated prematurely due to adverse events, 1 withdrew consent,

and 1 was lost to follow-up.

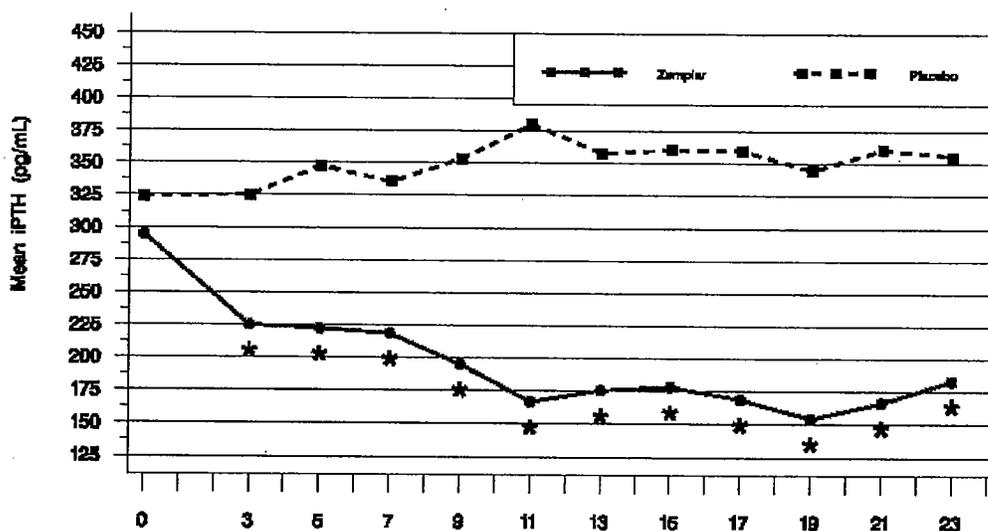
Subject Demographics: The baseline patient demographics were well-matched between groups. The mean age was 64 years; 69% of the subjects were male, approximately 68% were Caucasian and 30% African-American; and the average years since CKD diagnosis was about 5.

Primary Efficacy Outcome (ITT): The mean baseline levels of iPTH were 287.1 pg/mL (range: 151.0 to 701.0 pg/mL) in the Zemplar group and 329.1 pg/mL (range: 147.0 to 697.5 pg/mL) in the placebo group. The difference between the treatment groups in baseline iPTH was not statistically significant.

Ninety-two percent of the Zemplar-treated subjects and 12% of the placebo subjects achieved at least 2 consecutive $\geq 30\%$ decreases from baseline in iPTH levels ($p < 0.001$).

Secondary Efficacy Outcomes (ITT): Seventy-two percent of the Zemplar-treated patients vs. none of the placebo subjects had at least 4 consecutive $> 30\%$ decreases from baseline in iPTH levels (nominal $p < 0.001$). The Zemplar group experienced a mean decrease of -58.1 pg/mL from baseline to the Final Visit in iPTH while the placebo group experienced a mean increase of 50.4 pg/mL (nominal $p < 0.001$). The corresponding mean percent decreases from baseline to Final Visit were -19% and 17% in the Zemplar and placebo groups, respectively.

The following figure shows the mean values for iPTH over the course of the study for the Zemplar and placebo groups (*nominal $p < 0.05$).



In general, the mean levels of the biochemical markers of bone turnover improved to a greater extent in the Zemplar vs. the placebo-treated subjects, although the differences between groups were of statistical significance when the changes were analyzed from baseline to Final visit, but not from baseline to Week 11.

Safety Evaluation

Adverse Events

One Zemplar-treated patient died from cardiac arrest during conduct of the study. No placebo patients died during the trial.

Nine Zemplar and 9 placebo subjects reported at least one serious adverse event (including the death mentioned above). The greatest proportion of subjects in the Zemplar group reported serious adverse events associated with the cardiovascular body system. The greatest proportion of subjects in the placebo group reported serious adverse events associated with the metabolic and nutritional body system. The majority of the events were serious because of hospitalization or prolonged hospitalization.

One Zemplar and two placebo patients reportedly discontinued prematurely from the study due to an adverse event.

A total of 79% of the Zemplar-treated subjects and 64% of the placebo-treated patients reported at least one treatment-emergent adverse event.

The most common adverse events that occurred with a greater frequency in the Zemplar vs. the placebo group were: pain (10% vs. 3%), pharyngitis (10% vs. 8%), viral infection (10% vs. 6%), constipation (8% vs. 3%), depression (8% vs. 0%), headache (8% vs. 3%), hypertension (8% vs. 3%), infection (8% vs. 3%), rhinitis (8% vs. 3%), and vertigo (8% vs. 0%).

Laboratory Parameters

As shown in the following table, the mean changes from baseline to Final Visit were larger for the Zemplar than the placebo-treated subjects; however, the differences were not statistically significant.

Mean Change from Baseline to Final Visit in Serum Calcium, Phosphorus, and Ca x P ion product

	Zemplar (N = 38) ^a	Placebo (N = 35) ^b	ANOVA P-value ^c
Calcium (mg/dL)			
Mean Baseline Value	9.30	9.37	0.464
Baseline Range	8.4–10.0	8.0–10.0	
Mean Final Value	9.46	9.44	
Change from Baseline (SE)	0.16 (0.061)	0.07 (0.063)	0.313
Phosphorus (mg/dL)			
Mean Baseline Value	3.99	4.21	0.063
Baseline Range	2.8–4.8	3.1–5.6	
Mean Final Value	4.42	4.45	

Mean Change from Baseline to Final Visit in Serum Calcium, Phosphorus, and Ca x P ion product

	Zemplar (N = 38) ^a	Placebo (N = 35) ^b	ANOVA P-value ^c
Change from Baseline (SE)	0.43 (0.145)	0.24 (0.152)	0.365
CaxP (mg²/dL²)			
Mean Baseline Value	36.78	39.12	0.051
Baseline Range	25.0-45.3	28.7-48.9	
Mean Final Value	41.92	41.91	
Change from Baseline (SE)	5.14 (1.365)	2.79 (1.422)	0.236

The mean levels of serum alkaline phosphatase decreased from baseline to Final Visit by a statistically significantly greater extent in the Zemplar compared with the placebo groups. This reflects the reduction in bone specific alkaline phosphatase levels observed with Zemplar treatment.

There were no significant differences between treatment groups in the changes from baseline to Final Visit in any of the standard hematology and clinical chemistry variables (other than those mentioned above). There were also no significant differences between groups in the mean changes from baseline to Final Visit in 24-hour urinary calcium, phosphorus, creatinine, creatinine clearance, or estimated GFR.

One Zemplar-treated patient and none of the placebo subjects developed 2 consecutive serum calcium values > 10.5 mg/dl. Five Zemplar and 1 placebo subject developed a single serum calcium value > 10.5 mg/dl. The latter is the more meaningful analysis since dose adjustments were to be made in the event that a subject developed a serum calcium value greater than 10.5 mg/dl.

There were no clinically meaningful changes in vital signs between the treatment groups.

III. SUMMARY OF THE MAJOR EFFICACY AND SAFETY FINDINGS FROM THE THREE PHASE 3 TRIALS

Abbott has submitted ample evidence that Zemplar capsules lower serum levels of iPTH by a clinically and statistically significant amount compared with placebo. Approximately 90% of the subjects treated with Zemplar (daily or TIW) and 13% of the placebo-treated patients had 2 consecutive $\geq 30\%$ from baseline in iPTH during the trials. The mean percent change from baseline to Final visit in serum iPTH levels was -21% in the Zemplar groups and +15% in the placebo groups. Although some of the analyses of the changes in biochemical markers of bone turnover indicated favorable changes in the Zemplar relative to the placebo groups, these data do not substitute for bone histomorphometric data and do not allow one to make accurate judgments about Zemplar's effects on bone structure or pathology.

The major safety issues with active vitamin D and the vitamin D analogues are hypercalcemia, increased Ca X P ion product, and oversuppression of iPTH levels.

Eighteen percent of the Zemplar subjects vs. 3% of the placebo subjects developed at least one serum calcium value > 10.5 mg/dl during the studies. The incidence of a single episode of hypercalcemia was somewhat higher in the subjects who received Zemplar QD vs. TIW (23% vs. 16%).

Twenty-six percent of the Zemplar subjects and 17% of the placebo subjects developed at least one single episode of $\text{Ca} \times \text{P} > 55$ mg^2/dl^2 .

A larger proportion of the Zemplar subjects compared with the placebo subjects had at least one iPTH level < 60 pg/ml.

VI. LABELING

Dr. Golden has conducted a thorough review of the clinical aspects of the proposed labeling and the various review disciplines have met to discuss all parts of the proposed labeling.

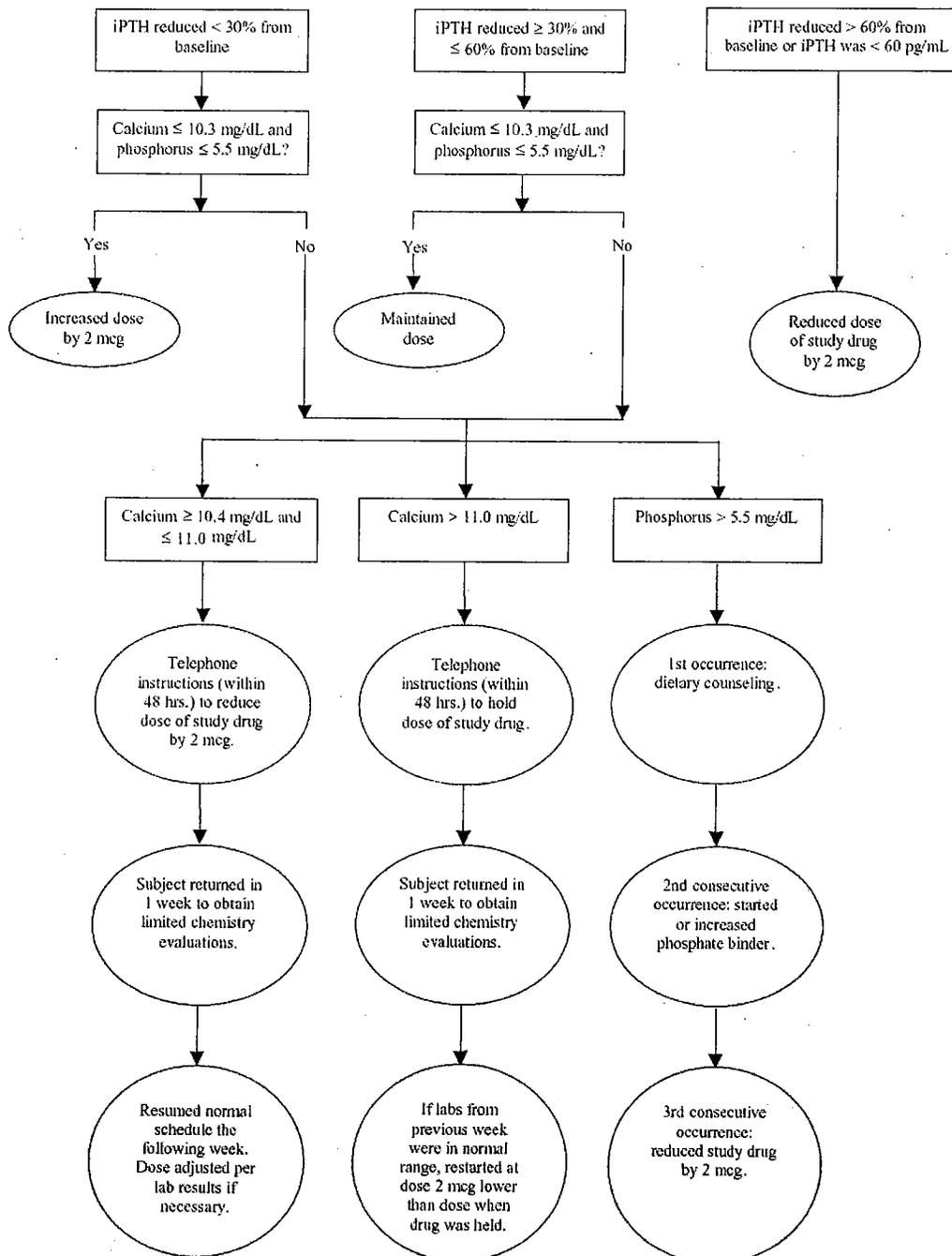
A copy of the review team's proposed labeling is included in the Appendix.

VII. REGULATORY RECOMMENDATION

Approve.

Appendix

Dosing Decision Algorithm.



15 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

**This is a representation of an electronic record that was signed electronically and
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/s/

Eric Colman
5/26/05 10:08:01 AM
MEDICAL OFFICER

David Orloff
6/3/05 12:38:50 PM
MEDICAL OFFICER

I concur with Dr. Colman. His memo will serve
as the Division memo for this application.

CLINICAL REVIEW

Application Type NDA
Submission Number 21-606
Submission Code N

Letter Date 07/28/2004
Stamp Date 07/30/2004
PDUFA Goal Date 5/30/2005

Reviewer Name Julie Golden, M.D.
Review Completion Date 4/15/2005

Established Name Paricalcitol Capsules
(Proposed) Trade Name Zemplar Capsules
Therapeutic Class Vitamin D Analog
Applicant Abbott Laboratories

Priority Designation S

Formulation Capsule
Dosing Regimen 1 or 2 μg p.o. QD or 2 or 4 μg p.o.
TIW
Indication Secondary Hyperparathyroidism
Intended Population CKD Stage 3 and 4

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The application should be Approved, based on the following:

- The Sponsor has demonstrated substantial evidence of effectiveness. The claim that subjects with chronic kidney disease (CKD) Stages 3 and 4 taking paricalcitol (Zemplar®) capsules achieve two consecutive 30% decreases in serum intact parathyroid hormone (iPTH) to a statistically significant degree over those taking placebo has been demonstrated. In addition, the Sponsor has shown that a greater number of subjects taking active drug than placebo achieved one and four consecutive 30% decreases in iPTH from baseline, and that the mean decrease in iPTH over the course of the study was greater in those taking active drug than those taking placebo.
- Paricalcitol capsule is safe for its intended use as recommended in the labeling. Safety was assessed primarily by changes in laboratory values [serum calcium, serum phosphorus, serum calcium/phosphorus product (Ca x P), measures of kidney function] and adverse events. The use of all vitamin D analogs, including paricalcitol capsule, is limited by the tendency to raise serum calcium and Ca x P, potentially leading to such consequences as metastatic calcification and accelerated cardiovascular disease. Serum calcium and Ca x P can be adequately monitored. Adynamic bone disease is a potential risk of iPTH oversuppression, although not much is known about this condition in this patient population (CKD Stage 3 and 4). Oversuppression of iPTH should be avoided as outlined in the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) Work Group guidelines¹. Although vertigo was a statistically significantly more common event in paricalcitol capsule-treated subjects than placebo, a causal relationship was not established.

Because dosing is titrated based on serum levels of iPTH, calcium, and phosphorus, the safe and effective use of paricalcitol capsule, perhaps more so than other medications, relies heavily upon use by a learned intermediary. Studies were performed examining three-times-per-week (TIW) and daily (QD) dosing schema. Both regimens appear to provide adequate iPTH suppression with similar safety outcomes. The Sponsor recommends the daily dosing regimen be used initially, as they believe it will enhance compliance; however, no direct evidence of this was provided in the NDA.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No specific risk management activity has been recommended.

1.2.2 Required Phase 4 Commitments

Decisions regarding the Pediatric Research Equity commitment were summarized in the NDA as follows: on February 8, 2002, the Agency granted a waiver for pediatric studies in subjects from birth to 11 years of age and a deferral for pediatric studies in subjects from 12 to 16 years of age until December 31, 2004.

In addition, a request to defer the requirement for pediatric data to be submitted by December 31, 2004 was submitted. On March 17, 2004, the Agency granted an extension of the deferral for conducting the pediatric studies in pre-dialysis CKD patients aged 12-16 years until December 31, 2008, by which time clinical and pharmacokinetic data from adults with pre-dialysis CKD will have been reviewed.

1.2.3 Other Phase 4 Requests

No other Phase 4 commitments were requested.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The drug under review is paricalcitol capsule (currently marketed in injection formulation for patients with CKD Stage 5 as Zemplar), a synthetic analog of ergocalciferol (vitamin D₂). The proposed indication is treatment of secondary hyperparathyroidism in patients with CKD Stage 3 and 4. Three pivotal trials were conducted with 220 subjects total (107 paricalcitol, 113 placebo). The overall number of patients in the safety database is 672 (healthy volunteers, and patients with CKD Stage 3 and 4 and CKD Stage 5) with approximately 43.2 patient-years of exposure. The other pertinent data source is post-marketing adverse event reporting from the Zemplar injection program.

1.3.2 Efficacy

Three pivotal trials were designed to compare the efficacy of paricalcitol capsule in decreasing serum iPTH levels as compared to placebo in subjects with CKD Stage 3 and 4. Each study was approximately six months in duration with the primary efficacy endpoint of two consecutive 30% decreases in iPTH. These trials, and the primary endpoint, were designed prior to the release of the K/DOQI guidelines, which provide specific guidance on target iPTH values in each CKD stage. While the outcome is clinically relevant, and its achievement signifies efficacy, responders under the K/DOQI guidelines are those that achieve an iPTH 35-70 pg/mL in CKD Stage 3, and 70-110 pg/mL in CKD Stage 4; in addition, iPTH levels to initiate and discontinue drug are dependent on CKD level in the guidelines. CKD levels 3 and 4 were not differentiated in these pivotal studies. Furthermore, whereas iPTH is a generally agreed upon

measure of therapeutic response, absolute and relative changes in iPTH do not in-and-of themselves signal clinically significant improvements in bone structure/quality or reductions in fracture risk. As with previously approved vitamin D analogs, the paricalcitol development program did not include histological bone or fracture data to support the benefit of the drug, although improvement (decrease) in markers of bone turnover was demonstrated.

1.3.3 Safety

The primary safety concern with paricalcitol is hypercalcemia.

Paricalcitol capsule has been shown to be more calcemic than placebo, both in responder analyses (single serum calcium levels > 10.5 mg/dL, $p < 0.001$; and ≥ 11 mg/dL, $p = 0.02$), and in analyses comparing differences of mean change. The Sponsor's contention, that clinically-significant hypercalcemia (two consecutive calcium values > 10.5) is not statistically significant, may be inappropriate for clinical practice based on these findings. A related safety concern is elevation of the calcium/phosphorus product. Although a statistically significant difference between serum $\text{Ca} \times \text{P} > 55$ was not evident, the studies were not designed to detect a difference. The clinical consequences of hypercalcemia and elevated $\text{Ca} \times \text{P}$ are concerning in this population; however, paricalcitol capsule dose is titrated according to serum iPTH, calcium, phosphorus, and $\text{Ca} \times \text{P}$ values and can be adequately monitored by the managing physician.

Adynamic bone disease is a potential risk of over-suppression of iPTH, although less is known about the absolute levels of iPTH that lead to adynamic bone disease in patients with stage 3 and 4 CKD than in patients with stage 5 CKD. Clearly, there is value to avoiding over-suppression of iPTH: in addition to the potential for adynamic bone disease, iPTH change (decrease) appears to be correlated to higher serum calcium levels.

_____ would be incorporated into the label.

1.3.4 Dosing Regimen and Administration

The initial dose in patients with secondary hyperparathyroidism and CKD Stage 3 or 4 is 2 mcg p.o. TIW or 1 mcg p.o. QD for serum iPTH level ≤ 500 pg/mL, and 4 mcg p.o. TIW or 2 mcg p.o. QD for serum iPTH level > 500 pg/mL. The dose is titrated based on serum iPTH, calcium, phosphorus, and $\text{Ca} \times \text{P}$ levels: ± 2 mcg p.o. for those on the TIW regimen and ± 1 mcg p.o. for those on the QD regimen.

1.3.5 Drug-Drug Interactions

Drug interaction potential was studied *in vitro* in cytochrome P450 assays, as well as in pharmacokinetic studies of paricalcitol with concomitant omeprazole or ketoconazole. Paricalcitol is not expected to inhibit the clearance of drugs metabolized by cytochrome P450

enzymes CYP3A, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1, nor induce the clearance of drug metabolized by CYP2B6, CYP2C9 or CYP3A. The pharmacokinetics of paricalcitol were unaffected when co-administered with omeprazole; however, the $AUC_{0-\infty}$ of paricalcitol approximately doubled in the presence of ketoconazole.

Despite a relatively small sample size in the pivotal studies, there may be a clinically important interaction between paricalcitol and high-ceiling diuretic use in serum calcium response (users of high-ceiling diuretics may be predisposed to hypercalcemia while taking paricalcitol), although inherent differences between groups (users and non-users) may explain this finding.

1.3.6 Special Populations

Race, gender, and age

The Sponsor has performed subpopulation analyses for race, gender, and age. There were no obvious clinically relevant differences in efficacy or safety variables based on race, gender, or age, although several of the subpopulations were very small.

Hepatic and renal insufficiency

The target population for this drug is patients with CKD Stage 3 and 4 (GFR 15 – 60 mL/min). The pharmacokinetics of paricalcitol are similar across CKD Stages 3 to 5. No statistically significant difference was found for $AUC_{0-\infty}$ between subjects with mild and moderate hepatic impairment and healthy subjects. No dosing adjustment is required in patients with mild to moderate hepatic impairment. The influence of severe hepatic impairment on the pharmacokinetics of paricalcitol is not known.

Pregnancy and lactation

Only four female subjects of childbearing age (15-45 years old) were enrolled in the pivotal CKD Stage 3 and 4 studies. No studies have been conducted in pregnant women, and none of the women enrolled in any paricalcitol studies were pregnant or became pregnant. According to the Sponsor, no adverse events related to pregnancy have been reported during post-marketing surveillance of paricalcitol injection. It is unknown whether paricalcitol is excreted in human milk.

2 INTRODUCTION AND BACKGROUND

Please note: Direct quotes from the Sponsor's IND are italicized and Reviewer's comments are bolded.

2.1 Product Information

The clinical promise of vitamin D analogs resides in their ability to decrease intact parathyroid hormone (iPTH) similarly to the endogenous hormone, calcitriol, while potentially lessening the risk of side effects such as hypercalcemia and its attendant consequences. Vitamin D₃ (cutaneous synthesis and animal sources) or D₂ (plant sources) is hydroxylated in the liver in the 25-position to its major storage form, and again in the kidney in the 1-position, into its biologically active form. 1,25-(OH)₂ vitamin D exerts its action on the vitamin D receptor (VDR) in parathyroid, bone, and intestinal tissue to maintain calcium homeostasis. In patients with renal dysfunction, the ability to activate 25-OH vitamin D becomes impaired, leading to hypocalcemia, secondary hyperparathyroidism, and ultimately, bone disease.

Paricalcitol (19-nor-1 α , 25-dihydroxyvitamin D₂) is a synthetic vitamin D analog (selective VDR agonist), and is currently marketed as Zemplar injection for intravenous administration. The pharmacologic class is hormone. Zemplar injection is indicated for the prevention and treatment of secondary hyperparathyroidism associated with stage 5 chronic kidney disease (CKD) chronic renal failure (Approved April 17, 1998). In this Review, the terms paricalcitol and Zemplar will be used interchangeably.

Abbott Laboratories seeks to add a new dosage form (capsule), as well as the following new indication:

Zemplar® Capsules are indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 3 and 4.

Paricalcitol capsule will be supplied in 1, 2 and 4 mcg capsules with a recommended starting dose of either 1 mcg daily or 2 mcg three times a week (not to be administered more often than every other day) for those with iPTH level \leq 500 pg/mL, and either 2 mcg daily or 4 mcg three times a week (not to be administered more often than every other day) for those with iPTH level $>$ 500 pg/mL. The label includes instructions for titration of the dose based on serum iPTH, calcium, and calcium-phosphorus product (Ca x P).

2.2 Currently Available Treatment for Indications

There are three other vitamin D analogs currently approved in the US: Calcijex (calcitriol, injectable) from Abbott, Rocaltrol (calcitriol, oral solution) from Roche, and Hectorol (doxercalciferol, injectable and capsule) from Bone Care International. All three analogs are

active forms of vitamin D (Calcijex and Rocaltrol are 1- and 25-hydroxylated, Hectorol is 1-hydroxylated with activation by 25-hydroxylation in the liver). Rocaltrol and Hectorol are approved and indicated for the treatment of secondary hyperparathyroidism in patients with stage 3 and 4 CKD.

2.3 Availability of Proposed Active Ingredient in the United States

Paricalcitol is currently available in an injectable dosage form and is indicated for the prevention and treatment of secondary hyperparathyroidism associated with stage 5 CKD.

2.4 Important Issues with Pharmacologically Related Products

Clinical issues include oversuppression of iPTH with resultant exacerbation of metabolic bone disease; hypercalcemia, increased Ca x P ion product, and systemic calcification; and the lack of head-to-head data comparing the efficacy and safety of the drugs approved to treat secondary hyperparathyroidism in patients with stage 3-5 CKD. The entire field suffers from the lack of data on the effects of treatment with active vitamin D compounds on long-term outcomes such as fractures and cardiovascular disease.

2.5 Presubmission Regulatory Activity

The initial IND (IND 60,672) for Zemplar (paricalcitol) capsule was submitted on July 28, 2000. Paricalcitol is also marketed in the United States under NDA 20-819 as Zemplar injection, approved April 17, 1998.

Abbott submitted a Type B meeting request on May 4, 2001, to discuss proceeding directly from Phase 1 to Phase 3 development. Initially the meeting was deemed unnecessary and Abbott was instructed to submit Phase 3 protocols for review under the "Special Protocol Amendment" (SPA) provision of FDAMA. On September 28, 2001, Abbott submitted the request for SPA for the Phase 3 clinical studies in _____ and CKD patients. During the Agency's 45-day review period of the SPA, Abbott was requested to schedule an End-of-Phase 2 Meeting.

The December 11, 2001, End-of Phase 2 Meeting agreements are as follows:

1. The pharmacology/toxicology data from Zemplar injection NDA 20-819 are adequate to support an NDA _____ Carcinogenicity studies are needed for NDA filing.
2. Bioequivalence differences observed between the 1, 2, and 4 mcg capsules may be addressed in a concurrent Phase 3 short-term clinical study.
3. Dosing regimens and dose titration were acceptable if the bioequivalence issue was resolved.
4. Investigational plan supports the proposed indication: For the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease.

5. Pediatric studies are deferred until results from the adult clinical trials using the oral formulation and the ongoing injection pediatric studies are complete.
6. — stability data are acceptable for the NDA exhibit batches. These data are to be supported by — of stability data on the Phase 3 batches (1 lot of each strength. 4 strengths) submitted during the NDA review.

End-of Phase 2 Meeting Action Items:

1. A draft proposal will be submitted to the Division for review to address the different capsule strength bioavailability issue.
2. Concerning the pediatric rule and request for waiver, provide information on how the 0-11 year age group can be studied and propose a deferral date for pediatric studies.
 - a. Abbott submitted a request for a pediatric deferral and partial waiver for conducting pediatric studies using paricalcitol capsule on July 31, 2001.
 - b. On February 8, 2002, the Agency granted a waiver for pediatric studies in subjects from birth to 11 years of age and a deferral for pediatric studies in subjects from 12 to 16 years of age until —

c.

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On March 17, 2004, the Agency granted an extension of the deferral for conducting the pediatric studies in pre-dialysis CKD patients aged 12-16 years until clinical and pharmacokinetic data from adults with pre-dialysis CKD have been reviewed, until December 31, 2008.

3. Provide additional information on related substances in the drug product.
 - a. A teleconference was held March 26, 2002, during which time the Agency indicated that Abbott's response on February 28, 2002, to chemistry topics (related substances, proposed dissolution testing procedure, proposed in-process — and proposed specifications for controlling quality of the drug product) were acceptable and there were no further issues with regards to related substances and dissolution-testing procedures.

A Pre-NDA Meeting was held to discuss —
— on September 23, 2002. —

A Pre-NDA Meeting for the CKD Stage 3 and 4 patient populations was held on March 1, 2004, followed by a teleconference on April 6, 2004, during which time the following agreements were made:

1. Preclinical Studies – No outstanding issues with the capsule formulation.
2. Clinical Pharmacology – Two additional clinical pharmacology studies are to be conducted and submitted within the first 3 months following the NDA submission: 1) *in vivo* study examining the interaction potential of paricalcitol with the CYP3A4 inhibitor

- ketoconazole; 2) *in vitro* study examining the metabolic enzyme induction potential of paricalcitol with primary cultured human liver cells.
3. Clinical Studies support the proposed indication.
 4. Clinical Studies (Special Populations) to be submitted in the NDA include Geriatric: The Division agreed there are sufficient numbers of geriatric patients represented in the CKD pivotal studies to allow adequate assessment of safety and efficacy in the population.
 5. Financial disclosure to be included for the three Phase 3 pivotal CKD Stage 3 and 4 trials.
 6. Statistical Analysis Plan – Provide additional analyses of single incidences of calcium > 10.5 mg/dL in the Primary Safety Analysis, including descriptive data.
 7. The schedule for submitting the stability data for the 2 and 4 mcg strengths, stability data for two lots of the 1 mcg strength and data for one lot of the 1 mcg strength within six months after the original NDA submission for the exhibit batches is acceptable to support a 24-month expiration period.
 8. The Zemplar Injection data can be incorporated by cross-referencing NDA 20-819.
 9. The Division agrees with the proposal to provide publications upon request.
 10. Zemplar Injection and paricalcitol capsule will be presented separately in the ISS. Within the data presentation for paricalcitol capsule, safety data for CKD Stage 3 and 4 will be presented separately, and also integrated with the safety data for CKD Stage 5.
 11. The ISE will focus on the three Phase 3 pivotal trials.
 12. The requirement for a full paper review is waived and only one paper copy of Volume 1, Item 4-Chemistry section, Clinical Pharmacology studies, Pharmacokinetics/Pharmacodynamics (PK/PD) study reports, Bio-analytical reports, and the Phase 3 pivotal study reports will be required.
 13. Patient profiles will not be included, as Abbott is providing CRT datasets. Additionally, the content and structure of the analysis-ready datasets presented in the Pre-NDA Meeting package are acceptable for submission.
 14. It is acceptable to submit case report forms for only deaths and discontinuations due to adverse events; organized as one file per subject, by study and site.
 15. The overall outline of the NDA is acceptable.
 16. The detailed description of Electronic NDA Navigation with regards to e-authored and scanned documents, (~40%) is to be included in the e-NDA. The level of navigation is acceptable.

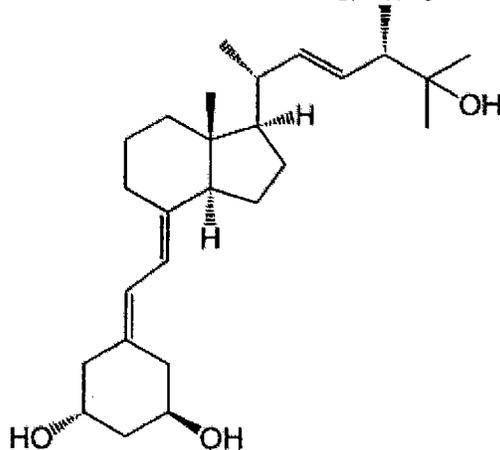
2.6 Other Relevant Background Information

Paricalcitol capsule has not been approved for marketing in any country. As of June 1, 2004, Zemplar Injection has been approved in 25 countries outside the United States, and is marketed in Spain.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

Please refer to Dr. Ding's review for a more detailed chemistry evaluation. The chemical name is 19-nor-1 α , 3 β , 25-trihydroxy-9,10-secoergosta-5(Z), 7(E), 22(E)-triene. It has a molecular weight of 416.64 and its molecular formula is C₂₇H₄₄O₃. Its structural formula is the following:



3.2 Animal Pharmacology/Toxicology

Please refer to Dr. Davis-Bruno's review for a more detailed toxicology evaluation. Effects seen in the toxicology studies were attributable to the pharmacologic action of the drug; specifically, calcification or indirect effects of calcification such as increases of BUN and creatinine as a result of kidney calcification. Effects not clearly related to hypercalcemia included decreased WBC counts in dogs, thymic atrophy in dogs, and altered APTT values in dogs and rats. The NTEL in an oral repeated-dose study was 60 mcg/kg/dose in rats and 1.2 mcg/kg/dose in dogs. In a 6-month study, the NTEL for the oral formulation was determined to be 0.5 mg/kg/dose in rats and 0.06 mg/kg/dose in dogs.

Two-year carcinogenicity studies in mice demonstrated increased incidence of uterine leiomyoma and leiomyosarcoma in doses of 3 to 8 times a human dose of 14 mcg. In rats, 2-year carcinogenicity studies demonstrated increased incidence of benign adrenal pheochromocytoma at doses of < 1 to 7 times the human dose of 14 mcg. All mutagenicity studies were negative: Ames test, mutation potential at thymidine kinase locus in cultured mammalian cells, chromosomal aberrations, and the micronucleus test.

Reproduction studies demonstrated no effect on reproductive capabilities or on early embryo development at dosages up to 20 mg/kg/dose, no developmental toxicity up to 3.0 mg/kg/day,

and a minimal decrease in offspring viability at dose of 0.5 times the human dose of 14 mcg. A dose of 3.0 mg/kg was considered both the maternal and developmental NTEL.

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4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of data used in the review include: ten Phase 1 trials in healthy subjects and those with CKD Stages 3, 4, and 5; three Phase 3 studies conducted in CKD Stage 5 subjects in order to support the overall safety profile of paricalcitol capsule; and three pivotal Phase 3 trials in CKD Stage 3 and 4 subjects. In addition, the data from NDA 20-819 (Zemplar Injection) were cross-referenced. As of this writing, there are no publications of controlled studies of the efficacy and safety of paricalcitol when used to treat secondary hyperparathyroidism in patients with stage 3 or 4 CKD.

4.2 Tables of Clinical Studies

Overview Table of Paricalcitol Capsules Clinical Studies							
Protocol Number/ Investigator/ Country/Status (Completion Date)	Study Design	Objective	Drug (Dose)	Number of Subjects	Mean Age in Years (Range)	Gender	Race/ Ethnicity
M95-018/ — /USA/ Complete (6/25/95) Cross Reference: NDA 20-819, 01/17/97, Original Submission, vol. 31 pgs. 140-261	Single and multiple dose, randomized, double-blind, placebo-controlled escalating dose study. 3 groups, 6 subjects each (4 active treatment, 2 placebo)	To assess 1) safety of paricalcitol injection 2) pharmacokinetic and pharmacodynamic profiles of single and multiple doses	Group 1: 0.04 mcg/kg QOD x 3 doses Group 2: 0.08 mcg/kg QOD x 3 doses Group 3: 0.16 mcg/kg QOD x 3 doses	Overall: 18	27 (18 – 44)	28% F 72% M	Not Described
96016/ — Scotland/ Complete (11/06/96) Cross Reference: NDA 20-819, 01/17/97, Original Submission, vol 35 pgs. 2-132	Open label, single dose, fasting, single center study in healthy males	To investigate the disposition of [³ H]-paricalcitol in healthy adult males following a single intravenous dose.	Single dose of [³ H]- paricalcitol 0.16 mcg/kg administered as an intravenous bolus	4	33 (30 – 46)	100% M	100% C

Overview Table of Paricalcitol Capsules Clinical Studies							
Protocol Number/ Investigator/ Country/Status (Completion Date)	Study Design	Objective	Drug (Dose)	Number of Subjects	Mean Age in Years (Range)	Gender	Race/ Ethnicity
M98-914/ — /USA/ Complete (02/24/99) Cross Reference: NDA 20-819, 04/14/00, S-007, 2 volumes	Single-dose, open-label, single-center study in subjects with normal hepatic function and with mild to moderate hepatic insufficiency.	To assess the safety and pharmacokinetics of a single dose of Zemplar (paricalcitol) injection in subjects with mild to moderate chronic hepatic insufficiency.	Group I: Mild hepatic insufficiency = single dose of 0.24 mcg/kg paricalcitol Group II: Moderate hepatic insufficiency = single dose of 0.24 mcg/kg paricalcitol Group III: Normal hepatic function = single dose of 0.24 mcg/kg paricalcitol	Overall 20 I = 5 II = 5 III = 10	I = 48.0 (41-64) II = 50.4 (40-55) III = 48.1 (36-60)	100% M	I: 80% C 20% B II: 80% C 20% B III: 90% C 10% B
2000005/ — /USA/ Complete (11/08/00)	Open-label, randomized, single-dose, two-period, crossover, non-fasting, two-center study.	To assess the safety and bioavailability of a paricalcitol capsule formulation relative to that of a paricalcitol IV formulation in subjects with ESRD who were undergoing HD. The safety of the paricalcitol capsule formulation was also assessed.	Regimen A: Paricalcitol capsule formulation (0.24 µg/kg) administered orally with 180 mL of water Regimen B: Paricalcitol IV formulation (0.24 µg/kg) administered as an IV bolus injection	Overall: 14	47 (30 - 62)	86% M 14% F	57% C 36% B 7% I
2000006/ — USA/ Complete (01/09/01)	Open-label, randomized, single-dose, two-period, crossover, non-fasting study.	To assess the bioavailability of a paricalcitol capsule formulation relative to that of a paricalcitol IV formulation in subjects with ESRD who were undergoing CPD treatment. The safety of the paricalcitol capsule formulation was also assessed.	Regimen A: Paricalcitol capsule formulation (0.24 mcg/kg) administered orally with 180 mL of water Regimen B: Paricalcitol IV formulation (0.24 mcg/kg) administered as an IV bolus injection	Overall: 8	47.3 (29 - 70)	12.5% M 87.5% F	37.5% C; 37.5% B; 25% I
2000007/ — USA/ Complete (11/28/00)	Single-dose, 4-period, partial crossover (Periods 1 to 3; crossover; Period 4: assess dose linearity), fasting and non-fasting, open-label, randomized, single-	To assess 1) the safety and bioavailability of a paricalcitol capsule formulation relative to that of a paricalcitol IV formulation, 2) the effect of food	Study Part I, Periods 1 to 3: Regimen A: 0.24 mcg/kg oral (nonfasting) Regimen B: 0.24 mcg/kg oral (fasting) Regimen C: 0.24 mcg/kg IV	Overall: 27	38 (21 - 54)	67% M 33% F	96% C 4% B

Overview Table of Paricalcitol Capsules Clinical Studies							
Protocol Number/ Investigator/ Country/Status (Completion Date)	Study Design	Objective	Drug (Dose)	Number of Subjects	Mean Age in Years (Range)	Gender	Race/ Ethnicity
	center study in healthy subjects.	on the bioavailability of the paricalcitol capsule formulation, and 3) whether there is pharmacokinetic dose-proportionality with the paricalcitol capsule formulation.	(nonfasting) Study Part II, Period 4: Regimen D: 0.06 mcg/kg oral (nonfasting) Regimen E: 0.12 mcg/kg oral (nonfasting) Regimen F: 0.48 mcg/kg oral (nonfasting)				
2001004/ — JSA Complete (03/23/01)	Open-label, randomized, single-dose, two-cohort, three-period, crossover, fasting study in 60 subjects	To assess the bioequivalence of three Paricalcitol capsule strengths under fasting conditions.	Subjects received one of three sequences: Regimen A: 8 x 1 mcg Regimen B: 4 x 2 mcg Regimen C: 2 x 4 mcg For a total of 8 mcg paricalcitol dose per period. Each regimen was administered with 240 mL of water after a 10-hour fast and approximately 4 hours prior to lunch.	Overall: 60	37.0 (18-55)	50%M 50%F	75%C 25%B
2001005/ — USA/Complete (08/19/02)	Single and multiple-dose, open-label, randomized study will be conducted according to a two-period, crossover design.	To assess the single and multiple dose safety and pharmacokinetics of the Paricalcitol capsule following 4 mcg daily (QD) and 8 mcg three times-a-week (TIW) administration	Regimen A: One 4 mcg paricalcitol capsule on Study Day 1 and one 4 mcg paricalcitol capsule QD for 11 doses on Study Days 3 through 13 Regimen B: Two 4 mcg paricalcitol capsules TIW for 6 doses on Study Days 1, 3, 5, 8, 10, and 12	Overall: 20	32.2 (18-53)	85%M 15%F	80%C 20%B

Overview Table of Paricalcitol Capsules Clinical Studies							
Protocol Number/ Investigator/ Country/Status (Completion Date)	Study Design	Objective	Drug (Dose)	Number of Subjects	Mean Age in Years (Range)	Gender	Race/ Ethnicity
M001030/ — Scotland/ Complete (12/04/01)	An open-label randomized, single-dose, fasting, parallel, single-center study in healthy male subjects.	To investigate the absorption and disposition of [³ H]-paricalcitol in healthy male subjects following either a single oral dose or single IV dose in healthy adults.	Group A: Single dose of 0.48 mcg /kg [³ H]-paricalcitol (oral) Group B: Single dose of 0.48 mcg/kg [³ H]-paricalcitol (IV)	Overall: 12	42.3 (36 - 53)	100% M	92% C 8% B
M02-435/ — JSA/ Complete (07/24/02)	Single-dose, open-label, randomized, fasting, 3-cohort, 4-period, crossover dose strength linking, single-center study in healthy subjects.	To assess the bioequivalency of 1 mcg (#3 SEC), 1 mcg (#2 SEC), 2 mcg (#3 SEC), and 4 mcg (#3 SEC) dosage strengths of paricalcitol capsules under fasting conditions.	Regimen A: eight 1 mcg (#3 SEC) paricalcitol capsules Regimen B: 1 mcg (#2 SEC) paricalcitol capsules Regimen C: four 2 mcg (#3 SEC) paricalcitol capsules Regimen D: two 4 mcg (#3 SEC) paricalcitol capsules administered orally with 240 mL of water after a 10-hour fast	Overall: 88	37.8 (19 - 54)	48% M 52% F	88% C 10% B 2% O
M02-436/ — JSA/ Complete (05/30/02)	An open-label, randomized, single-dose, two-period, crossover, fasting, single-center, drug interaction, pharmacokinetics study in healthy subjects.	To assess the effect of omeprazole on the pharmacokinetics of paricalcitol. In addition, the safety of the co-administration of paricalcitol with omeprazole will be evaluated.	Regimen A: Four 4 mcg paricalcitol capsules (16 mcg) to be administered under fasting conditions Regimen B: One 40 mg omeprazole capsule to be administered under fasting conditions followed by four 4 mcg paricalcitol capsules (16 mcg) to be administered under fasting conditions	Overall: 26	40.3 (23 - 54)	50% M 50% F	96% C 4% B
M02-437/ — /USA/ Complete (06/25/02)	An open-label, randomized, single-dose, three-period, cross-over, fasting and non-fasting, single center, bioequivalence, food effect study in healthy subjects.	To evaluate the bioavailability of paricalcitol commercial capsule relative to paricalcitol clinical capsule and to evaluate the effect of food on the bioavailability of	Regimen A: Two 4 mcg paricalcitol capsules, clinical formulation, administered under fasting conditions Regimen B: Two 4 mcg paricalcitol capsules, commercial	Overall: 60	44 (19 - 55)	43% M 57% F	93% C 7% B

Overview Table of Paricalcitol Capsules Clinical Studies							
Protocol Number/ Investigator/ Country/Status (Completion Date)	Study Design	Objective	Drug (Dose)	Number of Subjects	Mean Age in Years (Range)	Gender	Race/ Ethnicity
		paricalcitol commercial capsule. The safety of paricalcitol administrations will also be evaluated.	formulation, administered under fasting conditions Regimen C: Two 4 mcg paricalcitol capsules, commercial formulation, administered under non-fasting conditions				
M03-633 USA/ Complete (2/29/04)	Phase 1, open-label, single and multiple dose, multicenter study in 15 subjects with moderate renal impairment (CKD Stage 3) (GFR of 30 - 60 mL/min) and 15 subjects with severe renal impairment (CKD Stage 4) (GFR < 30 mL/min, not requiring dialysis)	To evaluate the safety, pharmacokinetics and pharmacodynamics of single and multiple doses of Paricalcitol Capsule in subjects with moderate to severe chronic renal impairment.	Group 1: Moderate renal impairment. Administered 4 mcg Paricalcitol Capsule on Study Day 1 and 4 mcg QD for 6 doses on Study Days 3-8. Doses were administered orally with 180 mL of water, 30 minutes after breakfast. Group 2: Severe renal impairment. Administered 3 mcg Paricalcitol Capsule on Study Day 1 and 3 mcg QD for 6 doses on Study Days 3-8. Doses were administered orally with 180 mL of water, 30 minutes after breakfast.	Overall: 29	62 (39 - 76)	66%M 34%F	52%C 41%B 3%A 3%I
95022/ USA/ Complete (2/12/96) Cross Reference: NDA 20-819, 01/17/97, Original Submission, vols. 39-42	Phase 2, single and multiple dose, double-blind, placebo-controlled, escalating dose study.	To determine the safety and efficacy of paricalcitol (paricalcitol) in patients with end-stage renal disease requiring hemodialysis. In addition, the pharmacokinetics of paricalcitol were investigated.	Subjects received an IV bolus dose three times a week of 0.04, 0.08, 0.16, 0.24 mcg/kg or placebo in 4 groups for a total of 4 weeks.	22	46 (18 - 74)	50% F 50% M	88% B 12% O

Overview Table of Paricalcitol Capsules Clinical Studies							
Protocol Number/ Investigator/ Country/Status (Completion Date)	Study Design	Objective	Drug (Dose)	Number of Subjects	Mean Age in Years (Range)	Gender	Race/ Ethnicity
97005/ — USA/ Complete (05/20/97)	Single dose, open-label, single-center study.	To determine the dialyzability of paricalcitol when administered to CKD Stage 5 subjects undergoing hemodialysis (HD).	Single 0.08 µg/kg intravenous dose of paricalcitol 2-4 hrs prior to hemodialysis	6	74 (69 - 79)	67% M 33%F	100% C
2001013/ Multi-center 13 investigators/ USA/Complete (01/07/03)	Prospective, randomized, placebo-controlled, double-blind, 12-week, multi- center study to evaluate safety and efficacy in ESRD subjects on HD with 2° HPT.	To determine the safety and efficacy of Paricalcitol Capsules as compared to placebo for the treatment of 2° HPT by decreasing iPTH levels in ESRD subjects on HD.	Group 1 - Paricalcitol Capsule Group 2 - Placebo Capsule The initial dose was based on the formula [baseline iPTH/60]. Subsequent doses were titrated in 2 mcg increments, based on weekly iPTH, Ca, and Ca×P. Dosing interval: 3 times weekly after HD session	Overall: 77	56.7 (21 - 84)	62%M 38%F	43%C 54%B 3%A
2001014/ Multi-center 15 investigators/ USA/Complete (12/17/02)	Prospective, randomized, placebo controlled, double-blind, 12- week, multi-center study to evaluate safety and efficacy in ESRD subjects on HD with 2° HPT.	To determine the safety and efficacy of Paricalcitol Capsules as compared to placebo for the treatment of 2° HPT by decreasing iPTH levels in ESRD subjects on HD.	Group 1 - Paricalcitol Capsule Group 2 - Placebo Capsule The initial dose was based on the formula [baseline iPTH/60]. Subsequent doses were titrated in 2 mcg increments, based on weekly iPTH, Ca, and Ca×P. Dosing interval: 3 times weekly after HD session	Overall: 74	59.6 (27 - 87)	62%M 38%F	47%C 50%B 3%A
2001015/ Multi-center 25 investigators/ USA, Poland/ Complete (01/08/03)	Prospective, placebo-controlled, double-blind, 12- week, randomized, multi-center study to evaluate safety and efficacy in ESRD subjects on PD with 2° HPT.	To determine the safety and efficacy of Paricalcitol Capsules as compared to placebo for the treatment of 2° HPT by decreasing iPTH levels in ESRD subjects on PD.	Group 1 - Paricalcitol Capsule Group 2 - Placebo Capsule The initial dose was based on the formula [baseline iPTH/60]. Subsequent doses are titrated in 2 mcg increments, based on weekly iPTH, Ca, and Ca×P. Dosing	Overall: 75	51.0 (20 - 79)	44%M 56%F	49.3%C 49.3%B 1.3%A

Overview Table of Paricalcitol Capsules Clinical Studies							
Protocol Number/ Investigator/ Country/Status (Completion Date)	Study Design	Objective	Drug (Dose)	Number of Subjects	Mean Age in Years (Range)	Gender	Race/ Ethnicity
			interval: 3 times weekly after PD session				
2001019/ Multi-center 15 investigators/ USA, Poland/ Complete (01/29/04)	Prospective, randomized, placebo-controlled, double-blind, multi- center study to determine the safety and efficacy of Paricalcitol Capsule (dosed three times weekly) in reducing elevated serum intact parathyroid hormone levels in subjects with chronic kidney disease.	To determine the safety and efficacy of Paricalcitol Capsules as compared to placebo in reducing elevated PTH levels in subjects with CKD.	Group 1 - Paricalcitol Capsule Group 2 - Placebo Capsule The initial dose was based on average iPTH from PTV1 & PTV2 ≤ 500 = 2 mcg TIW, > 500 = 4 mcg TIW. Subsequent doses are titrated in 2 mcg increments, based on bi-weekly iPTH, Ca, and P. Dose increases could occur no more frequently than every 4 weeks. Dose decreases could occur at any visit.	Overall: 75	64.1 (22 - 90)	69.3%M 30.7%F	68%C 29.3%B 2.7%A
2001020/ Multi-center 15 investigators/ USA, Poland/ Complete (02/23/04)	Prospective, randomized, placebo-controlled, double-blind, multi- center study to determine the safety and efficacy of Paricalcitol Capsule (dosed three times weekly) in reducing elevated serum intact parathyroid hormone levels in subjects with chronic kidney disease.	To determine the safety and efficacy of Paricalcitol Capsules as compared to placebo in reducing elevated PTH levels in subjects with CKD.	Group 1 - Paricalcitol Capsule Group 2 - Placebo Capsule The initial dose was based on average iPTH from PTV1 & PTV2 ≤ 500 = 2 mcg TIW, > 500 = 4 mcg TIW. Subsequent doses are titrated in 2 mcg increments, based on bi-weekly iPTH, Ca, and P. Dose increases could occur no more frequently than every 4 weeks. Dose decreases could occur at any visit.	Overall: 70	60.1 (30 - 91)	35.7%M 64.3%F	65.7%C 32.9%B 1.4%A

Overview Table of Paricalcitol Capsules Clinical Studies							
Protocol Number/ Investigator/ Country/Status (Completion Date)	Study Design	Objective	Drug (Dose)	Number of Subjects	Mean Age in Years (Range)	Gender	Race/ Ethnicity
2001021/ Multi-center 14 investigators/ USA, Poland/ Complete (03/03/04)	Prospective, randomized, placebo-controlled, double-blind, multi- center study to determine the safety and efficacy of Paricalcitol Capsule (dosed every day) in reducing elevated serum intact parathyroid hormone levels in subjects with chronic kidney disease.	To determine the safety and efficacy of Paricalcitol Capsules as compared to placebo in reducing elevated PTH levels in subjects with CKD.	Group 1 - Paricalcitol Capsule Group 2 - Placebo Capsule The initial dose was based on average iPTH from PTV1 & PTV2 ≤ 500 = 1 mcg daily, > 500 = 2 mcg daily. Subsequent doses are titrated in 1 mcg increments, based on bi-weekly iPTH, Ca, and P. Dose increases could occur no more frequently than every 4 weeks. Dose decreases could occur at any visit.	Overall: 75	63.7 (32 - 93)	69.3%M 30.7%F	80%C 16%B 1.3%A 2.7%I
M98015/ Multi-center 15 investigators/ USA/Complete (10/99) Cross Reference: NDA 20-819, 06/09/00, S-008	Phase IV, double- blind, randomized, multi-center, 12- week, active control trial comparing two initial starting dose regimens in ESRD subjects	To determine whether a starting dose based on baseline iPTH (baseline iPTH/80) is equivalent in the incidence rate of hypercalcemia (single incidence) to the approved method based on body weight (0.04 mcg/kg).	Regimen A: Paricalcitol initially dosed according to iPTH/80 and placebo dose according to 0.04 mcg/kg, dose titration in 2 mcg increments Regimen B: Paricalcitol initially dosed according to patient weight 0.04 mcg/kg and placebo dosed according to iPTH/80, dose titration in 2 mcg increments	Overall 125 A: 64 B: 61	A: 56.1 (21.1 - 81.0) B: 55.2 (23.4 - 81.1)	A: 56%M 44%F B: 48%M 52%F	A: 84%B 11%C 5%H B: 84%B 11%C 5%H
2° HPT = Secondary Hyperparathyroidism; Ca = Calcium; Ca×P = Calcium Phosphorous product; CKD = Chronic Kidney Disease; CPD = Continuous Peritoneal Dialysis; ESRD = End Stage Renal Disease; HD = Hemodialysis; iPTH = Intact Serum Parathyroid Hormone; IV = intravenous; kg = kilogram; mg = milligram; mL = milliliters; QD = once daily; PD = Peritoneal Dialysis; SEC = soft elastic capsule; TIW = three times weekly; PTV1 = Pre-Treatment Visit 1; PTV2 = Pre-Treatment Visit 2; (Gender: M = Male; F = Female); (Race: C = Caucasian; B = Black; O = Other; A = Asian; I = American Indian/Alaska Native, H=Hispanic).							

4.3 Review Strategy

All clinical data submitted in this NDA were considered when formulating a conclusion of Zemplar's safety. The three pivotal studies were reviewed for efficacy as they were the only randomized controlled trials that studied the proposed dosage form (capsule) for the proposed

indication (CKD Stages 3 and 4). In addition, previous FDA reviews and current labels for paricalcitol injection and other approved vitamin D analogs were reviewed. All supporting literature supplied by Abbott was reviewed.

4.4 Data Quality and Integrity

The Division of Scientific Investigation completed an audit of the following three clinical sites: Dr. Daniel Battle, Chicago, IL, Dr. Hanna Abboud, San Antonio, TX, and Dr. Barton Levine, Los Angeles, CA. These sites were chosen as they enrolled the largest number of subjects in each respective pivotal study (2001019, 2001020, and 2001021).

An audit report of Dr. Battle's site inspection revealed two protocol violations: subject 802 had a history of cardiac graft and a cholecystectomy that was not recorded on the CRF, and the study coordinator was not listed on Form FDA 1572 as a sub-investigator (for which a 1-item Form FDA 483 was issued). Data from the site were found to be acceptable.

An audit report of Dr. Abboud's site inspection revealed general adherence to applicable statutory requirements as well as FDA regulations governing the conduct of clinical investigations and the protection of human subjects. Form FDA 483 was not issued. Data from the site were found to be acceptable.

An audit report of Dr. Levine's site inspection revealed several protocol violations: subjects 901, 902, and 905 had dosage changes that were not per protocol, and a 3-item Form FDA 483 was issued. The audit report acknowledged that in general, data in source documents and CRFs matched the data in sponsor provided data listings. Data from the site were found to be acceptable.

4.5 Compliance with Good Clinical Practices

All pivotal study informed consent forms were reviewed. Although evidently approved by the individual sites' IRBs, several issues with the informed consent were identified by this Reviewer:

1. The Risks and Discomforts section did not specifically list the potential side effects of hypercalcemia.
2. Zemplar IV was listed as an example of alternative treatment for people with Stage 3/4 CKD, which is misleading (it has not been approved for this indication).
3. It is unclear from the submitted form what the actual amount of subject reimbursement was, since this area was left blank.

The following tables summarize the number of protocol violations by investigator. Protocol violations appear generally balanced between subjects on active drug and subjects on placebo.

Protocol Violations by Investigator (the following are Reviewer-generated tables):

Study 2001019

Investigator	N Total	N Paricalcitol	N Placebo
(22030)	24	14	10
(19147)	28	11	17
(19148)	12	12†	0
(11460)	31	13	18
(8800)	19	12	7
(18802)	11	11*	0
(1472)	20	13	7
(18814)	14	7	7
(19154)	23	9	14
(19155)	33	16	17
(18815)	31	16	15
(19159)	93	47	46
(19163)	19	4	15
Total	358	185	173

† These 12 protocol deviations came from one subject

* These 11 protocol deviations came from two subjects

Study 2001020

Investigator	N Total	N Paricalcitol	N Placebo
(11396)	46	18	28
(19150)	19	6	13
(8818)	21	11	10
(18801)	51	28	23
(19153)	22	6	16
(18813)	4	0	4
(11478)	8	0	8
(11479)	11	11†	0
(11264)	57	22	35
(16504)	18	7	11
(9345)	14	0	14
(19156)	10	3	7
(962)	12	7	5
(11450)	14	12*	2
(20224)	5	0	5
Total	312	131	181

† These 11 protocol deviations came from one subject

* These 12 protocol deviations came from four subjects

Study 2001021

Investigator	N Total	N Paricalcitol	N Placebo
(18799)	13	7	6
(18848)	15	5	10
pouris (18819)	8	0	8
(18809)	38	21	17
(11432)	76	49	27
(531)	70	31	39
(19157)	27	5	22
(158)	18	8	10
(27074)	14	7	7
(19160)	14	7	7
(20223)	35	20	15
(19161)	31	19	12
(19162)	19	13	6
(11457)	43	17	26
Total	421	209	212

Additionally, the data were evaluated for evidence of differential entrance criteria noncompliance by randomization status. All studies had subjects who violated inclusion or exclusion criteria (15-21% of total subjects), but these subjects were distributed equally in each treatment group:

2001019

All Criteria Met?	N Total	N Paricalcitol	N Placebo
NO	12	6	6
YES	63	33	30

2001020

All Criteria Met?	N Total	N Paricalcitol	N Placebo
NO	9	4	5
YES	61	29	32

2001021

All Criteria Met?	N Total	N Paricalcitol	N Placebo
NO	13	7	6
YES	62	28	34

Finally, the data were evaluated for evidence of differential premature discontinuation from the study between treatment groups. Subjects randomized to the paricalcitol group did not prematurely discontinue from their respective study to a greater extent than those in the placebo group:

2001019

Premature discontinuation?	N Total	N Paricalcitol	N Placebo
NO	57	30	27
YES	18	9	9

p-value = 1.00 (Fisher's exact test)

2001020

Premature discontinuation?	N Total	N Paricalcitol	N Placebo
NO	60	27	33
YES	10	6	4

p-value = 0.50 (Fisher's exact test)

2001021

Premature discontinuation?	N Total	N Paricalcitol	N Placebo
NO	58	25	33
YES	17	10	7

p-value = 0.28 (Fisher's exact test)

4.6 Financial Disclosures

A Form 3454 was submitted by Laura Williams (Global Project Head, Renal) certifying that she did not enter into any financial agreement with any of the listed clinical investigators that could influence the outcome of the study.

A Form 3455 was submitted by Dr. Williams indicating that _____, an investigator on study _____ received unrestricted grant support (\$18,000), equipment (\$6000), compensation for consulting work, and honoraria for speaking engagements. The sponsor did state that Dr. _____ site conducted the study in accordance with the protocol, ICH, GCP guidelines, FDA regulations, and guidelines governing clinical study conduct, ethical principles having their origin in the Declaration of Helsinki (1989 revision) and all applicable local regulations. Dr. _____ did not randomize any subjects in study _____ therefore the outcome of the study was unaffected by his financial arrangements with Abbott.

5 CLINICAL PHARMACOLOGY

Please refer to Dr. Wei's review for a more detailed clinical pharmacology evaluation.

5.1 Pharmacokinetics

Absorption – The absolute bioavailability was not assessed in CKD Stage 3 and 4 subjects, but is expected to be between 72-86%, based on absolute bioavailability data for healthy and CKD Stage 5 subjects. Paricalcitol capsule can be administered without regard for food.

Distribution – The distribution phase after oral administration is not observed. Paricalcitol is extensively bound (> 99.9%) to plasma proteins in healthy and CKD Stage 3 and 4 subjects; gender did not have an effect on drug distribution.

Metabolism – There are two circulating metabolites in plasma in low concentrations: one that is non-polar that has not been identified, and the other – 24(R)-hydroxyparicalcitol – that has the lower concentration. According to the Sponsor, the 24(R)-hydroxyparicalcitol metabolite is less active than paricalcitol in an *in vivo* rat model of PTH suppression.

Elimination – Over the 336-hour sampling interval after oral administration of 0.48 mcg/kg [³H]paricalcitol, approximately 18% of total radioactivity was excreted in urine and 70% in feces. No parent drug was excreted in urine. About 2% of dose radioactivity was unchanged parent in feces; about 8 fecal metabolites were discerned, which represented about 40% of total fecal radioactivity.

Clearance – In healthy subjects, the mean apparent clearance calculated for single oral doses of 0.06, 0.12, 0.24, and 0.48 mcg/kg was 4.0, 3.6, 3.6, and 4.5 L/h, respectively. Clearance decreases with renal disease (there is some increased clearance with HD and PD). In pivotal studies (CKD Stage 3 and 4) there was an indication of hysteresis in iPTH and calcium dose response over time. No demographic covariate studied had a significant effect on iPTH dose response.

Bioavailability/Bioequivalence – Results of a pilot dose-strength-linking study showed that the 1 mcg SEC #3 formulation was not bioequivalent to the 2 or 4 mcg SEC #3 formulation when adjusted for dose; therefore, the 1 mcg formulation was reformulated and manufactured as a 1 mcg capsule SEC #2. The results of a bioequivalence study showed that the 1 mcg SEC #2 formulation was bioequivalent to the 2 and 4 mcg SEC #3 formulations when adjusted for dose. A pivotal bioequivalence study was conducted to link the clinical lot capsule used in the Phase 3 studies and the to-be-marketed lot capsule, which demonstrated the bioequivalence of the two lots using the 4 mcg SEC #3 formulation.

5.2 Pharmacodynamics

Pharmacodynamic drug effects are discussed in detail in the Integrated Summaries of Efficacy (changes in iPTH and markers of bone turnover) and Safety (changes in serum calcium, phosphorus, and Ca x P).

There were no QT studies done, however, given the mechanism of the drug and previous experience with vitamin D and other analogs, these studies are not required. This issue is elaborated further in Section 7.1.9.

5.3 Exposure-Response Relationships

Because dose was titrated to outcome, exposure-response was not explicitly studied. Dosing criteria were developed based on previous knowledge of vitamin D and its analogs: that is, increased dose leads to greater iPTH suppression and hypercalcemia.

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6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Zemplar® Capsules are indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 3 and 4.

6.1.1 Methods

The data used for this review of efficacy are from the three pivotal trials, Study 2001019, 2001020, and 2001021 (see Appendix for full review of each of the three studies). Data from the three studies were combined, analyzed by dosing regimen, and analyzed by subpopulation.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint was two consecutive $\geq 30\%$ decreases from baseline in iPTH. Secondary hyperparathyroidism (HPT) is a well-described and recognized phenomenon of progressive kidney disease ultimately resulting in renal osteodystrophy. Intact PTH is the generally accepted method of monitoring this disease and guidelines exist (the NKF K/DOQI taskforce) describing the treatment of secondary hyperparathyroidism with vitamin D and its analogs. The primary efficacy criterion has been selected in this drug development program for its acceptance as a clinically significant and meaningful treatment effect for the management of secondary HPT. The Zemplar Injection clinical studies similarly used a 30% reduction in iPTH as its primary efficacy outcome. According to the Sponsor, the two consecutive values represent a measurable change in iPTH that can be detected outside the range of assay variability.

The primary efficacy analysis was conducted in the Intent-to-Treat population, which included subjects who had been randomized and had a baseline and at least two on-treatment iPTH values. Secondary analyses attempt to address the inherent limitations of a responder analysis (e.g., an unanticipated result, such as an increase from baseline; or the variability of response) with absolute and mean percent changes in serum iPTH.

Secondary efficacy analyses with ANOVA, using treatment as the factor, included mean change and mean percent change of iPTH, mean values of iPTH over time, and change in bone biochemical markers. iPTH change was evaluated both using Final Visit and Last On-Treatment Visit to calculate change from baseline. The rationale of the Last On-Treatment Visit analysis is it is more suggestive of an actual treatment effect (it also captures those subjects who discontinued prematurely). ANCOVA was performed using baseline iPTH as a covariate. Analysis of this endpoint used the All-Treated population (all randomized subjects who had received at least one dose of drug). It should be noted that correlative data of serum bone markers with bone histology for Stages 3 and 4 of CKD are not available; therefore,

interpretation of these results is not definitive. Additionally, it is difficult to conclude that decreases in levels of bone markers in the setting of vitamin D therapy are purely favorable, since over-treatment can lead to adynamic bone disease. Therefore, the bone marker data should be interpreted with caution. As a final comment regarding this issue, it should be noted that all endpoints, including the primary endpoint, are “surrogates” and no conclusion should be drawn regarding this particular therapy on bone outcomes, per se. These limitations notwithstanding, the endpoints evaluated in the paricalcitol pivotal trials represent the standard measures used to support approval of prior therapies for secondary hyperparathyroidism, as stated above.

Finally, the dosing regimen can be considered a separate efficacy outcome, as both daily and three times per week schedules were evaluated. Data from published literature support a pulsed dosing regimen for efficacy and safety of vitamin D and its analogs. The sponsor sought to evaluate a QD regimen as a possible alternative, in particular to enhance compliance in this patient population. See Section 6.1.3, Study Design, for the results of compliance analyses. There is only one QD regimen pivotal study, whereas there are two TIW pivotal studies.

6.1.3 Study Design

Three Phase 3, prospective, randomized, placebo-controlled, double-blind, multi-center trials evaluated the safety and efficacy of paricalcitol capsule in reducing elevated serum iPTH levels (average of two values ≥ 150 pg/mL, all values must be ≥ 120 pg/mL) in CKD Stage 3 and 4 subjects; two (studies 2001019 and 2001020) dosed subjects TIW, one (study 2001021) dosed subjects QD.

Sample size was determined as follows: a Fisher’s exact test with a 0.05 2-sided significance level would have 90% power to reject the null hypothesis that the incidence rates of two consecutive $\geq 30\%$ decreases from baseline in iPTH between the two treatment groups were equal (assumed success rate in placebo was 20% and success rate in Zemplar group was 60%). This resulted in a target sample size of 34 subjects in each treatment group.

Comment: This calculation did not take potential drop-outs into account.

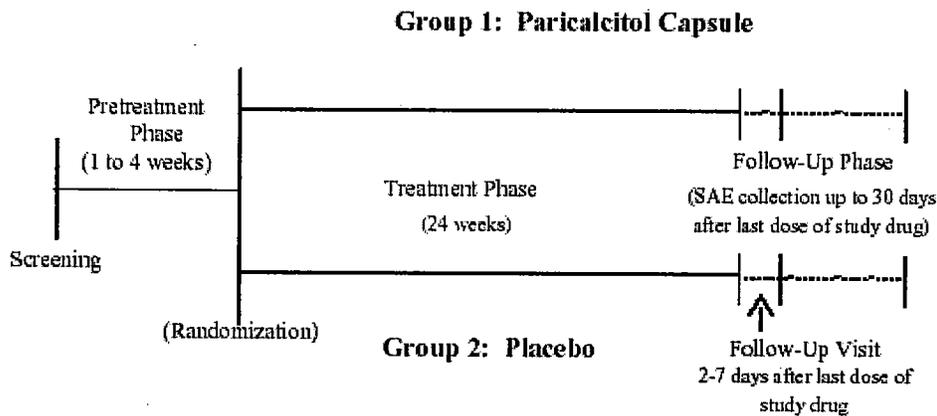
Placebo and study drug were administered in a double-blind, parallel-group design. Although two of the pivotal studies used a TIW dosing regimen and one provided drug daily, these regimens were not compared head-to-head in a single study.

To enter the Pre-Treatment Phase, subjects must not have been on pharmacological vitamin D therapy for at least four weeks, must have had an iPTH value ≥ 120 pg/mL, and must have had an eGFR 15 to 60 mL/min.

Comment: The inclusion iPTH value is higher than that recommended for starting treatment by the K/DOQI (CKD Stage 3, iPTH > 70; CKD Stage 4, iPTH > 110), which is a more conservative approach.

Comment: Baseline 25-OH vitamin D levels are not provided (nor were they measured); this is potentially important given low 25-OH vitamin D can increase iPTH. According to the Sponsor (based on an ongoing community-based non-interventional observational study), only 31-46% of individuals with a GFR 20-59 have adequate levels of serum 25-OH vitamin D₃, with greater levels of insufficiency seen as the GFR decreases. Therefore, patients with secondary HPT who are candidates for vitamin D or an analog should have 25-OH vitamin D levels checked prior to starting an active vitamin D metabolite. No comments regarding safety or efficacy dependent upon baseline 25-OH vitamin D status can be made.

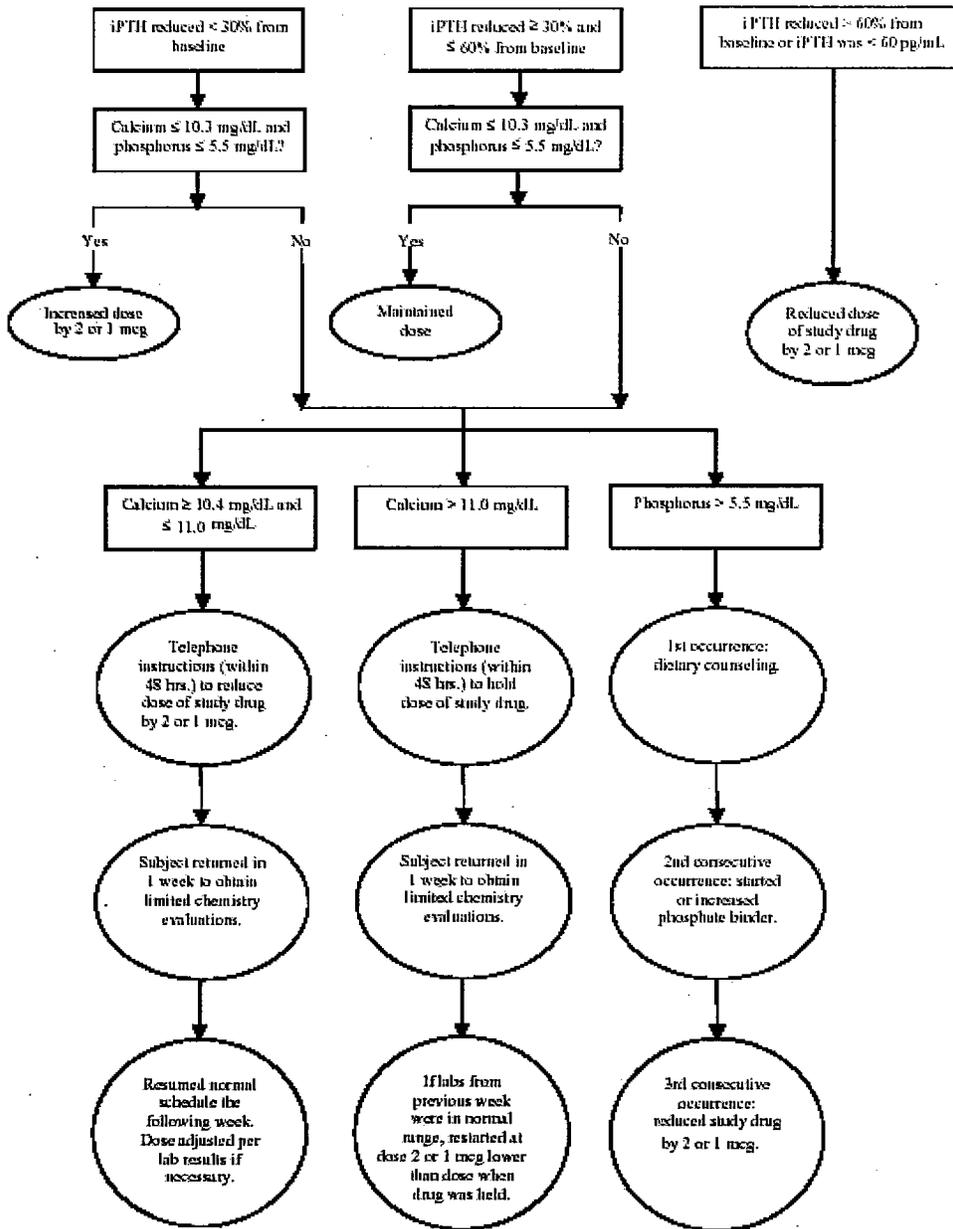
The duration of the Treatment Phase was 24 weeks; the following is the Study Design schematic:



Initial dosing was based on baseline iPTH value:

Paricalcitol Capsule Initial Dose		
	Baseline iPTH Level	Initial Dose
Study 2001019 and Study 2001020		
	≤ 500 pg/mL	2 mcg
	> 500 pg/mL	4 mcg
Study 2001021		
	≤ 500 pg/mL	1 mcg
	> 500 pg/mL	2 mcg

Dose titration (2 mcg in Study 2001019 and Study 2001020 and 1 mcg in Study 2001021) was determined based on iPTH, serum calcium, and serum phosphorus. Dose decreases could have occurred weekly and dose increases could have occurred no more frequently than every four weeks beginning with Week 5. The dosing algorithm is described in the following schematic:



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Comment: The dosing algorithm did not allow for the temporary discontinuation of the study drug due to inappropriately low iPTH levels (it only allowed for a dose decrease). It is not known at what iPTH level an individual with CKD Stage 3 or 4 is at increased risk for adynamic bone disease; however, the K/DOQI guidelines recommend a target iPTH 35-70 pg/mL for CKD Stage 3 and 70-110 pg/mL for CKD Stage 4.

Comment: Because investigators were adjusting drug based on the outcome (iPTH values), the possibility of investigator “unblinding” was considered. Investigators conceivably would have been able to determine whether a subject was on drug or placebo based on iPTH lowering. However, there is no obvious evidence that this altered treatment decisions, given that: 1) the placebo group did not have more subjects prematurely withdrawn (see Subject Disposition below), and 2) protocol violations were generally balanced between groups.

Baseline Demographic Characteristics

No statistically significant differences in baseline demographic characteristics existed between the two groups in the three studies combined. The only baseline characteristic difference noted in the individual pivotal trials is discussed in the Review of Study 2001020 (see Appendix 10.1): the number of years since CKD was diagnosed was greater in the placebo group than the paricalcitol group.

Demographics in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (All Treated Subjects)				
	Paricalcitol Capsule	Placebo	Total	
	(N = 107)	(N = 113)	(N = 220)	p-value^a
Gender				0.886
Female	34 (32%)	37 (33%)	71 (32%)	
Male	73 (68%)	76 (67%)	149 (68%)	
Race				0.242
Black	28 (26%)	29 (26%)	57 (26%)	
Other	5 (5%)	1 (1%)	6 (3%)	
White	74 (69%)	83 (73%)	157 (71%)	
Tobacco Use				0.583
Nonsmoker	41 (38%)	48 (42%)	89 (40%)	
Smoker (includes ex-smokers)	66 (62%)	65 (58%)	131 (60%)	
Alcohol Use				1.000
Nondrinker	39 (36%)	42 (37%)	81 (37%)	
Drinker (includes ex-drinkers)	68 (64%)	71 (63%)	139 (63%)	
Age (years)				0.313
Mean (SE)	63.6 (1.27)	61.8 (1.16)	62.7 (0.86)	
Median	66.0	63.0	64.0	
Range	22 - 91	32 - 93	22 - 93	

Demographics in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (All Treated Subjects)				
	Paricalcitol Capsule	Placebo	Total	p-value^a
	(N = 107)	(N = 113)	(N = 220)	
Age Group				
< 65	51 (48%)	62 (55%)	113 (51%)	0.345
≥ 65	56 (52%)	51 (45%)	107 (49%)	
< 75	85 (79%)	97 (86%)	182 (83%)	0.218
≥ 75	22 (21%)	16 (14%)	38 (17%)	
Time Since CKD Diagnosis (years)				
	(N=106)	(N=112)	(N=218)	0.452
Mean (SE)	5.37 (0.631)	6.09 (0.709)	5.74 (0.476)	
Median	3.50	3.65	3.60	
Range	0.2 – 51.4	0.2 – 38.7	0.2 – 51.4	
Baseline Phosphate Binder Usage				
				0.859
Calcium-Based Phosphate Binders/ Calcium Supplement	22 (21%)	27 (24%)	49 (22%)	
Non-Calcium-Based Phosphate Binders	2 (2%)	2 (2%)	4 (2%)	
None	83 (78%)	84 (74%)	167 (76%)	
Baseline eGFR (mL/min/1.73m²)				
				0.956
Mean (SE)	23.09 (0.783)	23.03 (0.733)	23.06 (0.534)	
Median	20.90	20.40	20.65	
Range	10.0 – 55.1	13.0 – 49.0	10.0 – 55.1	
Diabetic Status at Baseline				
				0.785
Diabetic	64 (60%)	65 (58%)	129 (59%)	
Non-Diabetic	43 (40%)	48 (43%)	91 (41%)	
Baseline Body Weight (kg)				
	(N=107)	(N=112)	(N=219)	0.380
Mean (SE)	92.68 (2.108)	89.91 (2.332)	91.26 (1.575)	
Median	91.17	85.28	88.91	
Range	44.5 – 152.0	40.8 – 172.4	40.8 – 172.4	

CKD = chronic kidney disease

a. p-values for race, gender, tobacco use, alcohol use, diabetic status at baseline, phosphate binder use at baseline, and age group are derived from Fisher's exact test. p-values for mean age, time since first CKD diagnosis, baseline eGFR, and baseline weight are from F-test testing equality of means between treatment groups.

Exposure to Study Drug

Because doses for placebo were to be increased in the same algorithm as treatment drug, paricalcitol would, on average, be expected to have lower doses than placebo if paricalcitol was

more effective in lowering iPTH. This is corroborated in the tables below, although a p-value for between group differences is not provided.

Exposure to Study Drug – Range (Reviewer-generated table)

Study Drug Administration Over a Two-Week Duration in the Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies (All Treated Subjects)		
Treatment Group	Two-week minimum prescribed dose, mcg	Two-week maximum prescribed dose, mcg
Paricalcitol	1	89
Placebo	2	150

Exposure to Study Drug – TIW Dosing

Study Drug Administration in the Double-Blind, Placebo-Controlled, Pivotal Phase 3 Study 2001019 and Study 2001020 - TIW Treatment Regimen (All Treated Subjects)		
	Paricalcitol Capsule (N = 72)	Placebo (N = 73)
Overall Average Weekly Dose (mcg/week)		
Mean (SD)	9.5 (3.60)	17.3 (5.32)
Median	8.9	18.4
Range of Overall Average Weekly Dose	2.0 - 21.0	2.0 - 27.6
Days from First Dose to Last Dose of Study Drug		
Mean (SD)	147.8 (42.65)	152.0 (40.65)
Median	166	167
Range	1 - 178	1 - 183

Exposure to Study Drug – QD Dosing

Study Drug Administration in the Double-Blind, Placebo-Controlled, Phase 3 Study 2001021 - QD Treatment Regimen (All Treated Subjects)		
	Paricalcitol Capsule (N = 35)	Placebo (N = 40)
Overall Average Weekly Dose (mcg/week)		
Mean (SD)	9.6 (4.30)	19.0 (5.97)
Median	9.3	21.2
Range of Overall Average Weekly Dose	3.1 - 22.3	4.0 - 24.9
Days from First Dose to Last Dose of Study Drug		
Mean (SD)	146.1 (41.71)	148.4 (47.20)
Median	167	168
Range	19 - 178	4 - 176

Comment: The mean average weekly dose and days from first dose to last dose of study drug is essentially equivalent between the TIW and QD dosing regimens in the paricalcitol capsule group.

The databased compliance measure was whether or not the subject was at least 60% compliant with the study drug. Using this dichotomous variable as the outcome variable and QD versus TIW dosing as the grouping variable, subjects on the QD regimen were not more compliant than those on the TIW regimen. This was also true when analyzing for those randomized to paricalcitol only.

60% Compliance, All Subjects

At least 60% Compliant?	NO	YES	TOTAL
TIW regimen	13 (8.3%)	144 (91.7%)	157
QD regimen	9 (10.7%)	75 (89.3%)	84

p = 0.64

60% Compliance, Paricalcitol-Treated Subjects Only

At least 60% Compliant?	NO	YES	TOTAL
TIW regimen	8 (10.0%)	72 (90.0%)	80
QD regimen	4 (10.3%)	35 (89.7%)	39

P = 1.00

Subject Disposition

Two hundred twenty (220) subjects were randomized in all three studies, and all 220 subjects received at least one dose of study drug; 107 received paricalcitol capsule and 113 received placebo. Of the 107 subjects randomized into the study and treated with paricalcitol, 82 (77%) completed 24 weeks of treatment, and 25 (23%) terminated prematurely from the study. Of the 113 subjects randomized into a placebo group, 93 (82%) completed 24 weeks of treatment, and 20 (18%) were terminated prematurely. The following table describes the numbers of subjects included in each of the various efficacy evaluations.

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Numbers of Subjects Included in the Efficacy Evaluations of iPTH in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined		
Analysis	Paricalcitol Capsule	Placebo
All Randomized and Treated	107	113
Primary Analysis of Efficacy (Intent-to-Treat Population) ^a	101	108
Secondary Efficacy Analyses (All Treated Subject Population)		
iPTH	Final Visit ^b	105
	Last On-Treatment Visit ^c	104
		111
		110

a. Six (6) paricalcitol capsule subjects and 5 placebo subjects were excluded from the Intent-to-Treat population because they did not have at least 2 on-treatment values of iPTH.

b. Two (2) paricalcitol capsule subjects and 2 placebo subjects were excluded from the change from baseline to the Final Visit analysis of iPTH because they had no iPTH values following their first dose of study drug.

c. Three (3) paricalcitol capsule subjects and 3 placebo subjects were excluded from the change from baseline to the Last On-Treatment Visit analysis of iPTH because they did not have any iPTH values following their first dose of study drug or obtained while on treatment.

6.1.4 Efficacy Findings

Primary Efficacy Outcome

In the primary efficacy analysis, the paricalcitol group had a significantly greater number of subjects achieving two consecutive $\geq 30\%$ decreases from baseline in iPTH compared with placebo, as shown in the following table.

Percent of Patients with 2 Consecutive $\geq 30\%$ decreases from baseline in iPTH Studies 2001019, 2001020, and 2001021			
	Zemplar (N = 101) Count (%)	Placebo (N = 108) Count (%)	p-value*
Yes	92 (91.1)	14 (13.0)	<0.001
No	9 (8.9)	94 (87.0)	

* p-value derived from Fisher's exact test

Further analysis demonstrated that 28%, 68%, and 77% of paricalcitol-treated subjects achieved the first of two consecutive $\geq 30\%$ decreases from baseline in iPTH by Weeks 5, 9, and 11, respectively, and that 69% of paricalcitol capsule-treated subjects maintained $\geq 30\%$ decreases in iPTH for at least 10 weeks. Analyses were significant at $p < 0.001$.

In order to account for drop-out bias, an analysis was performed to assume drop-outs (i.e., those not included in ITT analysis) either failed to meet (paricalcitol) or achieved (placebo) endpoint (i.e., a "worst-case scenario"). As noted in Section 4.5, subjects randomized to the paricalcitol group did not prematurely discontinue from their respective study to a greater extent than those in the placebo group. The following table describes the result of the worst-case scenario analysis:

Proportion of Subjects Who Achieved 2 Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Treatment Group in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (All Treated Subjects)			
	Paricalcitol Capsule (N = 107)	Placebo (N = 113)	p-value^a
Subject achieved 2 consecutive $\geq 30\%$ decreases from baseline in iPTH	92 (86%)	19 (17%)	< 0.001

a. p-value derived from Fisher's exact test.

The QD and TIW treatment regimens were very similar in their potential to lower serum iPTH levels: 91% of the paricalcitol-treated subjects dosed QD or TIW achieved the primary efficacy endpoint; whereas 11% of the placebo subjects dosed QD and 14% dosed TIW achieved the primary endpoint.

Proportion of Subjects Who Achieved 2 Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Treatment Regimen (TIW and QD) in the Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies (Intent-to-Treat Population)							
	TIW Treatment Regimen (N = 138)			QD Treatment Regimen (N = 71)			Homogeneity p-value^b
	Paricalcitol Capsule (N = 68)	Placebo (N = 70)	p-value^a	Paricalcitol Capsule (N = 33)	Placebo (N = 38)	p-value^a	
2 consecutive $\geq 30\%$ decreases from Baseline in iPTH	62 (91%)	10 (14%)	< 0.001	30 (91%)	4 (11%)	< 0.001	0.745

a. p-value derived from a Fisher's exact test.

b. p-value for the Breslow-Day test of odds ratio homogeneity.

Subgroup Analyses

Results of the primary efficacy endpoints in the three studies combined were analyzed for subpopulations of the following baseline and demographic characteristics: gender, age, race, years since CKD diagnosis at baseline, disease severity at baseline, diabetic status at baseline, with and without the concomitant use of phosphate binders, baseline body weight, geographic region, alcohol use, and tobacco use. In general, the proportion of paricalcitol-treated subjects vs. the proportion of placebo-treated subjects who achieved two consecutive $\geq 30\%$ reductions from baseline in iPTH was similar across the various subgroups of patients. In addition, high-ceiling diuretic use did not appear to affect efficacy. Due to very small sample sizes, however, little can be said regarding the relative efficacy of paricalcitol in non-Black, non-Caucasian races and in patients who weigh less than 50 kg.

Secondary Efficacy Outcomes

In an ancillary analysis evaluating for robustness of response, as shown below, nearly 75% of the paricalcitol-treated patients and none of the placebo subjects achieved four consecutive $\geq 30\%$ decreases from baseline in iPTH.

Proportion of Subjects Who Achieved 4 Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Treatment Group in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)			
	Paricalcitol Capsule (N = 101)	Placebo (N = 108)	p-value^a
Subject achieved 4 consecutive $\geq 30\%$ decreases from baseline in iPTH	75 (74%)	0 (0%)	< 0.001

a. p-value derived from Fisher's exact test.

This Reviewer also performed an analysis between Zemplar and placebo subjects who achieved at least one $\geq 30\%$ decrease in iPTH. The following table demonstrates that patients taking Zemplar demonstrate a statistically significant difference in iPTH reduction in comparison to placebo subjects.

Proportion of Subjects Who Achieved One $\geq 30\%$ Decrease from Baseline in iPTH by Treatment Group in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (All-Treated Population)			
	Paricalcitol Capsule (N = 105)	Placebo (N = 111)	p-value^a
Subject achieved one $\geq 30\%$ decrease from baseline in iPTH	97 (92%)	51 (46%)	< 0.001

a. p-value derived from Fisher's exact test.

This Reviewer also performed exploratory analyses using the K/DOQI guidelines for goal iPTH values. As noted previously, the guidelines recommend that patients with CKD Stage 3 (eGFR 30-60 mls/min/1.73 m²) target iPTH in the range of 35-70 pg/mL, and those with CKD Stage 4 (eGFR 15-30 mls/min/1.73 m²) target iPTH 70-110 pg/mL. The following analyses describe the differences between treatment groups for those that achieved iPTH at least once and those that achieved target at last On-Treatment Visit.

Proportion of Subjects Who Achieved One iPTH Within Target by Treatment Group in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (CKD Stages 3 and 4 Only)			
	Paricalcitol Capsule (N = 105)	Placebo (N = 111)	p-value^a
Subject achieved one iPTH within target	20 (24%)	3 (3%)	< 0.001

a. p-value derived from Fisher's exact test.

Proportion of Subjects Who Achieved iPTH Within Target At Last On-Treatment Visit by Treatment Group in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (CKD Stages 3 and 4 Only)			
	Paricalcitol Capsule (N = 105)	Placebo (N = 111)	p-value^a
Subject achieved iPTH within target at last on-treatment visit	20 (19%)	3 (3%)	< 0.001

a. p-value derived from Fisher's exact test.

Comment: This Reviewer acknowledges that the pivotal studies were not designed to test the above outcome; however, even with fewer subjects achieving “target” values than the primary efficacy outcome, the result is still strongly statistically significant. Therefore, on balance, the multiple statistically significant responder analyses support the claim of drug efficacy.

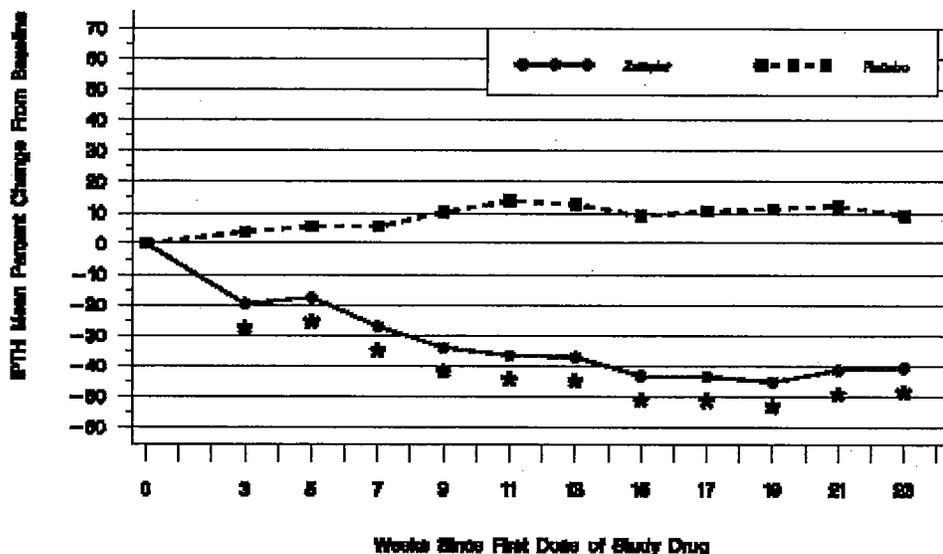
Further secondary analyses evaluated change in iPTH over time. There was a statistically significant difference between the paricalcitol and placebo treatment groups in mean absolute and percent changes from baseline to endpoint in iPTH levels.

Mean Change and Percent Change from Baseline to the Final Visit in iPTH in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (All Treated Subjects)						
Treatment group	N	Baseline mean	Final Visit mean	% change mean	% change SE	ANOVA p-value
Zemplar	105	265.3	203.9	-21.4	3.42	<0.001
Placebo	111	279.7	318.5	15.2	3.33	

Results were similar when the changes in iPTH levels from baseline to Final Visit were adjusted for baseline iPTH level.

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Mean Percent Change From Baseline in iPTH Over Time During Treatment Phase in the 3 Double - Blind, Placebo - Controlled, Pivotal Phase 3 Studies Combined



Week	0	3	5	7	9	11	13	15	17	19	21	23
Paricalcitol Capsule N	107	102	103	99	98	92	96	93	90	86	87	80
Placebo N	113	106	108	104	98	104	99	100	93	94	93	93

* Statistically significant ($p \leq 0.05$) difference in mean percent change from baseline between the paricalcitol capsule and placebo treatment groups. At each visit, percent change from baseline is calculated for subjects who had data at that visit.

This Reviewer's analysis of mean percent change from baseline in iPTH over time using the Last On-Treatment analysis (All-Treated subjects) produced similar results.

Biochemical Markers of Bone Turnover

Statistically significant differences were observed between the paricalcitol capsule and placebo treatment groups in mean change from baseline to Week 11 and Final Visit in the biochemical bone activity marker of bone-specific alkaline phosphatase using ANOVA with treatment as the factor. Additionally, urinary deoxypyridinoline was significantly different between treatments at Week 11, and serum osteocalcin and urinary pyridinoline were significantly different between treatments at Final Visit. Results were similar using ANCOVA with treatment as the factor and baseline value as the covariate.

Comment: Biochemical markers, while suggesting an improvement in bone turnover in the Zemplar-treated subjects versus the placebo-treated subjects, do not have proven equivalence to histological data. In addition, the relevance of bone marker data in subjects with renal impairment (in particular, urinary markers) is not clear.

Mean Change from Baseline to Week 11 and Final Visit in Biochemical Bone Activity Marker Variables in the Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (All Treated Subjects)			
	Paricalcitol Capsule	Placebo	ANOVA p-value^a
Serum Bone-Specific Alkaline Phosphatase (mcg/L)			
Number of Subjects	86	95	
Mean Baseline Value	16.669	18.499	
Mean Change from Baseline to Week 11 (SE)	-5.024 (0.6279)	-1.749 (0.5974)	< 0.001
Number of Subjects	101	107	
Mean Baseline Value	17.090	18.843	
Mean Change from Baseline to Final (SE)	-7.890 (0.7596)	-1.444 (0.7380)	< 0.001
Serum Osteocalcin (ng/mL)			
Number of Subjects	87	93	
Mean Baseline Value	62.47	69.63	
Mean Change from Baseline to Week 11 (SE)	-3.94 (2.431)	1.30 (2.351)	0.123
Number of Subjects	100	104	
Mean Baseline Value	62.70	70.92	
Mean Change from Baseline to Final (SE)	-21.64 (2.706)	10.74 (2.654)	< 0.001
Urinary Deoxypyridinoline (nmol/mg Creat)			
Number of Subjects	86	88	
Mean Baseline Value	0.0665	0.0560	
Mean Change from Baseline to Week 11 (SE)	-0.0155 (0.00433)	0.0024 (0.00429)	0.004
Number of Subjects	96	100	
Mean Baseline Value	0.0644	0.0542	
Mean Change from Baseline to Final (SE)	-0.0058 (0.00514)	0.0033 (0.00504)	0.208
Urinary Pyridinoline (nmol/mmol Creat)			
Number of Subjects	87	93	
Mean Baseline Value	37.94	34.45	
Mean Change from Baseline to Week 11 (SE)	-5.21 (1.938)	-1.80 (1.875)	0.207
Number of Subjects	99	104	
Mean Baseline Value	37.95	33.78	
Mean Change from Baseline to Final (SE)	-3.61 (1.896)	3.77 (1.850)	0.006

a. One-way ANOVA with treatment as the factor.

6.1.5 Clinical Microbiology

Not applicable (the compound is not an antimicrobial nor an injectable drug).

6.1.6 Efficacy Conclusions

Three double-blind, placebo-controlled, multi-center studies were performed to support the efficacy of paricalcitol capsule to treat secondary hyperparathyroidism in patients with CKD

Stages 3 and 4. Two of the studies (2001019 and 2001020) were conducted under identical protocols utilizing a TIW dosing regimen; the third (2001021) was conducted using a QD dosing regimen. The studies were 24 weeks in duration, with doses titrated by iPTH levels, in addition to serum calcium and phosphorus levels. Primary efficacy was defined as two consecutive $\geq 30\%$ decreases from baseline in the level of iPTH. This analysis was performed combined as well as stratified by treatment regimen, gender, age, race, baseline body weight, geographic region, history of alcohol abuse, history of tobacco use, years since CKD diagnosis, baseline disease severity, baseline diabetic status, concomitant phosphate binder use, and concomitant high-ceiling diuretic use. Additional efficacy analyses included: 1) one and four consecutive $\geq 30\%$ decreases in iPTH from baseline, 2) achievement of target iPTH, 3) change and percent change from baseline analyses in iPTH using Final Visit and Last On-Treatment analyses, and 4) change from baseline of biochemical bone activity markers to Week 11 and Final Visit.

Sponsor's efficacy conclusions:

1. Paricalcitol capsule provides a rapid and sustained reduction of intact parathyroid hormone (iPTH) throughout the Treatment Phase.
 - a. In these pivotal Phase 3 studies, 91% of paricalcitol capsule-treated subjects vs. 13% of placebo subjects achieved the primary endpoint of 2 consecutive $\geq 30\%$ decreases from baseline in iPTH ($p < 0.001$). In addition, 74% of paricalcitol capsule-treated subjects vs. 0% of placebo subjects achieved 4 consecutive $\geq 30\%$ decreases from baseline in iPTH demonstrating the robustness of response.
 - b. Kaplan-Meier estimates demonstrated that 28%, 68%, and 77% of paricalcitol capsule-treated subjects achieved the first of 2 consecutive $\geq 30\%$ decreases from baseline in iPTH by Weeks 5 (Day 35), 9 (Day 63), and 11 (Day 77), respectively. Also, Kaplan-Meier estimates demonstrated that 69% of paricalcitol capsule-treated subjects maintained $\geq 30\%$ decreases in iPTH for at least 10 weeks (70 days).
2. Paricalcitol capsule has a similar efficacy profile with either a daily (QD) or three times a week (TIW) dosing regimen and the effectiveness is consistent across all subpopulations studied.
 - a. The results of these trials indicate that paricalcitol capsule, dosed as either a TIW or QD regimen, has a similar efficacy profile. In both treatment regimens, 91% of paricalcitol capsule-treated subjects achieved 2 consecutive $\geq 30\%$ decreases from baseline in iPTH. A 30% mean reduction of iPTH occurred by Week 7 with the QD regimen and by Week 9 with the TIW regimen. These reductions were sustained throughout the remainder of the Treatment Phase.
 - b. The effectiveness of paricalcitol capsule was demonstrated to be consistent across subpopulations of age, gender, race, baseline body weight, geographic region, alcohol use, tobacco use, years since CKD at diagnosis at baseline. The treatment effect is consistent regardless of disease severity and diabetic status at baseline. Also, concomitant use of calcium-based phosphate binders, or lack thereof, did not impact the efficacy of paricalcitol capsule.

3. Paricalcitol capsule decreases serum bone-specific alkaline phosphatase and osteocalcin levels,
 - a. Paricalcitol capsule treatment resulted in statistically significant mean decreases in serum bone-specific alkaline phosphatase and osteocalcin compared with placebo.

Medical Officer's conclusions:

Paricalcitol capsule has been shown to be effective when compared with placebo in the primary efficacy analysis of two consecutive $\geq 30\%$ decreases in iPTH from baseline. This definition of efficacy was agreed upon by the Division in the End-of-Phase 2 meeting that the clinical studies support the proposed indication. This endpoint does not capture a potential two-sided result, that is, an increase of iPTH from baseline; nor does it capture the variability of response. Secondary analyses have attempted to address these limitations with absolute and percent change of iPTH from baseline. An additional limitation of the primary endpoint evaluation is the requirement for including only those subjects with two consecutive iPTH on-treatment values ("Intent-to-Treat"); this analysis eliminated those subjects that did not meet that criterion, introducing a possible source of bias. This limitation has been addressed with the use of an All-Treated subject population in a separate "worst-case scenario" analysis. Finally, the concern that efficacy definitions have changed since the publication of the K/DOQI guidelines was addressed with exploratory analyses of target iPTH achievement by CKD stage. All the efficacy analyses were strongly statistically significant.

Dosing was determined by iPTH, calcium, and phosphorus levels, and based upon dosing schedule (QD vs. TIW). A limitation for dosing determinations is that there was only one trial evaluating efficacy of the QD dosing regimen. However, given similar (and strong) results among the three studies, efficacy may be extrapolated to this regimen. The dosing algorithm differs somewhat from that recommended by the National Kidney Foundation K/DOQI guidelines for treatment of secondary HPT in CKD Stage 3 and 4 with vitamin D sterols in that inclusion into the study was based on a higher iPTH than is currently recommended for this patient population (CKD Stage 3, > 70 ; Stage 4, > 110). As the pivotal clinical trials used a more conservative approach, labeling should reflect what was used in the studies. The Sponsor may wish to expand inclusion criteria for broader usage in future studies. Separate dosing algorithms were not performed for the two stages of CKD.

_____ should be adequately addressed in label.

Although the case can be made for efficacy of paricalcitol in decreasing biochemical markers of bone turnover, no conclusion can be drawn about their relationship to bone changes without bone histology or fracture data.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The following parameters were used to evaluate the overall safety of paricalcitol capsule:

1. Adverse events profile
 - a. deaths and serious adverse events
 - b. adverse events leading to premature discontinuation
 - c. common adverse events
 - d. adverse events deemed to occur to a greater extent in paricalcitol group versus placebo
 - e. events that are presumed likely due to paricalcitol or its pharmacologic action

Adverse events in this clinical development program were coded using the COSTART system. It is noted that MEDRA was used for coding of adverse events in the Zemplar Injection post-marketing surveillance program. All post-marketing adverse events are listed in Appendix F.

Comment: In the midst of this clinical review, the Sponsor made some modifications to adverse event coding following an inquiry by this Reviewer. Although updated case report tabulations were not provided, it is not expected that the Sponsor's changes would substantively impact the Reviewer's own analyses or overall safety review. Changes provided by the Sponsor are outlined in the appropriate sections below.

2. Primary safety endpoint "clinically meaningful hypercalcemia"
 - a. two consecutive serum calcium levels > 10.5 mg/dL
3. Laboratory parameter evaluation
 - a. calcium
 - b. phosphorus
 - c. calcium/phosphorus product (Ca x P)
 - d. lowest iPTH achieved
 - e. estimated glomerular filtration rate (eGFR)
 - f. creatinine
 - g. urinary variables: calcium, phosphorus, calcium-to-creatinine ratio, hemoglobin, protein

7.1.1 Deaths

Clinical pharmacology studies:

No subjects died during or within 30 days of participating in any of the studies.

Pivotal Phase 3 CKD Stage 3 and 4 studies:

There were three deaths, two paricalcitol-treated subjects and one placebo-treated subject, one subject from each study.

Study 2001019 – Paricalcitol Subject 507, a 71-year old black male was hospitalized on Day 151 with chest pain that started on Day 150 and swollen side of face; the subject died on Day 155. The subject's cause of death was cardiopulmonary arrest due to probable MI, and CRFs indicate that the subject had not been feeling well for several months prior to the incident, with malaise, poor eating, weight loss, difficulty walking, facial edema, navel infection, and depression. The death occurred 14 days after the last documented dose of the study drug. The subjects' maximum serum calcium was 9.6 mg/dL and maximum Ca x P was 59.52 mg²/dL² as provided in the case report tabulations. These values were noted on Week 5 of the study.

Study 2001020 – Placebo Subject 1406, a 67-year old white male was discovered dead at his home on Day 177 (posttreatment Day 10). The subject's cause of death was cardiac arrest.

Study 2001021 – Paricalcitol Subject 401, a 74-year old white male, died on treatment Day 77 (posttreatment Day 6) due to hepatic encephalopathy. The subject was admitted to the study despite the protocol violation of chronic liver disease. He had a GI bleed due to a Mallory-Weiss tear on treatment Day 67, which likely precipitated the encephalopathy.

Phase 3 CKD Stage 5 studies (not the subject of this NDA):

Study 2001013 – Placebo Subject 305, a 71 year old Asian male on hemodialysis, died on treatment Day 80 during hospitalization for *Staphylococcus aureus* septicemia.

Study 2001014 – Zemplar Subject 108, a 67 year old black female on hemodialysis was found unresponsive in her home on treatment Day 30 and died the next day reportedly due to electromechanical dissociation. At the time of the event, the patient was receiving 10 mcg of study drug. Upon review of her laboratory values, six days prior to the death, her normalized serum calcium was 10.1 mg/dL, CaxP was 45.5 mg²/dL², phosphorus was 4.5 mg/dL, iPTH was — mg/dL, and PTH percent change from baseline was -50.23%. Of note, two days prior to her death, a protocol violation was reported that the subject's dose was increased to 10 mcg when she was supposed to have been maintained on 8 mcg according to the algorithm.

Study 2001015 – There were no deaths reported.

7.1.2 Other Serious Adverse Events

If an adverse event met any of the following criteria, it was to be reported to the Sponsor as a serious adverse event (SAE): death, life-threatening, hospitalization, prolongation of

hospitalization, congenital anomaly, persistent or significant disability/incapacity, important medical event requiring medical or surgical intervention to prevent serious outcome, spontaneous abortion, or elective abortion.

Phase 1 Clinical Pharmacology Studies

In the Phase 1 clinical pharmacology studies, the SAEs only occurred in CKD Stage 5 subjects and none were considered by the investigator to be related to study drug (although one was noted to be “probably not related”). Four of 337 (1%) subjects reported an SAE, with events classified as serious due to subject hospitalization. Serious adverse events included nausea, vomiting, abdominal pain, chest pain, dehydration, bacteremia, worsening CAD, and diarrhea.

Phase 3 CKD Stage 3 and 4 Studies (Pivotal Trials)

In the Phase 3 CKD Stage 3 and 4 studies, 22 (21%) of the 107 paricalcitol capsule-treated subjects (see Appendix E) and 19 (17%) of the 113 placebo-treated subjects reported a serious adverse event (including the three deaths). The following are the most common serious adverse events in the paricalcitol capsule-treated group, as calculated by this Reviewer:

COSTART V term	Organ System	N, Total	N, Paricalcitol	N, Placebo
Uremia	Metabolic and nutritional disorders	11	8	3
Accidental injury	Body as a whole	3	3	0
Chest pain	Body as a whole	3	2	1
Hypertension	Cardiovascular system	2	2	0
Myocardial infarct	Cardiovascular system	2	2	0

The one SAE that was considered to be related to the study drug (“possibly related”) was for paricalcitol subject (502) in Study 2001019 with elevated liver enzymes. The alternate explanation for this event was passive liver congestion due to bradycardia from cardiac medications. The narrative for this patient is as follows:

Paricalcitol subject 502 (study 2001019) is a 56 year-old black male with a past medical history significant for hypertension, diabetes, chronic kidney disease; and cerebrovascular accident. The subject was initially admitted to the hospital on treatment Day 38 for increased blood pressure, headaches, nausea, and vomiting. He received 12 mcg of Zemplar between Days 36 and 50. The patient developed deterioration of his renal function after aggressive antihypertensive treatment from a baseline serum creatinine of 3.0, to a level of 6.5 in 2 days. The subject was discharged on treatment Day 41 with a slight improvement of serum creatinine to 6.1. The subject presented to the emergency room with bradycardia (heart rate in the 40s) on treatment Day 84. He received 24 mcg Zemplar between Days 78 and 84. Diltiazem, metoprolol, and clonidine were held with improvement of bradycardia, but he experienced an episode of

tachycardia (heart rate up to 170) and increased blood pressure. He was restarted on a low dose beta blocker. During this hospitalization, the subject developed nausea, hyperkalemia, elevated WBC count (17,300), anasarca, and elevated liver enzymes (AST 425 U/L, ALT 470 U/L, alkaline phosphatase 170 U/L, and GGTP 256 U/L). He was diagnosed with pneumonia and heart failure. It was thought that the elevated liver enzymes may have been due to heart failure with passive liver congestion. The subject was treated with Levofloxacin and intravenous diuretics. The subject had an unrevealing abdominal ultrasound, normal liver profile, and was ruled out for myocardial infarction. The study drug, in addition to his lipid-lowering agent, simvastatin, was held. His liver enzymes on Day 86 were AST 57 U/L, ALT 227 U/L, alkaline phosphatase 118 U/L, and GGTP 169 U/L. His serum calcium throughout the hospitalization was 8.0-8.3 mg/dL. The nausea, hyperkalemia, pneumonia, anasarca, and passive congestion secondary to heart failure were resolved on Day 90. The subject was discontinued from the study. Of note, the subject was hospitalized 5 days later (13 days after his last dose of study drug) with uremia, and hemodialysis was initiated.

Comment: Given the multiple medical issues during the second hospitalization, it is virtually impossible to pinpoint an exact etiology of the elevated enzymes. However, it is likely that at least some of the reason for the elevation can be attributed to congestive heart failure. In addition, the subject was taking a statin concomitantly, so while a drug-related etiology cannot be ruled out, it is not possible from the data presented to determine which drug contributed in this case. A rechallenge was not attempted, although liver enzymes were improving. According to the case report tabulations, on the Final Visit (after this event had occurred), AST was 14 IU/L and ALT was 30 IU/L.

Phase 3 CKD Stage 5 Studies

In the Phase 3 CKD Stage 5 studies, 33 (30%) of the 109 paricalcitol capsule-treated subjects and 24 (21%) of the 115 placebo-treated subjects reported a serious adverse event. The following are the most common serious adverse events in the paricalcitol capsule-treated group, as calculated by this Reviewer:

COSTART V term	Organ System	N, Total	N, Paricalcitol	N, Placebo
Kidney failure	Urogenital system	5	4	1
Hypotension	Cardiovascular system	3	3	0
Cerebrovascular accident	Cardiovascular system	2	2	0
Chest pain	Body as a whole	3	2	1
Congestive heart failure	Cardiovascular system	3	2	1
Diarrhea	Digestive system	2	2	0
Dizziness	Nervous system	2	2	0
Fever	Body as a whole	2	2	0
Hemorrhage	Cardiovascular system	2	2	0

COSTART V term	Organ System	N, Total	N, Paricalcitol	N, Placebo
Hernia	Body as a whole	2	2	0
Lung edema	Respiratory system	2	2	0
Sepsis	Body as a whole	5	2	3
Thrombosis	Cardiovascular system	3	2	1

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Reasons for Premature Termination from the Study (All Treated Subjects) in CKD Stage 3 and 4 Pivotal Trials Combined		
	Paricalcitol (n = 107)	Placebo (n = 113)
Reason for Premature Termination		
Adverse event	6 (6%)	5 (4%)
Withdrew consent	3 (3%)	4 (4%)
Other	13 (12%)	8 (7%)
Total Terminated Prematurely	25 (23%)	20 (18%)
Total Completed 24 Weeks of Treatment	82 (77%)	93 (82%)

Those randomized to Zemplar who completed prematurely due to an adverse event are as follows: one subject (502) with abnormal liver function tests; two subjects (Study 2001020, subject 1403 and Study 2001021, subject 102) with uremia; one subject (202) with back pain, hematuria, and contusion to renal cyst; one subject (401) with hepatic encephalopathy; and one subject (604) with allergic reaction. Further description is provided in Section 7.1.3.2, Adverse events associated with dropouts.

Those randomized to Zemplar and terminated due to “other” reasons are as follows: six subjects (801, 809, 708, 1303, 503 and 1404) required dose reduction to 0 mcg; three subjects (101, 404, and 1405) had a history of kidney stones; one subject (507) died (**comment: it is not clear why this was not classified as an adverse event**); one subject (504) had a history of kidney stones and a Pre-Treatment calcium value of > 10.0 mg/dL, one subject (801) received prednisone and had increased calcium values, and one subject (1402) used an exclusionary drug (Advair) during the study.

The percent of subjects remaining in the pivotal studies over time is represented in the following table:

Percent of Subjects in CKD Stage 3 and 4 Studies Over Time		
	Paricalcitol	Placebo
	(N = 107)	(N = 113)
≥ 28 Days	101/107 (94%)	108/113 (96%)
≥ 56 Days	101/107 (94%)	103/113 (91%)
≥ 84 Days	93/107 (87%)	102/113 (90%)
≥ 112 Days	89/107 (83%)	101/113 (89%)
≥ 140 Days	84/107 (79%)	95/113 (84%)
≥ 168 Days	28/107 (26%)	33/113 (29%)

7.1.3.2 Adverse events associated with dropouts

There were 7 of 337 (2%) subjects who prematurely terminated the study due to adverse events in the Phase 1 clinical pharmacology studies. None of these adverse events were determined by the Investigator to have a causal relationship to study drug.

In the Phase 3 CKD Stage 3 and 4 studies, 6 of the 107 (6%) paricalcitol and 5 of the 113 (4%) placebo subjects discontinued prematurely due to an adverse event. A Fisher's exact test was performed by this Reviewer to assess whether this difference was statistically significant:

	D/C due to adverse event	Did not D/C due to adverse event	p-value
Zemplar	6 (6%)	101 (94%)	0.69
Placebo	5 (4%)	108 (96%)	

D/C = discontinue/d

Two of these events were considered to have a causal relationship to the study drug by the Investigator. One paricalcitol subject (502) had elevated liver enzymes that were considered by the Investigator to be possibly related to study drug (see Section 7.1.2, above), and one paricalcitol subject (604) had an allergic reaction with a maculopapular rash that was considered to be probably related to study drug.

Adverse Events Leading to Premature Termination from the Study (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; Paricalcitol-Treated Subjects)							
Subject Number	Gender/ Age	Adverse Event Description/Final Diagnosis	COSTART	Study Day Onset^a	Study Day End^a	Severity	Investigator Alternative Etiology
Study 2001019							
502	M/56	Elevated liver enzymes/passive congestion	Liver function tests abnormal	84	90	Moderate	Drug toxicity ^b

Adverse Events Leading to Premature Termination from the Study (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; Paricalcitol-Treated Subjects)							
Subject Number	Gender/ Age	Adverse Event Description/Final Diagnosis	COSTART	Study Day Onset^a	Study Day End^a	Severity	Investigator Alternative Etiology
		secondary to heart failure					
Study 2001020							
1403	F/81	Weakness, SOB, fluid overload /chronic renal failure	Uremia	77	Ongoing as of Day 86 (9)	Severe	ESRD
Study 2001021							
102	F/84	Dizziness, poor appetite, nausea, weakness, unable to walk/stand, mild headache/uremic nephropathy	Uremia	107	114 (7)	Severe	Uremia due to progressing kidney failure
202	M/67	Worsening of back/flank pain/ contusions to renal cyst w/severe flank pain and hematuria	Back pain Hematuria Accidental injury	62	73	Severe	History of back pain
401 ^c	M/74	Increasing confusion and somnolence, slurred speech, agitated, not alert or oriented/hepatic encephalopathy	Encephalopathy	71	77 (6)	Severe	Intraluminal blood
604	M/68	Allergic reaction – maculopapular eruption on legs, chest, and arms/ allergic reaction due to study medication	Allergic reaction	19	27 (8)	Mild	Not required

M/F = Male/Female; SOB = shortness of breath; CRF = chronic renal failure; ESRD = end-stage renal disease

a. Numbers in parentheses represent number of days since last dose of study drug.

b. The Abbott alternative etiology was: bradycardia associated with cardiac meds led to liver congestion resulting in elevated liver enzymes.

c. Subject died (hepatic encephalopathy).

Further evaluation of case report forms revealed that four paricalcitol subjects and three placebo subjects discontinued the study because of dialysis initiation.

7.1.3.3 Other significant adverse events

The patients studied in the pivotal trials have multiple co-morbidities and therefore experience many significant adverse events. Attention has been focused on those adverse events possibly related to study drug (e.g., allergy or hypercalcemia) and those events which appear to occur with greater frequency in paricalcitol group versus placebo. These adverse events are described in other sections.

7.1.4 Other Search Strategies

As stated above, attention was paid to adverse events and their relationship to the primary adverse pharmacological effect of vitamin D (or its analog): hypercalcemia. Therefore, all subjects with serious adverse events were examined for possible relationships between laboratory abnormalities and the event (typically via review of the CRF). There was no obvious relationship between hypercalcemia and serious adverse events or adverse events leading to drop-out.

Further search strategies attempted to determine if a cluster of adverse events that may be a result of a paricalcitol-related “syndrome” (i.e., early signs and symptoms of hypercalcemia and symptoms that could be suggestive of an allergic reaction) were performed by this Reviewer and shown in the following table:

Early signs and symptoms of hypercalcemia	Paricalcitol (N=107)	Placebo (N=113)
asthenia	3 (3%)	2 (2%)
headache	5 (5%)	5 (4%)
constipation	4 (4%)	4 (4%)
dry mouth	1 (1%)	3 (3%)
nausea	6 (6%)	4 (4%)
vomiting	6 (6%)	5 (4%)
myalgia	2 (2%)	5 (4%)
taste perversion	1 (1%)	2 (2%)
TOTAL	28 (26%)	30 (27%)
Signs and symptoms of a potential allergic reaction	Paricalcitol (N=107)	Placebo (N=113)
allergic reaction	6 (6%)	2 (2%)
face edema	1 (1%)	0 (0%)
dyspnea	1 (1%)	0 (0%)
angioedema	0 (0%)	1 (1%)
pruritus	3 (3%)	3 (3%)
rash	6 (6%)	3 (3%)
urticaria	1 (1%)	0 (0%)
vesiculobullous rash	2 (2%)	1 (1%)
conjunctivitis	1 (1%)	1 (1%)
TOTAL	21 (20%)	11 (10%)

The majority of the greater AEs seen under the “allergy” subheading above for paricalcitol may be attributable to an allergy to paricalcitol therapy. The Sponsor provided information on the allergenic potential of paricalcitol and the excipients in the proposed formulation in response to the Reviewer’s request. Four cases of possible allergy were reviewed from the Sponsor’s post-marketing database, all related to difficulty breathing; two of which were associated with facial and oral edema and hives, and two cases involving throat tightness, one associated with itching. In one of the facial edema cases, the reporter did not offer an opinion on causality, and in the other case, the symptoms recurred after rechallenge with paricalcitol. Similarly, causality was not provided for one of the two cases of throat tightness, but the other noted recurrence of itching upon rechallenge. Three of the four subjects reported allergy to penicillin. Based on the Sponsor’s review of the four cases, an update to the Safety Report will be submitted to NDA 20-819.

Paricalcitol capsules contain alcohol, BHT, medium chain triglycerides, gelatin, glycerin, titanium oxide, iron oxide, and . Isolated reports of adverse skin reactions have been reported with BHT use. Gelatin in capsule formulations has not been implicated in allergic reactions and there have been no reports of allergic reactions to medium chain triglycerides.

Pre-clinical toxicity studies conducted in different animal species showed no indication of allergic reactions to paricalcitol. According to the Sponsor: *Based on Abbott’s current data, the paricalcitol capsule formulation is not believed to be associated with allergic reactions.*

The proposed label states that Zemplar Capsules should not be given to patients with hypersensitivity to any ingredient in this product.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events could have been reported in response to a query, observed by site personnel, or reported spontaneously by the subject. The method by which subjects were queried was not described.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

After detailed review of adverse event coding by the Sponsor, a request was generated for further clarification of certain adverse events and their codes. After reviewing the itemized adverse event clarifications, it appears that much of the apparent discrepancy is due to the final diagnosis on the CRF, which is occasionally different than the brief description on the case report tabulations. This final diagnosis is what the Sponsor uses to match to the coding dictionary’s (COSTART) preferred term. In addition, the COSTART preferred term does not always seem adequate or appropriate for a given clinical situation (for example, upper respiratory infection is

mapped to COSTART term “pharyngitis”). The Sponsor acknowledges and the Reviewer concedes the limitations of this coding dictionary. After the Sponsor’s review of the adverse events, several of the pivotal trials’ and CKD Stage 5 trials’ adverse events were recorded.

Comment: The recoding does not appear to make a substantive change to the overall safety evaluation, so all analyses using the provided CRTs (prior to the changes) will stand. The Sponsor’s effort towards consistency of adverse event reporting and coding is satisfactory.

The Sponsor did provide tables with analyses of the changes made to coding as shown below:

CKD Stage 3 and 4				
COSTART Code	Before		After	
	Paricalcitol Capsule (N = 107)	Placebo (N = 113)	Paricalcitol Capsule (N = 107)	Placebo (N = 113)
Gastroenteritis	3 (3%)	3 (3%)	3 (3%)	2 (2%)
Gastritis	2 (2%)	4 (4%)	1 (1%)	5 (4%)
Eructation	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Flatulence	0 (0%)	2 (2%)	1 (1%)	2 (2%)
Somnolence	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Uremia	7 (7%)	9 (8%)	6 (6%)	9 (8%)
Hyperglycemia	0 (0%)	2 (2%)	0 (0%)	1 (1%)
Headache	5 (5%)	5 (4%)	5 (5%)	6 (5%)
Dyspepsia	2 (2%)	2 (2%)	3 (3%)	2 (2%)

CKD Stage 5				
COSTART Code	Before		After	
	Paricalcitol Capsule (N = 110)	Placebo (N = 115)	Paricalcitol Capsule (N = 110)	Placebo (N = 115)
Accidental Injury	4 (4%)	4 (3%)	5 (5%)	5 (4%)
Stupor	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Heart Arrest	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Pain	13 (12%)	13 (11%)	12 (11%)	12 (10%)
Tendon Disorder	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Thyroid Adenoma	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Adenoma	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Taste Loss	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Taste Perversion	0 (0%)	1 (1%)	1 (1%)	1 (1%)
Abdominal Pain	9 (8%)	2 (2%)	9 (8%)	3 (3%)
Urticaria	2 (2%)	1 (1%)	1 (1%)	0 (0%)
Pruritus	4 (4%)	2 (2%)	4 (4%)	3 (3%)
Skin Disorder	0 (0%)	1 (1%)	1 (1%)	1 (1%)
Electrolyte Depletion	0 (0%)	1 (1%)	0 (0%)	0 (0%)

CKD Stage 5				
COSTART Code	Before		After	
	Paricalcitol Capsule (N = 110)	Placebo (N = 115)	Paricalcitol Capsule (N = 110)	Placebo (N = 115)
Nausea	9 (8%)	8 (7%)	10 (9%)	8 (7%)
Viral Infection	5 (5%)	4 (3%)	5 (5%)	2 (2%)
Diarrhea	7 (6%)	4 (3%)	7 (6%)	6 (5%)
Myalgia	1 (1%)	1 (1%)	1 (1%)	2 (2%)
Dehydration	2 (2%)	1 (1%)	3 (3%)	1 (1%)
Dizziness	5 (5%)	4 (3%)	5 (5%)	3 (3%)
Infection	9 (8%)	2 (2%)	10 (9%)	3 (3%)
Rhinitis	1 (1%)	2 (2%)	1 (1%)	1 (1%)
Diabetes Mellitus	2 (2%)	0 (0%)	1 (1%)	0 (0%)

7.1.5.3 Incidence of common adverse events

The most commonly experienced treatment-emergent adverse events among subjects who received paricalcitol capsule in the pivotal Phase 3 CKD Stage 3 and 4 studies were pharyngitis (10%; placebo = 11%), accidental injury (9%; placebo = 7%), pain, viral infection, diarrhea, edema, hypertension, uremia (7% each; placebo incidence = 6%, 7%, 4%, 4%, 4%, and 8%, respectively), allergic reaction, nausea, rash, vomiting (6% each; placebo incidence = 2%, 4%, 3%, and 4%, respectively), arthritis, dizziness, headache, hypotension, rhinitis, and vertigo (5% each; placebo incidence = 1%, 4%, 4%, 3%, 4%, and 0%, respectively).

Common adverse events were also evaluated by treatment regimen (TIW vs. QD). The most commonly experienced adverse events among paricalcitol subjects dosed on the TIW regimen were pain, pharyngitis, uremia, and viral infection (8% each; placebo incidence = 3%, 10%, 7%, and 5%, respectively). The most commonly experienced adverse events among paricalcitol subjects dosed on the QD regimen were accidental injury (17%; placebo = 8%), pharyngitis (14%; placebo = 13%), diarrhea, edema, rash, vomiting (11% each; placebo incidence = 8%, 8%, 3%, and 8%, respectively), allergic reaction, nausea, abdominal pain, and cough increased (9% each; placebo incidence = 0%, 5%, 3%, and 0%, respectively). Although the relative risk of “skin and appendages” events and “cough increased” was statistically greater in the QD regimen group than the TIW group, these were not considered clinically relevant differences.

Evaluation by organ system demonstrates greater reports of treatment-emergent adverse events than placebo in the cardiovascular system (25% versus 17%), musculoskeletal system (11% versus 8%), nervous system (17% versus 11%), respiratory system (24% versus 22%), and skin and appendages (16% versus 9%).

Comment: Although conceivably long-term treatment with paricalcitol may predispose to increased cardiovascular events, this would be expected to be due to a prolonged elevation

of the calcium/phosphorus product, which will be monitored by the prescribing health care professional.

7.1.5.4 Common adverse event tables

Overall

Treatment-Emergent Adverse Events in Body Systems by Paricalcitol Capsule Group Occurring in ≥ 3% of Subjects in Either Treatment Group (Double-Blind, Placebo Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)		
Body System^a	Paricalcitol Capsule (N = 107)	Placebo (N = 113)
COSTART V Term		
Overall N (%)	88 (82%)	86 (76%)
Body as a Whole	49 (46%)	40 (35%)
Accidental Injury	10 (9%)	8 (7%)
Pain	8 (7%)	7 (6%)
Viral Infection	8 (7%)	8 (7%)
Allergic Reaction	6 (6%)	2 (2%)
Headache	5 (5%)	5 (4%)
Abdominal Pain	4 (4%)	2 (2%)
Back Pain	4 (4%)	1 (1%)
Infection	4 (4%)	4 (4%)
Asthenia	3 (3%)	2 (2%)
Chest Pain	3 (3%)	1 (1%)
Fever	3 (3%)	1 (1%)
Infection Fungal	3 (3%)	0 (0%)
Cardiovascular	27 (25%)	19 (17%)
Hypertension	7 (7%)	4 (4%)
Hypotension	5 (5%)	3 (3%)
Syncope	3 (3%)	1 (1%)
Congestive Heart Failure	2 (2%)	5 (4%)
Peripheral Vascular Disorder	0 (0%)	3 (3%)
Digestive	29 (27%)	31 (27%)
Diarrhea	7 (7%)	5 (4%)
Nausea	6 (6%)	4 (4%)
Vomiting	6 (6%)	5 (4%)
Constipation	4 (4%)	4 (4%)
Gastroenteritis	3 (3%)	3 (3%)
Gastritis	2 (2%)	4 (4%)
Dry Mouth	1 (1%)	3 (3%)
Hemic and Lymphatic	4 (4%)	10 (9%)
Ecchymosis	2 (2%)	4 (4%)
Hypervolemia	2 (2%)	4 (4%)
Metabolic and Nutritional Disorders	24 (22%)	34 (30%)
Edema	7 (7%)	5 (4%)
Uremia	7 (7%)	9 (8%)
Gout	4 (4%)	6 (5%)
Dehydration	3 (3%)	1 (1%)

Treatment-Emergent Adverse Events in Body Systems by Paricalcitol Capsule Group Occurring in ≥ 3% of Subjects in Either Treatment Group (Double-Blind, Placebo Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)		
Body System^a COSTART V Term	Paricalcitol Capsule (N = 107)	Placebo (N = 113)
Hyperkalemia	2 (2%)	3 (3%)
Hyperphosphatemia	2 (2%)	4 (4%)
Hypoglycemia	2 (2%)	4 (4%)
Hyperlipemia	1 (1%)	3 (3%)
Peripheral Edema	1 (1%)	3 (3%)
Musculoskeletal	12 (11%)	9 (8%)
Arthritis	5 (5%)	1 (1%)
Leg Cramps	3 (3%)	0 (0%)
Myalgia	2 (2%)	5 (4%)
Nervous	18 (17%)	12 (11%)
Dizziness	5 (5%)	5 (4%)
Vertigo*	5 (5%)	0 (0%)
Depression	3 (3%)	0 (0%)
Respiratory	26 (24%)	25 (22%)
Pharyngitis	11 (10%)	12 (11%)
Rhinitis	5 (5%)	4 (4%)
Bronchitis	3 (3%)	1 (1%)
Cough Increased	3 (3%)	2 (2%)
Sinusitis	3 (3%)	1 (1%)
Lung Disorder	1 (1%)	3 (3%)
Skin and Appendages	17 (16%)	10 (9%)
Rash	6 (6%)	3 (3%)
Pruritus	3 (3%)	3 (3%)
Skin Ulcer	3 (3%)	0 (0%)
Urogenital	10 (9%)	10 (9%)
Urinary Tract Infection	3 (3%)	1 (1%)

* Statistically significant difference between treatment groups at p ≤ 0.05 level.

a. Includes all subjects with events in that body system.

Comment: The current proposed label uses _____ of subjects experiencing treatment-emergent adverse events; use of _____ ≥ 2% treatment-emergent adverse events in the paricalcitol-treated group, is recommended. The Sponsor's assertion, that _____ is more clinically meaningful because of the underlying health status of the CKD Stage 3 and 4 patient population, is not taking into account the relatively small number of patients in these pivotal trials.

Comment: See Section 7.1.5.5 for a discussion of vertigo, which was found to be statistically significantly greater in those on paricalcitol vs. those on placebo.

Severity

The most common treatment-emergent adverse events deemed “severe” by the Investigator are presented below:

Severe Treatment-Emergent Adverse Events in Descending Frequency by Paricalcitol Capsule Group (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)				
COSTART V Term	Number (%) of Subjects			
	Paricalcitol Capsule (N = 107)		Placebo (N = 113)	
Overall	16	(15%)	10	(9%)
Uremia	4	(4%)	2	(2%)
Accidental Injury	2	(2%)	1	(1%)
Back Pain	2	(2%)	0	(0%)
Myocardial Infarction	2	(2%)	0	(0%)
Neck Pain	1	(1%)	0	(0%)
Pain	1	(1%)	0	(0%)
Viral Infection	1	(1%)	0	(0%)
Angina Pectoris	1	(1%)	0	(0%)
Congestive Heart Failure	1	(1%)	0	(0%)
Heart Arrest	1	(1%)	1	(1%)
Syncope	1	(1%)	0	(0%)
Dehydration	1	(1%)	1	(1%)
Gout	1	(1%)	0	(0%)
Hypoglycemia	1	(1%)	1	(1%)
Encephalopathy	1	(1%)	0	(0%)
Acute Kidney Failure	1	(1%)	2	(2%)
Hematuria	1	(1%)	0	(0%)
Kidney Pain	1	(1%)	0	(0%)
Cerebral Ischemia	0	(0%)	1	(1%)
Diabetes Mellitus	0	(0%)	1	(1%)
Hypervolemia	0	(0%)	1	(1%)
Hyperglycemia	0	(0%)	1	(1%)
Confusion	0	(0%)	1	(1%)
Lung Edema	0	(0%)	1	(1%)
Conjunctivitis	0	(0%)	1	(1%)
Glaucoma	0	(0%)	1	(1%)

7.1.5.5 Identifying common and drug-related adverse events

The only adverse event that was determined to be significantly higher in paricalcitol-treated subjects than placebo was vertigo. Review of these cases by the Sponsor indicated no apparent link between the occurrence of vertigo and the use of paricalcitol capsule, including dose, serum calcium, and treatment duration. In all cases, the symptoms resolved while the subjects

continued on paricalcitol. In addition, there are no reports in the literature of an increased association with vitamin D or its analogs and vertigo.

Although not statistically significant, there was a greater occurrence of allergic reaction and arthritis in those subjects treated with paricalcitol capsule (allergy: 6, 6%; arthritis: 5, 5%) versus placebo (allergy: 2, 2%; arthritis: 1, 1%). Allergy is also discussed in Section 7.1.4, Other Search Strategies. For those paricalcitol-treated subjects experiencing allergy, three were on the TIW regimen and three on the QD regimen. Only one reaction (maculopapular rash, severity described as “mild”) was considered by the Investigator to be probably related to study drug (and the subject was prematurely discontinued due to this adverse event). The other reactions included: nasal congestion, seasonal allergy, skin peeling on hands/arms (considered by the Investigator to be due to allopurinol), and possible hay fever. At the treatment week in which the events occurred, all but one subject had serum calcium values within the normal range; one subject had serum calcium 10.4 mg/dL and was receiving paricalcitol capsule 1 mcg QD (this was not the subject discontinued because of maculopapular rash). For those subjects experiencing arthritis, no events were considered severe and no events were considered by the Investigator to have a causal relationship to study drug. Three subjects received paricalcitol capsule on the TIW regimen and two on the QD regimen. Serum calcium range during the reported events was 8.4-10.2 mg/dL.

Eleven (10%) paricalcitol capsule subjects and 12 (11%) placebo subjects experienced at least one treatment-emergent adverse event considered by the Investigator to have a causal relationship to study drug; see table below:

Treatment-Emergent Adverse Events Considered to Have a Causal Relationship to Treatment in Descending Frequency by Paricalcitol Capsule Group (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)				
	Number (%) of Subjects			
	Paricalcitol Capsule		Placebo	
COSTART V Term	(N = 107)		(N = 113)	
Overall	11	(10%)	12	(11%)
Rash	2	(2%)	0	(0%)
Allergic Reaction	1	(1%)	0	(0%)
Constipation	1	(1%)	1	(1%)
Dry Mouth	1	(1%)	0	(0%)
Dyspepsia	1	(1%)	0	(0%)
Gastritis	1	(1%)	0	(0%)
Liver Function Tests Abnormal	1	(1%)	0	(0%)
Leg Cramps	1	(1%)	0	(0%)
Dizziness	1	(1%)	0	(0%)
Pruritus	1	(1%)	2	(2%)
Urticaria	1	(1%)	0	(0%)
Taste Perversion	1	(1%)	1	(1%)

Treatment-Emergent Adverse Events Considered to Have a Causal Relationship to Treatment in Descending Frequency by Paricalcitol Capsule Group (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)				
	Number (%) of Subjects			
	Paricalcitol Capsule		Placebo	
COSTART V Term	(N = 107)		(N = 113)	
Hyperphosphatemia	0	(0%)	3	(3%)
Headache	0	(0%)	2	(2%)
Hypotension	0	(0%)	1	(1%)
Palpitation	0	(0%)	1	(1%)
Flatulence	0	(0%)	1	(1%)
Gastroenteritis	0	(0%)	1	(1%)
Nausea	0	(0%)	1	(1%)
Vomiting	0	(0%)	1	(1%)
Ecchymosis	0	(0%)	1	(1%)

7.1.5.6 Additional analyses and explorations

There are too few events to perform additional analyses on the above data for dose dependency, adaptation, or interactions. The CRF for the maculopapular rash (paricalcitol) adverse event was reviewed. The event was described as an allergic reaction starting on March 29, 2003 and ending April 6, 2003. The eruption occurred on the subject's legs, chest, and arms, was mild, and the action taken was that study drug was discontinued. The subject was treated with oral Benadryl as needed from March 30 – April 6, 2003.

The CRF for elevated liver function tests (paricalcitol) adverse event was reviewed. The explanation of bradycardia, hypertension, and congestive heart failure leading to liver congestion is a plausible alternative to drug-related, although it is difficult to determine conclusively. See the narrative of this subject in Section 7.1.2 for further details.

7.1.6 Less Common Adverse Events

It is difficult to attribute those adverse events of significant concern that are rare, given that the number of subjects in the entire development program is relatively small. Rare events that are deemed by the Investigator to be temporally-related to the use of paricalcitol, are of some concern, and did not occur in the placebo group of the pivotal studies include allergic reaction (1%) and abnormal liver function tests (1%), see Section 7.1.5. Given the experience with the active compound (Zemplar Injection) as well as similar vitamin D analogs, there is no reason to anticipate the emergence of unexpected events postmarketing.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

During the Phase 3 CKD 3 and 4 trials, samples for analysis of primary chemistry variables (calcium, phosphorus, Ca x P, and albumin) were collected throughout the study, while samples for analysis of secondary chemistry (alkaline phosphatase, cholesterol, chloride, CO₂, glucose, LDH, magnesium, sodium, potassium, SGOT, SGPT, total bilirubin, total protein, triglycerides, and uric acid), hematology (hematocrit, hemoglobin, MCH, MCHC, MCV, platelet count, RBC, and WBC), eGFR and serum creatinine, urinalysis, and 24-hour urine parameters (urinary calcium, phosphorus, and creatinine clearance) were collected at the Pretreatment and Follow-Up phases. Serum iPTH, used in exploratory analyses (lowest iPTH achieved), was also collected throughout the study. Spot urine for calcium/creatinine ratio was performed at Pretreatment Phase, Week 11, and the Follow-Up Phase. In the clinical pharmacology studies, hypercalcemia was defined as single serum calcium > 11.0 mg/dL. Clinically meaningful hypercalcemia in the pivotal studies was defined as at least two consecutive calcium values > 10.5 mg/dL.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The three pivotal CKD Stage 3 and 4 studies were pooled for the analyses of laboratory values as well as examined by dosing regimen. For several critical variables, laboratory values from Phase 3 CKD Stage 5 studies were also examined.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 *Analyses focused on measures of central tendency*

Calcium

Although not a strict measure of central tendency, “clinically meaningful hypercalcemia” (two consecutive calcium levels > 10.5 mg/dL, a responder analysis), is the primary safety outcome identified. Therefore, the results of this and other important responder analyses will be discussed here.

Proportion of Subjects Who Developed Hypercalcemia (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)			
Variable	Paricalcitol Capsule (N = 106) ^b	Placebo (N = 111) ^c	p-value 95% CI ^a
Hypercalcemia (at least 2 consecutive calcium values > 10.5 mg/dL)	2 (2%)	0 (0%)	0.237 (-0.7%, 4.5%)

CI = confidence interval
 a. Normal approximation of a 95% two-sided confidence for the difference in the incidence of clinically meaningful hypercalcemia.
 b. One paricalcitol subject had no chemistry data following the first dose of study drug; therefore, only 106 subjects (versus 107) are included in this analysis.
 c. Two placebo subjects had no chemistry data following the first dose of study drug; therefore, only 111 subjects (versus 113) are included in this analysis.

Comment: These studies were not designed to specifically test this outcome. Based on the incidence of hypercalcemia from studies of Zemplar injection, the sample size from the capsule development program is too small to detect anything other than very large differences in the incidence of hypercalcemia (as defined by the Sponsor) between treatment groups.

In analyses separated by treatment regimen, the incidence of clinically meaningful hypercalcemia was 3% for paricalcitol-treated subjects who received the TIW regimen, 0% among those on the QD regimen, and 0% for either placebo-treated regimen.

An analysis was performed to assess hypercalcemia occurring at least once in the Phase 3 CKD Stages 3 and 4 studies:

Proportion of Subjects Who Developed at Least One Elevated Calcium Value (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)			
Variable	Paricalcitol Capsule (N = 106) ^b	Placebo (N = 111) ^c	p-value 95% CI ^a
Elevated Calcium (at least one calcium value > 10.5 mg/dL)	19 (18%)	3 (3%)	< 0.001 (7.3%, 23.1%)

CI = confidence interval
 a. Normal approximation of a 95% two-sided confidence for the difference in the incidence of a single calcium elevation > 10.5 mg/dL.
 b. One paricalcitol subject had no chemistry data following the first dose of study drug; therefore, only 106 subjects (versus 107) are included in this analysis.
 c. Two placebo subjects had no chemistry data following the first dose of study drug; therefore, only 111 subjects (versus 113) are included in this analysis.

Comment: The proposed labeling does not include the above finding.

Additionally, according to this Reviewer's analysis, only two placebo subjects, rather than three as provided in the above table, developed at least one serum calcium > 10.5 (2/111, 2%).

The Sponsor was requested to also provide the analysis of single episodes of Ca > 10.5 mg/dL by treatment regimen. The results are as follows:

Proportion of Subjects Who Developed At Least One Calcium Value > 10.5 mg/dL By Treatment Regimen							
	TIW Regimen (N = 142)			QD Regimen (N = 75)			Homogeneity p-value
	Paricalcitol Capsule (N = 71)	Placebo (N = 71)	p-value	Paricalcitol Capsule (N = 35)	Placebo (N = 40)	p-value	
One or more Calcium Value > 10.5 mg/dL	11 (15.5%)	3 (4.2%)	0.046	8 (22.9%)	0 (0.0%)	0.001	0.126

One paricalcitol subject and 2 placebo subjects had no chemistry data following the first dose of study drug and are excluded from this analysis.

This Reviewer also performed an analysis of single serum calcium ≥ 11.0 mg/dL in the subjects on paricalcitol versus placebo:

Proportion of Subjects Who Developed at Least 1 Calcium Value ≥ 11.0 mg/dL (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)			
Variable	Paricalcitol Capsule	Placebo	p-value
Elevated Calcium (at least one calcium value ≥ 11.0 mg/dL)	(N = 106) ^a 5 (5%)	(N = 111) ^b 0 (0%)	0.027

a. One paricalcitol subject had no chemistry data following the first dose of study drug; therefore, only 106 subjects (versus 107) are included in this analysis.
b. Two placebo subjects had no chemistry data following the first dose of study drug; therefore, only 111 subjects (versus 113) are included in this analysis.

Because the review of study 2001020 revealed a difference in concomitant high-ceiling diuretic use, the Sponsor was asked to repeat analyses in users vs. non-users of high-ceiling diuretics. Significant differences were seen in users of high-ceiling diuretics in the proportion of subjects who developed one serum calcium value > 10.5 mg/dL (in addition to one $\text{Ca} \times \text{P} > 55 \text{ mg}^2/\text{dL}^2$); differences were not seen in non-users. Only the combined analysis is provided below:

Proportion of Subjects Who Achieved at Least One Elevated Serum Calcium, Phosphorus and Ca×P Value by Concomitant High-Ceiling Diuretic Usage							
Combined Studies (Studies 2001019, 2001020 & 2001021)							
	User (N = 157)			Non-User (N = 60)			Homogeneity p-value
	Paricalcitol Capsule (N = 79)	Placebo (N = 78)	p-value	Paricalcitol Capsule (N = 27)	Placebo (N = 33)	p-value	
Calcium (> 10.5 mg/dL)	19 (24.1%)	3 (3.8%)	< 0.001	0 (0.0%)	0 (0.0%)	NA	NA
Phosphorus (> 5.5 mg/dL)	30 (38.0%)	21 (26.9%)	0.173	3 (11.1%)	6 (18.2%)	0.495	0.187
Ca×P (> 55 mg^2/dL^2)	26 (32.9%)	14 (17.9%)	0.043	2 (7.4%)	5 (15.2%)	0.442	0.079

One paricalcitol subject and 2 placebo subjects had no chemistry data following the first dose of study drug and are excluded from this analysis.

Comment: The use of high-ceiling diuretics in these studies appears to predispose individuals to single episodes of hypercalcemia. This may be due to volume depletion,

although eGFR and serum creatinine change did not appear to be statistically significantly affected by high-ceiling diuretic use. According to the Sponsor, baseline calcium was higher in the users of a high-ceiling diuretic compared with non-users. In analyses performed by this Reviewer, high-ceiling diuretic use no longer predicted a single episode of hypercalcemia when adjusted for baseline serum calcium. Nevertheless, these findings underscore the importance of calcium monitoring – clearly, baseline calcium, even if within normal limits, predicts calcium responses to paricalcitol (and likely other vitamin D analogs). Despite the tendency for high-ceiling diuretics to increase urinary calcium excretion (and therefore are used therapeutically to treat hypercalcemia), it may be that those taking these medications chronically may have slightly higher serum calcium levels (due to intravascular depletion or other mechanisms). Further research into predictive factors for developing hypercalcemia may broaden the therapeutic usefulness of these compounds.

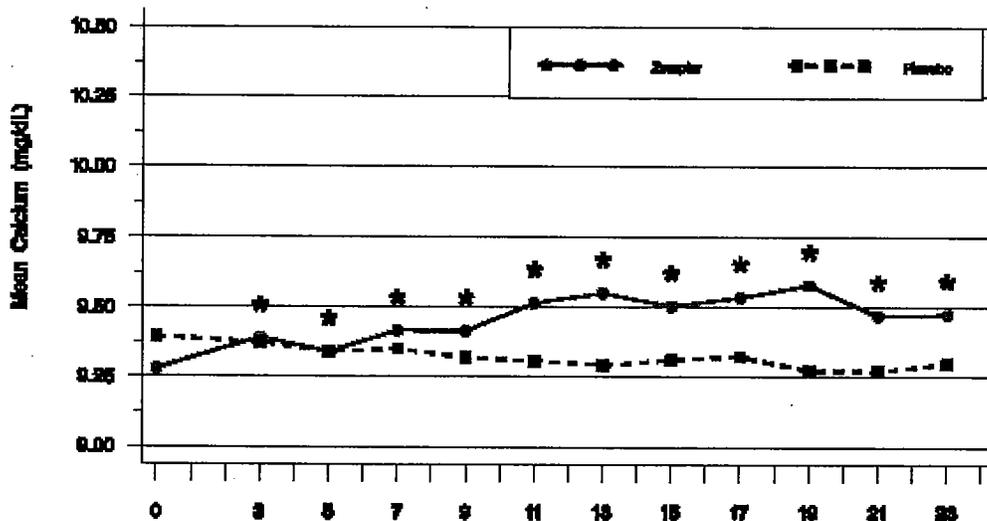
Mean Change in Calcium

The difference between the treatment groups in mean change from baseline to Final Visit was statistically significant ($p = 0.028$); when adjusted for baseline calcium, the difference between treatment groups was not statistically significant ($p = 0.058$). The difference between the treatment groups in mean change from baseline to Last On-Treatment Visit was statistically significant ($p < 0.001$); results were similar when adjusted for baseline calcium.

The following figure is taken from the NDA and describes serum calcium levels over time in each group. Mean calcium levels increased in the paricalcitol group throughout the study, in contrast to the placebo group. Both groups had mean calcium levels within the normal range at all timepoints.

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Mean Calcium Values Over Time During the Treatment Phase (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)



Week	0	3	5	7	9	11	13	15	17	19	21	23
paricalcitol N	107	103	103	99	98	92	95	93	90	86	88	80
Placebo N	113	106	109	105	99	103	99	100	93	93	93	93

* Statistically significant ($p \leq 0.05$) difference in mean change from baseline between the paricalcitol capsule and placebo treatment groups. At each visit, change from baseline is calculated for subjects who had data at that visit.

Calcium Normal Range: 8.4 to 10.3 mg/dL

Comment: In the pivotal studies combined, mean serum calcium is statistically significantly different than placebo starting at Week 11 and continuing throughout the study (as opposed to the above graph which demonstrates statistically significant differences as compared to baseline):

Treatment	N	Wk 3	Wk 5	Wk 7	Wk 9	Wk 11	Wk 13	Wk 15	Wk 17	Wk 19	Wk 21	Wk 23
Paricalcitol	107	9.39	9.34	9.42	9.42	9.52*	9.55*	9.51*	9.54*	9.58*	9.47*	9.48*
Placebo	113	9.37	9.34	9.35	9.32	9.31	9.29	9.31	9.32	9.27	9.27	9.30

* $p < 0.05$

CKD Stage 5

Similar analyses of serum calcium (relevant to the CKD Stage 5 patient population) were performed in the Phase 3 CKD Stage 5 studies:

Proportion of Subjects Who Developed at Least One Calcium Value ≥ 11.0 mg/dL (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 5 Studies; All Treated Subjects)			
Variable	Paricalcitol Capsule	Placebo	p-value
	(N = 109)	(N = 115)	<0.0001
Elevated Calcium (at least one calcium value ≥ 11.0 mg/dL)	25 (23%)	1 (0.9%)	

Ca x P

The calcium/phosphorus product (Ca x P) is an additional safety concern with the use of vitamin D compounds, and is thought to contribute to cardiovascular and tissue calcification. Similar to the analysis of clinically significant hypercalcemia in the section above, the Sponsor defined elevated Ca x P as at least two consecutive Ca x P values > 55 mg²/dL²:

Proportion of Subjects Who Developed at Least Two Consecutive Elevated Ca x P Values (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)			
Elevated Ca x P	Paricalcitol Capsule (N = 106) ^a	Placebo (N = 111) ^b	Fisher's exact test p-value
At least 2 consecutive Ca x P values > 55 mg ² /dL ²	13 (12%)	7 (6%)	0.161

a. One paricalcitol subject had no chemistry data following the first dose of study drug; therefore, only 106 subjects (versus 107) are included in this analysis.
 b. Two placebo subjects had no chemistry data following the first dose of study drug; therefore, only 111 subjects (versus 113) are included in this analysis.

Using a Last On-Treatment analysis (to include the values of those subjects who dropped-out prematurely), Ca x P increased in both treatment groups, although there was no statistical difference in the between-group comparison (p = 0.287). The results of the responder analysis are as follows:

Proportion of Subjects Who Developed at Least One Ca x P > 55 mg²/dL² (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)			
Variable	Paricalcitol Capsule	Placebo	p-value
	(N = 106) ^a	(N = 111) ^b	0.102
Elevated Ca x P (at least one Ca x P value > 55 mg ² /dL ²)	28 (26%)	19 (17%)	

a. One paricalcitol subject had no chemistry data following the first dose of study drug; therefore, only 106 subjects (versus 107) are included in this analysis.
 b. Two placebo subjects had no chemistry data following the first dose of study drug; therefore, only 111 subjects (versus 113) are included in this analysis.

Comment: Although a statistically significant difference between serum Ca x P > 55 is not evident, the studies were not designed to detect a difference. Serum phosphorus is expected

to increase during the natural course of CKD, and its increase in both groups may be attenuating the Ca x P difference.

Similarly, there were no statistically significant differences in the relative risk of elevated phosphorus and Ca x P values for paricalcitol capsule vs. placebo when evaluated by treatment regimen:

Proportion of Subjects Who Developed At Least One Elevated Ca x P Value By Treatment Regimen							
	TIW Regimen (N = 142)			QD Regimen (N = 75)			Homogeneity p-value
	Paricalcitol Capsule (N = 71)	Placebo (N = 71)	p-value	Paricalcitol Capsule (N = 35)	Placebo (N = 40)	p-value	
1 or more Ca x P > 55 mg ² /dL ²	22 (31.0%)	15 (21.1%)	0.251	6 (17.1%)	4 (10.0%)	0.500	0.895
One paricalcitol subject and 2 placebo subjects had no chemistry data following the first dose of study drug and are excluded from this analysis.							

Mean change from Baseline to Final Visit and Last On-Treatment visit was similarly not statistically significant:

Mean Change from Baseline to the Final Visit in Ca x P (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)			
Ca x P (mg ² /dL ²)	Paricalcitol Capsule	Placebo	ANOVA p-value
All Subjects	N = 106 ^a	N = 111 ^b	
Mean Baseline Value	36.65	36.88	0.751
Baseline Range	22.2 – 46.9	20.8 – 48.9	
Mean Final Value	38.99	39.33	
Change from Baseline (SE)	2.35 (0.785)	2.46 (0.767)	0.918
a. One paricalcitol subject had no chemistry data following the first dose of study drug; therefore, only 106 subjects (versus 107) are included in this analysis.			
b. Two placebo subjects had no chemistry data following the first dose of study drug; therefore, only 111 subjects (versus 113) are included in this analysis.			

Mean Change from Baseline to the Last On-Treatment Visit in Ca x P (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)			
Ca x P (mg ² /dL ²)	Paricalcitol Capsule	Placebo	ANOVA p-value
All Subjects	N = 104 ^a	N = 110 ^b	
Mean Baseline Value	36.65	36.88	
Mean Final Value	40.65	39.70	
Change from Baseline (SE)	3.96 (0.742)	2.86 (0.722)	0.287
a. Three paricalcitol subjects had no chemistry data while on-treatment; therefore, only 104 subjects (versus 107) are included in this analysis.			
b. Three placebo subjects had no chemistry data while on-treatment; therefore, only 110 subjects (versus 113) are included in this analysis.			

CKD Stage 5

Similar analyses of Ca x P (relevant to the CKD Stage 5 patient population) were performed in the Phase 3 CKD Stage 5 studies:

Proportion of Subjects Who Developed at Least One Ca x P Value $\geq 70 \text{ mg}^2/\text{dL}^2$ (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 5 Studies; All Treated Subjects)			
Variable	Paricalcitol Capsule	Placebo	p-value
	(N = 109)	(N = 115)	<0.0001
Elevated CaxP (at least one CaxP value $\geq 70 \text{ mg}^2/\text{dL}^2$)	48 (44%)	15 (13%)	

Kidney Function Parameters (eGFR and serum creatinine)

There were no statistically significant differences in mean change or percent change in eGFR or serum creatinine between paricalcitol and placebo. Both paricalcitol and placebo groups experienced mean percent decreases in eGFR and mean increases in serum creatinine from Baseline to Final Visit, as would be expected due to the natural course of CKD. It is noted that analyses for mean change and percent change from Baseline to Last On-Treatment Visit in eGFR and serum creatinine were not performed because Last On-Treatment values for eGFR and serum creatinine were not measured in the pivotal studies. All but one paricalcitol subject and two placebo subjects had a follow-up (final) visit within 30 days post-treatment.

Mean Change and Percent Change from Baseline to Final Visit in eGFR and Serum Creatinine (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; Subjects Who Completed 24 Weeks of Treatment)			
Variable (unit)	Paricalcitol Capsule (N = 82)	Placebo (N = 93)	ANOVA P-value ^a
eGFR (mL/min/1.73m²)			
Mean Baseline Value	23.90	23.44	—
Mean Final Value	21.38	21.87	NA
Mean Change from Baseline (SE)	-2.52 (0.526)	-1.57 (0.494)	0.187
Mean Percent Change from Baseline (SE)	-10.40 (2.268)	-6.95 (2.130)	0.269
Serum Creatinine (mg/dL)			
Mean Baseline Value	2.92	2.94	—
Mean Final Value	3.33	3.30	NA
Mean Change from Baseline (SE)	0.41 (0.085)	0.35 (0.080)	0.625
Mean Percent Change from Baseline (SE)	13.90 (2.521)	11.23 (2.367)	0.440

NA = Not Applicable
a. One-way ANOVA with treatment as the factor.

Mean Change and Percent Change from Baseline to Final Visit in eGFR and Serum Creatinine by Treatment Regimen (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4; Subjects Who Completed 24 Weeks of Treatment)			
TIW Subjects Who Completed 24 Weeks of Treatment			
	Paricalcitol Capsule	Placebo	ANOVA
eGFR (mL/min/1.73m²)	(N = 57)	(N = 60)	P-value^a
Mean Baseline Value	24.17	23.21	—
Mean Final Value	21.25	21.88	NA
Mean Change from Baseline (SE)	-2.92 (0.613)	-1.33 (0.597)	0.066
Mean Percent Change from Baseline (SE)	-12.27 (2.704)	-5.32 (2.636)	0.068
Serum Creatinine (mg/dL)			
Mean Baseline Value	2.91	3.01	—
Mean Final Value	3.37	3.30	NA
Mean Change from Baseline (SE)	0.46 (0.094)	0.29 (0.092)	0.181
Mean Percent Change from Baseline (SE)	15.70 (2.792)	9.10 (2.721)	0.093
QD Subjects Who Completed 24 Weeks of Treatment			
	Paricalcitol Capsule	Placebo	ANOVA
eGFR (mL/min/1.73m²)	(N = 25)	(N = 33)	P-value^a
Mean Baseline Value	23.30	23.85	—
Mean Final Value	21.68	21.86	NA
Mean Change from Baseline (SE)	-1.61 (1.011)	-1.99 (0.880)	0.780
Mean Percent Change from Baseline (SE)	-6.15 (4.135)	-9.92 (3.599)	0.496
Serum Creatinine (mg/dL)			
Mean Baseline Value	2.95	2.82	—
Mean Final Value	3.24	3.29	NA
Mean Change from Baseline (SE)	0.30 (0.178)	0.48 (0.155)	0.441
Mean Percent Change from Baseline (SE)	9.82 (5.189)	15.09 (4.516)	0.446
NA = Not Applicable			
a. One-way ANOVA with treatment as the factor.			

Comment: The p-value of 0.06 for mean change and mean percent change in eGFR between treatment groups in the TIW regimen is noted, although there is no reason to suspect the TIW regimen has greater risk of renal deterioration than the QD regimen.

Although paricalcitol subjects experienced a mean increase from baseline in urinary calcium and mean decrease in baseline in urinary phosphorus and creatinine clearance at the Final Visit, these differences were not statistically significantly different than placebo:

Mean Change from Baseline to Final Visit in 24-Hour Urine Collection Variables (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)			
Variable (unit)	Paricalcitol Capsule	Placebo	ANOVA P-value^a
Calcium (mg/24 hours)	(N = 74)	(N = 80)	
Mean Baseline Value	39.63	37.46	—
Mean Final Value	41.97	37.08	NA
Mean Change from Baseline (SE)	2.34 (3.042)	-0.38 (2.926)	0.521
Phosphorus (mg/24 hours)	(N = 74)	(N = 83)	
Mean Baseline Value	672.5	691.6	—
Mean Final Value	670.4	725.8	NA
Mean Change from Baseline (SE)	-2.1 (39.72)	34.2 (37.50)	0.508
Creatinine Clearance (mL/min/1.73m²)	(N = 85)	(N = 88)	
Mean Baseline Value	29.6	30.1	—
Mean Final Value	27.6	29.3	NA
Mean Change from Baseline (SE)	-2.0 (1.32)	-0.8 (1.29)	0.536

NA = Not Applicable
a. One-way ANOVA with treatment as the factor.

There was no statistically significant difference between treatment groups in urinary calcium-to-creatinine ratio:

Change From Baseline to Final Visit in Calcium/Creatinine Ratio, All Treated Subject Population							
Treatment Group	N	Baseline Mean	Visit Mean	Change From Baseline			Between Group Comparison
				Mean	SE	P-Value	Difference (95% CI) P-Value
Zemplar	102	0.02	0.02	-0.00	0.005	0.773	-0.01 (-0.03, 0.00)
Placebo	107	0.02	0.02	0.01	0.005	0.102	0.177

7.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

Calcium

The majority of subjects had normal calcium values at the Final Visit:

Shift Table for Serum Calcium in the CKD Stage 3 and 4 Studies Combined, %

	Paricalcitol capsule	Placebo
Normal calcium values at baseline and at Final Visit	88	92
Normal calcium values at baseline and high values at Final Visit	4	0
Normal calcium values at baseline and low values at Final Visit	6	4

Given the nature of CKD, the evaluation of shifts of certain laboratory values over time (e.g., hemoglobin, creatinine, etc.) must be compared between paricalcitol-treated subjects and those taking placebo due to changes consistent with the natural course of the disease. The proportions of all treated subjects with shifts from baseline to Final Visit relative to the normal range were generally similar between treatment groups. A greater proportion of paricalcitol-treated subjects had shifts from high at Baseline to normal at Final Visit for potassium and alkaline phosphatase levels. The latter is likely explained by the expected decrease in the bone fraction of the enzyme.

iPTH

A higher proportion of paricalcitol subjects vs. placebo subjects receiving the QD regimen had iPTH values < 60 pg/mL compared to the proportion of those receiving the TIW regimen. However, the relative risk between treatment regimens was not statistically significant:

Lowest iPTH Achieved by Treatment Regimen (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)					
Lowest iPTH Achieved (pg/mL)	Number (%) of Subjects				p-value ^a
	TIW Regimen		QD Regimen		
	Paricalcitol Capsule (N = 70)	Placebo (N = 71)	Paricalcitol Capsule (N = 35)	Placebo (N = 40)	
< 60	17 (24%)	1 (1%)	17 (49%)	0 (0%)	0.251
≥ 60	53 (76%)	70 (99%)	18 (51%)	40 (100%)	

a. p-value for test of odds ratio homogeneity from Breslow-Day Test.

Comment: Although not statistically significantly different from the TIW regimen, it is clinically relevant that almost 50% of those on the paricalcitol QD regimen had iPTH suppressed to < 60.

Urine Hemoglobin/Protein

The following analyses were performed on urine hemoglobin and protein to further characterize the safety of paricalcitol on kidney function.

Oral Zemplar (N=94) Shift in Urine Hemoglobin CKD Stages 3 and 4

Final \ Baseline	Negative	Trace	+	++	+++
Negative	71 (75.5)	1 (1.1)	2 (2.1)	0 (0.0)	0 (0.0)
Trace	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
+	0 (0.0)	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)
++	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
+++	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)

11 reduction (11.7%), 8 increase (8.5%), 75 no change (79.8%)

Oral Placebo (N=101) Shift in Urine Hemoglobin CKD Stages 3 and 4

Final \ Baseline	Negative	Trace	+	++	+++
Negative	68 (67.3)	7 (6.9)	2 (2.0)	0 (0.0)	1 (1.0)
Trace	0 (0.0)	3 (3.0)	2 (2.0)	0 (0.0)	1 (1.0)
+	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)
++	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
+++	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

12 reduction (11.9%), 16 increase (15.8%), 73 no change (72.3%)

Oral Zemplar (N=94) Shift in Urine Protein CKD Stages 3 and 4

CKD Stages 3 and 4

Final \ Baseline	Negative	Trace	+	++	+++
Negative	29(30.9)	4(4.3)	3(3.2)	1(1.1)	0(0.0)
Trace	5(5.3)	0(0.0)	3(3.2)	0(0.0)	0(0.0)
+	0(0.0)	1(1.1)	4(4.3)	0(0.0)	0(0.0)
++	3(3.2)	1(1.1)	1(1.1)	4(4.3)	7(7.4)
+++	0(0.0)	0(0.0)	1(1.1)	7(7.4)	10(10.6)

29 reduction (30.9%), 18 increase (19.1%), 47 no change (50%)

Oral Placebo (N=101) Shift in Urine Protein CKD Stages 3 and 4

Final \ Baseline	Negative	Trace	+	++	+++
Negative	29(28.7)	6(5.9)	1(1.0)	4(4.0)	0(0.0)
Trace	2(2.0)	2(2.0)	4(4.0)	2(2.0)	0(0.0)
+	1(1.0)	1(1.0)	3(3.0)	0(0.0)	0(0.0)
++	5(5.0)	3(3.0)	0(0.0)	13(12.9)	0(0.0)
+++	0(0.0)	0(0.0)	0(0.0)	3(3.0)	16(15.8)

15 reduction (14.9%), 23 increase (22.8%), 63 no change (62.3%)

Comment: These findings support the claim that paricalcitol does not negatively impact kidney function.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no dropouts for laboratory abnormalities in either the three pivotal trials or the three Phase 3 trials in CKD Stage 5 patients. The following narratives describe laboratory outliers with respect to calcium and iPTH. Hypercalcemia, elevated Ca x P, and over-suppression of iPTH are concerns with paricalcitol treatment.

Study 2001019: Paricalcitol subject 702, a 48 year old white male, had a serum calcium value of 11.0 mg/dL at Week 15, with a concomitant iPTH value of \sim μ g/mL, representing an iPTH change of -91%. Paricalcitol subject 1508, a 53 year old white female, had a calcium value of 11.1 mg/dL at Week 15, with an iPTH of \sim μ g/mL, representing a PTH change of -55%. There were no placebo subjects with calcium levels \geq 11.0 mg/dL.

Study 2001020: Paricalcitol subject 1301, a 52 year old white female, had a calcium value of 11.1 mg/dL at Week 19, with an iPTH of \sim μ g/mL, representing an iPTH change of -89%. There were no placebo subjects with calcium levels \geq 11.0 mg/dL.

Study 2001021: Paricalcitol subject 907, a 53 year old white male, had a calcium value of 11.6 mg/dL at Week 19, with an iPTH of \sim μ g/mL, representing a PTH change of -93%. This subject also had a very high calcium/phosphorus ratio at 95 mg²/dL² (see the table below for this subject's laboratory values over time). Paricalcitol subject 1001, a 62 year old black male, had a calcium value of 11.2 mg/dL at Week 13, with an iPTH of \sim μ g/mL, representing an iPTH change of -90%. There were no placebo subjects with calcium levels \geq 11.0 mg/dL.

Paricalcitol subject 907 (Study 2001021): Laboratory values longitudinally by week

	Baseline	5	7	9	11	13	15	17	19	21	23
Calcium	9.8	9.3	9.6	9.3	9.9	9.8	9.4	10.2	11.6	9.2	9.6
iPTH	246	246									
CaxP	45.8	53.01	45.12	40.92	60.39	55.86	42.3	48.96	95.12	32.2	42.24
Phosphorus	4.7	5.7	4.7	4.4	6.1	5.7	4.5	4.8	8.2	3.5	4.4
Paricalcitol dose	15	14	14	26	30	26	39	39	4	13	13

Comment: These trends highlight the dose-response relationship of paricalcitol to abnormal laboratory values as well as the rapid recovery with decreasing dose.

The following table was generated to demonstrate lowest iPTH value, and highest calcium, CaxP, and phosphorus values in any subject by treatment group:

	Minimum iPTH (pg/mL)	Maximum Calcium (mg/dL)	Maximum CaxP (mg ² /dL ²)	Maximum Phosphorus (mg/dL)
Paricalcitol	\sim	11.6	95.12	8.2
Placebo	\sim	10.9	83.6	9.1

The above table was also generated for the Phase 3 CKD Stage 5 studies; again, iPTH is suppressed to a lower minimum value, and maximum serum calcium, Ca x P, and phosphorus is higher in the paricalcitol-treated group than the placebo group.

	Minimum iPTH (pg/mL)	Maximum Calcium (mg/dL)	Maximum CaxP (mg ² /dL ²)	Maximum Phosphorus (mg/dL)
Paricalcitol	==	13.2	108.1	10.6
Placebo	—	11.6	86.1	9.6

Comment: Given the possibility of iPTH over-suppression to a greater extent with paricalcitol than placebo, is recommended.

7.1.7.4 Additional analyses and explorations

The analyses in this section are Reviewer-generated.

In order to assess the relationship between serum iPTH and serum calcium (i.e., whether hypercalcemia was dependent on percent change in iPTH), multiple regression analysis was performed. Serum calcium was regressed on percent change in serum iPTH (%ΔPTH), only when %ΔPTH was ≤ 0 (i.e., when iPTH was suppressed) in the three pivotal studies. The following analysis demonstrates that %ΔPTH, treatment group (where Zemplar = 1 and placebo = 2), and their interaction, are significant predictors of serum calcium (i.e., calcium increases as %ΔPTH becomes more negative; the effect is statistically significantly more pronounced in the paricalcitol-treated group, although the β-coefficients are small). This finding underscores the importance of vigilance with regard to iPTH monitoring with paricalcitol treatment, given the strong correlation to serum calcium.

$$\text{Serum Calcium} = 9.20 - 0.01(\% \Delta \text{PTH}) - 0.05(\text{Group}) - 0.002(\% \Delta \text{PTH} * \text{Group})$$

$$R^2 = 0.148, p < 0.0001$$

Analyses that examined whether subjects in the pivotal subjects randomized to paricalcitol that achieved the K/DOQI iPTH target (CKD Stage 3, iPTH 35-70 pg/mL, CKD Stage 4, iPTH 70-110 pg/mL) had higher mean and maximum serum calcium and CaxP on average than those that did not achieve target levels were performed.

Achieved K/DOQI iPTH Target?	N	Average [Mean Ca]	Average [Max Ca]	Average [Mean CaxP]	Average [Max CaxP]
YES	84	9.63**	9.72	41.3*	43.2
NO	196	9.41	9.75	39.3	45.1†

Between Yes-No: * p = 0.04; ** p < 0.0001; † p = 0.054

Given that subjects with diabetes mellitus made up a large proportion of total study participants (approximately 60%), and both subjects who developed “clinically significant hypercalcemia” were diabetic, exploratory analyses were performed by this Reviewer to evaluate changes in mean serum calcium and Ca x P. As seen in the following table, Zemplar-treated diabetic subjects had higher increases in serum calcium from Baseline to Final Visit than those without diabetes mellitus:

	Diabetes?	Mean Baseline Ca	Mean Ca, Final Visit	Mean Change Ca	Mean Baseline CaxP	Mean CaxP, Final Visit	Mean Change CaxP
Zemplar	No	9.24	9.35	0.11	35.27	36.97	1.79
Zemplar	Yes	9.30	9.54*	0.23*	37.59*	42.05†	4.31*
Placebo	No	9.41	9.34	-0.07	35.58	37.44	1.77
Placebo	Yes	9.37	9.30	-0.05	37.83*	39.45*	1.91

Between DM groups: * p < 0.05, † p < 0.001

Zemplar-treated diabetic subjects also had an overall greater maximum calcium and Ca x P than those without diabetes:

	Diabetes?	Max Ca	Max CaxP
Zemplar	No	10.8	58
Zemplar	Yes	11.6	95.12
Placebo	No	10.9	83.6
Placebo	Yes	10.6	80.08

Comment: The following results again underscore the importance of laboratory monitoring for safety. There is no reason to suspect that diabetic subjects would be more susceptible to hypercalcemia with paricalcitol than with another vitamin D analog.

Finally, in paricalcitol-treated subjects, analyses were performed to compare mean iPTH, calcium, Ca x P, or change, or percent change in any of these variables between those on the QD regimen and those on the TIW regimen. There were no statistically or clinically significant differences between dosing regimens in any of the above variables.

7.1.7.5 Special assessments

Cardiovascular markers pro-BNP and troponin-T were measured in a subset of subjects in each of the three pivotal trials. Those who had both baseline and Final Visit values were included in these analyses. No statistically significant differences in cardiovascular marker variables were observed between treatment groups in mean change from baseline to Week 11, Final Visit, or Final Visit using ANOVA and ANCOVA. A combined analysis was not performed by the sponsor.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse were measured in the Phase I clinical pharmacology studies. The following vital signs were measured in the pivotal studies at baseline, Week 7, Week 15, and the Final Visit: SBP, DBP, pulse, and weight (considered a vital sign in this NDA).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital sign summaries were presented for the pivotal studies (CKD Stage 3 and 4 subjects).

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

No statistically significant differences were observed between the treatment groups in mean change from baseline to Week 7, Week 15, or Final Visit for any vital sign when studies were combined (SBP, DBP, pulse, weight). The following table summarizes the Baseline to Final Visit blood pressure findings:

Change in Blood Pressure from Baseline to Final Visit			
	Zemplar (N = 105)	Placebo (N = 109)	p-value
SBP (mmHg)	1.32 +/- 22.13	-0.42 +/- 18.25	0.53
DBP (mmHg)	0.03 +/- 13.83	-0.82 +/- 11.81	0.62

Comment: These differences are not clinically significant.

In study 2001020, a statistically significant difference was noted between treatments groups in median weight change from baseline to Final Visit (-0.91 kg Zemplar, +1.0 kg placebo; $p = 0.014$). In addition, although not statistically significant, SBP and DBP were increased in the Zemplar group from baseline to Final Visit whereas the placebo group values were decreased, making the between-group differences 8.3 mmHg ($p = 0.13$) and 4.5 mmHg ($p = 0.14$).

In study 2001021, a statistically significant difference was noted between treatment groups for the mean change between baseline and Week 7 in DBP (-4.0 mmHg Zemplar, +1.9 mmHg placebo; $p = 0.040$); this difference was not noted at Week 15 or at the Final Visit.

Comment: These findings are not clinically significant.

7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

Subjects With Clinically Significant Vital Sign Abnormalities at Final Visit (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4; All Treated Subjects)						
Vital Sign	Paricalcitol Capsule			Placebo		
	(N = 107)			(N = 113)		
	N	Low	High	N	Low	High
Systolic Blood Pressure (Low: ≤ 90 mmHg and change -15 mmHg; High: ≥ 180 mmHg and change +15 mmHg)	105	3 (3%)	3 (3%)	109	1 (1%)	2 (2%)
Diastolic Blood Pressure (Low: ≤ 50 mmHg and change -15 mmHg; High: ≥ 105 mmHg and change +15 mmHg)	105	2 (2%)	0 (0%)	109	0 (0%)	0 (0%)
Pulse Rate (Low: ≤ 50 bpm and change -15 bpm; High: ≥ 120 bpm and change +15 bpm)	104	0 (0%)	0 (0%)	108	0 (0%)	0 (0%)

7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*

Examining the individual data sets for vital sign change as well as absolute values, the range was similar for all vital signs among studies between Zemplar and placebo. There were no dropouts for vital sign abnormalities.

7.1.8.4 Additional analyses and explorations

Given the low number of abnormal vital signs, no further analyses were pursued.

7.1.9 Electrocardiograms (ECGs)

Not Applicable. The Sponsor states: *No quantitative ECG analyses were performed on data from the clinical pharmacology studies. No ECGs were performed as part of the pivotal Phase 3 CKD Stage 3 and 4 studies.*

QT studies were not required given the mechanism of action of paricalcitol and experience with vitamin D and other analogs. Hypercalcemia, the primary laboratory abnormality associated with use of these drugs, has well-described ECG effects, namely, QT interval shortening (as opposed to *hypocalcemia*, which has been demonstrated to cause QT prolongation, a condition that renders one vulnerable to torsades de pointes and sudden death). Increased arrhythmogenic

potential in the setting of hypercalcemia may occur with concomitant use of digitalis, as noted in the package insert.

7.1.10 Immunogenicity

Not applicable given that paricalcitol is not a therapeutic protein.

7.1.11 Human Carcinogenicity

Extensive studies have been conducted examining the properties of paricalcitol, including carcinogenicity studies. Based upon these data, orally administered paricalcitol's safety profile has been appropriately established. Furthermore, many vitamin D analogs have been studied and/or are in development for treatment of a variety of treatment-refractory cancers.

Comment: Although beyond the scope of this review, it is a promising area of research.

7.1.12 Special Safety Studies

No additional safety studies were performed to address safety concerns common to this pharmaceutical class (except for laboratory values described above) or to demonstrate a safety advantage over therapeutic alternatives.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Therapy with Vitamin D has a low potential for abuse based on historical experience. No studies were performed looking at rebound or withdrawal effects. Studies reported in the literature have shown that iPTH levels rebound after vitamin D treatment was interrupted.

7.1.14 Human Reproduction and Pregnancy Data

Minimal decreases in fetal viability have been shown in rabbits dosed 0.5 times that of human dose and rats dosed 2 times human dose. At the highest dose tested (13 times human dose), there was a significant increase in the mortality of newborn rats.

Paricalcitol capsule was administered to four women of childbearing age. No comments can be made about adverse drug reactions in this group. No studies have been conducted in pregnant women. Zemplar Injection is classified as a Pregnancy Category C. According to the Sponsor, no adverse events related to pregnancy have been reported in post-marketing surveillance of Zemplar Injection.

It is not known whether paricalcitol is excreted in human milk, although in rodent studies of radioactive-labeled drug, radioactivity was present in milk.

7.1.15 Assessment of Effect on Growth

Not applicable (studies were not performed on children).

7.1.16 Overdose Experience

The risk of acute overdosage of paricalcitol is hypercalcemia, and chronic administration may lead to hypercalcemia, elevated calcium/phosphorus product, and metastatic calcification. The NDA does not provide a dosage at which hypercalcemia is likely to occur, although it is noted that serum calcium and phosphorus levels should be monitored during dose adjustment. Particular concern is made for those patients receiving digitalis, for which hypercalcemia may precipitate fatal arrhythmias.

7.1.17 Postmarketing Experience

Paricalcitol capsule has not been approved in any country and no post-marketing data are available.

Post-marketing data are available regarding the experience with paricalcitol injection in CKD Stage 5 subjects. AERS Datamart lists 72 adverse events (although several appear to be duplicates) associated with the use of Zemplar injection. These events are listed in Appendix F.

In many of the AERS reports, patients were on multiple medications. Very few reports had additional information. Although these are open label reports, given the high prevalence out of total reported events, dysgeusia (26%), dermatitis (14%), and pruritus (13%) may be due to use of the drug.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Summary of the Number of Subjects Exposed to Paricalcitol Capsule by Study Phase and Subject Type			
Study Phase	Subject Type	Number of Subjects	% of Total
Phase 1	Healthy (single dose)	384	(57%)
Phase 1	Healthy (multiple dose)	20	(3%)
Phase 1	CKD Stage 3 and 4 (multiple dose)	29	(4%)
Phase 1	CKD Stage 5 (single dose)	22	(3%)
Phase 3	CKD Stage 3 and 4 – TIW treatment regimen*	72	(11%)
Phase 3	CKD Stage 3 and 4 – QD treatment regimen*	35	(5%)
Phase 3	CKD Stage 5-HD	73	(11%)
Phase 3	CKD Stage 5-PD	37	(6%)
	Total**	672	(100%)

* Phase 3, pivotal studies in CKD Stage 3 and 4 subjects for the indication of prevention and treatment of secondary hyperparathyroidism.
** Twelve of the same subjects were exposed to paricalcitol capsule in two different phase 1 studies. One additional subject was exposed to paricalcitol capsule in one of the phase 1 studies and also one of the phase 3 studies.
CKD = chronic kidney disease; HD = hemodialysis; PD = peritoneal dialysis; QD = daily dosing; TIW = 3 times a week (no more often than every other day)

7.2.1.2 Demographics

There were no significant differences between baseline demographic characteristics (gender, race, tobacco use, alcohol use, age, age group, time since CKD diagnosis, baseline phosphate binder usage, baseline eGFR, diabetic status at baseline, baseline body weight) in all studies combined, see Section 6.1.3.

7.2.1.3 Extent of exposure (dose/duration)

The average weekly dose was similar between the two dosing regimens; see Section 6.1.3 for charts of study drug administration (overall average weekly dose and days from first dose to last dose of study drug) and see Appendix G for the average weekly dose. The TIW regimen dose peak occurs at week 14 and the QD regimen dose peak occurs at week 9. Both treatment regimens saw decreases in mean weekly dosing thereafter until the end of the study. Reasons for this may have included: those subjects on higher doses may have been discontinued first, or the algorithm may have been too aggressive, leading to an “overshoot” of paricalcitol dosing.

Comment: Although either of these explanations may have contributed to the dosing pattern seen with paricalcitol, the rapid response in iPTH and serum calcium to dosing adjustments assures that there will not be prolonged exposure to excessive dosing with careful monitoring. Frequent monitoring is warranted until paricalcitol dose is stabilized.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There were no other studies to evaluate.

7.2.2.2 Postmarketing experience

See section 7.1.17.

7.2.2.3 Literature

Five randomized controlled trials²⁻⁶ were reviewed examining secondary hyperparathyroidism outcomes with paricalcitol as one of the treatment arms. All trials utilized intravenous paricalcitol in a CKD Stage 5 (ESRD) patient population. All five studies demonstrated paricalcitol was efficacious in lowering iPTH. Three studies^{3,5,6} compared paricalcitol with calcitriol, and found fewer episodes of hyperphosphatemia, hypercalcemia, or calcium/phosphorus product (or combinations of these) than with calcitriol therapy.

7.2.3 Adequacy of Overall Clinical Experience

Adequacy of subject numbers including adequate numbers of various demographic subsets and people with pertinent risk factors

Although the numbers of subjects are considerably below that for either short-term or long-term intended drug usage as recommended by the ICH Guidance, given the experience both with the injectable formulation, other drugs of this class, as well as the limited patient population, the number of exposed subjects is acceptable.

Adequacy of doses and durations of exposure for the intended use

Given the high degree of physician involvement in drug monitoring and titration, the 24-week data presented are adequate.

Adequacy of study design to answer critical questions

As demonstrated in the efficacy portion of this NDA, the outcome data are very strong. The safety signals are reflective of the pharmacologic action of the drug.

Evaluation of class effects and whether problems suggested by preclinical data were assessed

Consideration of hypercalcemia (the primary class effect) and its attendant consequences were adequately addressed in the NDA. Preclinical effects were expected based on the pharmacologic activity of the drug.

Evaluation of whether patients excluded from the study limit the relevance of safety assessments

The main exclusions were of subjects who would be predisposed to hypercalcemia, rapid progression of renal failure, and kidney stones. Given that these subjects should not be administered paricalcitol (as stated in the label), it is reasonable that they were excluded from the study protocol. While inclusion would have provided some useful information on those with liver disease and glucocorticoid use; the existence of such exclusion criteria does not limit the relevance of the overall safety assessments.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

As stated above, all preclinical effects were expected based on the pharmacologic activity of the drug. Please see Dr. Davis-Bruno's review for details.

7.2.5 Adequacy of Routine Clinical Testing

Clinical testing appears adequate given the experience with this drug.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Because paricalcitol is used in patients with renal disease, attention to pharmacokinetics in this patient population and renal clearance was particularly important. Study M03-633 evaluated the PK and PD of single- and multiple-doses of paricalcitol capsule in CKD Stage 3 and 4 subjects. The pharmacokinetics of paricalcitol capsule were similar in CKD Stage 3 and 4 patients to those of CKD Stage 5 subjects; the mean half-life was 16 to 23 hours and steady state was reached by Study Day 6.

Metabolism and Elimination

After oral administration of ³H-paricalcitol, approximately 18% of total radioactivity was excreted in urine and about 70% was excreted in the feces. No parent drug was excreted in the urine and about 2% of dose radioactivity was unchanged parent in the feces. Circulating plasma metabolites include 24(R)-hydroxyparicalcitol and an unidentified non-polar metabolite. At least eight fecal metabolites were discerned.

Clearance

Mean ± SD Paricalcitol CL/F Following Single and Multiple Oral Dose for Different Populations		
	CL/F	
	Single Dose	Multiple Dose
Healthy	3.95 ± 1.19	4.33 ± 2.08
CKD Stage 3	1.77 ± 0.50	2.01 ± 0.77
CKD Stage 4	1.52 ± 0.36	1.75 ± 0.39
CKD Stage 5 with HD	1.82 ± 0.75	NS
CKD Stage 5 with CPD	1.76 ± 0.77	NS

NS = Not studied.

Hepatic Impairment

Although paricalcitol capsule has not been studied in patients with hepatic impairment, a study involving Zemplar Injection was performed in patients with no, mild, and moderate hepatic impairment, and demonstrated that the PK of plasma unbound paricalcitol was similar across groups. It is therefore expected that paricalcitol capsule will be safe and well-tolerated in patients with hepatic impairment, since the PK profile is similar between the injection and capsule formulations.

Drug Interactions

Paricalcitol is not an inhibitor of CYP3A, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, or CYP2E1 in *in vitro* evaluations at concentrations up to 50 nM. Two of the elimination pathways for paricalcitol, CYP3A and 24-hydroxylase, are inhibited by ketoconazole.

The PK of paricalcitol (16 mcg) was unaffected when orally co-administered with omeprazole (40 mg). Additionally, a study was performed (M04-692) evaluating the interaction between paricalcitol (4 mcg) and ketoconazole (CYP3A inhibitor; administered 200 mg BID), in an open-label, sequential design. The C_{max} of paricalcitol was minimally affected by ketoconazole, but the AUC_{0-∞} approximately doubled.

Comment: Given that dosing is titrated to iPTH levels, specific recommendations for dosing change in the case of concomitant ketoconazole therapy are probably not needed. However, monitoring should be increased in this situation.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Adverse events of concern for this drug class are primarily related to the incidence of hypercalcemia, Ca x P and the consequences thereof, or over-suppression of iPTH. As expected, calcium did rise in the group treated with active drug as compared with placebo, but the limited number of subjects made it difficult to draw any conclusions about the adverse consequences of raised serum calcium levels in this population. It is clear that as drug dose is decreased or withdrawn as a result of either high serum calcium or Ca x P, the adverse laboratory test sequelae reverse. Longer-term effects of either elevated calcium or suppression of iPTH cannot be determined from these studies.

7.2.8 Assessment of Quality and Completeness of Data

The database appears clean with very little missing data in the pivotal trials. Data quality and integrity was addressed in Section 4.4.

7.2.9 Additional Submissions, Including Safety Update

The 120-Day Safety Report was submitted to the Electronic Document Room on November 10, 2004. The data presented are the results of two Clinical Pharmacology studies (M04-692 and M04-693) and the results are incorporated into data descriptions in above sections. M04-692 studied the interaction of paricalcitol capsule with ketoconazole; M04-693 was a bioequivalence study comparing paricalcitol capsule from different dosage strengths. The results of study M04-692 is reported above under the section of drug interactions. Otherwise, data in the safety update do not suggest new or unexpected safety concerns.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The relatively small number of subjects enrolled in the pivotal studies is an important limitation to the safety evaluation. As discussed in previous sections, individual adverse events of interest include allergy and increased serum transaminases (although the relationship of paricalcitol in the one case seen was debatable). There did not appear to be a greater number of adverse events associated with the primary laboratory event, hypercalcemia. In addition, there did not appear to be a greater number of events of renal failure. Progression of CKD is part of the natural history of this disease and although hypercalcemia can contribute to CKD worsening, there was no evidence that this occurred in the pivotal studies due to appropriate monitoring. Although there were a greater number of cardiovascular events in the paricalcitol group as compared with the

placebo group, this difference was not statistically significant and there was no evidence that these events were related to paricalcitol use; specifically, an increased Ca x P.

In conclusion, there were few important drug-related adverse events. Dose titration and clinical monitoring by a medical professional should ensure the safe use of paricalcitol capule.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The benefit of pooling the data is that increased power allows for better evaluation of safety and efficacy outcomes. Although no comparison of baseline characteristics, outcomes, or adverse events was performed between studies, dose and outcomes were similar across pivotal studies.

The drawback of pooling data is that two of the three studies used a TIW dosing regimen, whereas the third study utilized a QD dosing regimen. Some of the concerns are outlined in the Integrated Summary of Efficacy.

The majority of the analyses evaluated in the Integrated Reviews were pooled by combining all pivotal studies. Several analyses were performed by combining studies by treatment regimen (TIW vs. QD).

7.4.1.2 Combining data

In pooling the data across the three pivotal trials, the studies were simply combined (i.e., not weighted), given the similar sample sizes and protocols (2001019 and 2001020 had identical TIW dosing protocols; 2001021 was dosed QD).

7.4.2 Explorations for Predictive Factors

As stated elsewhere, the primary adverse event of concern from vitamin D or any of its analogs, is hypercalcemia (and the signs and symptoms directly or indirectly related to hypercalcemia). Dose and duration of use of paricalcitol or a similar drug impacts the likelihood of developing hypercalcemia. However, the monitoring of calcium, phosphorus, Ca x P, and iPTH in order to adjust dose should help to lessen the adverse biochemical effects.

7.4.2.1 Explorations for dose dependency for adverse findings

Because dose changed depending on serum iPTH response, analysis was performed evaluating adverse events for subjects experiencing the spectrum of iPTH levels. Statistically significant adverse events were seen between the various levels of iPTH reduction (< 60, ≥ 60 – ≤ 150, and > 150 pg/mL) in the overall adverse event incidence, as well as for bradycardia:

Statistically Significant Differences Between Groups for Treatment-Emergent Adverse Events by Minimum iPTH Level Achieved (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)							
COSTART V Term	< 60 pg/mL		≥ 60 – ≤ 150 pg/mL		> 150 pg/mL		p-value ^a
	Paricalcitol Capsule (N = 34)	Placebo (N = 1)	Paricalcitol Capsule (N = 58)	Placebo (N = 38)	Paricalcitol Capsule (N = 13)	Placebo (N = 72)	
Overall	32 (94%)	0 (0%)	45 (78%)	29 (76%)	11 (85%)	56 (78%)	0.015
Bradycardia	0 (0%)	0 (0%)	0 (0%)	1 (3%)	1 (8%)	0 (0%)	0.013

a. p-value for test of odds ratio homogeneity from Breslow-Day Test.

Comment: These results do not appear to be clinically meaningful. Statistically significant results on adverse events overall are likely being driven by the relatively large number of subjects who achieved iPTH < 60 pg/mL, as compared with those taking placebo. There are too few subjects to make any determinations about bradycardia. Differences between minimum iPTH level achieved (< 60 pg/mL, ≥ 60 - ≤ 150 pg/mL, and > 150 pg/mL) in the paricalcitol capsule-treated group do not appear to be practically important.

7.4.2.2 Explorations for time dependency for adverse findings

No clinically relevant trends were apparent when adverse events were summarized according to time of event and treatment regimen.

Prevalence of Treatment-Emergent Adverse Events Phase 3 Dosing Regimen TIW All Treated Subject Population			
Group	Days 1-56	Days 1-112	Days 1-End
	New N (Zemplar) = 72 N (Placebo) = 73	Cumulative N (Zemplar) = 72 N (Placebo) = 73	Cumulative N (Zemplar) = 72 N(Placebo) = 73
TIW: Zemplar	37 (51%)	54 (75%)	56 (78%)
TIW: Placebo	35 (48%)	50 (68%)	52 (71%)

Prevalence of Treatment-Emergent Adverse Events Phase 3 Dosing Regimen QD All Treated Subject Population			
Group	Days 1-56	Days 1-112	Days 1-End
	New N (Zemplar) = 35 N (Placebo) = 40	Cumulative N (Zemplar) = 35 N (Placebo) = 40	Cumulative N (Zemplar) = 35 N (Placebo) = 40
QD: Zemplar	19 (54%)	31 (89%)	32 (91%)
QD: Placebo	20 (50%)	33 (83%)	34 (85%)

7.4.2.3 Explorations for drug-demographic interactions

The difference between groups in treatment-emergent adverse events was relatively small, which precludes meaningful assessment by subgroup analysis.

7.4.2.4 Explorations for drug-disease interactions

The difference between groups in treatment-emergent adverse events was relatively small, which precludes meaningful assessment by subgroup analysis.

7.4.2.5 Explorations for drug-drug interactions

The difference between groups in treatment-emergent adverse events was relatively small, which precludes meaningful assessment by subgroup analysis.

7.4.3 Causality Determination

As stated previously, adverse events related to hypercalcemia are biologically plausible. The Sponsor's definition of "clinically meaningful hypercalcemia" (two consecutive episodes of serum calcium > 10.5 mg/dL) was only seen in 2/106 paricalcitol subjects and 0/111 placebo subjects. It is therefore difficult to evaluate the frequency and expected adverse events that will likely be seen when the drug is in the marketplace. Nevertheless, one can expect that hypercalcemia will be seen due to the use of this drug.

Other potential biologically plausible events include adynamic bone disease due to iPTH oversuppression and cardiovascular disease due to elevated calcium/phosphorus product. These are potential consequences known from use of other drugs in this class and may be monitored by laboratory measurements.

Other elements of causality determination include investigator-deemed potential causality and statistically different rates of an AE between paricalcitol and placebo. For a table of adverse events deemed by the Investigator to possibly be related to use of drug, see section 7.1.5.5, Identifying common and drug-related adverse events. As stated in a previous section, allergy is a

potential adverse event attributable to use of drug. Only one allergic reaction, maculopapular rash, was deemed due to use of paricalcitol.

The only adverse event that was determined to be statistically significantly higher in paricalcitol-treated subjects than placebo was vertigo. Review of these cases by the Sponsor indicated no apparent link between the occurrence of vertigo and the use of paricalcitol capsule, including dose, serum calcium, and treatment duration. In all cases, the symptoms resolved while the subjects continued on paricalcitol. In addition, there are no reports in the literature of an increased association with vitamin D or its analogs and vertigo.

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8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The initial dose is based on baseline iPTH levels: ≤ 500 pg/mL, 1 mcg QD or 2 mcg TIW; > 500 pg/mL, 2 mcg QD or 4 mcg TIW. However, there is no iPTH lower limit specified at which Zemplar should not be administered. Dose titration is individualized based on iPTH levels according to the following algorithm:

iPTH Level Relative to Baseline	Zemplar® Capsule Dose	Dose Adjustment at 2 to 4 Week Intervals	
		Daily Dosage	Three Times a Week Dosage*
The same or increased	Increase	1 mcg	2 mcg
Decreased by $< 30\%$			
Decreased by $\geq 30\%$, $\leq 60\%$	Maintain		
Decreased $> 60\%$	Decrease	1 mcg	2 mcg
iPTH < 60 pg/mL			

If a patient is taking the lowest dose on the daily or three times a week regimen, and a dose reduction is needed, dosing frequency can be decreased.
 * To be administered not more often than every other day

Furthermore, the label suggests that serum calcium and phosphorus should be closely monitored after initiation of Zemplar capsules and during dose titration periods. However, there is no instruction on at what levels and how much to dose reduce or withhold: *Serum calcium and phosphorus levels should be closely monitored after initiation of Zemplar® Capsules and during dose titration periods.*

Comment: Because dose titration based on laboratory measurements is such an important part of the appropriate use of this drug,

Comment: The optimal dosing regimen is still unclear based on the pivotal studies.

there are no head-to-head data either demonstrating improved compliance or similar safety/efficacy for the QD versus the TIW regimens. Combined analyses seem to indicate similar outcomes with the two regimens and the individual QD study seems to indicate that it is safe and effective in this population; however, literature suggests that daily dosing of calcitriol or its analogs may predispose to hypercalcemia.

8.2 Drug-Drug Interactions

Drug interaction potential was studied *in vitro* in cytochrome P450 assays, as well as in PK studies of paricalcitol with omeprazole and ketoconazole. Paricalcitol is not expected to inhibit the clearance of drugs metabolized by cytochrome P450 enzymes CYP3A, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1, nor induce the clearance of drug metabolized by CYP2B6, CYP2C9 or CYP3A. The pharmacokinetics of paricalcitol were unaffected when co-administered with omeprazole; however, the AUC_{0-∞} of paricalcitol approximately doubled in the presence of ketoconazole. The label also provides the following precaution: “Digitalis toxicity is potentiated by hypercalcemia of any cause, so caution should be applied when digitalis compounds are prescribed concomitantly with paricalcitol.”

Because of the relatively low sample size, it was not possible to determine whether there were any clinically important interactions between concomitant medication use and paricalcitol.

8.3 Special Populations

Race, gender, and age

The Sponsor has performed subpopulation analyses for race, gender, and age. The relatively small sample size for several of the subpopulations is noted (e.g., primary efficacy in “other” race category).

The following tables attempt to describe safety and effectiveness by race:

Proportion of Subjects Who Achieved Two Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Race in the Three Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)										
	White (N = 147)			Black (N = 56)			Other (N = 6)			Homogeneity p-value^b
	Paricalcitol Capsule (N = 69)	Placebo (N = 78)	p-value^a	Paricalcitol Capsule (N = 27)	Placebo (N = 29)	p-value^a	Paricalcitol Capsule (N = 5)	Placebo (N = 1)	p-value^a	
2 consecutive $\geq 30\%$ decreases from Baseline in iPTH	62 (90%)	9 (12%)	< 0.001	25 (93%)	5 (17%)	< 0.001	5 (100%)	0 (0%)	0.167	0.905

a. p-value derived from Fisher's exact test.
b. p-value for the Breslow-Day test of odds ratio homogeneity between White and Black subgroups only.

Proportion of Subjects Who Achieved Two Consecutive Elevated Calcium, Phosphorus, and CaxP Values by Race (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)

Chemistry Variable	White Only		Black Only		Other Races		p-value ^a
	Paricalcitol Capsule (N = 72)	Placebo (N = 80)	Paricalcitol Capsule (N = 27)	Placebo (N = 29)	Paricalcitol Capsule (N = 5)	Placebo (N = 1)	
Calcium (> 10.5 mg/dL) ^b	1 (1%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	Not performed
Phosphorus (> 5.5 mg/dL)	5 (7%)	9 (11%)	4 (15%)	3 (10%)	2 (40%)	1 (100%)	0.344
CaxP (> 55 mg ² /dL ²)	6 (8%)	5 (6%)	5 (19%)	2 (7%)	2 (40%)	0 (0%)	0.452

a. p-value for test of odds ratio homogeneity between White and Black groups only from Breslow-Day Test.

b. Breslow-Day Test was not computed on calcium data because the data were too sparse to calculate.

Lowest iPTH Achieved by Race (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)

Lowest iPTH Achieved (pg/mL)	Number (%) of Subjects						p-value ^a
	White		Black		Other Races		
	Paricalcitol Capsule (N = 73)	Placebo (N = 81)	Paricalcitol Capsule (N = 27)	Placebo (N = 29)	Paricalcitol Capsule (N = 5)	Placebo (N = 1)	
< 60	28 (38%)	1 (1%)	3 (11%)	0 (0%)	3 (60%)	0 (0%)	0.784
≥ 60	45 (62%)	80 (99%)	24 (89%)	29 (100%)	2 (40%)	1 (100%)	

a. p-value for test of odds ratio homogeneity between White and Black groups only from Breslow-Day Test.

The following tables describe safety and efficacy for gender:

Proportion of Subjects Who Achieved Two Consecutive ≥ 30% Decreases from Baseline in iPTH by Gender in the Three Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)

	Male (N = 142)			Female (N = 67)			Homogeneity p-value ^b
	Paricalcitol Capsule (N = 69)	Placebo (N = 73)	p-value ^a	Paricalcitol Capsule (N = 32)	Placebo (N = 35)	p-value ^a	
2 consecutive ≥ 30% decreases from Baseline in iPTH	63 (91%)	8 (11%)	< 0.001	29 (91%)	6 (17%)	< 0.001	0.523

a. p-value derived from a Fisher's exact test.

b. p-value for the Breslow-Day test of odds ratio homogeneity.

Summary of Subjects Who Experienced Two Consecutive Elevations in Calcium by Gender; Phase 3 (Intent-to-Treat Population)							
2 consecutive calcium > 10.5 mg/dL	Male (N=146)			Female (N= 68)			Between Group P-Value#
	Oral Zemplar (N=71) N (%)	Placebo (N=75) N (%)	P-Value@	Oral Zemplar (N=33) N (%)	Placebo (N=35) N (%)	P-Value@	
YES	0 (0.0%)	0 (0.0%)	NA	2 (6.1%)	0 (0.0%)	0.232	NA
NO	71 (100.0%)	75 (100.0%)		31 (93.9%)	35 (100.0%)		

@ p-value is derived from Fisher's exact test.
p-value is derived from Breslow-Day test. Breslow-Day test is not computed because the data are sparse.

Summary of Subjects Who Experienced Two Consecutive Elevations in Phosphorus or CaxP By Gender; Phase 3 (Intent-to-Treat Population)							
2 consecutive elevations in chemistry	Male (N=146)			Female (N= 68)			Between Group p-value#
	Oral Zemplar (N=71) N (%)	Placebo (N=75) N (%)	P-Value@	Oral Zemplar (N=33) N (%)	Placebo (N=35) N (%)	P-Value@	
phosphorus (>5.5 mg/dL)							
YES	7 (9.9%)	10 (13.3%)	0.610	4 (12.1%)	3 (8.6%)	0.705	0.446
NO	64 (90.1%)	65 (86.7%)		29 (87.9%)	32 (91.4%)		
CaxP (>55 mg ² /dL ²)							
YES	7 (9.9%)	6 (8.0%)	0.776	6 (18.2%)	1 (2.9%)	0.051+	0.132
NO	64 (90.1%)	69 (92.0%)		27 (81.8%)	34 (97.1%)		

@ p-value is derived from Fisher's exact test.
p-value is derived from Breslow-Day test.
***, **, *, + statistically significant at p=0.001, 0.01, 0.05, 0.10 levels, respectively.

Lowest iPTH Achieved by Gender (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)					
Lowest iPTH Achieved (pg/mL)	Number (%) of Subjects				p-value ^a
	Male		Female		
	Paricalcitol Capsule (N = 72)	Placebo (N = 75)	Paricalcitol Capsule (N = 33)	Placebo (N = 36)	
< 60	23 (32%)	0 (0%)	11 (33%)	1 (3%)	0.172
≥ 60	49 (68%)	75 (100%)	22 (67%)	35 (97%)	

a. p-value for test of odds ratio homogeneity from Breslow-Day Test.

The following tables describe safety and efficacy for age:

Proportion of Subjects Who Achieved Two Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Age Group (< 65 years and ≥ 65 years) in the Three Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)							
	Age < 65 years (N = 110)			Age ≥ 65 years (N = 99)			Homogeneity p-value ^b
	Paricalcitol Capsule (N = 49)	Placebo (N = 61)	p-value ^a	Paricalcitol Capsule (N = 52)	Placebo (N = 47)	p-value ^a	
2 consecutive $\geq 30\%$ decreases from Baseline in iPTH	45 (92%)	9 (15%)	< 0.001	47 (90%)	5 (11%)	< 0.001	0.833

a. p-value derived from a Fisher's exact test.
b. p-value for the Breslow-Day test of odds ratio homogeneity.

Proportion of Subjects Who Achieved Two Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Age Group (< 75 years and ≥ 75 years) in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)							
	Age < 75 years (N = 173)			Age ≥ 75 years (N = 36)			Homogeneity p-value ^b
	Paricalcitol Capsule (N = 79)	Placebo (N = 94)	p-value ^a	Paricalcitol Capsule (N = 22)	Placebo (N = 14)	p-value ^a	
2 consecutive $\geq 30\%$ decreases from Baseline in iPTH	73 (92%)	12 (13%)	< 0.001	19 (86%)	2 (14%)	< 0.001	0.481

a. p-value derived from a Fisher's exact test.
b. p-value for the Breslow-Day test of odds ratio homogeneity.

Lowest iPTH Achieved by Age Group (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)					
Lowest iPTH Achieved (pg/mL)	Number (%) of Subjects				p-value ^a
	< 65 Years of Age		≥ 65 Years of Age		
	Paricalcitol Capsule (N = 50)	Placebo (N = 62)	Paricalcitol Capsule (N = 55)	Placebo (N = 49)	
< 60	22 (44%)	1 (2%)	12 (22%)	0 (0%)	0.565
≥ 60	28 (56%)	61 (98%)	43 (78%)	49 (100%)	

a. p-value for test of odds ratio homogeneity from Breslow-Day Test.

Lowest iPTH Achieved by Age Group (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)					
Lowest iPTH Achieved (pg/mL)	Number (%) of Subjects				p-value ^a
	< 75 Years of Age		≥ 75 Years of Age		
	Paricalcitol Capsule (N = 83)	Placebo (N = 96)	Paricalcitol Capsule (N = 22)	Placebo (N = 15)	
< 60	30 (36%)	1 (1%)	4 (18%)	0 (0%)	0.799
≥ 60	53 (64%)	95 (99%)	18 (82%)	15 (100%)	

a. p-value for test of odds ratio homogeneity from Breslow-Day Test.

Proportion of Subjects Who Achieved Two Consecutive Elevated Calcium, Phosphorus, and Ca x P Values by Age Group (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)					
Chemistry Variable	< 65 Years of Age		≥ 65 Years of Age		p-value ^a
	Paricalcitol Capsule (N = 50)	Placebo (N = 61)	Paricalcitol Capsule (N = 54)	Placebo (N = 49)	
Calcium (> 10.5 mg/dL) ^b	1 (2%)	0 (0%)	1 (2%)	0 (0%)	Not performed
Phosphorus (> 5.5 mg/dL)	9 (18%)	9 (15%)	2 (4%)	4 (8%)	0.287
Ca x P (> 55 mg ² /dL ²)	11 (22%)	5 (8%)	2 (4%)	2 (4%)	0.273

a. p-value for test of odds ratio homogeneity from Breslow-Day Test.

b. Breslow-Day Test was not computed on calcium data because the data were too sparse to calculate.

Proportion of Subjects Who Achieved Two Consecutive Elevated Calcium, Phosphorus, and Ca x P Values by Age Group (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)					
Chemistry Variable	< 75 Years of Age		≥ 75 Years of Age		p-value ^a
	Paricalcitol Capsule (N = 82)	Placebo (N = 95)	Paricalcitol Capsule (N = 22)	Placebo (N = 15)	
Calcium (> 10.5 mg/dL)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	Not performed
Phosphorus (> 5.5 mg/dL)	11 (13%)	13 (14%)	0 (0%)	0 (0%)	Not performed
Ca x P (> 55 mg ² /dL ²)	13 (16%)	7 (7%)	0 (0%)	0 (0%)	Not performed

a. Breslow-Day Test was not computed because the data were too sparse to calculate.

Hepatic and renal insufficiency

The target population for this drug is patients with CKD Stage 3 and 4 (GFR 15 – 59). The pharmacokinetics of paricalcitol are similar across CKD Stages 3 to 5, as shown in the following tables:

Mean ± SD Paricalcitol CL Following Single IV Dose for Different Populations		
Population	CL (L/h)	Study Number
Healthy	2.6 ± 1.1	2000007
CKD Stage 5 on HD	1.5 ± 0.6	2000005
CKD Stage 5 on CPD	1.5 ± 1.0	2000006

Mean ± SD Paricalcitol CL/F Following Single and Multiple Oral Dose for Different Populations		
Population	CL/F	
	Single Dose	Multiple Dose
Healthy	3.95 +/- 1.19	4.33 +/- 2.08
CKD Stage 3	1.77 +/- 0.50	2.01 +/- 0.77
CKD Stage 4	1.52 +/- 0.36	1.75 +/- 0.39
CKD Stage 5 with HD	1.82 +/- 0.75	NS
CKD Stage 5 with CPD	1.76 +/- 0.77	NS

NS = Not studied.

No statistically significant difference was found for AUC_{0-∞} between subjects with mild and moderate hepatic impairment and healthy subjects in Study M98-914 (NDA 20-819). No dosing adjustment is required in patients with mild to moderate hepatic impairment. The influence of severe hepatic impairment in the pharmacokinetics of paricalcitol is not known.

Pregnancy and lactation

Only four female subjects of childbearing age (15-45 years old) were enrolled in the pivotal Phase 3 CKD Stage 3 and 4 studies. No studies have been conducted in pregnant women, and none of the women enrolled in any paricalcitol studies were pregnant or became pregnant. According to the Sponsor, no adverse events related to pregnancy have been reported during post-marketing surveillance of paricalcitol injection. It is unknown whether paricalcitol is excreted in human milk.

8.4 Pediatrics

Agreements related to pediatric studies reached at the End-of-Phase 2 meeting are outlined in section 2.5.

8.5 Advisory Committee Meeting

Not applicable, as there are no issues in this application that require Advisory Committee input or discussion.

8.6 Literature Review

See section 7.2.2.3 for a review of the literature as it related to paricalcitol safety.

8.7 Postmarketing Risk Management Plan

Not applicable, as no plan was submitted by the Sponsor, nor is one deemed necessary by the Division.

8.8 Other Relevant Materials

A consult from the Division of Medication Errors and Technical Support was reviewed regarding container label, carton, and insert labeling revision recommendations.

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9 OVERALL ASSESSMENT

9.1 Conclusions

Abbott has demonstrated the general safety and effectiveness of Zemplar capsules in treating secondary hyperparathyroidism in patients with CKD Stage 3 and 4. The primary differences between the Reviewer's conclusions and those of the Sponsor are highlighted in the labeling review (see section 9.4).

9.2 Recommendation on Regulatory Action

This Reviewer recommends that this NDA be Approved. This Reviewer agrees with the Sponsor that the risk of this drug (namely, hypercalcemia) is outweighed by the benefit (reduction of secondary hyperparathyroidism) in the proposed patient population.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No specific risk management activity has been recommended.

9.3.2 Required Phase 4 Commitments

Decisions regarding the Pediatric Research Equity commitment was summarized in the NDA as follows: on February 8, 2002, the Agency granted a waiver for pediatric studies in subjects from birth to 11 years of age and a deferral for pediatric studies in subjects from 12 to 16 years of age until _____

_____ In addition, a request to defer the requirement for pediatric data to be submitted by _____ was submitted. On March 17, 2004, the Agency granted an extension of the deferral for conducting the pediatric studies in pre-dialysis CKD patients aged 12-16 years until December 31, 2008, by which time clinical and pharmacokinetic data from adults with pre-dialysis CKD will have been reviewed.

9.3.3 Other Phase 4 Requests

No other Phase 4 commitments were requested.

9.4 Labeling Review

The following is a summary of the salient issues from the labeling review (section 10.2):

- The _____ have not been clinically demonstrated.
- Statements _____ are misleading.
- The pivotal study design should be described in more detail given that guidelines for treatment of SHPT in CHD Stage 3 and 4 have been published subsequent to the start of these studies.
- _____
- The fact that baseline 25-OH vitamin D levels of the study participants are unknown should be stated explicitly.
- Hypercalcemia, _____ should be defined, as these values (two consecutive elevations) are more stringent than values that were used for dose adjustment in the clinical studies. Further information regarding safety laboratory values ! _____ would provide a more complete safety profile.
- _____
- The Warnings section should be strengthened.
- Language should be updated for consistency with labeling of similar drugs.
- The adverse event table should be changed to: Treatment - Emergent Adverse Events by Body System Occurring with Greater Frequency in $\geq 2\%$ of Subjects in the Zemplar Treatment Group.
- Because of the importance of clinical monitoring for proper use of this drug, ; _____

9.5 Comments to Applicant

Comments to the applicant are limited to the labeling changes as described in Section 9.4.

10 APPENDICES

10.1 Review of Individual Study Reports

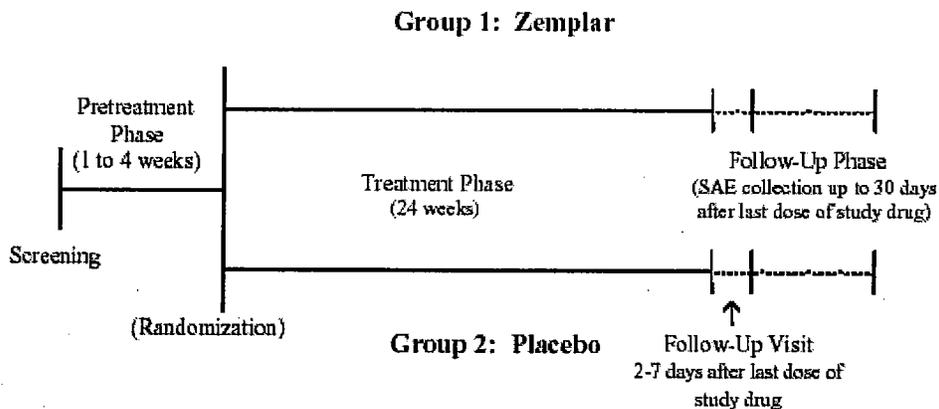
Study 2001-019

Study Title: A Phase 3, Prospective, Randomized, Placebo-Controlled, Double-Blind, Multi-Center Study to Determine the Safety and Efficacy of Zemplar Capsule (Dosed 3 Times Weekly) in Reducing Elevated Serum Intact Parathyroid Hormone Levels in Subjects with Chronic Kidney Disease

Primary Objectives: To determine the safety and efficacy of Zemplar Capsule as compared to placebo in reducing serum iPTH levels in subjects with Stage 3 and 4 CKD.

Secondary Objectives: NA

Design: Phase 3, prospective, randomized, placebo-controlled, double-blind, 24-week treatment phase, multi-center study in Stage 3 and 4 CKD subjects with elevated iPTH levels (≥ 150 pg/mL). Study drug is administered TIW.



Patient Population:

To enter Pre-Treatment Phase, subjects must:

1. not have been on pharmacological vitamin D therapy for at least four weeks
2. have had an iPTH value ≥ 120 pg/mL
3. have had an eGFR of 15 to 60 mL/min
4. not have been expected (in the opinion of the Investigator) to begin dialysis for at least six months

To enter Treatment Phase, subjects must:

1. have had two consecutive iPTH measurements that averaged ≥ 150 pg/mL (all values must have been ≥ 120 pg/mL)
2. have had two consecutive results for calcium levels 8.0 to 10.0 mg/dL
3. have had two consecutive results for phosphorus levels ≤ 5.2 mg/dL
4. have satisfied inclusion and exclusion criteria after a minimum of one week in the Pre-Treatment Phase (see Appendix A)

Treatment Groups: Approximately 68 subjects were assigned in an equal ratio (1:1) to either Zemplar capsule or placebo capsule.

The initial dose was either 2 or 4 mcg, based on baseline iPTH according to the criteria presented in the following table:

Zemplar Initial Dose	
Initial Dose	Baseline iPTH Level
2 mcg	≤ 500 pg/mL
4 mcg	> 500 pg/mL

At the start of the Treatment Phase, eligible subjects were assigned a unique 4-digit number in ascending numerical sequence per investigative site, which randomized them to treatment with Zemplar or placebo.

Endpoints: The primary efficacy endpoint was the achievement of two consecutive $\geq 30\%$ decreases from baseline iPTH levels. Safety was assessed through an evaluation of clinically meaningful hypercalcemia (two consecutive calcium results > 10.5 mg/dL), the incidence of adverse events, the change from baseline in chemistry, hematology, and urinalysis laboratory values, the change from baseline in subject vital signs, and progressive changes in kidney function observed via changes in eGFR.

Procedures	Schedule of Assessments					
	Screening Visit	Pre-Treatment Phase (weeks) ^a		Treatment Phase (weeks)		Follow-Up Phase ^b
		1	2 to 4	1	2 to 24	
Informed consent ^c	X					
Medical history		X				
Concurrent medications		X ^d	X	X	X	
Physical examination		X			X	
Vital signs		X			X ^e	
Serum pregnancy test ^f		X				
Complete Chemistry and Hematology		X		X ^{g,h}	X ^h	
Limited Chemistry: Calcium, ⁱ Phosphorus, iPTH, albumin	X ^j		X ^k		X ^l	

Schedule of Assessments						
Procedures	Screening Visit	Pre-Treatment Phase (weeks) ^a		Treatment Phase (weeks)		Follow-Up Phase ^b
Urinary pyridinoline, deoxypyridinoline, serum bone-specific alkaline phosphatase, serum osteocalcin				X ^g	X ^m	X
Serum creatinine, BUN, albumin	X ⁿ					
Urinalysis				X ^g		X
Spot urine for calcium/creatinine ratio	X				X ⁿ	X
24 hr. urine collection (calcium, phosphorus, Ccr)		X ⁿ				X
Study drug administration ^o				X	X	
Study drug compliance assessment					X	X
Adverse event monitoring ^p				X	X	X
Serious adverse event monitoring ^q	X	X	X	X	X	X

a. Duration was dependent on the length of time it took for the subject's laboratory values to reach the levels required for entering into the Treatment Phase.
b. Performed at the Follow-Up Visit; should have occurred approximately 2 to 7 days following final dose of study drug for all subjects who completed or prematurely discontinued the study.
c. Prior to the performance of any study procedures.
d. Assessed at every visit.
e. At Weeks 7 and 15 visits only.
f. All women.
g. Prior to study drug administration.
h. Results used in eGFR calculation derived from MDRD study.
i. All calcium results were to be corrected.
j. iPTH only.
k. Serum creatinine was also to be measured if 24-hour urine collections were done at second Pre-Treatment Visit.
l. Every 2 weeks (office visits typically occurred on odd-numbered weeks).
m. At Week 11 visit.
n. Any time during Pre-Treatment.
o. 3 times per week on Monday, Wednesday, and Friday.
p. Collected at start of study drug administration through 30 days following the last dose of study drug.
q. Collected from the time of informed consent through 30 days following the last dose of study drug.

Statistical Analyses:

Primary Efficacy Assessment – The efficacy endpoint was a dichotomous endpoint, that is, each subject must have either achieved or failed to achieve the efficacy endpoint throughout the trial. Percent change from baseline in iPTH was $((\text{value}-\text{base})/\text{base}) \times 100$, where “base” is baseline iPTH and “value” represents subsequent iPTH assessments during the treatment phase. Missing values were excluded. The primary efficacy endpoint was evaluated with statistical hypothesis testing utilizing subjects in the Intent-to-Treat Population. A Fisher’s exact test was used to test for a difference between treatment groups in the proportion of subjects achieving the primary efficacy endpoint.

An exploratory analysis was performed to evaluate the robustness of the primary efficacy analysis results; a comparison between the Zemplar and placebo treatment groups of the

proportion of subjects achieving four consecutive decreases from baseline in iPTH of at least \geq 30% were performed using the Fisher's exact test.

Secondary Efficacy Analyses – These analyses were performed to assess the change and percent change from baseline iPTH. The final visit measurement was defined as the last iPTH measurement following the first dose of study drug; subjects who did not have both a baseline and a Final Visit measurement were not included in this analysis. Longitudinal analyses were analyses of data collected at scheduled visits of the Treatment Phase following the first dose of study drug; subjects who did not have both a baseline and at least one measurement following the first dose of study drug were not included in these analyses. The change and percent change from baseline in iPTH was compared between Zemplar and placebo using ANOVA with treatment as the factor, and ANCOVA with baseline as the second factor. Both “observed value” and “LOCF” methods were used for analyses.

Dosing day intervals that were used to select data that corresponded to the visits at which iPTH was measured were defined as shown below:

Scheduled Visit Week	"Observed Value" Dosing Day Interval	"Last Observation Carried Forward" Dosing Day Interval
3	[8, 21]	[2, 21]
5	[22,35]	[2, 35]
7	[36,49]	[2, 49]
9	[50,63]	[2, 63]
11	[64,77]	[2, 77]
13	[78,91]	[2, 91]
15	[92,105]	[2, 105]
17	[106,119]	[2, 119]
19	[120,133]	[2, 133]
21	[134,147]	[2, 147]
23	[148,161]	[2, 161]

Exploratory Efficacy Analyses – These analyses were performed on change from baseline in the biochemical markers (serum bone-specific alkaline phosphatase, serum osteocalcin, urinary pyridinoline, and deoxypyridinoline) by treatment group. Changes from baseline to Week 11 Visit and to Final Visit were compared between Zemplar and placebo using ANOVA with treatment as the factor; also, the changed from baseline to Week 11 Visit and to Final Visit were compared using ANCOVA with baseline as the second factor.

Safety Assessment – Descriptive statistics (frequency, means, standard error, standard deviation, and range) were performed on the incidence rate of adverse events, the change in baseline in laboratory assessments, and vital signs. Safety endpoints were evaluated utilizing subjects in the All-Treated Subject Population.

- **Hypercalcemia:** clinically meaningful hypercalcemia was defined as 2 consecutive calcium levels > 10.5 mg/dL.

- eGFR: a descriptive summary was generated for the change from baseline in eGFR (using the MDRD equation) by treatment group.
- Adverse events: adverse events were mapped by the COSTART V dictionary. Analyses of adverse events included treatment-emergent events and did not include adverse events that had an onset > 30 days after the last dose of study drug.
- Chemistry, hematology, and urinalysis assessments:
 - primary chemistry values
 - serum iPTH, serum total calcium (corrected to serum albumin), serum phosphorus, and Ca x P
 - the mean change from baseline was summarized quantitatively and graphically by treatment group and over time
 - secondary values
 - the secondary chemistry values were ALT; AST; alkaline phosphatase; BUN; chloride; total cholesterol; creatinine; total, direct, and indirect bilirubin; glucose; LDH; magnesium; potassium; carbon dioxide; sodium; total protein; triglycerides; and uric acid
 - hematology variables were hematocrit, hemoglobin, platelet count, RBC, WBC, and WBC differentials
 - routine urinalysis variables were pH, specific gravity, glucose, ketones, protein, and microscopic evaluation; other variables were 24-hour calcium, 24-hour phosphorus, 24-hour Ccr, and urinary calcium/creatinine ratio
- Vital signs:
 - Vital sign variables analyzed were SBP, DBP, HR, and weight
 - Changes from baseline to Week 7 and Week 15 Visits, and to Final Visit in vital sign variables were compared between Zemplar and placebo using an ANOVA with treatment as the factor; also ANCOVA was performed using baseline as the second factor
- Exploratory safety analyses – cardiovascular marker variables:
 - The cardiovascular marker variables analyzed were pro-B-type Natriuretic Peptide (pro-BNP), C-reactive protein (CRP)*, troponin T, and Myeloperoxidase (MPO)*
 - * CRP and MPO were not analyzed since there was insufficient evaluable data collected for these markers

Other Analyses – A descriptive summary was generated for the total number of subjects randomized and treated, including a breakdown of the treated subjects within each treatment group showing the numbers of subjects having two on-treatment iPTH values. A descriptive summary was generated for the disposition of All-Treated Subjects relative to study completion. Subject demographics, vital signs, medical history, and physical exam data were summarized descriptively for All-Treated Subjects by treatment group. Analysis of concurrent medication mapped to the World Health Organization drug dictionary was generated by treatment group for All-Treated Subjects. A descriptive summary was performed listing subject treatment numbers associated with each medication. Study drug administration was summarized descriptively for All-Treated Subjects by treatment group.

In an effort to assess robustness of ANOVA results and to accommodate departures from normality assumptions, the Wilcoxon rank-sum test was performed comparing changes from baseline to the Final Visit for the following variables: iPTH, serum total calcium, phosphorus, Ca x P, secondary chemistry variables, hematology variables, urinalysis variables, 24-hour urine collections, eGFR, serum creatinine, urinary calcium/creatinine ratio, cardiovascular markers, and vital signs.

Sample Size – With a sample size of 34 subjects in each group, a Fisher's exact test with a 0.05 2-sided significance level would have 90% power to reject the null hypothesis that the incidence rates of 2 consecutive $\geq 30\%$ decreases from baseline in iPTH between the two treatment groups were equal. This assumed the success rate in the placebo group was 20% and the success rate in the Zemplar group was 60%.

Protocol Amendments:

Amendment 1 (May 20, 2002):

- Modified the sign-off page
- Corrected the address of _____ M.D.
- Changed the Serious Adverse Event Reporting and Protocol Deviations contact name
- Modified the header
- Changed the exclusion criteria relating to the urine calcium-to-urine creatinine ratio from > 0.3 to > 0.2
- Clarified when subjects were assigned a unique 4-digit number

Amendment 2 (May 9, 2003):

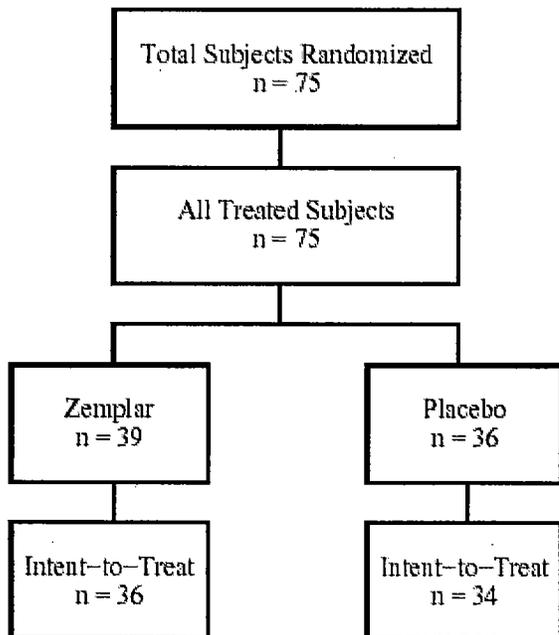
- Modified the sign-off page
- Corrected Abbott Department number
- Corrected the title of _____
- Removed hyperphosphatemia as a primary safety variable. Rationale: Dietary phosphate restriction, phosphate binder compliance, and the degree of renal insufficiency have significant impact on serum phosphorus levels. In renal patients, the degree of compliance to diet and phosphate binders varied substantially (42-67%), even with close surveillance. The progressive decline of renal function in these patients causes phosphorus retention and, therefore, significant elevation in serum phosphorus levels. Currently there is no specifically defined and generally accepted value for hyperphosphatemia in CKD patients.
- Clarified Section 5.5.4

Results

Patient Demographics:

Variable	Zemplar N= 39	Placebo N= 36	Total N= 75	P-Value
Gender				1.000 #
Female	12 (30.8%)	11 (30.6%)	23 (30.7%)	
Male	27 (69.2%)	25 (69.4%)	52 (69.3%)	
Race				0.596 #
Asian Only	2 (5.1%)	0 (0.0%)	2 (2.7%)	
Black Only	12 (30.8%)	10 (27.8%)	22 (29.3%)	
White Only	25 (64.1%)	26 (72.2%)	51 (68.0%)	
Tobacco				0.815 #
Nonsmoker	17 (43.6%)	14 (38.9%)	31 (41.3%)	
Smoker \$	22 (56.4%)	22 (61.1%)	44 (58.7%)	
Alcohol				1.000 #
Drinker &	25 (64.1%)	23 (63.9%)	48 (64.0%)	
Non drinker	14 (35.9%)	13 (36.1%)	27 (36.0%)	
Age Group				0.819 #
< 65 Yr	17 (43.6%)	17 (47.2%)	34 (45.3%)	
>= 65 Yr	22 (56.4%)	19 (52.8%)	41 (54.7%)	
Age (Years)				0.699 ##
Mean	63.5	64.7	64.1	
Se	2.41	1.81	1.51	
Median	66.0	65.0	65.0	
Range	22 - 89	46 - 90	22 - 90	
Time Since CKD (Years)				0.850 ##
N	38	35	73	
Mean	4.86	5.11	4.98	
Se	0.807	1.065	0.657	
Median	3.50	2.50	2.80	
Range	0.5 - 22.8	0.6 - 26.0	0.5 - 26.0	
# P-Value For Race, Gender, Tobacco, Alcohol And Age Group Derived From Fisher's Exact Test.				
## P-Value From F-Test Testing Equality Of Means Among Treatment Groups.				
\$ Includes Ex-Tobacco Users.				
& Includes Ex-Drinkers.				

Patient Disposition:



Protocol Violations:

There were no subjects for whom the blind was broken.

Six Zemplar subjects and six placebo subjects did not meet the inclusion/exclusion criteria of the study.

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Subjects Not Meeting Inclusion/Exclusion Criteria		
Inclusion Criteria	Zemplar	Placebo
8-For entry into Pre-Treatment Phase, subject had an iPTH value \geq 120 pg/mL and an eGFR of 15 to 60 mL/min, and was not expected to begin dialysis for at least 6 months.	202 ^a , 1501 ^a	501 ^a
9-For entry into Treatment Phase, subject had an average of 2 consecutive iPTH values \geq 150 pg/mL taken at least 1 day apart (all values must have been \geq 120 pg/mL), 2 consecutive corrected serum calcium levels of \geq 8.0 to \leq 10.0 mg/dL, and 2 consecutive phosphorus levels of \leq 5.2 mg/dL.	702 ^b	703 ^c , 704 ^e , 1506 ^d
Exclusion Criteria		
4-Subject had a spot urine result demonstrating a urine calcium-to-urine creatinine ratio of $>$ 0.2 or had a history of kidney stones.	101, 404, 1510	802, 1502
<small>a. eGFR was $<$ 15 mL/min/1.73m². b. Serum calcium $>$ 10.0 mg/dL. c. Serum phosphorus $>$ 5.2 mg/dL. d. Average iPTH $<$ 150 pg/mL.</small>		

Concomitant Medication Use:

From the time of Screening, subjects must not have taken vitamin D medication, calcitonin, bisphosphonates, maintenance oral or IV glucocorticoids, or other drugs that could affect calcium or bone metabolism. Multivitamin supplements containing \leq 400 IU of vitamin D were not restricted.

Most commonly used drugs

Drug	Zemplar	Placebo
ACE-I and/or ARBs	82%	75%
Cholesterol and TG reducers	82%	56%
High-ceiling diuretics	72%	78%
ACE-I only	59%	47%
Antithrombotic agents	56%	67%
Beta-blocking agents	51%	56%
Antianemic preparations	51%	42%

Phosphate binder usage

Overall	Zemplar (N=39)	Placebo (N=36)
Baseline	8 (21%)	4 (11%)
Final Visit	15 (38%)	10 (28%)

Phosphate binder at Final Visit	Zemplar (N=15)	Placebo (N=10)
Calcium-based	11 (73%)	7 (70%)
Non-calcium based (sevelamer hydrochloride)	4 (27%)	3 (30%)

Of the subjects who were taking phosphate binders at baseline, all remained on the same type of phosphate binder throughout the study and only one subject (Zemplar 1509) required a dose change (decrease).

Elemental calcium usage

Overall	Zemplar (N=39)	Placebo (N=36)
Baseline	8 (21%)	6 (17%)
Final Visit	11 (28%)	10 (28%)

Of the subjects who were taking elemental calcium at baseline, all remained on the same dose throughout the study except for one subject (Zemplar 1509) who required a dose decrease.

Primary Efficacy Outcome:

The primary efficacy endpoint was two consecutive $\geq 30\%$ decreases from baseline in iPTH. The difference between the treatment groups in baseline iPTH was not statistically significant (see Appendix B).

Summary of iPTH Response - Primary Efficacy Analysis Intent-to-Treat Population					
	Zemplar (N= 36)		Placebo (N= 34)		p-value #
	Count	(%)	Count	(%)	
Subject achieved two consecutive 30% decreases from baseline in iPTH?					
Yes	33	(91.7%)	4	(11.8%)	<0.001***
No	3	(8.3%)	30	(88.2%)	

p-value is derived from Fisher's exact test.

Exploratory analyses were performed to assess the proportion of subjects in each treatment group who had four consecutive $\geq 30\%$ decreases from baseline in iPTH in order to assess the robustness of the results.

Four Consecutive 30% Decreases In iPTH – Intent-To-Treat Population					
	Zemplar (N= 36)		Placebo (N= 34)		p-value #
Subject Achieved Four Consecutive 30% Decreases From Baseline In iPTH ?	Count	(%)	Count	(%)	
Yes	26	(72.2%)	0	(0.0%)	<0.001***
No	10	(27.8%)	34	(100.0%)	

p-value is derived from Fisher's exact test.

Secondary Efficacy Outcomes:

Mean Change and Percent Change from Baseline to Final Visit in iPTH (All Treated Subjects)			
iPTH (pg/mL)	Zemplar (N = 37) ^a	Placebo (N = 35) ^b	ANOVA P-value ^c
Mean Baseline Value	285.9	324.8	0.214
(Baseline Range)	(151.0-701.0)	(147.0-697.5)	
Mean Final Value	227.8	375.3	NA
Mean Change from Baseline (SE)	-58.1 (19.03)	50.4 (19.57)	< 0.001
Mean Percent Change from Baseline (SE)	-19.2 (6.33)	16.9 (6.51)	< 0.001

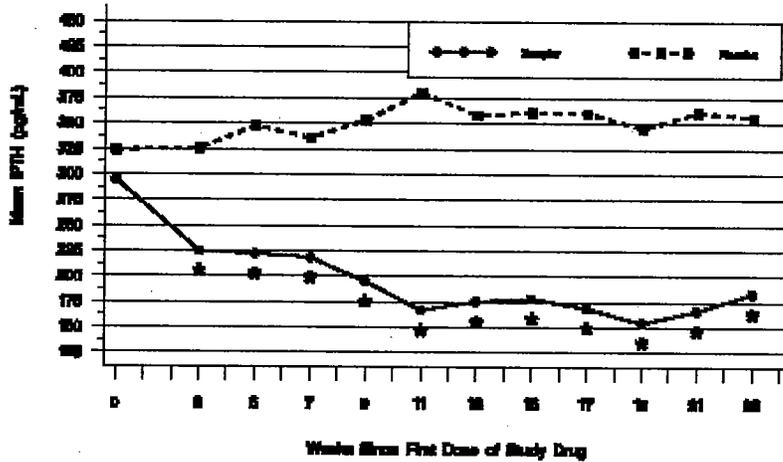
NA = Not Applicable
a. Zemplar Subjects 404 and 1202 had no iPTH measurements following the first dose of study medication; therefore, only 37 subjects (versus 39) are included in this analysis.
b. Placebo Subject 902 had no iPTH measurements following the first dose of study medication; therefore, only 35 subjects (versus 36) are included in this analysis.
c. One-way ANOVA with treatment as the factor.

Results were similar using ANCOVA with treatment as the factor and baseline iPTH as the covariate. Additionally, results were statistically significant when using Last On-Treatment Visit instead of Final Visit.

The following graph shows the mean values in iPTH over time for observed values:

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Mean Values of iPTH Over Time During Treatment Phase



Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	39	35	36	35	35	34	32	33	31	32	31	29
Placebo N	36	32	34	33	29	32	29	30	30	28	28	29

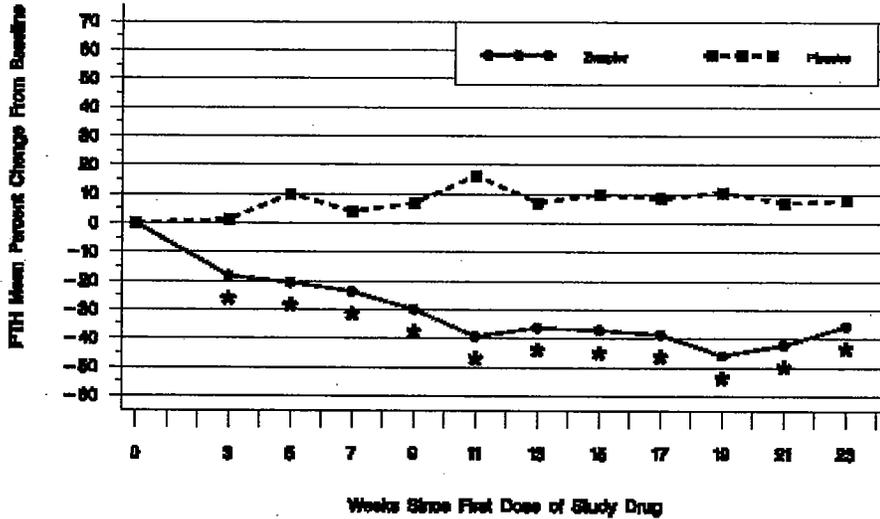
* Statistically significant ($p \leq 0.05$) difference in mean change from baseline between the Zemplar and placebo treatment groups. At each visit, change from baseline is calculated for subjects who had data at the corresponding timepoint.

Results were similar using observed value ANCOVA with treatment as the factor and baseline iPTH as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline iPTH as the covariate.

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The following graph shows the mean percent change from baseline in iPTH over time for observed values:

Mean Percent Change From Baseline in iPTH Over Time During Treatment Phase



Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	39	35	36	35	35	34	32	33	31	32	31	29
Placebo N	36	32	34	33	29	32	29	30	30	28	28	29

* Statistically significant ($p \leq 0.05$) difference in mean percent change from baseline between the Zemplar and placebo treatment groups. At each visit, percent change from baseline is calculated for subjects who had data at the corresponding timepoint.

Results were similar using observed value ANCOVA with treatment as the factor and baseline iPTH as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline iPTH as the covariate.

The differences between the treatment groups in mean change from baseline to Final Visit in the biochemical bone activity markers were statistically significant using ANOVA with treatment as the factor; the Zemplar group experienced mean decreases in all markers while the placebo group experienced mean increases or no change, see table below:

Mean Change from Baseline to Week 11 and Final Visit in Biochemical Bone Activity Marker Variables			
	Zemplar	Placebo	ANOVA P-value ^a
Serum Bone-Specific Alkaline Phosphatase (mcg/L)			
Number of Subjects	31	30	
Mean Baseline Value	15.971	21.450	
Change from Baseline (SE) to Week 11	-4.673 (1.2590)	-1.462 (1.2798)	0.079
Number of Subjects	36	35	
Mean Baseline Value	16.317	22.014	
Change from Baseline (SE) to Final	-7.922 (1.3520)	-2.278 (1.3712)	0.005
Serum Osteocalcin (ng/mL)			
Number of Subjects	32	27	
Mean Baseline Value	57.91	78.00	
Change from Baseline (SE) to Week 11	-4.23 (4.386)	2.47 (4.774)	0.306
Number of Subjects	35	32	
Mean Baseline Value	59.70	81.85	
Change from Baseline (SE) to Final	-19.00 (4.381)	14.56 (4.581)	< 0.001
Urinary Deoxypyridinoline (nmol/mg Creat)			
Number of Subjects	32	27	
Mean Baseline Value	0.0500	0.0525	
Change from Baseline (SE) to Week 11	-0.0116 (0.00354)	0.0026 (0.00385)	0.009
Number of Subjects	35	31	
Mean Baseline Value	0.0476	0.0502	
Change from Baseline (SE) to Final	-0.0084 (0.00375)	0.0034 (0.00398)	0.033
Urinary Pyridinoline (nmol/mmol Creat)			
Number of Subjects	33	28	
Mean Baseline Value	35.92	36.20	
Change from Baseline (SE) to Week 11	-5.46 (2.545)	-5.86 (2.763)	0.916
Number of Subjects	36	33	
Mean Baseline Value	35.47	34.85	
Change from Baseline (SE) to Final	-4.06 (2.276)	2.73 (2.377)	0.043

a. One-way ANOVA with treatment as the factor.

Safety Data

Deaths:

There was one death in a Zemplar subject (507), due to cardiopulmonary arrest. The death occurred 14 days after the last documented dose of study drug. The investigator described the final diagnosis as probably acute MI. The known cardiovascular disease for this subject included hypertension and congestive heart failure. The subject also had a history of diabetes and hyperlipidemia. Chronic kidney disease was thought due to diabetes. The subject's iPTH at baseline was 309.5 pg/mL and ranged during the study from — pg/mL. His baseline serum

calcium was 8.9 mg/dL and ranged during the study from 8.6 to 9.6 mg/dL. His baseline Ca x P was 40.5 mg²/dL² and ranged during the study from 36.54 to 59.52 mg²/dL² (the 59.52 mg²/dL² value was noted at the second post-baseline measurement, after which it subsequently decreased).

Serious Adverse Events:

Serious Adverse Events Reported During the Treatment and Follow-Up Phases							
Subject Number	Gender/ Age	Serious Adverse Event Description	Study Day Onset^a	Study Day End^a	Severity	Relationship (Investigator-determined)	Reason Serious
Zemplar							
502	M/56	Decreased renal function	38	Ongoing as Of Day 93 (3)	Moderate	Not related	HS
		Increased blood pressure, headaches, nausea and vomiting	38	39	Mild	Not related	HS
		Bradycardia	84	90	Moderate	Probably not	HS
		Elevated liver enzymes ^b	84	90	Moderate	Possibly	PH
		Anasarca	84	90	Moderate	Probably not	PH
		Nausea	84	90	Mild	Probably not	PH
		Hypertension, uncontrolled with bradycardia	84	90	Moderate	Probably not	PH
		Decreased kidney function	84	90	Mild	Probably not	PH
		Elevated WBC count	84	90	Mild	Probably not	PH
		Elevated laboratory values for hyperkalemia	84	90	Moderate	Probably not	PH
		Nausea and vomiting	95 (5)	Ongoing as Of Day 97 (7)	Moderate	Probably not	HS
504	M/77	SOB	103	109	Moderate	Not related	HS
		Chest pain left sided	104	Ongoing as Of Day 174 (7)	Mild	Not related	HS
507	M/71	Chest pain, swollen face ^c	151 (10)	155 (14)	Severe	Not related	HS, DE
509	M/69	Sharp pain from right hip to right leg to right foot	129	158	Moderate	Not related	HS
807	M/84	Confusion altered mental status	63	63	Severe	Not related	HS
1101	M/89	Felt faint getting out of car	55	65	Severe	Not related	HS
1402	M/48	Intermittent purulent drainage from right scrotal area	7	7	Moderate	Not related	RI
		Worsening dizziness, nausea and vomiting, and dyspnea	13	21	Moderate	Not related	HS
1508	F/53	Dehydration with nausea and vomiting	116	117	Severe	Not related	HS
		Elevated BUN and serum creatinine, dehydration	116	117	Severe	Not related	HS, RI

Serious Adverse Events Reported During the Treatment and Follow-Up Phases							
Subject Number	Gender/Age	Serious Adverse Event Description	Study Day Onset^a	Study Day End^a	Severity	Relationship (Investigator-determined)	Reason Serious
1509	M/73	SOB, Pain radiating to throat and fatigue	29	33	Severe	Not related	HS, RI, LT
Placebo							
501	M/59	Nausea, vomiting, and near syncope	34 (1)	37 (4)	Mild	Not related	HS
		Very high intraocular pressure	38 (5)	Ongoing as Of Day 66 (33)	Severe	Not related	HS
		Hyperglycemia, dehydration, and confusion leading to acute on chronic renal failure ^b	49 (16)	55 (22)	Severe	Not related	HS, RI, LT
503	M/62	Severe pain and swelling of right wrist and left foot	93	97	Mild	Not related	HS
505	M/65	Occlusion and stenosis of left carotid artery	125	145	Moderate	Not related	HS
512	M/84	Sharp pains in stomach area	82	87	Moderate	Not related	HS
704	F/53	Diabetic coma	71 (16)	78 (23)	Severe	Not related	HS
		ESRD	76 (21)	Ongoing as Of Day 92 (37)	Severe	Not related	PH, RI
705	F/80	GFR 15mL/min, gradual symptoms of uremia	147 (20)	153 (26)	Severe	Not related	HS
901	M/67	Left knee sprain, left arm and leg weakness, intermittent light headedness and nausea	10	18	Mild	Probably not	HS
902	F/72	SOB	1	3	Moderate	Probably not	HS
		SOB, hyponatremia, sinus bradycardia	12	22	Moderate	Not related	HS
1401	F/61	Potassium 6.1 mEq/L asymptomatic	90	92	Moderate	Not related	HS
M/F = Male/Female; WBC = white blood cell; BUN = blood urea nitrogen; SOB = shortness of breath; ESRD = end-stage renal disease; HS = hospitalization; PH = prolonged hospitalization; DE = Death; RI = required intervention; LT = life threatening a. Numbers in parentheses represent number of days since last dose of study drug. b. Event led to premature termination. c. Subject died 14 days after the last documented dose of study drug.							

Adverse Events that Led to Study Withdrawal:

Adverse Events Leading to Premature Termination from Study Drug							
Subject Number	Gender/ Age	Adverse Event Description	Study Day Onset^a	Study Day End^a	Severity	Relationship (Investigator-determined)	Investigator Alternative Etiology
Zemplar							
502	M/56	Elevated liver enzymes	84	90	Mod	Possibly	Drug toxicity ^b
Placebo							
501	M/59	Hyperglycemia, dehydration, and confusion leading to acute on chronic renal failure	49 (16)	55 (22)	Sev	Not related	Diabetes
705	F/80	Weight increase, more SOB, intermittent chest pain	128 (1)	Ongoing as of Day 133 (6)	Sev	Not related	Progression of CRF
M/F = Male/Female; Mod = moderate; Sev = severe; SOB = shortness of breath; CRF = chronic renal failure							
a. Numbers in parentheses represent number of days since last dose of study drug.							
b. The Abbott alternative etiology was: bradycardia associated with cardiac meds led to liver congestion resulting in elevated liver enzymes							

Treatment-Emergent Adverse Events:

Overall Summary of Treatment-Emergent Adverse Events (All Treated Subjects)		
	Zemplar (N = 39)	Placebo (N = 36)
Number of Subjects Reporting Adverse Events	31 (79%)	23 (64%)
Number of Events Reported	111	75
Number of Serious Adverse Events Reported	22	16
Number of Subjects Reporting		
0 Events	8 (21%)	13 (36%)
1 Event	8 (21%)	3 (8%)
> 1 Event	23 (59%)	20 (56%)
Severity of Event		
Mild	45 (41%)	31 (41%)
Moderate	53 (48%)	35 (47%)
Severe	13 (12%)	9 (12%)
Investigator-Determined Relationship to Study Drug		
Probably Related	1 (1%)	0 (0%)
Possibly Related	6 (5%)	2 (3%)
Probably Not Related	10 (9%)	5 (7%)
Not Related	94 (85%)	68 (91%)

Laboratory Parameters:

Proportions of Subjects Who Developed Clinically Meaningful Hypercalcemia (All Treated Subject Population)			
Variable	Zemplar ^a (N = 38)	Placebo ^b (N = 35)	P-value ^c
Clinically Meaningful Hypercalcemia (at least 2 consecutive calcium values > 10.5 mg/dL)			1.000
Yes	1 (3%)	0 (0%)	
No	35 (97%)	35 (100%)	

a. Zemplar Subject 1202 had no calcium measurements following the first dose of study medication; therefore, only 38 subjects (versus 39) are included in this analysis.
b. Placebo Subject 902 had no calcium measurements following the first dose of study medication; therefore, only 35 subjects (versus 36) are included in this analysis.
c. Fisher's exact test.

One Zemplar subject (405), a 74-year old black female, experienced two consecutive serum calcium values > 10.5 mg/dL at Weeks 13 (10.6 mg/dL) and 14 (10.6 mg/dL). The subject's baseline iPTH was 701 pg/mL and calcium was 8.9 mg/dL. At Week 13, her iPTH was — pg/mL and study drug was reduced from 8 mcg/dose to 6 mcg/dose. At Week 14, her calcium was 10.6 mg/dL. Study drug was further reduced to 4 mcg/dose. At Week 15, her calcium returned to normal (9.6 mg/dL). No subject had hypercalcemia reported as an adverse event.

Comment: Five Zemplar-treated subjects and one placebo-treated subject had single calcium values > 10.5:

Proportions of Subjects Who Developed Single Calcium Values > 10.5 (All Treated Subject Population*)			
Variable	Zemplar (N = 39)	Placebo (N = 36)	P-value ^a
At least 1 consecutive calcium value > 10.5 mg/dL)			0.202
Yes	5 (13%)	1 (3%)	
No	34 (87%)	35 (97%)	

a. Fisher's exact test.

*Results similar using Intent-to-Treat population.

Mean Change from Baseline to Final Visit in Calcium, Phosphorus, CaXP and Albumin			
	Zemplar (N = 38) ^a	Placebo (N = 35) ^b	ANOVA P-value ^c
Calcium (mg/dL)			
Mean Baseline Value	9.30	9.37	0.464
Baseline Range	8.4-10.0	8.0-10.0	
Mean Final Value	9.46	9.44	
Change from Baseline (SE)	0.16 (0.061)	0.07 (0.063)	0.313

Mean Change from Baseline to Final Visit in Calcium, Phosphorus, CaxP and Albumin			
	Zemplar (N = 38)^a	Placebo (N = 35)^b	ANOVA P-value^c
Phosphorus (mg/dL)			
Mean Baseline Value	3.99	4.21	0.063
Baseline Range	2.8-4.8	3.1-5.6	
Mean Final Value	4.42	4.45	
Change from Baseline (SE)	0.43 (0.145)	0.24 (0.152)	0.365
Ca×P (mg²/dL²)			
Mean Baseline Value	36.78	39.12	0.051
Baseline Range	25.0-45.3	28.7-48.9	
Mean Final Value	41.92	41.91	
Change from Baseline (SE)	5.14 (1.365)	2.79 (1.422)	0.236
Albumin (g/dL)			
Mean Baseline Value	3.81	3.79	0.807
Baseline Range	2.8-4.6	2.4-4.5	
Mean Final Value	3.84	3.84	
Change from Baseline (SE)	0.03 (0.042)	0.05 (0.043)	0.678
<p>a. Zemplar Subject 1202 had no primary chemistry measurements following the first dose of study medication; therefore, only 38 subjects (versus 39) are included in this analysis.</p> <p>b. Placebo Subject 902 had no primary chemistry measurements following the first dose of study medication; therefore, only 35 subjects (versus 36) are included in this analysis.</p> <p>c. One-way ANOVA with treatment as the factor.</p>			

Similar results were observed using ANCOVA with treatment as the factor and baseline value as the covariate.

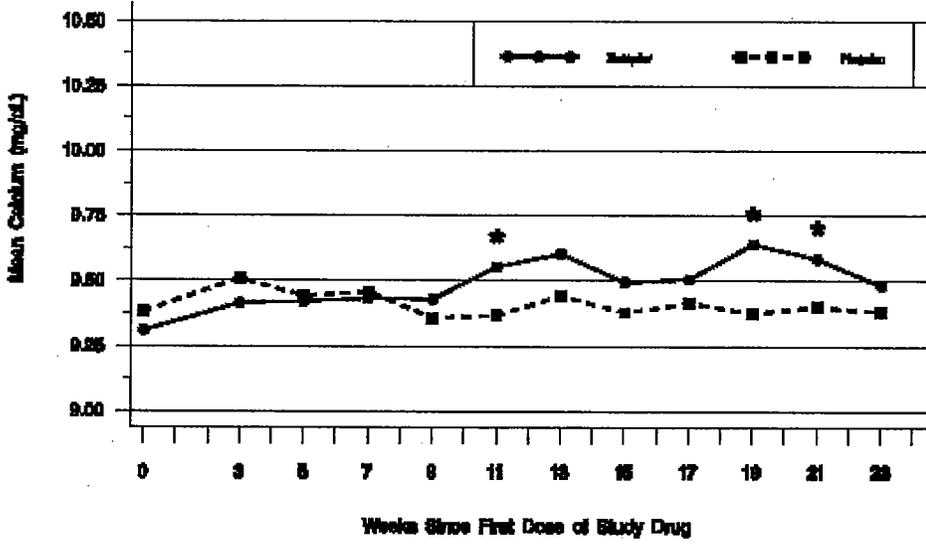
Mean Change from Baseline to Last On-Treatment Visit in Calcium, Phosphorus, CaxP and Albumin			
	Zemplar (N = 36)^a	Placebo (N = 35)^b	ANOVA P-value^c
Calcium (mg/dL)			
Mean Baseline Value	9.33	9.37	
Mean Last On-Treatment Value	9.47	9.40	
Change from Baseline (SE)	0.14 (0.069)	0.03 (0.070)	0.269
Phosphorus (mg/dL)			
Mean Baseline Value	3.99	4.21	
Mean Last On-Treatment Value	4.46	4.71	
Change from Baseline (SE)	0.47 (0.144)	0.49 (0.146)	0.904
Ca×P (mg²/dL²)			
Mean Baseline Value	36.92	39.12	
Mean Last On-Treatment Value	42.42	43.98	

Mean Change from Baseline to Last On-Treatment Visit in Calcium, Phosphorus, Ca _x P and Albumin			
	Zemplar (N = 36) ^a	Placebo (N = 35) ^b	ANOVA P-value ^c
Change from Baseline (SE)	5.51 (1.378)	4.87 (1.398)	0.745
Albumin (g/dL)			
Mean Baseline Value	3.81	3.79	
Mean Last On-Treatment Value	3.82	3.81	
Change from Baseline (SE)	0.01 (0.048)	0.02 (0.049)	0.930

a. Zemplar Subject 1202 had no primary chemistry measurements following the first dose of study medication and Subjects 101 and 404 had no primary chemistry measurements collected prior to the last dose of study drug; therefore, only 36 subjects (versus 39) are included in this analysis.
 b. Placebo Subject 902 had no primary chemistry measurements following the first dose of study medication; therefore, only 35 subjects (versus 36) are included in this analysis.
 c. One-way ANOVA with treatment as the factor.

Similar results were observed using ANCOVA with treatment as the factor and baseline value as the covariate.

Mean Calcium Values Over Time During Treatment Phase



Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	39	36	36	35	35	34	32	33	31	32	32	29
Placebo N	36	32	34	33	30	32	29	31	30	28	28	29

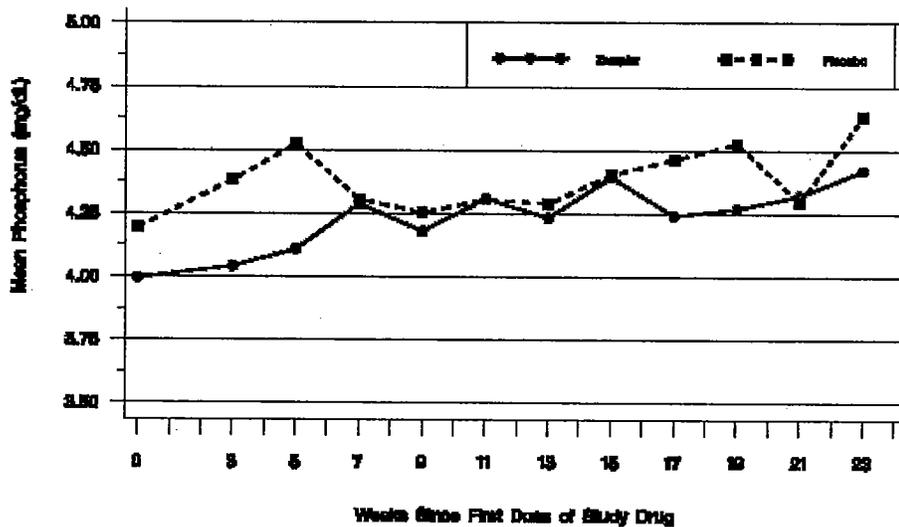
* Statistically significant (p ≤ 0.05) difference in mean change from baseline between the Zemplar and placebo treatment groups. At each visit, change from baseline is calculated for subjects who had data at the corresponding timepoint.

Calcium Normal Range: 8.0 to 10.3 mg/dL

Results were similar using observed value ANCOVA with treatment as the factor and baseline calcium as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline calcium as the covariate.

Comment: Calcium range for Zemplar subjects was 7.9 – 11.1 mg/dL; for placebo subjects 7.1 – 10.6 mg/dL.

Mean Phosphorus Values Over Time During Treatment Phase



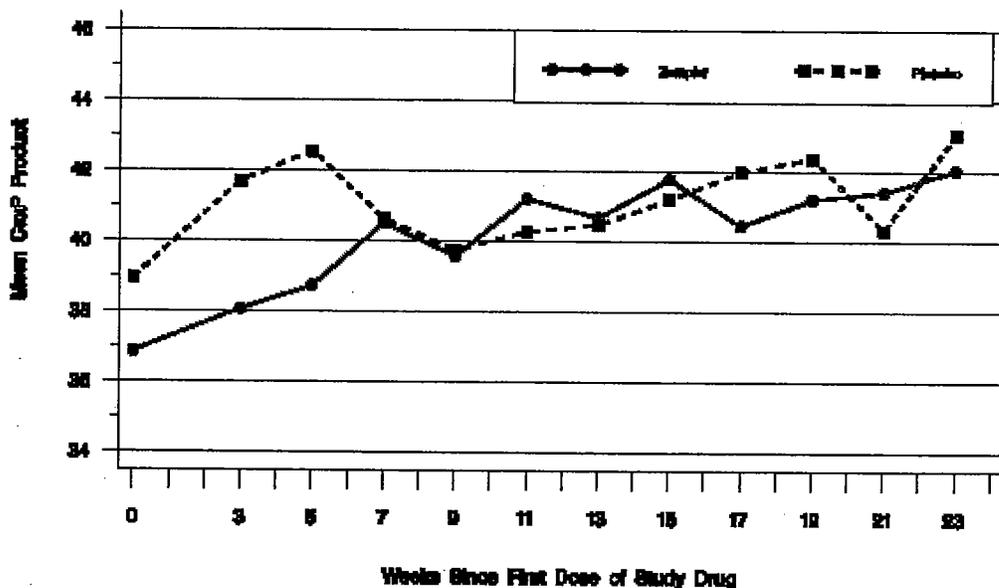
Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	39	36	36	35	35	34	32	33	31	32	32	29
Placebo N	36	32	34	33	30	32	29	31	30	28	28	29

* Statistically significant ($p \leq 0.05$) difference in mean change from baseline between the Zemplar and placebo treatment groups. At each visit, change from baseline is calculated for subjects who had data at the corresponding timepoint.

Phosphorus Normal Range: 2.2 to 5.1 mg/dL

Results were similar using observed value ANCOVA with treatment as the factor and baseline calcium as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline phosphorus as the covariate.

Mean CaxP Values Over Time During Treatment Phase



Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	39	36	36	35	35	34	32	33	31	32	32	29
Placebo N	36	32	34	33	30	32	29	31	30	28	28	29

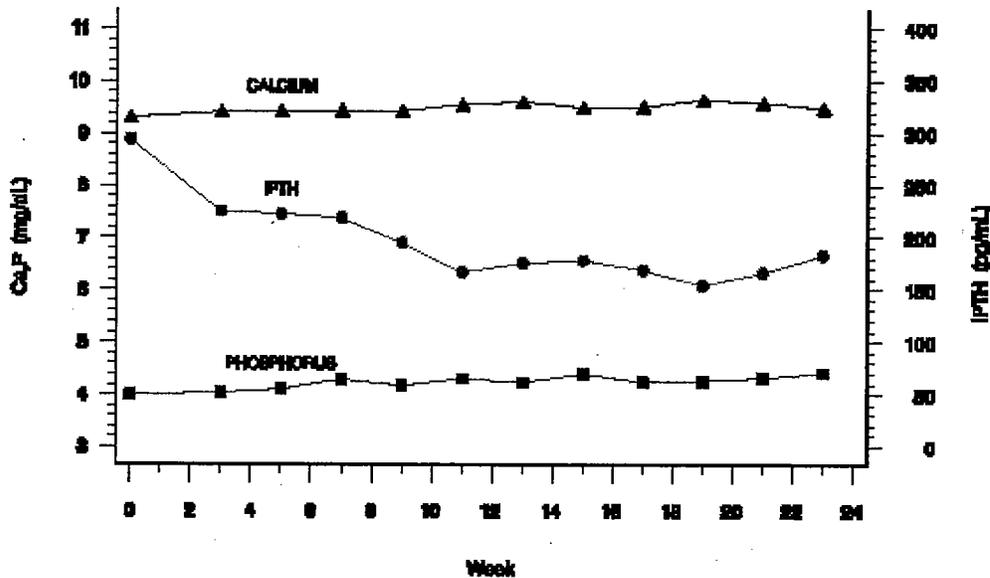
* Statistically significant ($p \leq 0.05$) difference in mean change from baseline between the Zemplar and placebo treatment groups. At each visit, change from baseline is calculated for subjects who had data at the corresponding timepoint.

CaxP Normal Range: 17.6 to 52.5

Results were similar using observed value ANCOVA with treatment as the factor and baseline calcium as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline CaxP as the covariate.

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Mean Calcium, Phosphorus, and iPTH Values Over Time, Zemplar-Treated Subjects



Except for the following (see table), there were no secondary chemistry variables that exhibited statistically significant differences between treatment groups in mean change from baseline to Final Visit using ANOVA.

Statistically Significant Differences Between Treatment Groups for Mean Change from Baseline to Final Visit in Secondary Chemistry Variables		
Variable (unit)	Zemplar	Placebo
Alkaline Phosphatase (IU/L)***	(N = 35)	(N = 34)
Mean Baseline Value	102.80	114.94
Mean Final Value	82.29	117.18
Mean Change from Baseline (SD)	-20.51 (17.950)	2.24 (25.872)
Nonfasting Triglycerides (mg/dL)**	(N = 35)	(N = 34)
Mean Baseline Value	244.49	211.79
Mean Final Value	291.49	194.94
Mean Change from Baseline (SD)	47.00 (100.794)	-16.85 (71.802)

** , *** = statistically significant difference between treatment groups at the 0.01 and 0.001 levels, respectively, using a contrast within the one-way ANOVA.

Results were similar when secondary chemistry variables were analyzed using ANCOVA, except that statistically significant differences were observed in mean change from baseline to Final Visit in uric acid [Zemplar group small mean increase (0.31 mg/dL), p = 0.028] and potassium [Zemplar group had a small mean decrease (-0.20 mEq/L), p = 0.037]. Results were similar using ANCOVA.

There were no hematology or urinalysis (pH and specific gravity) variables that exhibited statistically significant differences between treatment groups in mean change from baseline to Final Visit using ANOVA or ANCOVA.

Mean Change from Baseline to Final Visit in 24-Hour Urine Collections (All Treated Subjects)			
	Zemplar	Placebo	ANOVA P-value^a
Calcium (mg/24 hours)	(N = 27)	(N = 25)	
Mean Baseline Value	39.97	31.38	—
Mean Final Value	39.03	39.67	NA
Mean Change from Baseline (SE)	-0.94 (5.959)	8.30 (6.192)	0.287
Phosphorus (mg/24 hours)	(N = 27)	(N = 25)	
Mean Baseline Value	675.6	772.6	—
Mean Final Value	669.7	801.6	NA
Mean Change from Baseline (SE)	-5.9 (55.10)	29.0 (57.27)	0.663
Creatinine Clearance (mL/min/1.73m²)	(N = 29)	(N = 25)	
Mean Baseline Value	28.2	30.3	—
Mean Final Value	25.0	29.9	NA
Mean Change from Baseline (SE)	-3.1 (2.11)	-0.4 (2.27)	0.388

NA = Not Applicable
a. One-way ANOVA with treatment as the factor.

Although not statistically different, as the above table demonstrates, Zemplar-treated subjects experienced mean decreases from baseline to Final Visit in urinary calcium, phosphorus, and Ccr, whereas placebo-treated subjects experienced mean increases from baseline for urinary calcium, and phosphorus and a mean decrease in Ccr. Results were similar using ANCOVA.

Mean Change and Percent Change from Baseline to Final Visit in eGFR and Creatinine (All Subjects Who Completed 24 Weeks of Treatment)			
	Zemplar	Placebo	ANOVA P-value^a
eGFR (mL/min/1.73m²)	(N = 30)	(N = 27)	
Mean Baseline Value	22.30	21.70	-
Mean Final Value	20.46	20.87	NA
Mean Change from Baseline (SE)	-1.84 (0.745)	-0.83 (0.785)	0.355
Mean Percent Change from Baseline (SE)	-8.36 (3.201)	-6.15 (3.374)	0.637
Creatinine (mg/dL)			
Mean Baseline Value	2.96	3.10	-
Mean Final Value	3.30	3.47	NA
Mean Change from Baseline (SE)	0.34 (0.119)	0.36 (0.126)	0.895
Mean Percent Change from Baseline (SE)	11.69 (3.660)	9.04 (3.858)	0.620

NA = Not Applicable
a. One-way ANOVA with treatment as the factor.

Results of the above table were similar using ANCOVA.

Urinary Calcium/Creatinine Ratio: No statistically significant differences were observed between the treatment groups in mean change from baseline to Week 11 or to Final Visit in urinary calcium/creatinine ratio using ANOVA or ANCOVA.

Cardiovascular Marker Variables: Eighteen subjects (9 Zemplar and 9 placebo) who had both baseline and Final Visit pro-BNP and troponin-T values were included in these analyses. No statistically significant differences in cardiovascular marker variables were observed between treatment groups in mean change from baseline to Week 11, Final Visit, or Final Visit that was at least 161 after the last dose of study drug using ANOVA and ANCOVA.

Vital Signs:

ANOVA Of Changes From Baseline To Final Visit In Vital Sign Variables, All Treated Subject Population								
					Change From Baseline			Between Group Comparison
Variables	Treatment Group	N	Baseline Mean	Visit Mean	Mean	Se	P-Value	Difference (95% CI)
								P-Value (HO:Difference=0)
Weight (Kg)								
	Zemplar	38	96.8	97.1	0.3	0.88	0.757	0.8 (-1.7, 3.3)
	Placebo	35	92.5	92.0	-0.5	0.92	0.565	0.529
Pulse (Bpm)								
	Zemplar	37	72.2	71.9	-0.3	1.62	0.842	0.3 (-4.3, 5.0)
	Placebo	34	72.4	71.7	-0.6	1.69	0.703	0.891
Systolic Blood Pressure (mmHg)								
	Zemplar	38	140.6	135.8	-4.7	3.02	0.121	-3.1 (-11.8, 5.6)
	Placebo	35	143.0	141.4	-1.6	3.15	0.613	0.474
Diastolic Blood Pressure (mmHg)								
	Zemplar	38	76.6	75.0	-1.5	1.93	0.432	1.7 (-3.9, 7.3)
	Placebo	35	76.3	73.1	-3.2	2.01	0.113	0.544

Note: Results Are Based On A One-Way Anova With Treatment As The Factor.

Results were similar using ANCOVA with treatment as the factor and baseline value as covariate. In addition, there statistically significant differences were not observed between the treatment groups for the mean change from baseline to Week 7, or Week 15 in systolic blood pressure, diastolic blood pressure, pulse, and weight using ANOVA or ANCOVA.

Special Safety Studies: NA

Other: NA

Company's Conclusions (emphasis added, indicating the Company's interpretations):

1. Thirty-six Zemplar subjects and 34 placebo subjects had a baseline and at least two on-treatment iPTH measurements. Thirty-three of 36 (92%) subjects who received Zemplar

- achieved two consecutive $\geq 30\%$ decreases from baseline in iPTH compared to 4 of 34 (12%) of subjects who received placebo. This difference was statistically significant.
2. At the Final Visit, subjects who received Zemplar had a statistically significant mean reduction in iPTH compared to a mean increase observed for subjects who received placebo [-58.1 pg/mL (-19.2%) versus 50.4 pg/mL (16.9%)]. When analyses were performed using iPTH data collected at the Last On-Treatment Visit, Zemplar-treated subjects had a statistically significant mean decrease [-95.7 pg/mL (-33%)] in iPTH compared with a mean increase [32.5 pg/mL (11.2%)] among placebo-treated subjects.
 3. Statistically significant differences were observed between the Zemplar and placebo treatment groups at all scheduled visits of the Treatment Phase for both change and percent change from baseline in iPTH.
 4. Statistically significant differences from baseline to Final Visit between treatment groups were observed in all four biochemical bone marker variables. Reductions from baseline to the Final Visit were observed in all four variables in Zemplar-treated subjects; increases from baseline in urinary deoxypyridinoline, urinary pyridinoline, serum osteocalcin, and a small decrease in serum bone-specific alkaline phosphatase were observed in placebo-treated subjects. The test comparing changes from baseline to Final Visit for urinary pyridinoline between Zemplar and placebo treatment groups demonstrated a non-significant difference between groups when using the Wilcoxon rank-sum test. The results of the Wilcoxon rank-sum tests for the other bone markers were consistent with the results using the ANOVA.
 5. ~~_____~~
~~_____~~
~~_____~~
 6. No statistically significant differences were observed between the treatment groups for the proportion of subjects with at least two consecutive calcium values > 10.5 mg/dL (1/38, 3% Zemplar versus 0% placebo).
 7. Mean serum calcium levels increased minimally during treatment in both the Zemplar (0.16 mg/dL) and placebo (0.07 mg/dL) groups; the difference between the treatment groups in mean change from baseline to Final Visit or Last On-Treatment Visit in calcium was not statistically significant.
 8. No statistically significant differences were observed between the treatment groups for mean changes from baseline to any of the scheduled visits of the Treatment Phase, Final Visit, or Last On-Treatment Visit for phosphorus or CaxP.
 9. No statistically significant differences were observed between the treatment groups in mean change and mean percent change from baseline to Final Visit in eGFR and creatinine. No statistically significant difference was observed between the treatment groups in mean change from baseline to Final Visit in 24-hour urine collection variables (calcium,

phosphorus, Ccr) or urinary calcium/creatinine ratio.

10. Evaluations of other laboratory analyses, vital signs, and physical examinations revealed no clinically meaningful changes as a result of Zemplar treatment.
11. No statistically significant differences were observed between the treatment groups for the overall incidence of adverse events or for the incidence of any specific adverse event. These data are indicative of the overall tolerability of Zemplar in this patient population.
12. Zemplar Capsule is safe and well tolerated for the treatment and prevention of 2° HPT in CKD (stages 3 and 4) subjects.
13. Zemplar Capsule is effective for the treatment and prevention of 2° HPT in CKD (Stages 3 and 4) subjects.

Medical Officer's Conclusions:

1. **Statistical analyses demonstrating Zemplar's efficacy in decreasing iPTH compared with placebo are very strong.**
2. **Final Visit and Last On-Treatment analyses lose within-study measurement information. Therefore, in addition to mean change from baseline, in particular when evaluating measures for safety, it is important to assess mean values over time.**
3. **Biochemical markers, while suggesting an improvement in bone turnover in the Zemplar-treated subjects versus the placebo-treated subjects, do not have proven equivalence to histological data. In addition, the relevance of bone marker data in subjects with renal impairment (in particular, urinary markers) is not clear.**
4. **Dosing changes are made for single calcium levels ≥ 10.4 mg/dL. Therefore, the designation of two consecutive calcium levels > 10.5 as clinically relevant is somewhat misleading. An analysis was performed with single calcium values > 10.5 . Although difference between groups was not statistically significant, it may be clinically significant (five Zemplar subjects with at least one calcium > 10.5 mg/dL versus one placebo subject). In addition, although there is not a statistically significant difference in mean serum calcium levels, a trend toward increased mean calcium levels in Zemplar-treated subjects compared to those treated with placebo appears to exist. This study was not powered to detect a statistically significant difference. The majority of calcium values remained in the normal range for both Zemplar- and placebo-treated subjects.**
5. **There were no statistically or clinically significant differences observed between the treatment groups for mean changes from baseline to any of the scheduled visits for phosphorus, CaxP, eGFR, or creatinine.**
6. **Evaluations of other laboratory analyses, vital signs, and physical examinations revealed no clinically meaningful changes as a result of Zemplar treatment.**
7. **It does not appear that there was an imbalance of baseline characteristics or concomitant medication use for either treatment group.**
8. **Although there were more adverse events in the Zemplar group than the placebo group, this difference does not appear to be particularly imbalanced or clinically concerning.**

- 9. Based on this single study, Zemplar Capsule appears safe to administer TIW to patients with CKD Stages 3 and 4 with 2° HPT with careful monitoring of calcium and CaxP levels and subsequent dose titration. Given the potential for hypercalcemia, Zemplar Capsules should not be administered to subjects with hypercalcemia at baseline.**

**APPEARS THIS WAY
ON ORIGINAL**

Appendix A. Inclusion and Exclusion Criteria

Inclusion Criteria

1. Male or female subjects ≥ 18 years
2. Subject had been in the care of a physician ≥ 2 months (for CKD) prior to entry into the study
3. Subject had not been on active vitamin D therapy for at least 4 weeks prior to the Screening Visit
4. If female, subject was either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or was of childbearing potential and practicing one of the following methods of birth control:
 - a. Condoms, sponge, foams, jellies, diaphragm, or intrauterine device
 - b. Contraceptives (oral or parenteral) for 3 months prior to study drug administration
 - c. Maintained a monogamous relationship with vasectomized partner
 - d. Total abstinence from sexual intercourse
5. If female, subject must have had a negative serum pregnancy test prior to the Treatment Phase
6. If female, subject was not breastfeeding
7. For those subjects taking phosphate binders, the subject had been on a stable regimen at least 4 weeks prior to the Screening Visit
8. For entry into the Pre-Treatment Phase, the subject must have had:
 - a. iPTH value ≥ 120 pg/mL
 - b. eGFR of 15 to 60 mL/min and subject was not expected to begin dialysis for at least 6 months (in the opinion of the Investigator)
9. For entry into the Treatment Phase, the subject must have had:
 - a. Average of 2 consecutive iPTH values of ≥ 150 pg/mL, taken at least 1 day apart (all values must have been ≥ 120 pg/mL)
 - b. 2 consecutive serum calcium levels of ≥ 8.0 to ≤ 10.0 mg/dL
 - c. 2 consecutive serum phosphorus levels of ≤ 5.2 mg/dL
10. Subject had voluntarily signed and dated an informed consent form, approved by an IRB/IEC, after the nature of the study had been explained and the subject had the opportunity to ask questions. The informed consent must have been signed before any study-specific procedures were performed.

Exclusion Criteria

1. Subject had a history of an allergic reaction or significant sensitivity to drugs similar to study drug
2. Subject had acute renal failure within 12 weeks of the study
3. Subject had chronic gastrointestinal disease that, in the Investigator's opinion, may have caused significant gastrointestinal malabsorption
4. Subject had a spot urine result demonstrating a urine calcium-to-creatinine ratio of > 0.2 or had a history of kidney stones

5. Within the last 12 weeks prior to Screening, subject had taken aluminum-containing phosphate binders, or required such medication ≥ 3 weeks during the course of the study
6. Subject had a current malignancy or clinically significant liver disease
7. Subject had an active granulomatous disease (e.g., tuberculosis, sarcoidosis)
8. Subject had a history of drug or alcohol abuse within 6 months prior to the Screening Visit
9. Subject had evidence of poor compliance with diet or medication that, in the Investigator's opinion, could have interfered with adherence to the protocol
10. Subject had received any investigational drug or participated in any device trial within 30 days prior to study drug administration
11. Subject was taking maintenance calcitonin, bisphosphonates, or drugs that could have affected calcium or bone metabolism, other than females on stable estrogen and/or progestin therapy
12. Subject had been on glucocorticoids for a period of > 14 days within the last 6 months
13. For any reason, subject was considered by the Investigator to be an unsuitable candidate to receive study drug or was put at risk by study procedures
14. Subject was known to be human immunodeficiency virus (HIV) positive

Appendix B. Comparison of Baseline iPTH

VISIT	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SE	BASELINE RANGE		BETWEEN GROUP DIFFERENCE
					MIN	MAX	P-VALUE
iPTH (pg/mL)							
ALL TREATED SUBJECTS	ZEMPLAR	39	294.6	21.39	151.0	711.0	0.367
	PLACEBO	36	323.6	23.92	147.0	697.5	
ALL SUBJECTS WITH POST DOSE MEASURE	ZEMPLAR	37	285.9	19.24	151.0	701.0	0.214
	PLACEBO	35	324.8	24.59	147.0	697.5	
INTENT-TO-TREAT SUBJECTS	ZEMPLAR	36	287.1	19.74	151.0	701.0	0.188
	PLACEBO	34	329.1	24.93	147.0	697.5	
NOTE: RESULTS ARE BASED ON A ONE-WAY ANOVA WITH TREATMENT AS THE FACTOR.							

Study 2001-020

Study Title: A Phase 3, Prospective, Randomized, Placebo-Controlled, Double-Blind, Multi-Center Study to Determine the Safety and Efficacy of Zemplar Capsule (Dosed 3 Times Weekly) in Reducing Elevated Serum Intact Parathyroid Hormone Levels in Subjects with Chronic Kidney Disease

Primary Objectives: To determine the safety and efficacy of Zemplar Capsule as compared to placebo in reducing serum iPTH levels in subjects with Stage 3 and 4 CKD.

Secondary Objectives: NA

The study design, patient population, treatment groups, endpoints, statistical analyses, and protocol amendments are equivalent to those of study 2001019. Please see the previous study report for details.

Results

Patient Demographics:

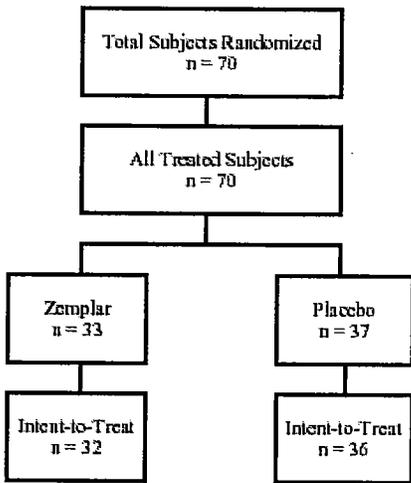
Variable	Zemplar N= 33	Placebo N= 37	Total N= 70	P-value
Gender				
Female	12 (36.4%)	13 (35.1%)	25 (35.7%)	1.000 #
Male	21 (63.6%)	24 (64.9%)	45 (64.3%)	
Race				
Asian only	1 (3.0%)	0 (0.0%)	1 (1.4%)	0.800 #
Black only	11 (33.3%)	12 (32.4%)	23 (32.9%)	
White only	21 (63.6%)	25 (67.6%)	46 (65.7%)	
Tobacco				
Nonsmoker	8 (24.2%)	16 (43.2%)	24 (34.3%)	0.131 #
Smoker \$	25 (75.8%)	21 (56.8%)	46 (65.7%)	
Alcohol				
Drinker &	18 (54.5%)	22 (59.5%)	40 (57.1%)	0.810 #
Nondrinker	15 (45.5%)	15 (40.5%)	30 (42.9%)	
Age group				
< 65 yr	20 (60.6%)	26 (70.3%)	46 (65.7%)	0.455 #
>= 65 yr	13 (39.4%)	11 (29.7%)	24 (34.3%)	
Age (years)				
N	33	37	70	
Mean	62.5	57.9	60.1	0.123 ##
Se	2.36	1.85	1.50	
Median	59.0	61.0	59.5	
Range	30 - 91	37 - 79	30 - 91	
Time since CKD (years)				
N	33	37	70	
Mean	4.17	7.76	6.07	0.031* ##

Variable	Zemplar N= 33	Placebo N= 37	Total N= 70	P-value
SE	0.490	1.477	0.837	
Median	3.50	4.60	4.00	
Range	0.2 - 11.0	0.2 - 38.7	0.2 - 38.7	

P-value for race, gender, tobacco, alcohol and age group derived from Fisher's exact test.
 ## p-value from f-test testing equality of means among treatment groups.
 \$ includes ex-tobacco users.
 & includes ex-drinkers.

Comment: Mean time since CKD is significantly different between groups and may impact safety evaluation (i.e., placebo group may appear "sicker" in comparison with Zemplar group).

Patient Disposition:



Protocol Violations:

There were no subjects for whom the blind was broken.

Four Zemplar subjects and five placebo subjects did not meet the inclusion/exclusion criteria of the study.

Subjects Not Meeting Inclusion/Exclusion Criteria		
Inclusion Criteria	Zemplar	Placebo
8 - For entry into Pre-Treatment Phase, subject had an iPTH value \geq 120 pg/mL and an eGFR of 15 to 60 mL/min, and was not expected to begin dialysis for at least 6 months.	1303 ^a	
Exclusion Criteria		
2 - Subject had acute renal failure within 12 weeks of the study.		705
4 - Subject had a spot urine result demonstrating a urine calcium-to-urine creatinine ratio of $>$ 0.2 or had a history of kidney stones.	1403, 1405, 301	1406, 1407, 1201
10 - Subject had received any investigational drug or participated in any device trial within 30 days prior to study drug administration.		1302

a. eGFR was $<$ 15 mL/min/1.73 m².

Concomitant Medication Use:

From the time of Screening, subjects must not have taken vitamin D medication, calcitonin, bisphosphonates, maintenance oral or IV glucocorticoids, or other drugs that could affect calcium or bone metabolism. Multivitamin supplements containing \leq 400 IU of vitamin D were not restricted.

Most commonly used drugs

Drug	Zemplar	Placebo
High-ceiling diuretics	85%	65%
ACE-I and/or ARBs	73%	68%
Cholesterol and TG reducers	61%	68%
Beta-blocking agents	61%	51%
Antithrombotic agents	58%	49%

Comment: The higher frequency of high-ceiling diuretics use in the Zemplar-treated group may have affected the incidence of hypercalcemia. This is addressed in the Integrated Review of Safety (see Section 7).

Phosphate binder usage

Overall	Zemplar (N=33)	Placebo (N=37)
Baseline	5 (15%)	5 (14%)
Final Visit	9 (27%)	7 (19%)

Phosphate binder at Final Visit	Zemplar (N=9)	Placebo (N=7)
Calcium-based	9 (100%)	6 (86%)
Non-calcium based (sevelamer hydrochloride)	0 (0%)	1 (14%)

Of the subjects who were taking phosphate binders at baseline, all remained on the same type of phosphate binder throughout the study and only two subjects (Zemplar 1303 and placebo 1901) required a dose change (increase).

Elemental calcium usage

Overall	Zemplar (N=39)	Placebo (N=36)
Baseline	8 (21%)	6 (17%)
Final Visit	11 (28%)	10 (28%)

Of the subjects who were taking elemental calcium at baseline, all remained on the same dose throughout the study except for one subject (Zemplar 1509) who required a dose decrease.

Primary Efficacy Outcome:

The primary efficacy endpoint was two consecutive $\geq 30\%$ decreases from baseline in iPTH. The difference between the treatment groups in baseline iPTH was not statistically significant (see Appendix C).

Summary of iPTH Response - Primary Efficacy Analysis Intent-to-Treat Population					
	Zemplar (N= 36)		Placebo (N= 34)		P-Value #
	Count	(%)	Count	(%)	
Subject achieved two consecutive 30% decreases from baseline in iPTH?					
Yes	29	(90.6%)	6	(16.7%)	<0.001***
No	3	(9.4%)	30	(83.3%)	

P-value is derived from Fisher's exact test.

Exploratory analyses were performed to assess the proportion of subjects in each treatment group who had four consecutive $\geq 30\%$ decreases from baseline in iPTH in order to assess the robustness of the results.

Summary Of PTH Response: Four Consecutive 30% Decreases In iPTH Intent-To-Treat Population					
	Zemplar (n= 36)		Placebo (n= 34)		P-value #
	Count	(%)	Count	(%)	
Subject Achieved Four Consecutive 30% Decreases From Baseline In iPTH ?					
Yes	26	(81.3%)	0	(0.0%)	<0.001***
No	6	(18.8%)	36	(100.0%)	

p-value is derived from Fisher's exact test.

Secondary Efficacy Outcomes:

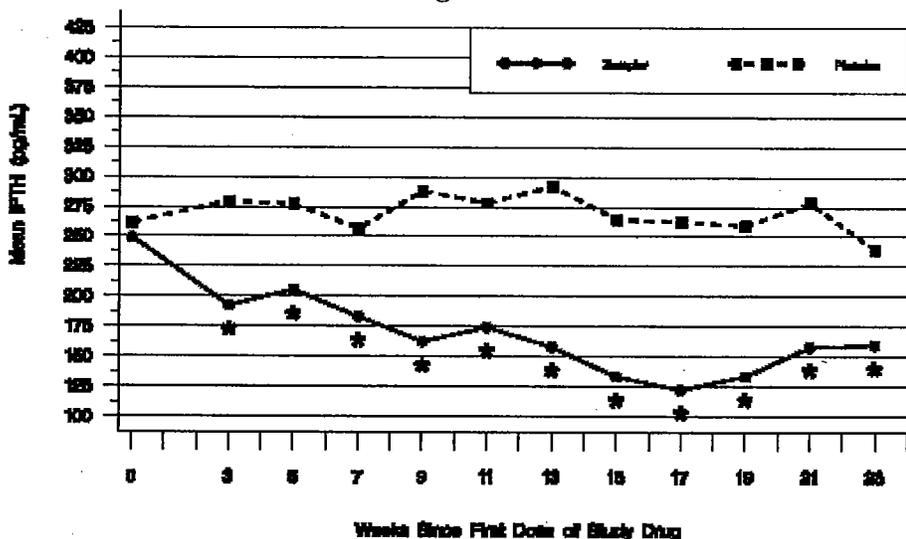
Mean Change and Percent Change from Baseline to Final Visit in iPTH (All Treated Subjects)			
iPTH (pg/mL)	Zemplar (N = 37)^a	Placebo (N = 35)^b	ANOVA P-value^c
Mean Baseline Value	248.9	263.1	0.552
(Baseline Range)	(152.5-442.0)	(150.0-625.0)	
Mean Final Value	168.3	275.3	NA
Mean Change from Baseline (SE)	-80.7 (15.45)	12.2 (14.79)	< 0.001
Mean Percent Change from Baseline (SE)	-30.3 (5.70)	9.4 (5.46)	< 0.001

NA = Not Applicable
 a. Placebo Subject 1407 had no iPTH measurements following the first dose of study medication; therefore, only 36 subjects (versus 37) are included in this analysis.
 b. One-way ANOVA with treatment as the factor.

Results were similar using ANCOVA with treatment as the factor and baseline iPTH as the covariate. Additionally, results were statistically significant when using Last On-Treatment Visit instead of Final Visit.

The following graph shows the mean values in iPTH over time for observed values:

Mean Values of iPTH Over Time During Treatment Phase



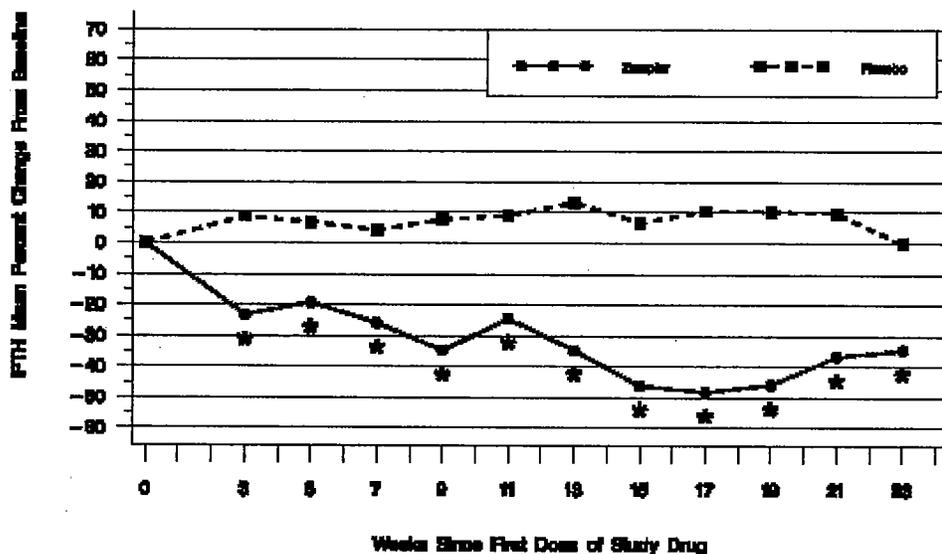
Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	33	33	33	32	32	29	32	29	29	27	30	26
Placebo N	37	36	35	35	34	36	36	35	30	33	33	32

* Statistically significant ($p \leq 0.05$) difference in mean change from baseline between the Zemplar and placebo treatment groups. At each visit, change from baseline is calculated for subjects who had data at the corresponding timepoint.

Results were similar using observed value ANCOVA with treatment as the factor and baseline iPTH as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline iPTH as the covariate.

The following graph shows the mean percent change from baseline in iPTH over time for observed values:

Mean Percent Change From Baseline in iPTH Over Time During Treatment Phase



Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	33	33	33	32	32	29	32	29	29	27	30	26
Placebo N	37	36	35	35	34	36	36	35	30	33	33	32

* Statistically significant ($p \leq 0.05$) difference in mean percent change from baseline between the Zemplar and placebo treatment groups. At each visit, percent change from baseline is calculated for subjects who had data at the corresponding timepoint.

Results were similar using observed value ANCOVA with treatment as the factor and baseline iPTH as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline iPTH as the covariate.

The differences between the treatment groups in mean change from baseline to Final Visit in the biochemical bone activity markers were statistically significant using ANOVA with treatment as the factor; the Zemplar group experienced mean decreases in all markers while the placebo group experienced mean increases or no change, see table below:

Mean Change from Baseline to Week 11 and Final Visit in Biochemical Bone Activity Marker Variables			
	Zemplar	Placebo	ANOVA P-value^a
Serum Bone-Specific Alkaline Phosphatase (mcg/L)			
Number of Subjects	29	32	
Mean Baseline Value	16.277	17.247	
Change from Baseline (SE) to Week 11	-5.078 (0.9420)	-1.448 (0.8968)	0.007
Number of Subjects	32	35	
Mean Baseline Value	17.007	17.543	
Change from Baseline (SE) to Final	-8.179 (1.2010)	-1.781 (1.1484)	< 0.001
Serum Osteocalcin (ng/mL)			
Number of Subjects	29	33	
Mean Baseline Value	55.31	56.12	
Change from Baseline (SE) to Week 11	-6.96 (3.259)	3.98 (3.055)	0.017
Number of Subjects	32	35	
Mean Baseline Value	56.09	55.44	
Change from Baseline (SE) to Final	-18.92 (3.973)	11.35 (3.799)	< 0.001
Urinary Deoxypyridinoline (nmol/mg Creat)			
Number of Subjects	28	28	
Mean Baseline Value	0.0698	0.0479	
Change from Baseline (SE) to Week 11	-0.0144 (0.00813)	0.0005 (0.00813)	0.199
Number of Subjects	31	33	
Mean Baseline Value	0.0682	0.0464	
Change from Baseline (SE) to Final	-0.0082 (0.00620)	-0.0034 (0.00601)	0.091
Urinary Pyridinoline (nmol/mmol Creat)			
Number of Subjects	28	32	
Mean Baseline Value	38.75	29.81	
Change from Baseline (SE) to Week 11	-4.87 (3.725)	-0.65 (3.484)	0.411
Number of Subjects	31	35	
Mean Baseline Value	38.60	29.17	
Change from Baseline (SE) to Final	-7.11 (2.828)	1.95 (2.662)	0.023

a. One-way ANOVA with treatment as the factor.

Safety Data

Deaths:

There was one death in a placebo subject (1406), due to cardiac arrest. The subject was a 67 year old male. The death occurred 10 days after the last dose of study drug. The investigator described the final diagnosis as suspected acute MI. The known cardiovascular disease for this subject included cardiac disease, congestive heart failure, and atrial fibrillation. The subject also had a history of diabetes and hyperlipidemia. Chronic kidney disease was thought due to diabetes. The subject's iPTH at baseline was 293.5 pg/mL and ranged during the study from — to — pg/mL. His baseline serum calcium was 9.2 mg/dL and ranged during the study from 8.9 to 9.6 mg/dL. His baseline CaxP was 31.7 mg²/dL² and ranged during the study from 30.36 to 44.59 mg²/dL².

Serious Adverse Events:

Serious Adverse Events Reported During the Treatment and Follow-Up Phases							
Subject Number	Gender/ Age	Serious Adverse Event Description	Study Day Onset^a	Study Day End^a	Severity	Investigator-determined Relationship	Reason Serious
Zemplar							
301	F/56	Complication from cholecystectomy	190 (24)	Ongoing as of Day 199 (33)	Moderate	Not related	HS
		Worsening of chronic renal failure	194 (28)	Ongoing as of Day 195 (29)	Severe	Not related	PH
803	F/59	Subject with ESRD secondary to diabetic nephropathy who had an arterial venous fistula placed in preparation of hemodialysis	65	66	Mild	Not related	HS
		Subject presented to ER with complaints of chest pain, diaphoresis, and abdominal fullness. She was admitted to the hospital. An EKG, chest x-rays and lab tests were performed. A kidney, ureter, and bladder x-ray showed her to be severely constipated. She was given magnesium citrate and water enemas which helped her to stool. Subject remained symptom free throughout remainder of admission	103	104	Mild	Not related	HS
1202	M/67	Chest pain, no diaphoresis, possible SOB	11	12	Severe	Not related	HS
1206	M/64	Admitted through ER with multiple complaints including chest pain, SOB, and abdominal pain	7	10	Moderate	Not related	HS
		Admitted with dizziness and blurred vision. No localizing symptoms	54	56	Moderate	Not related	HS
		Admitted with blurred vision and headache	76	89	Moderate	Not related	HS
1403	F/81	Weakness, SOB, fluid overload ^b	77	Ongoing as of Day 86 (9)	Severe	Not related	HS
		SOB, generalized fatigue, irregular heart rhythm	87 (10)	Ongoing as of Day 90 (13)	Moderate	Not related	HS
1405	F/58	Fluid overload, SOB, chest pain, orthopnea, dyspnea on exertion, pulmonary edema, decreased t-waves	57	59	Moderate	Not related	HS
Placebo							
1402	F/68	Facial droop, right sided weakness, excessive drooling, and mild chest pain	132 (5)	140 (13)	Severe	Not related	HS

Clinical Review
 Golden, J.
 NDA 21-606
 Paricalcitol capsules, Zemplar®

Serious Adverse Events Reported During the Treatment and Follow-Up Phases							
Subject Number	Gender/Age	Serious Adverse Event Description	Study Day Onset ^a	Study Day End ^a	Severity	Investigator-determined Relationship	Reason Serious
1406 ^c	M/67	Cardiac arrest	177 (10)	Unknown	Severe	Not related	DE

M/F = Male/Female; SOB = shortness of breath; ESRD = end-stage renal disease; ER = emergency room; HS = hospitalization; PH = prolonged hospitalization; DE = Death
 a. Numbers in parentheses represent number of days since last dose of study drug.
 b. Event led to premature termination.
 c. Subject died (cardiac arrest).

Adverse Events that Led to Study Withdrawal:

Adverse Events Leading to Premature Termination from Study Drug							
Subject Number	Gender/Age	Adverse Event Description	Study Day Onset ^a	Study Day End ^a	Severity	Investigator-determined Relationship	Investigator Alternative Etiology
Zemplar							
1403	F/81	Weakness, SOB, fluid overload	77	Ongoing as of Day 86 (9)	Severe	Not related	ESRD
Placebo							
705	M/41	Placement of arterial venous fistula and right internal jugular catheter placement	97	Ongoing as of Day 104 (7)	Moderate	Not related	Preparation for imminent dialysis

M/F = Male/Female; SOB = shortness of breath; ESRD = end-stage renal disease
 a. Numbers in parentheses represent number of days since last dose of study drug.

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Treatment-Emergent Adverse Events:

Overall Summary of Treatment-Emergent Adverse Events (All Treated Subjects)		
	Zemplar (N = 33)	Placebo (N = 37)
Number of Subjects Reporting Adverse Events	25 (76%)	29 (78%)
Number of Events Reported	73	78
Number of Serious Adverse Events Reported	13	2
Number of Subjects Reporting		
0 Events	8 (24%)	8 (22%)
1 Event	9 (27%)	9 (24%)
> 1 Event	16 (48%)	20 (54%)
Severity of Event		
Mild	45 (62%)	51 (65%)
Moderate	25 (34%)	25 (32%)
Severe	3 (4%)	2 (3%)
Relationship to Study Drug		
Probably Related	1 (1%)	1 (1%)
Possibly Related	1 (1%)	3 (4%)
Probably Not Related	12 (16%)	12 (15%)
Not Related	59 (81%)	62 (79%)

Laboratory Parameters:

Proportions of Subjects Who Developed Clinically Meaningful Hypercalcemia (All Treated Subject Population)			
Variable	Zemplar^a (N = 38)	Placebo^b (N = 35)	P-value^c
Clinically Meaningful Hypercalcemia (at least 2 consecutive calcium values > 10.5 mg/dL)			0.478
Yes	1 (3%)	0 (0%)	
No	35 (97%)	35 (100%)	

a. Placebo Subject 1407 had no calcium measurements following the first dose of study medication; therefore, only 36 subjects (versus 37) are included in this analysis.
c. Fisher's exact test.

One Zemplar subject (1301), a 52 year old white female, experienced two consecutive serum calcium values > 10.5 mg/dL at Weeks 17 (10.8 mg/dL) and 19 (11.1 mg/dL). The subject's baseline iPTH was 266 pg/mL and calcium was 9.4 mg/dL. At Week 17, her iPTH was — pg/mL although the subject did not get the phone message to reduce her dose from 6 mcg to 2 mcg. At Week 19, her iPTH was — pg/mL. Study drug was reduced to 0 mcg/dose. At Week 21, her calcium returned to normal (9.7 mg/dL). She resumed dose on treatment week 23-24.

No subject had hypercalcemia reported as an adverse event.

Comment: Four Zemplar-treated subjects and one placebo-treated subject had single calcium values > 10.5:

Proportions of Subjects Who Developed Single Calcium Values > 10.5*			
Variable	Zemplar (N = 33)	Placebo (N = 36)	P-value^a
At least 1 consecutive calcium value > 10.5 mg/dL)			0.186
Yes	4 (12%)	1 (3%)	
No	29 (88%)	35 (97%)	

a. Fisher's exact test.

*Subjects with at least one on-treatment calcium value

Mean Change from Baseline to Final Visit in Calcium, Phosphorus, CaxP, and Albumin			
	Zemplar (N = 33)	Placebo (N = 36)^a	ANOVA P-value^b
Calcium (mg/dL)			
Mean Baseline Value	9.25	9.50	0.004
Baseline Range	8.3 - 10.0	9.0 - 10.0	
Mean Final Value	9.44	9.51	
Change from Baseline (SE)	0.18 (0.067)	0.01 (0.064)	0.067
Phosphorus (mg/dL)			
Mean Baseline Value	4.00	3.75	0.071
Baseline Range	2.8 - 4.9	2.3 - 4.8	
Mean Final Value	4.15	3.92	
Change from Baseline (SE)	0.15 (0.137)	0.17 (0.131)	0.938
CaxP (mg²/dL²)			
Mean Baseline Value	36.64	35.27	0.286
Baseline Range	24.1 - 46.3	20.8 - 43.9	
Mean Final Value	39.26	37.32	
Change from Baseline (SE)	2.62 (1.289)	2.04 (1.234)	0.747
Albumin (g/dL)			
Mean Baseline Value	3.80	3.97	0.122
Baseline Range	2.7 - 4.6	2.4 - 4.7	
Mean Final Value	3.82	3.88	
Change from Baseline (SE)	0.02 (0.048)	-0.09 (0.046)	0.108

a. Placebo Subject 1407 had no primary chemistry measurements following the first dose of study medication; therefore, only 36 subjects (versus 37) are included in this analysis.

b. One-way ANOVA with treatment as the factor.

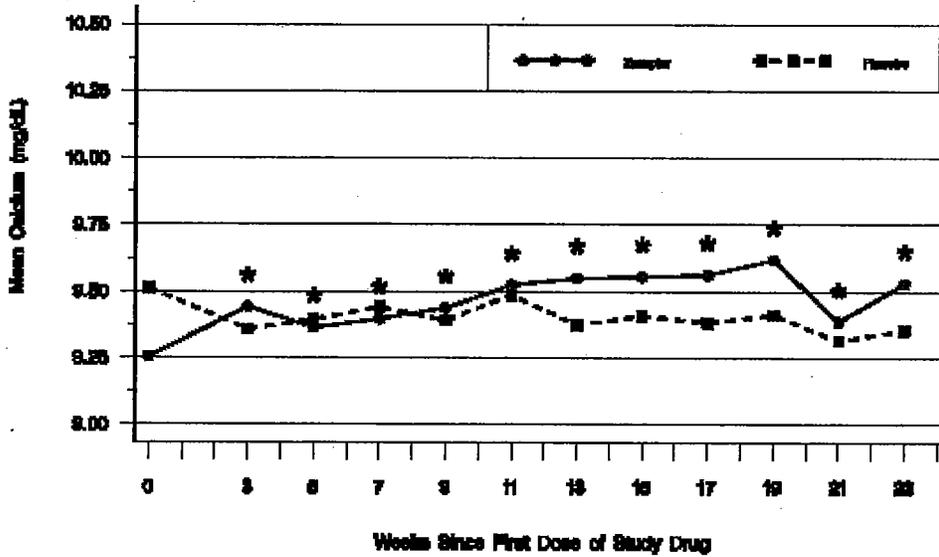
Similar results were observed using ANCOVA with treatment as the factor and baseline value as the covariate for phosphorus, CaxP, and albumin. In the calcium ANCOVA analysis, the difference in mean changes in treatment group when adjusting for baseline calcium is non-significant at p = 0.390.

Mean Change from Baseline to Last On-Treatment Visit in Calcium, Phosphorus, Ca×P, and Albumin			
	Zemplar	Placebo	ANOVA
	(N = 33)	(N = 36)^a	P-value^b
Calcium (mg/dL)			
Mean Baseline Value	9.25	9.50	
Mean Last On-Treatment Value	9.45	9.37	
Change from Baseline (SE)	0.19 (0.054)	-0.14 (0.052)	< 0.001
Phosphorus (mg/dL)			
Mean Baseline Value	4.00	3.75	
Mean Last On-Treatment Value	4.12	3.96	
Change from Baseline (SE)	0.12 (0.133)	0.20 (0.128)	0.648
Ca×P (mg²/dL²)			
Mean Baseline Value	36.64	35.27	
Mean Last On-Treatment Value	38.93	37.05	
Change from Baseline (SE)	2.30 (1.270)	1.78 (1.216)	0.770
Albumin (g/dL)			
Mean Baseline Value	3.80	3.97	
Mean Last On-Treatment Value	3.82	3.93	
Change from Baseline (SE)	0.02 (0.042)	-0.04 (0.041)	0.331
a. Placebo Subject 1407 had no primary chemistry measurements following the first dose of study medication; therefore, only 36 subjects (versus 37) are included in this analysis.			
b. One-way ANOVA with treatment as the factor.			

Similar results were observed using ANCOVA with treatment as the factor and baseline value as the covariate.

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Mean Calcium Values Over Time During Treatment Phase



Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	33	33	33	32	32	29	32	29	29	27	30	26
Placebo N	37	36	36	36	34	36	36	35	30	32	33	32

* Statistically significant ($p \leq 0.05$) difference in mean change from baseline between the Zemplar and placebo treatment groups. At each visit, change from baseline is calculated for subjects who had data at the corresponding timepoint.

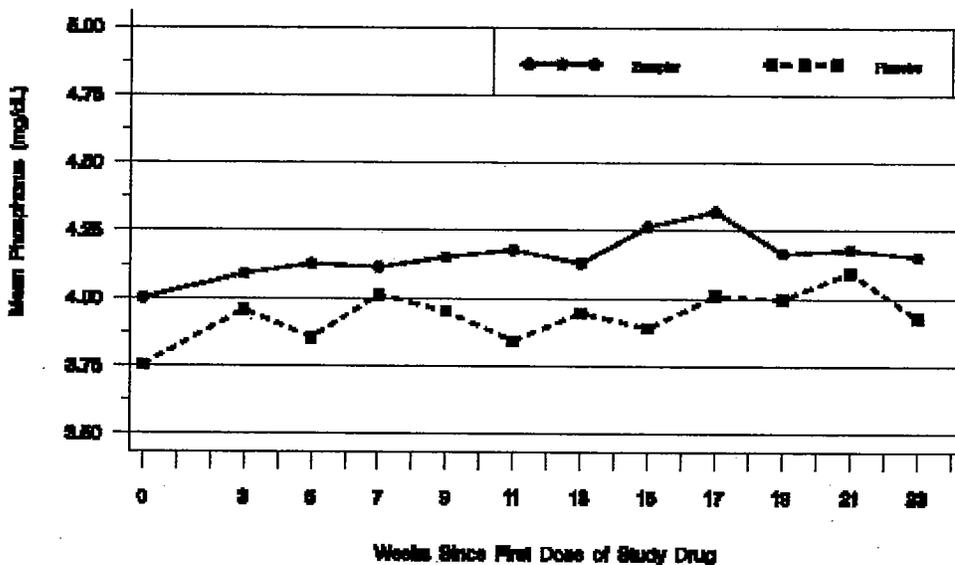
Calcium Normal Range: 8.0 to 10.3 mg/dL

Results were similar using observed value ANCOVA with treatment as the factor and baseline calcium as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline calcium as the covariate.

Comment: Calcium range for Zemplar subjects was 7.8 – 11.1 mg/dL; for placebo subjects 8.6 – 10.9 mg/dL.

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Mean Phosphorus Values Over Time During Treatment Phase



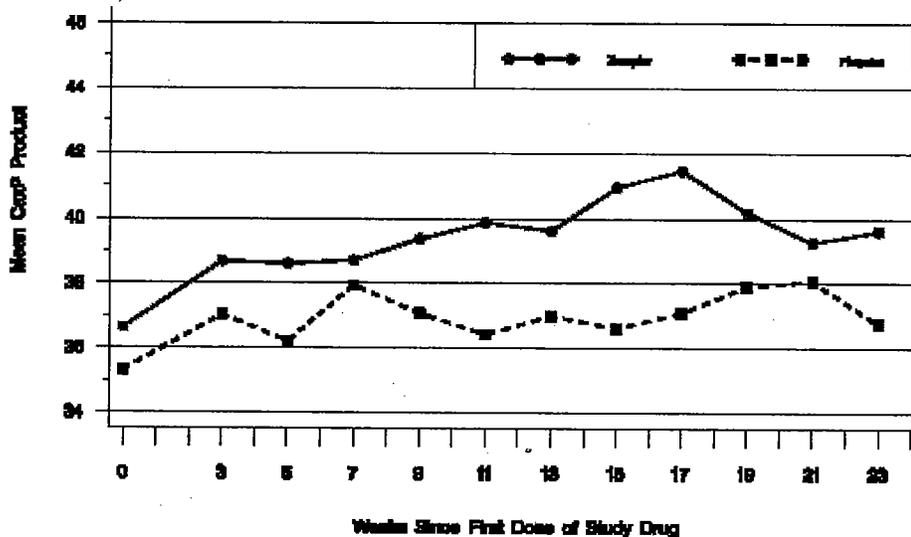
Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	33	33	33	32	32	29	32	29	29	27	30	26
Placebo N	37	36	36	36	34	36	36	35	31	33	33	31

At each visit, change from baseline is calculated for subjects who had data at the corresponding timepoint.
 Phosphorus Normal Range: 2.2 to 5.1 mg/dL

Results were similar using observed value ANCOVA with treatment as the factor and baseline calcium as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline phosphorus as the covariate.

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 ON ORIGINAL**

Mean CaxP Values Over Time During Treatment Phase



Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	33	33	33	32	32	29	32	29	29	27	30	26
Placebo N	37	36	36	36	34	36	36	35	30	32	33	31

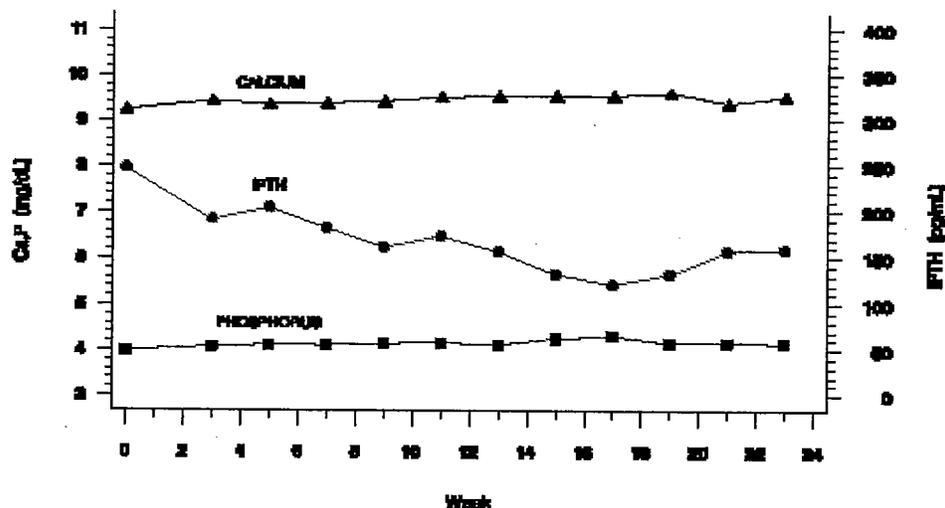
At each visit, change from baseline is calculated for subjects who had data at the corresponding timepoint.
 CaxP Normal Range: 17.6 to 52.5

Results were similar using observed value ANCOVA with treatment as the factor and baseline calcium as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline CaxP as the covariate. However, a statistically significant difference was observed between the Zemplar and placebo treatment groups at Week 11 using observed value ANCOVA.

Comment: A statistically significant result may not also have been seen at Week 17 due to a smaller sample size at this week.

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Mean Calcium, Phosphorus, and iPTH Values Over Time, Zemplar-Treated Subjects



Except for the alkaline phosphatase (see table), there were no secondary chemistry variables that exhibited statistically significant differences between treatment groups in mean change from baseline to Final Visit using ANOVA.

Statistically Significant Differences Between Treatment Groups for Mean Change from Baseline to Final Visit in Secondary Chemistry Variables		
Variable (unit)	Zemplar	Placebo
Alkaline Phosphatase (IU/L)***	(N = 32)	(N = 36)
Mean Baseline Value	104.31	92.92
Mean Final Value	86.53	95.69
Mean Change from Baseline (SD)	-17.78 (24.719)	2.78 (18.064)

*** = statistically significant difference between treatment groups at the 0.001 level, using a contrast within the one-way ANOVA.

Results were similar when secondary chemistry variables were analyzed using ANCOVA, except that a statistically significant difference was observed in mean change from baseline to Final Visit in potassium [Zemplar group had a small mean decrease (-0.07 mEq/L), $p = 0.016$]. Results were similar using ANCOVA.

There were no hematology or urinalysis (pH and specific gravity) variables that exhibited statistically significant differences between treatment groups in mean change from baseline to Final Visit using ANOVA. Results were similar using ANCOVA, except that a statistically significant difference in mean change from baseline to Final Visit in pH was observed (Zemplar group had a small mean increase 0.119, $p = 0.032$).

Mean Change from Baseline to Final Visit in 24-Hour Urine Collections (All Treated Subjects)			
	Zemplar	Placebo	ANOVA P-value^a
Calcium (mg/24 hours)	(N = 25)	(N = 27)	
Mean Baseline Value	39.06	39.54	—
Mean Final Value	42.80	37.67	NA
Mean Change from Baseline (SE)	3.74 (4.773)	-1.87 (4.592)	0.401
Phosphorus (mg/24 hours)	(N = 25)	(N = 29)	
Mean Baseline Value	688.9	684.6	—
Mean Final Value	679.8	762.8	NA
Mean Change from Baseline (SE)	-9.1 (55.29)	78.2 (51.34)	0.252
Creatinine Clearance (mL/min/1.73m²)	(N = 28)	(N = 32)	
Mean Baseline Value	30.7	29.2	—
Mean Final Value	28.8	30.7	NA
Mean Change from Baseline (SE)	-2.0 (2.15)	1.5 (2.01)	0.240

NA = Not Applicable
a. One-way ANOVA with treatment as the factor.

Although not statistically different, as the above table demonstrates, Zemplar-treated subjects experienced mean increases from baseline to Final Visit in urinary calcium, and mean decreases from baseline in urinary phosphorus, and Ccr; whereas placebo-treated subjects experienced mean decreases from baseline in urinary calcium, and mean increases in phosphorus and Ccr. Results were similar using ANCOVA.

Mean Change and Percent Change from Baseline to Final Visit in eGFR and Creatinine (All Subjects Who Completed 24 Weeks of Treatment)			
	Zemplar	Placebo	ANOVA P-value^a
eGFR (mL/min/1.73m²)	(N = 27)	(N = 33)	
Mean Baseline Value	26.24	24.44	—
Mean Final Value	22.12	22.70	NA
Mean Change from Baseline (SE)	-4.12 (0.965)	-1.74 (0.873)	0.073
Mean Percent Change from Baseline (SE)	-16.61 (4.379)	-4.64 (3.961)	0.047
Creatinine (mg/dL)			
Mean Baseline Value	2.84	2.94	—
Mean Final Value	3.44	3.16	NA
Mean Change from Baseline (SE)	0.60 (0.145)	0.22 (0.131)	0.060†
Mean Percent Change from Baseline (SE)	20.15 (4.226)	9.15 (3.823)	0.059‡

NA = Not Applicable
a. One-way ANOVA with treatment as the factor.
† When using Wilcoxon rank-sum test, p = 0.016
‡ When using Wilcoxon rank-sum test, p = 0.017

As noted by the Sponsor, more subjects in the Zemplar-treated group were taking high-ceiling diuretics and ACE-I and/or ARBs that may have contributed to the above findings. Results of the above table were similar using ANCOVA.

Urinary Calcium/Creatinine Ratio: No statistically significant differences were observed between the treatment groups in mean change from baseline to Week 11 or to Final Visit in urinary calcium/creatinine ratio using ANOVA or ANCOVA.

Cardiovascular Marker Variables: Fifteen subjects (7 Zemplar and 8 placebo) who had both baseline and Final Visit pro-BNP and troponin-T values were included in these analyses. No statistically significant differences in cardiovascular marker variables were observed between treatment groups in mean change from baseline to Week 11, Final Visit, or Final Visit that was at least 161 after the last dose of study drug using ANOVA and ANCOVA.

Vital Signs:

ANOVA Of Changes From Baseline To Final Visit In Vital Sign Variables All Treated Subject Population								
Variables	Treatment Group	N	Baseline Mean	Visit Mean	Change From Baseline			Between Group Comparison
					Mean	SE	P-Value	Difference (95% CI) P-Value (HO:Difference=0)
Weight (Kg)								
	Zemplar	32	93.3	93.3	-0.0	0.73	0.977	-1.3 (-3.3, 0.7)
	Placebo	34	92.7	94.0	1.3	0.70	0.071+	0.198†
Pulse (BPM)								
	Zemplar	32	71.6	72.6	1.0	2.26	0.660	1.7 (-4.6, 7.9)
	Placebo	35	72.1	71.4	-0.7	2.16	0.762	0.598
Systolic Blood Pressure (mmHg)								
	Zemplar	32	140.5	146.5	6.0	3.95	0.131	8.3 (-2.6, 19.2)
	Placebo	35	138.7	136.4	-2.3	3.77	0.542	0.131
Diastolic Blood Pressure (mmHg)								
	Zemplar	32	74.7	77.1	2.5	2.16	0.258	4.5 (-1.4, 10.5)
	Placebo	35	77.1	75.0	-2.1	2.07	0.323	0.135

***, **, *, + Statistically Significant At P=0.001, 0.01, 0.05, 0.10 Levels, Respectively.

Note: Results Are Based On A One-Way Anova With Treatment As The Factor.

†Wilcoxon-rank test, p = 0.014

Comment: Although differences were not statistically significant either in (Baseline to Final Visit nor in between-group comparisons), SBP and DBP increased in the Zemplar-treated group and decreased in the placebo treated group. However, there appears to be a lot of variability in the data. These data, taken together with blood pressure data from the other two pivotal studies, on balance do not suggest a clinically important blood pressure effect of Zemplar (see ISS).

Results were similar using ANCOVA with treatment as the factor and baseline value as covariate. In addition, there statistically significant differences were not observed between the

treatment groups for the mean change from baseline to Week 7, or Week 15 in systolic blood pressure, diastolic blood pressure, pulse, and weight using ANOVA or ANCOVA.

Special Safety Studies: NA

Other: NA

Company's Conclusions (emphasis added, indicating the Company's interpretations):

1. Thirty-two Zemplar subjects and 36 placebo subjects had a baseline and at least two on-treatment iPTH measurements. Twenty-nine of 32 (91%) subjects who received Zemplar achieved two consecutive $\geq 30\%$ decreases from baseline in iPTH compared to 6 of 36 (17%) of subjects who received placebo. This difference was statistically significant.
2. At the Final Visit, subjects who received Zemplar had a statistically significant mean reduction in iPTH compared to a mean increase observed for subjects who received placebo [-80.7 pg/mL (-30.3%) versus 12.2 pg/mL(9.4%)]. When analyses were performed using iPTH data collected at the Last On-Treatment Visit, Zemplar-treated subjects had a statistically significant mean decrease [-83.1 pg/mL (-33.4%)] in iPTH compared with a mean increase [10.1 pg/mL (2.9%)] among placebo-treated subjects.
3. Statistically significant differences were observed between the Zemplar and placebo treatment groups at all scheduled visits of the Treatment Phase for both change and percent change from baseline in iPTH.
4. Statistically significant differences from baseline to Final Visit between treatment groups were observed in all 2/4 biochemical bone marker variables (serum osteocalcin and serum BAP).
5. /
6. No statistically significant differences were observed between the treatment groups for the proportion of subjects with at least two consecutive calcium values > 10.5 mg/dL (1/33, 3% Zemplar versus 0% placebo).
7. Mean change from baseline serum calcium to Last On-Treatment Visit was statistically significantly different between the treatment groups (Zemplar group mean = +0.19 mg/dL; placebo group mean = -0.14 mg/dL).
8. Statistically significant differences between the treatment groups were observed at every scheduled visit of the Treatment Phase for mean change from baseline in calcium values; mean increases were seen in Zemplar group and mean decreases were seen in placebo group.

9. No statistically significant differences were observed between the treatment groups for mean changes from baseline to any of the scheduled visits of the Treatment Phase, Final Visit, or Last On-Treatment Visit for phosphorus or CaxP.
10. No statistically significant difference was observed between the treatment groups in mean change from baseline to Final Visit in 24-hour urine collection variables (calcium, phosphorus, Ccr) or urinary calcium/creatinine ratio.
11. A statistically significant difference between treatment groups was observed for mean percent change from baseline in eGFR (Zemplar = -16.61%, placebo = -4.64%; $p = 0.047$). The difference in mean change was not statistically significant. No statistically significant difference in serum creatinine was observed between treatment groups for those that completed 24 weeks of treatment using ANOVA and ANCOVA analyses. The Wilcoxon rank-sum test indicated a statistically significant difference between the treatment groups for mean change and mean percent change from baseline to Final Visit in creatinine.
12. Evaluations of other laboratory analyses, vital signs, and physical examinations revealed no clinically meaningful changes as a result of Zemplar treatment.
13. No statistically significant differences were observed between the treatment groups for the overall incidence of adverse events or for the incidence of any specific adverse event. These data are indicative of the overall tolerability of Zemplar in this patient population.
14. Zemplar Capsule is safe and well tolerated for the treatment and prevention of 2° HPT in CKD (stages 3 and 4) subjects.
15. Zemplar Capsule is effective for the treatment and prevention of 2° HPT in CKD (Stages 3 and 4) subjects.

Medical Officer's Conclusions:

1. **Statistical analyses demonstrating Zemplar's efficacy in decreasing iPTH compared with placebo are very strong.**
2. **Final Visit and Last On-Treatment analyses lose within-study measurement information. Therefore, in addition to mean change from baseline, in particular when evaluating measures for safety, it is important to assess mean values over time.**
3. **Biochemical markers, while suggesting an improvement in bone turnover in the Zemplar-treated subjects versus the placebo-treated subjects, do not have proven equivalence to histological data. In addition, the relevance of bone marker data in subjects with renal impairment is not clear.**
4. **Mean time since CKD is significantly different between groups and may impact safety evaluation (i.e., placebo group may appear "sicker" in comparison with Zemplar group).**
5. **The higher frequency of high-ceiling diuretics use in the Zemplar-treated group may have masked the incidence of hypercalcemia.**
6. **A statistically significant difference was observed in change in serum calcium from baseline to Last On-Treatment Visit between groups;**

Monitoring of calcium in dosing is critical.

7. Dosing changes are made for single calcium levels ≥ 10.4 mg/dL. Therefore, the designation of two consecutive calcium levels > 10.5 as clinically relevant is somewhat misleading. An analysis was performed with single calcium values > 10.5 . Although difference between groups was not statistically significant, it may be clinically significant (five Zemplar subjects with at least one calcium > 10.5 mg/dL versus one placebo subject). In addition, although there is not a statistically significant difference in mean serum calcium levels, a trend toward increased mean calcium levels in Zemplar-treated subjects compared to those treated with placebo appears to exist. This study was not powered to detect a statistically significant difference. The majority of calcium values remained in the normal range for both Zemplar- and placebo-treated subjects.
8. There were no statistically or clinically significant differences observed between the treatment groups for mean changes from baseline to any of the scheduled visits for phosphorus, Ca x P, eGFR, or creatinine.
9. Although differences were not statistically significant either in (Baseline to Final Visit nor in between-group comparisons), SBP and DBP increased in the Zemplar-treated group and decreased in the placebo treated group.
10. Although there are several baseline imbalances between groups, there is no reason to suspect that invalidating bias was introduced. Based on this single study, Zemplar Capsule appears safe to administer TIW to patients with CKD Stages 3 and 4 with 2° HPT with careful monitoring of calcium and Ca x P levels and subsequent dose titration. Given the potential for hypercalcemia, Zemplar capsules should not be administered to subjects with hypercalcemia at baseline.

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Appendix C. Comparison of Baseline iPTH

VISIT	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SE	BASELINE RANGE		BETWEEN GROUP DIFFERENCE
					MIN	MAX	P-VALUE
iPTH (pg/mL)							
ALL TREATED SUBJECTS	ZEMPLAR	33	248.9	12.68	152.5	442.0	0.593
	PLACEBO	37	261.5	19.11	150.0	625.0	
ALL SUBJECTS WITH POST DOSE MEASURE	ZEMPLAR	33	248.9	12.68	152.5	442.0	0.552
	PLACEBO	36	263.1	19.58	150.0	625.0	
INTENT-TO-TREAT SUBJECTS	ZEMPLAR	32	248.8	13.08	152.5	442.0	0.555
	PLACEBO	36	263.1	19.58	150.0	625.0	
NOTE: RESULTS ARE BASED ON A ONE-WAY ANOVA WITH TREATMENT AS THE FACTOR.							

**APPEARS THIS WAY
ON ORIGINAL**

Study 2001-021

Study Title: A Phase 3, Prospective, Randomized, Placebo-Controlled, Double-Blind, Multi-Center Study to Determine the Safety and Efficacy of Zemlar Capsule (Dosed Every Day) in Reducing Elevated Serum Intact Parathyroid Hormone Levels in Subjects with Chronic Kidney Disease

Primary Objectives: To determine the safety and efficacy of Zemlar Capsule as compared to placebo in reducing serum iPTH levels in subjects with Stage 3 and 4 CKD.

Secondary Objectives: NA

With the exception of study drug administration regimen (QD), the study design, patient population, treatment groups, endpoints, statistical analyses, and protocol amendments are equivalent to those of study 2001019. Please see the previous study report for details.

Results

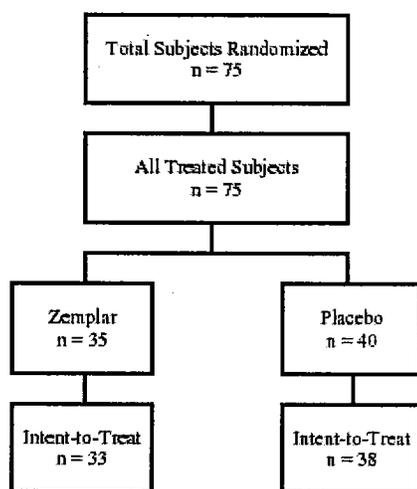
Patient Demographics:

Variable	Zemlar N= 35	Placebo N= 40	Total N= 75	P-Value
Gender				
Female	10 (28.6%)	13 (32.5%)	23 (30.7%)	0.804 #
Male	25 (71.4%)	27 (67.5%)	52 (69.3%)	
Race				
Asian Only	0 (0.0%)	1 (2.5%)	1 (1.3%)	0.468 #
Black Only	5 (14.3%)	7 (17.5%)	12 (16.0%)	
Am Indian-Alaska Native Only	2 (5.7%)	0 (0.0%)	2 (2.7%)	
White Only	28 (80.0%)	32 (80.0%)	60 (80.0%)	
Tobacco				
Nonsmoker	16 (45.7%)	18 (45.0%)	34 (45.3%)	1.000 #
Smoker \$	19 (54.3%)	22 (55.0%)	41 (54.7%)	
Alcohol				
Drinker &	25 (71.4%)	26 (65.0%)	51 (68.0%)	0.624 #
Nondrinker	10 (28.6%)	14 (35.0%)	24 (32.0%)	
Age Group				
< 65 Yr	14 (40.0%)	19 (47.5%)	33 (44.0%)	0.642 #
>= 65 Yr	21 (60.0%)	21 (52.5%)	42 (56.0%)	
Age (Years)				
N	35	40	75	
Mean	64.6	62.9	63.7	0.552 ##
SE	1.79	2.20	1.44	
Median	67.0	66.5	67.0	
Range	42 - 84	32 - 93	32 - 93	
Time Since CKD (Years)				

Variable	Zemplar N= 35	Placebo N= 40	Total N= 75	P-Value
N	35	40	75	
Mean	7.05	5.39	6.17	0.388 ##
SE	1.617	1.088	0.950	
Median	3.80	3.30	3.70	
Range	0.3 - 51.4	0.4 - 31.5	0.3 - 51.4	

Note: # P-Value For Race, Gender, Tobacco, Alcohol And Age Group Derived From Fisher's Exact Test.
 ## P-Value From F-Test Testing Equality Of Means Among Treatment Groups.
 \$ Includes Ex-Tobacco Users.
 & Includes Ex-Drinkers.

Patient Disposition:



Protocol Violations:

There were no subjects for whom the blind was broken.

Seven Zemplar subjects and six placebo subjects did not meet the inclusion/exclusion criteria of the study.

Subjects Not Meeting Inclusion/Exclusion Criteria		
Inclusion Criteria	Zemplar	Placebo
8 - For entry into Pre-Treatment Phase, subject had an iPTH value \geq 120 pg/mL and an eGFR of 15 to 60 mL/min, and was not expected to begin dialysis for at least 6 months.		105 ^a
9 - For entry into Treatment Phase, subject had an average of 2 consecutive iPTH values \geq 150 pg/mL taken at least 1 day apart (all values must have been \geq 120 pg/mL), 2 consecutive corrected serum calcium levels of \geq 8.0 to \leq 10.0 mg/dL, and 2 consecutive serum phosphorus levels of \leq 5.2 mg/dL.	504 ^b , 203 ^c , 901 ^d , 405 ^e	

Subjects Not Meeting Inclusion/Exclusion Criteria		
Exclusion Criteria		
4 - Subject had a spot urine result demonstrating a urine calcium-to-urine creatinine ratio of > 0.2 or had a history of kidney stones.	503, 504, 604	601, 406, 803, 1403
12 - Subject had been on glucocorticoids for a period of > 14 days within the last 6 months.	1405	802
a. eGFR was < 15 mL/min/1.73m ² . b. Serum calcium > 10.0 mg/dL. c. Serum calcium < 8.0 mg/dL. d. Serum phosphorus > 5.2 mg/dL. e. Average iPTH < 150 pg/mL.		

Concomitant Medication Use:

From the time of Screening, subjects must not have taken vitamin D medication, calcitonin, bisphosphonates, maintenance oral or IV glucocorticoids, or other drugs that could affect calcium or bone metabolism. Multivitamin supplements containing ≤ 400 IU of vitamin D were not restricted.

Most commonly used drugs during treatment

Drug	Zemplar	Placebo
High-ceiling diuretics	66%	70%
ACE-I and/or ARBs	57%	70%
Cholesterol and TG reducers	60%	58%
Beta-blocking agents	66%	65%
Antithrombotic agents	77%	65%

Phosphate binder usage

Overall	Zemplar (N=33)	Placebo (N=37)
Baseline	7 (20%)	9 (23%)
Final Visit	11 (31%)	10 (25%)

Phosphate binder at Final Visit	Zemplar (N=11)	Placebo (N=10)
Calcium-based	7 (64%)	9 (90%)
Non-calcium based (sevelamer hydrochloride)	4 (36%)	1 (10%)

Of the subjects who were taking phosphate binders at baseline, one subject (Zemplar 2211) discontinued binder use and one subject (placebo 904) required a dose increase. Two Zemplar subjects (202 and 1404) initiated calcium-based phosphate binders, three Zemplar subjects (907, 1001, and 1204) initiated non-calcium-based phosphate binders, and one placebo subject initiated a calcium-based phosphate binder during the study.

Elemental calcium usage

Overall	Zemplar (N=35)	Placebo (N=40)
Baseline	8 (23%)	11 (28%)
Final Visit	9 (26%)	11 (28%)

Of the subjects who were taking elemental calcium at baseline, two subjects (Zemplar 2211 and placebo 2203) discontinued calcium-containing medications. Placebo 904 required a dose increase during the study.

Primary Efficacy Outcome:

The primary efficacy endpoint was two consecutive $\geq 30\%$ decreases from baseline in iPTH. The difference between the treatment groups in baseline iPTH was not statistically significant (see Appendix D).

Summary Of iPTH Response - Primary Efficacy Analysis, Intent-To-Treat Population					
	Zemplar (N= 33)		Placebo (N= 38)		P-Value #
	Count	(%)	Count	(%)	
Subject Achieved Two Consecutive 30% Decreases From Baseline In iPTH?					
Yes	30	(90.9%)	4	(10.5%)	<0.001***
No	3	(9.1%)	30	(89.5%)	

P-Value Is Derived From Fisher's Exact Test.

Exploratory analyses were performed to assess the proportion of subjects in each treatment group who had four consecutive $\geq 30\%$ decreases from baseline in iPTH in order to assess the robustness of the results.

Summary Of iPTH Response - Four Consecutive 30% Decreases In iPTH, Intent-To-Treat Population					
	Zemplar (N= 33)		Placebo (N= 38)		P-Value #
	Count	(%)	Count	(%)	
Subject Achieved Four Consecutive 30% Decreases From Baseline In iPTH ?					
Yes	23	(69.7%)	0	(0.0%)	<0.001***
No	10	(30.3%)	36	(100.0%)	

P-Value Is Derived From Fisher's Exact Test.

Secondary Efficacy Outcomes:

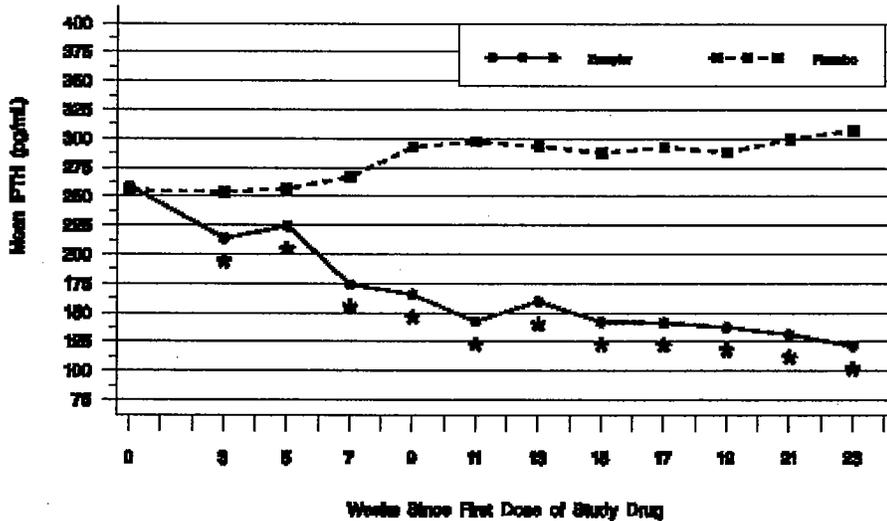
Mean Change and Percent Change from Baseline to Final Visit in iPTH (All Treated Subjects)			
iPTH (pg/mL)	Zemplar (N = 35)	Placebo (N = 40)	ANOVA P-value^a
Mean Baseline Value (Baseline Range)	259.1 (145.0-856.0)	255.1 (149.5-594.0)	0.879
Mean Final Value	212.2	307.7	NA
Mean Change from Baseline (SE)	-46.9 (15.65)	52.6 (14.64)	< 0.001
Mean Percent Change from Baseline (SE)	-15.2 (5.65)	19.1 (5.29)	< 0.001

NA = Not Applicable
a. One-way ANOVA with treatment as the factor.

Results were similar using ANCOVA with treatment as the factor and baseline iPTH as the covariate. Additionally, results were statistically significant when using Last On-Treatment Visit instead of Final Visit.

The following graph shows the mean values in iPTH over time for observed values:

Mean Values of iPTH Over Time During Treatment Phase



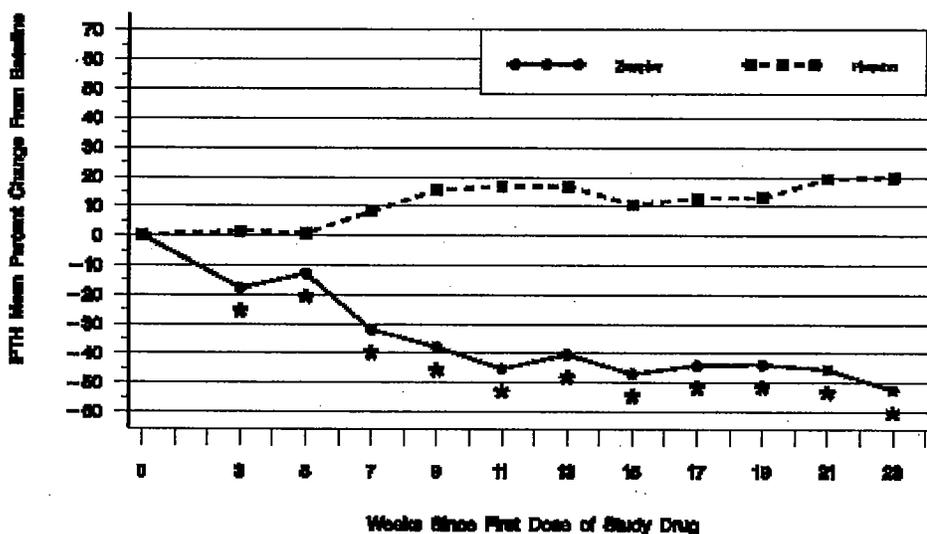
Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	35	34	34	32	31	29	32	31	30	27	26	25
Placebo N	40	38	39	36	35	36	34	35	33	33	32	32

* Statistically significant ($p \leq 0.05$) difference in mean change from baseline between the Zemplar and placebo treatment groups. At each visit, change from baseline is calculated for subjects who had data at the corresponding timepoint.

Results were similar using observed value ANCOVA with treatment as the factor and baseline iPTH as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline iPTH as the covariate.

The following graph shows the mean percent change from baseline in iPTH over time for observed values:

Mean Percent Change From Baseline in iPTH Over Time During Treatment Phase



Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	35	34	34	32	31	29	32	31	30	27	26	25
Placebo N	40	38	39	36	35	36	34	35	33	33	32	32

* Statistically significant ($p \leq 0.05$) difference in mean percent change from baseline between the Zemplar and placebo treatment groups. At each visit, percent change from baseline is calculated for subjects who had data at the corresponding timepoint.

Results were similar using observed value ANCOVA with treatment as the factor and baseline iPTH as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline iPTH as the covariate.

The differences between the treatment groups in mean change from baseline to Final Visit in the biochemical bone activity markers were statistically significant using ANOVA with treatment as the factor; the Zemplar group experienced mean decreases in all markers while the placebo group experienced mean increases or no change, see table below:

Mean Change from Baseline to Week 11 and Final Visit in Biochemical Bone Activity Marker Variables			
	Zemplar	Placebo	ANOVA P-value^a
Serum Bone-Specific Alkaline Phosphatase (mcg/L)			
Number of Subjects	26	33	
Mean Baseline Value	17.938	17.029	
Change from Baseline (SE) to Week 11	-5.383 (1.0482)	-2.302 (0.9304)	0.032
Number of Subjects	33	37	
Mean Baseline Value	17.945	17.074	
Change from Baseline (SE) to Final	-7.575 (1.3976)	-0.336 (1.3199)	< 0.001
Serum Osteocalcin (ng/mL)			
Number of Subjects	26	33	
Mean Baseline Value	76.07	76.28	
Change from Baseline (SE) to Week 11	-0.22 (4.968)	-2.35 (4.410)	0.749
Number of Subjects	33	37	
Mean Baseline Value	72.29	76.12	
Change from Baseline (SE) to Final	-27.07 (5.544)	6.87 (5.236)	< 0.001
Urinary Deoxypyridinoline (nmol/mg Creat)			
Number of Subjects	26	33	
Mean Baseline Value	0.0834	0.0659	
Change from Baseline (SE) to Week 11	-0.0216 (0.01018)	0.0039 (0.00903)	0.066
Number of Subjects	30	36	
Mean Baseline Value	0.0800	0.0648	
Change from Baseline (SE) to Final	0.0100 (0.01392)	0.0092 (0.01271)	0.968

a. One-way ANOVA with treatment as the factor.

Safety Data

Deaths:

There was one death in a Zemplar subject (401). This subject was a 74 year old male who fell at home due to loose carpeting and was hospitalized on treatment Day 48 with hip fracture requiring surgical intervention. The subject received 19 mcg of Zemplar between Days 44 and 58. The subject had been admitted to the study despite meeting the exclusion criterion of cirrhosis. His PMH was also significant for hepatitis C, esophageal varices, hepatic encephalopathy, and alcoholism. On treatment Day 67, the subject was hospitalized a second time with GI bleeding due to a Mallory-Weiss tear. The subject received 28 mcg Zemplar between Days 58 and 71. Four days later, the subject was readmitted with hepatic encephalopathy. He died on Day 77 (posttreatment Day 6).

Clinical Review
Golden, J.
NDA 21-606
Paricalcitol capsules, Zemplar®

Serious Adverse Events:

Serious Adverse Events Reported During the Treatment and Follow-Up Phases							
Subject Number	Gender/ Age	Serious Adverse Event Description	Study Day Onset^a	Study Day End^a	Severity	Relationship	Reason Serious
Zemplar							
102	F/84	Scalp laceration, bleeding, anemia, nausea, hematoma	77	79	Severe	Not related	HS
		Dizziness, poor appetite, nausea, weakness, unable to walk/stand, mild headache ^b	107 (1)	114 (8)	Severe	Not related	HS
202	M/67	Worsening of back/flank pain ^b	62	73	Severe	Not related	HS, RI
401 ^c	M/74	Pain in groin and elbow, unable to bear weight	48	54	Moderate	Not related	HS
		Vomiting, loose stool, bloody vomitus, coffee ground emesis	67	69	Moderate	Not related	HS
		Increasing confusion and somnolence, slurred speech, agitated, not alert or oriented ^b	71	77 (6)	Severe	Not related	HS, DE
603	M/66	Worsening CAD, fluid volume overload, dyspnea on exertion, low blood pressure	126	Ongoing as of Day 198 (30)	Moderate	Probably not related	HS
801	M/74	Fever	67	85	Moderate	Not related	HS
909	M/61	Knee pain - worsening from medical history (estimated)	7	141	Moderate	Not related	HS
2211	M/70	Sternocardial pain	151	157	Severe	Not related	HS, RI
Placebo							
204	M/66	Subject presented to ER with elevated blood glucose	153	Ongoing as of Day 183 (12)	Severe	Probably not related	HS
407	M/75	Severe SOB, CHF, left pleural effusion, mild mitral regurgitation, mild ventricular regurgitation, moderate pulmonary hypertension	16	18	Severe	Not related	HS
		Severe SOB, hypoxemia, CHF	44	46	Severe	Not related	HS
		Scheduled pacemaker replacement, upgrade to biventricular pacing because of CHF and limiting exertional symptoms of dyspnea	85	86	Mild	Not related	HS
		Severe SOB, poor ejection fraction 25%	138	140	Severe	Not related	HS
601	M/52	Worsening renal failure	177 (9)	Ongoing as of Day 199 (31)	Moderate	Probably not related	HS
903	M/62	Acute rise of creatinine from 4.2 mg/dL, increased BLE edema and abdominal girth	15	Ongoing as of Day 171 (4)	Severe	Probably not related	HS
908	M/79	Left eye irritation, red and puffy with drainage	22	24	Severe	Not related	HS

Clinical Review
Golden, J.
NDA 21-606
Paricalcitol capsules, Zemplar®

Serious Adverse Events Reported During the Treatment and Follow-Up Phases							
Subject Number	Gender/ Age	Serious Adverse Event Description	Study Day Onset ^a	Study Day End ^a	Severity	Relationship	Reason Serious
1003	F/61	Subject reportedly complained of moderate to severe chest pain. She was brought to the hospital and was subsequently admitted for fluid overload ^b	113	127 (14)	Moderate	Probably not related	HS
1505	F/70	Abdominal and back pain, diarrhea, increased blood pressure (220/125 mmHg)	66	73	Moderate	Probably not related	HS
2203	M/69	Erysipelas, left shank pain, reddening	73	83	Moderate	Not related	HS

M/F = Male/Female; BLE = bilateral lower extremity; CAD = coronary artery disease; CHF = congestive heart failure; SOB = shortness of breath; ER = emergency room; HS = hospitalization; RI = required intervention; DE = Death
a. Numbers in parentheses represent number of days since last dose of study drug.
b. Event led to premature termination.
c. Subject died (hepatic encephalopathy).

Adverse Events that Led to Study Withdrawal:

Adverse Events Leading to Premature Termination from Study Drug							
Subject Number	Gender/ Age	Adverse Event Description	Study Day Onset	Study Day End ^a	Severity	Relationship	Investigator Alternative Etiology
Zemplar							
102	F/84	Dizziness, poor appetite, nausea, weakness, unable to walk/stand, mild headache	107	114 (7)	Severe	Not related	Uremia due to progressing kidney failure
202	M/67	Worsening of back/flank pain	62	73	Severe	Not related	History of back pain
401 ^b	M/74	Increasing confusion and somnolence, slurred speech, agitated, not alert or oriented	71	77 (6)	Severe	Not related	Intraluminal blood
604	M/68	Allergic reaction - maculopapular eruption on legs, chest, and arms	19	27 (8)	Mild	Probably related	Not required
Placebo							

Adverse Events Leading to Premature Termination from Study Drug							
Subject Number	Gender/ Age	Adverse Event Description	Study Day Onset	Study Day End^a	Severity	Relationship	Investigator Alternative Etiology
1003	F/61	Subject reportedly complained of moderate to severe chest pain. She was brought to the hospital and was subsequently admitted for fluid overload	113	127 (14)	Moderate	Probably not related	Underlying chronic renal insufficiency
1403	M/77	Generalized weakness with increased difficulty walking and decreased appetite	5	29 (10)	Mild	Probably not related	Progression of underlying disease

M/F = Male/Female
a. Numbers in parentheses represent number of days since last dose of study drug.
b. Subject died (hepatic encephalopathy).

Treatment-Emergent Adverse Events:

Overall Summary of Treatment-Emergent Adverse Events (All Treated Subjects)		
	Zemplar (N = 35)	Placebo (N = 40)
Number of Subjects Reporting Adverse Events	32 (91%)	34 (85%)
Number of Events Reported	111	103
Number of Serious Adverse Events Reported	14	10
Number of Subjects Reporting		
0 Events	3 (9%)	6 (15%)
1 Event	6 (17%)	7 (18%)
> 1 Event	26 (74%)	27 (68%)
Severity of Event		
Mild	74 (67%)	68 (66%)
Moderate	29 (26%)	30 (29%)
Severe	8 (7%)	5 (5%)
Relationship to Study Drug		
Probably Related	1 (1%)	0 (0%)
Possibly Related	3 (3%)	10 (10%)
Probably Not Related	33 (30%)	32 (31%)
Not Related	74 (67%)	61 (59%)

Laboratory Parameters:

Proportions of Subjects Who Developed Clinically Meaningful Hypercalcemia (All Treated Subject Population)			
Variable	Zemplar (N = 35)	Placebo (N = 40)	P-value ^a
Clinically Meaningful Hypercalcemia (at least 2 consecutive calcium values > 10.5 mg/dL)			N/A
Yes	0 (0%)	0 (0%)	
No	35 (100%)	40 (100%)	

a. Fisher's exact test.

No subject had hypercalcemia reported as an adverse event.

Comment: Eight Zemplar-treated subjects and no placebo-treated subjects had single calcium values > 10.5, as seen in table below. This is clinically important, as a purported benefit of Zemplar is its low risk of hypercalcemia.

Proportions of Subjects Who Developed Single Calcium Values > 10.5*			
Variable	Zemplar (N = 35)	Placebo (N = 40)	P-value ^a
At least 1 consecutive calcium value > 10.5 mg/dL)			0.0014
Yes	8 (23%)	0 (0%)	
No	27 (77%)	40 (100%)	

a. Fisher's exact test.

*Subjects with at least one on-treatment calcium value

Mean Change from Baseline to Final Visit in Calcium, Phosphorus, CaxP, and Albumin			
	Zemplar (N = 35)	Placebo (N = 40)	ANOVA P-value ^a
Calcium (mg/dL)			
Mean Baseline Value	9.27	9.30	0.808
Baseline Range	8.2 - 10.1	8.3 - 10.0	
Mean Final Value	9.20	9.14	
Change from Baseline (SE)	-0.07 (0.073)	-0.16 (0.068)	0.380
Phosphorus (mg/dL)			
Mean Baseline Value	3.98	3.95	0.814
Baseline Range	2.5 - 5.2	3.2 - 5.1	
Mean Final Value	3.85	4.26	
Change from Baseline (SE)	-0.13 (0.140)	0.31 (0.131)	0.028
Ca×P (mg²/dL²)			
Mean Baseline Value	36.51	36.36	0.900
Baseline Range	22.2 - 46.9	29.1 - 47.7	
Mean Final Value	35.56	38.90	
Change from Baseline (SE)	-0.95 (1.352)	2.54 (1.264)	0.063

Mean Change from Baseline to Final Visit in Calcium, Phosphorus, CaP, and Albumin			
	Zemplar (N = 35)	Placebo (N = 40)	ANOVA P-value^a
Albumin (g/dL)			
Mean Baseline Value	3.94	4.00	0.645
Baseline Range	2.4 - 4.8	1.9 - 4.7	
Mean Final Value	3.83	3.93	
Change from Baseline (SE)	-0.10 (0.046)	-0.07 (0.043)	0.579

a. One-way ANOVA with treatment as the factor.

Similar results were observed using ANCOVA with treatment as the factor and baseline value as the covariate.

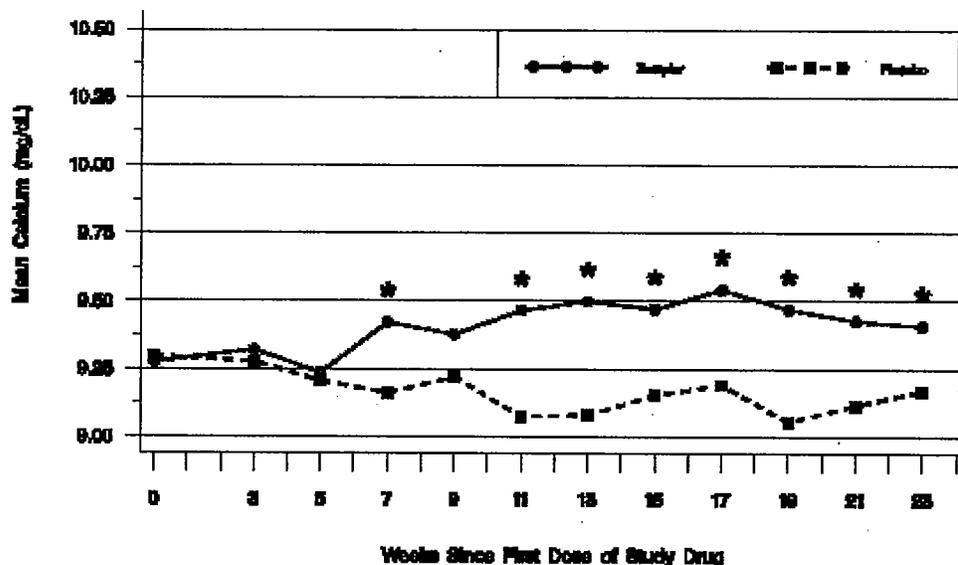
Mean Change from Baseline to Last On-Treatment Visit in Calcium, Phosphorus, CaP, and Albumin			
	Zemplar (N = 35)	Placebo (N = 39)^a	ANOVA P-value^b
Calcium (mg/dL)			
Mean Baseline Value	9.27	9.29	
Mean Last On-Treatment Value	9.49	9.17	
Change from Baseline (SE)	0.21 (0.062)	-0.12 (0.059)	< 0.001
Phosphorus (mg/dL)			
Mean Baseline Value	3.98	3.94	
Mean Last On-Treatment Value	4.27	4.18	
Change from Baseline (SE)	0.29 (0.121)	0.24 (0.115)	0.752
Ca×P (mg²/dL²)			
Mean Baseline Value	36.51	36.26	
Mean Last On-Treatment Value	40.46	38.31	
Change from Baseline (SE)	3.94 (1.176)	2.05 (1.114)	0.246
Albumin (g/dL)			
Mean Baseline Value	3.94	4.00	
Mean Last On-Treatment Value	3.93	4.02	
Change from Baseline (SE)	-0.01 (0.046)	0.02 (0.044)	0.650

a. Placebo Subject 803 had no primary chemistry measurements while on-treatment; therefore, only 39 subjects (versus 40) are included in this analysis.
 b. One-way ANOVA with treatment as the factor.

Similar results were observed using ANCOVA with treatment as the factor and baseline value as the covariate.

Comment: The strong difference in calcium change in the On-Treatment group is noted.

Mean Calcium Values Over Time During Treatment Phase



Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	35	34	34	32	31	29	31	31	30	27	26	25
Placebo N	40	38	39	36	35	35	34	34	33	33	32	32

* Statistically significant ($p \leq 0.05$) difference in mean change from baseline between the Zemplar and placebo treatment groups. At each visit, change from baseline is calculated for subjects who had data at the corresponding timepoint.

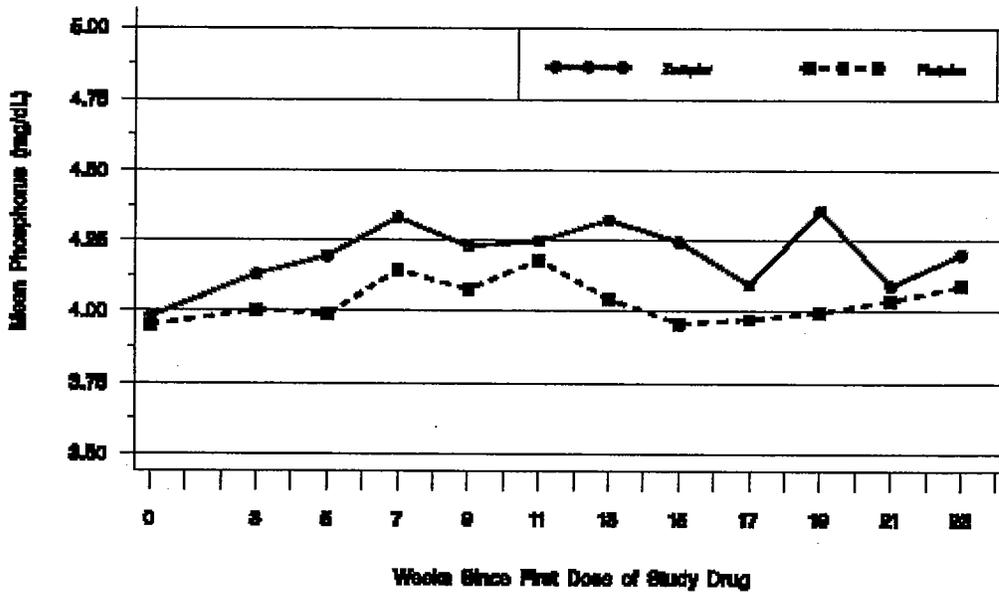
Calcium Normal Range: 8.0 to 10.3 mg/dL

Results were similar using observed value ANCOVA with treatment as the factor and baseline calcium as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline calcium as the covariate.

Comment: Calcium range for Zemplar subjects was 7.7 – 11.6 mg/dL; for placebo subjects 7.7 – 10.2 mg/dL.

**APPEARS THIS WAY
ON ORIGINAL**

Mean Phosphorus Values Over Time During Treatment Phase



Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	35	34	34	32	31	29	31	31	30	27	26	25
Placebo N	40	38	39	36	35	35	34	34	33	33	32	32

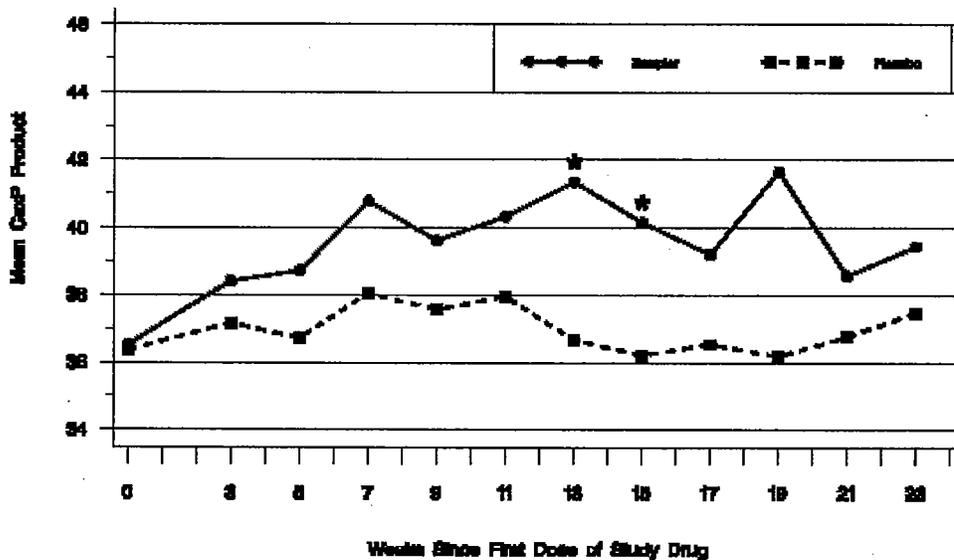
At each visit, change from baseline is calculated for subjects who had data at the corresponding timepoint.

Phosphorus Normal Range: 2.2 to 5.1 mg/dL

Results were similar using observed value ANCOVA with treatment as the factor and baseline calcium as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline phosphorus as the covariate.

**APPEARS THIS WAY
 ON ORIGINAL**

Mean CaxP Values Over Time During Treatment Phase



Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	35	34	34	32	31	29	31	31	30	27	26	25
Placebo N	40	38	39	36	35	35	34	34	33	33	32	32

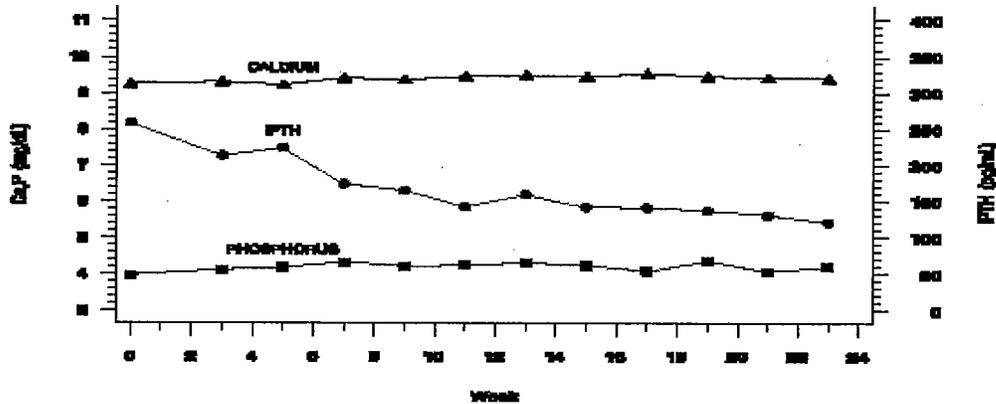
* Statistically significant ($p \leq 0.05$) difference in mean change from baseline between the Zemplar and placebo treatment groups. At each visit, change-from baseline is calculated for subjects who had data at the corresponding timepoint.

CaxP Normal Range: 17.6 to 52.5

Results were similar using observed value ANCOVA with treatment as the factor and baseline calcium as the covariate, last value carried forward ANOVA with treatment as the factor, and last value carried forward ANCOVA with treatment as the factor and baseline CaxP as the covariate. However, a statistically significant difference was observed between the Zemplar and placebo treatment groups at Weeks 5 and 9 using observed value ANCOVA.

APPEARS THIS WAY
 ON ORIGINAL

Mean Calcium, Phosphorus, and iPTH Values Over Time, Zemplar-Treated Subjects



Except for alkaline phosphatase (see table), there were no secondary chemistry variables that exhibited statistically significant differences between treatment groups in mean change from baseline to Final Visit using ANOVA.

Statistically Significant Differences Between Treatment Groups for Mean Change from Baseline to Final Visit in Secondary Chemistry Variables		
Variable (unit)	Zemplar (N = 33)	Placebo (N = 37)
Alkaline Phosphatase (IU/L)***		
Mean Baseline Value	97.85	95.59
Mean Final Value	82.03	101.05
Mean Change from Baseline (SD)	-15.82 (30.540)	5.46 (22.078)

*** = statistically significant difference between treatment groups at the 0.001 level, using a contrast within the one-way ANOVA.

Results were similar when secondary chemistry variables were analyzed using ANCOVA.

A statistically significant difference was observed between treatment groups in mean change from baseline to Final Visit in RBC (Zemplar: $-0.20 \times 10^{12}/L$, placebo: $+0.02 \times 10^{12}/L$; $p = 0.026$) for all treated subjects using ANOVA. Mean changes in hemoglobin and hematocrit were not statistically significant between treatment groups ($p = 0.085$ and 0.099 , respectively). Results were similar using ANCOVA.

There were no urinalysis variables (pH and specific gravity) that exhibited statistically significant differences between treatment groups using both ANOVA and ANCOVA.

Zemplar subjects experienced mean increases from baseline to Final Visit in urinary calcium and phosphorus and a mean decrease in Ccr. Placebo-treated subjects experienced mean decreases in urinary calcium, phosphorus, and Ccr. None of the differences were statistically significant between treatment groups using ANOVA or ANCOVA.

Mean Change from Baseline to Final Visit in 24-Hour Urine Collections (All Treated Subjects)			
	Zemplar	Placebo	ANOVA P-value^a
Calcium (mg/24 hours)	(N = 22)	(N = 28)	
Mean Baseline Value	39.86	40.88	—
Mean Final Value	44.64	34.20	NA
Mean Change from Baseline (SE)	4.78 (4.782)	-6.68 (4.238)	0.079
Phosphorus (mg/24 hours)	(N = 22)	(N = 29)	
Mean Baseline Value	649.8	628.8	—
Mean Final Value	660.4	623.4	NA
Mean Change from Baseline (SE)	10.6 (95.90)	-5.5 (83.52)	0.900
Creatinine Clearance (mL/min/1.73m²)	(N = 28)	(N = 31)	
Mean Baseline Value	29.8	30.8	—
Mean Final Value	29.1	27.3	NA
Mean Change from Baseline (SE)	-0.7 (2.57)	-3.5 (2.44)	0.432
NA = Not Applicable			

a. One-way ANOVA with treatment as the factor.

Mean Change and Percent Change from Baseline to Final Visit in eGFR and Serum Creatinine (All Subjects Who Completed 24 Weeks of Treatment)			
	Zemplar	Placebo	ANOVA P-value^a
eGFR (mL/min/1.73m²)	(N = 25)	(N = 33)	
Mean Baseline Value	23.30	23.85	—
Mean Final Value	21.68	21.86	NA
Mean Change from Baseline (SE)	-1.61 (1.011)	-1.99 (0.880)	0.780
Mean Percent Change from Baseline (SE)	-6.15 (4.135)	-9.92 (3.599)	0.496
Serum Creatinine (mg/dL)			
Mean Baseline Value	2.95	2.82	—
Mean Final Value	3.24	3.29	NA
Mean Change from Baseline (SE)	0.30 (0.178)	0.48 (0.155)	0.441
Mean Percent Change from Baseline (SE)	9.82 (5.189)	15.09 (4.516)	0.446
NA = Not Applicable			

a. One-way ANOVA with treatment as the factor.

Results of the above table were similar using ANCOVA.

Urinary Calcium/Creatinine Ratio: No statistically significant differences were observed between the treatment groups in mean change from baseline to Week 11 or to Final Visit in urinary calcium/creatinine ratio using ANOVA or ANCOVA.

Cardiovascular Marker Variables: Nineteen subjects (9 Zemplar and 10 placebo) who had both baseline and Final Visit pro-BNP and troponin-T values were included in these analyses. No statistically significant differences in cardiovascular marker variables were observed between

treatment groups in mean change from baseline to Week 11, Final Visit, or Final Visit that was at least 161 after the last dose of study drug using ANOVA and ANCOVA.

Vital Signs:

ANOVA Of Changes From Baseline To Final Visit In Vital Sign Variables								
All Treated Subject Population								
Variables	Treatment Group	N	Baseline Mean	Visit Mean	Change From Baseline			Between Group Comparison
					Mean	SE	P-Value	Difference (95% CI) P-Value (Ho:Difference=0)
Weight (Kg)								
	Zemplar	35	88.8	87.9	-0.9	0.60	0.138	-0.8 (-2.5, 0.9)
	Placebo	39	85.1	84.9	-0.1	0.57	0.844	0.344
Pulse (BPM)								
	Zemplar	35	71.8	72.6	0.8	1.57	0.599	-1.5 (-5.8, 2.9)
	Placebo	39	70.6	72.9	2.3	1.48	0.129	0.503
Systolic Blood Pressure (mmHg)								
	Zemplar	35	129.3	132.9	3.6	3.28	0.277	1.3 (-7.8, 10.3)
	Placebo	39	129.8	132.1	2.3	3.11	0.456	0.780
Diastolic Blood Pressure (mmHg)								
	Zemplar	35	73.9	73.4	-0.5	2.37	0.829	-3.0 (-9.5, 3.6)
	Placebo	39	71.0	73.4	2.4	2.25	0.283	0.370

Note: Results Are Based On A One-Way ANOVA With Treatment As The Factor.

Results were similar using ANCOVA with treatment as the factor and baseline value as covariate. There was a statistically significant difference at Week 7 in DBP between treatment groups using ANOVA: Zemplar mean = -4.0 mmHg, placebo mean = +1.9 mmHg, p = 0.04.

Special Safety Studies: NA

Other: NA

Company's Conclusions (emphasis added, indicating the Company's interpretations):

1. Thirty-three Zemplar subjects and 38 placebo subjects had a baseline and at least two on-treatment iPTH measurements. Thirty of 33 (91%) subjects who received Zemplar achieved two consecutive $\geq 30\%$ decreases from baseline in iPTH compared to 4 of 38 (11%) of subjects who received placebo. This difference was statistically significant.
2. At the Final Visit, subjects who received Zemplar had a statistically significant mean reduction in iPTH compared to a mean increase observed for subjects who received placebo [-46.9 pg/mL (-15.2%) versus 52.6 pg/mL(19.1%)]. When analyses were performed using iPTH data collected at the Last On-Treatment Visit, Zemplar-treated subjects had a statistically significant mean decrease [-130.8 pg/mL (-50.0%)] in iPTH compared with a mean increase [61.1 pg/mL (21.4%)] among placebo-treated subjects.

3. Statistically significant differences were observed between the Zemplar and placebo treatment groups at all scheduled visits of the Treatment Phase for both change and percent change from baseline in iPTH.
4. Statistically significant differences from baseline to Final Visit between treatment groups were observed in all 2/4 biochemical bone marker variables (serum osteocalcin and serum BAP).
5. /
6. No statistically significant differences were observed between the treatment groups for the proportion of subjects with at least two consecutive calcium values > 10.5 mg/dL (0/35, 0% Zemplar versus 0/40, 0% placebo). This is clinically meaningful because the primary safety concern of any vitamin D therapy is hypercalcemia.
7. Mean change from baseline serum calcium to Last On-Treatment Visit was statistically significantly different between the treatment groups (Zemplar group mean = $+0.21$ mg/dL; placebo group mean = -0.12 mg/dL).
8. Statistically significant differences between the treatment groups were observed at Weeks 7, 11, 13, 15, 17, 19, 21, and 23 during the Treatment Phase for mean change from baseline in calcium values; mean increases were seen in Zemplar group and mean decreases were seen in placebo group.
9. Other than the statistically significant differences noted between the Zemplar and placebo groups at Weeks 13 and 15 of the Treatment Phase for CaxP, no other statistically significant differences between the Zemplar and placebo groups were observed during the Treatment Phase for phosphorus or CaxP.
10. A statistically significant difference was observed between the Zemplar and placebo treatment groups in mean change from baseline to Final Visit in phosphorus (Zemplar mean change: -0.13 mg/dL, placebo mean change: 0.31 mg/dL). No statistically significant differences were observed between treatment groups in mean change from baseline to Last On-Treatment Visit in Ca x P and phosphorus using ANOVA with treatment as the factor.
11. No statistically significant difference was observed between the treatment groups in mean change from baseline to Final Visit in eGFR and serum creatinine for all subjects who completed 24 weeks of treatment; nor 24-hour urine collection variables (calcium, phosphorus, Ccr) or urinary calcium/creatinine ratio.
12. /

13. No statistically significant differences were observed between the treatment groups for the overall incidence of adverse events or for the incidence of any specific adverse event. These data are indicative of the overall tolerability of Zemplar in this patient population.
14. The only event leading to premature termination considered by the Investigator to have a causal relationship to study drug was allergic reaction, which was reported by one Zemplar subject.
15. Zemplar Capsule is safe and well tolerated for the treatment and prevention of 2° HPT in CKD (stages 3 and 4) subjects.
16. Zemplar Capsule is effective for the treatment and prevention of 2° HPT in CKD (Stages 3 and 4) subjects.

Medical Officer's Conclusions:

1. **Statistical analyses demonstrating Zemplar's efficacy in decreasing iPTH compared with placebo are very strong.**
 2. **Final Visit and Last On-Treatment analyses lose within-study measurement information. Therefore, in addition to mean change from baseline, in particular when evaluating measures for safety, it is important to assess mean values over time.**
 3. **Biochemical markers, while suggesting an improvement in bone turnover in the Zemplar-treated subjects versus the placebo-treated subjects, do not have proven equivalence to histological data. In addition, the relevance of bone marker data in subjects with renal impairment is not clear.**
 4. **A statistically significant difference was observed in change in serum calcium from baseline to Last On-Treatment Visit between groups;**
- /
-
- Monitoring of calcium in dosing is therefore critical.
5. **Dosing changes are made for single calcium levels ≥ 10.4 mg/dL. Therefore, the designation of two consecutive calcium levels > 10.5 as clinically relevant is somewhat misleading. An analysis was performed with single calcium values > 10.5 . Eight Zemplar-treated subjects and no placebo-treated subjects had single calcium values > 10.5 . This is clinically important, as a purported benefit of Zemplar is its low risk of hypercalcemia.**
 6. **Although the majority of calcium values remained in the normal range for both Zemplar- and placebo-treated subjects, maximum calcium level in the Zemplar-treated group was as high as 11.6.**
 7. **CaxP was statistically higher than baseline in Zemplar group as compared to placebo group for several intrastudy weeks. This underscores the importance of vigilant calcium and phosphorus monitoring.**
 8. **There is no mean change difference in eGFR, or creatinine between Zemplar and placebo treatment groups; but this is comparing just those subjects who completed 12 weeks of treatment. Last observation (Last On-Treatment) analyses should be performed.**

- 9. Evaluations of other laboratory analyses, vital signs, and physical examinations revealed no clinically meaningful changes as a result of Zemplar treatment.**
- 10. The premature discontinuation due to allergy is noted.**
- 11. Further analyses of TIW versus QD regimens should be performed to determine if the QD regimen predisposes to greater risk of hypercalcemia or increased calcium/phosphorus product.**

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Appendix D. Comparison of Baseline iPTH

VISIT	TREATMENT GROUP	N	BASELINE MEAN	BASELINE SE	BASELINE RANGE		BETWEEN GROUP DIFFERENCE
					MIN	MAX	P-VALUE
iPTH (pg/mL)							
ALL TREATED SUBJECTS	ZEMPLAR	35	259.1	21.49	145.0	856.0	0.879
	PLACEBO	40	255.1	15.26	149.5	594.0	
ALL SUBJECTS WITH POST DOSE MEASURE	ZEMPLAR	35	259.1	21.49	145.0	856.0	0.879
	PLACEBO	40	255.1	15.26	149.5	594.0	
INTENT-TO-TREAT SUBJECTS	ZEMPLAR	33	260.7	22.53	145.0	856.0	0.691
	PLACEBO	38	250.0	15.58	149.5	594.0	

NOTE: RESULTS ARE BASED ON A ONE-WAY ANOVA WITH TREATMENT AS THE FACTOR.

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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Clinical Review
Golden, J.
NDA 21-606
Paricalcitol capsules, Zemplar®

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11 APPENDIX E.

Serious Adverse Events Reported During the Treatment and Follow-Up Phases (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; Paricalcitol-Treated Subjects)							
Subject Number	Gender/ Age	Serious Adverse Event Description/ Final Diagnosis	COSTART	Study Day Onset ^a	Study Day End ^a	Severity	Reason Serious
Study 2001019							
502	M/56	Decreased renal function/acute on chronic renal failure	Uremia	38	Ongoing as of Day 93 (3)	Moderate	Hospitalization
		Increased blood pressure, headaches, nausea and vomiting/uncontrolled hypertension	Hypertension	38	39	Mild	Hospitalization
		Bradycardia/bradycardia	Bradycardia	84	90	Moderate	Hospitalization
		Elevated liver enzymes ^b /passive congestion secondary to heart failure	Liver function tests abnormal	84	90	Moderate	Prolonged Hospitalization
		Nausea/nausea	Nausea	84	90	Mild	Prolonged Hospitalization
		Hypertension, uncontrolled with bradycardia/hypertension	Hypertension	84	90	Moderate	Prolonged Hospitalization
		Decreased kidney function/chronic renal failure	Uremia	84	90	Mild	Prolonged Hospitalization
		Elevated WBC count/pneumonia	Pneumonia	84	90	Mild	Prolonged Hospitalization
		Elevated laboratory values for hyperkalemia/hyperkalemia	Hyperkalemia	84	90	Moderate	Prolonged Hospitalization
		Nausea and vomiting/uremia	Uremia	95 (5)	Ongoing as of Day 97 (7)	Moderate	Hospitalization
Anasarca/anasarca	Generalized edema	84	90	Moderate	Prolonged Hospitalization		
504	M/77	SOB/acute bronchitis	Bronchitis	103	109	Moderate	Hospitalization
		Chest pain left sided	Chest pain	104	Ongoing as of	Mild	Hospitalization
507 ^c	M/71	Chest pain, swollen face/cardiopulmonary arrest due to renal failure	Heart arrest	151 (10)	155 (14)	Severe	Hospitalization, Death
509	M/69	Sharp pain from right hip to right leg to right foot/thrombosis of right femoral bypass	Arterial thrombosis	129	158	Moderate	Hospitalization
807	M/84	Confusion altered mental status/hypoglycemia	Hypoglycemia	63	63	Severe	Hospitalization
1101	M/89	Felt faint getting out of car/near syncope secondary to aggressive diuresis	Syncope	55	65	Severe	Hospitalization
1402	M/48	Intermittent purulent drainage from right	Infection Cyst	7	7	Moderate	Required Intervention

Serious Adverse Events Reported During the Treatment and Follow-Up Phases (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; Paricalcitol-Treated Subjects)							
Subject Number	Gender/ Age	Serious Adverse Event Description/ Final Diagnosis	COSTART	Study Day Onset^a	Study Day End^a	Severity	Reason Serious
		scrotal area/worsening of sebaceous cyst of right scrotum					
		Worsening dizziness, nausea and vomiting, and dyspnea/vertigo	Vertigo	13	21	Moderate	Hospitalization
1508	F/53	Dehydration with nausea and vomiting/dehydration secondary to viral syndrome	Dehydration Viral infection	116	117	Severe	Hospitalization
		Elevated BUN and serum creatinine, dehydration/acute on chronic renal failure	Acute kidney failure Uremia	116	117	Severe	Hospitalization, Required Intervention
1509	M/73	SOB, Pain radiating to throat and fatigue/myocardial infarction	Myocardial infarction	29	33	Severe	Hospitalization, Required Intervention, Life Threatening
Study 2001020							
301	F/56	Complication from cholecystectomy/cholelithiasis	Cholelithiasis	190 (24)	Ongoing as of Day 199 (33)	Moderate	Hospitalization
		Worsening of chronic renal failure/chronic renal failure	Uremia	194 (28)	Ongoing as of Day 195 (29)	Severe	Prolonged Hospitalization
803	F/59	Subject with ESRD secondary to diabetic nephropathy who had an arterial venous fistula placed in preparation of hemodialysis/ESRD	Uremia	65	66	Mild	Hospitalization
		Subject presented to ER with complaints of chest pain, diaphoresis, and abdominal fullness. She was admitted to the hospital. An EKG, chest x-rays and lab tests were performed. A kidney, ureter, and bladder x-ray showed her to be severely constipated. She was given magnesium citrate and water enemas which helped her to stool. Subject remained symptom free throughout remainder of admission/abdominal discomfort secondary to constipation	Abdominal pain Constipation	103	104	Mild	Hospitalization
1202	M/67	Chest pain, no diaphoresis,	Angina pectoris	11	12	Severe	Hospitalization

Serious Adverse Events Reported During the Treatment and Follow-Up Phases (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; Paricalcitol-Treated Subjects)							
Subject Number	Gender/ Age	Serious Adverse Event Description/ Final Diagnosis	COSTART	Study Day Onset^a	Study Day End^a	Severity	Reason Serious
		possible SOB/angina					
1206	M/64	Admitted through ER with multiple complaints including chest pain, SOB, and abdominal pain/chest pain	Chest pain	7	10	Moderate	Hospitalization
		Admitted with dizziness and blurred vision. No localizing symptoms/dizziness and blurred vision	Dizziness Amblyopia	54	56	Moderate	Hospitalization
		Admitted with blurred vision and headache/retinopathy	Retinal disorder	76	89	Moderate	Hospitalization
1403	F/81	Weakness, SOB, fluid overload ^b /chronic renal failure	Uremia	77	Ongoing as of Day 86 (9)	Severe	Hospitalization
		SOB, generalized fatigue, irregular heart rhythm/hypotension due to ultrafiltration	Hypotension	87 (10)	Ongoing as of Day 90 (13)	Moderate	Hospitalization
1405	F/58	Fluid overload, SOB, chest pain, orthopnea, dyspnea on exertion, pulmonary edema, decreased t-waves/diastolic heart failure	Heart failure	57	59	Moderate	Hospitalization
Study 2001021							
102	F/84	Scalp laceration, bleeding, anemia, nausea, hematoma/right scalp laceration	Accidental injury	77	79	Severe	Hospitalization
		Dizziness, poor appetite, nausea, weakness, unable to walk/stand, mild headache ^b /uremic neuropathy	Uremia	107 (1)	114 (8)	Severe	Hospitalization
202	M/67	Worsening of back/flank pain ^b /contusions to renal cyst with severe flank pain and hematuria	Back pain Hematuria Accidental injury	62	73	Severe	Hospitalization, Required Intervention
401 ^c	M/74	Pain in groin and elbow, unable to bear weight/hip fracture	Pathological fracture	48	54	Moderate	Hospitalization
		Vomiting, loose stool, bloody vomitus, coffee ground emesis	Diarrhea Vomiting Hematemesis	67	69	Moderate	Hospitalization
		Increasing confusion and somnolence, slurred speech, agitated, not alert or oriented ^b / ^{hepatic} encephalopathy	Encephalopathy	71	77 (6)	Severe	Hospitalization, Death
603	M/66	Worsening CAD, fluid volume overload,	Coronary artery disorder	126	Ongoing as of	Moderate	Hospitalization

Serious Adverse Events Reported During the Treatment and Follow-Up Phases (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; Paricalcitol-Treated Subjects)							
Subject Number	Gender/ Age	Serious Adverse Event Description/ Final Diagnosis	COSTART	Study Day Onset ^a	Study Day End ^a	Severity	Reason Serious
		dyspnea on exertion, low blood pressure/worsening CAD			Day 198 (30)		
801	M/74	Fever/lung infiltrate of unknown etiology	Lung disorder	67	85	Moderate	Hospitalization
909	M/61	Knee pain - worsening from medical history/worsening knee pain secondary to varus alignment of left femur and knee	Joint disorder	7 (estimated)	141	Moderate	Hospitalization
2211	M/70	Sternocardial pain/myocardial infarction	Myocardial infarction	151	157	Severe	Hospitalization, Required Intervention

M/F = Male/Female; WBC = white blood cell; SOB = shortness of breath; BUN = blood urea nitrogen; ESRD = end-stage renal disease; GFR = glomerular filtration rate;
 CVA = cardiovascular accident; COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; ER = emergency room; EKG = electrocardiogram;
 CAD = coronary artery disease; BLE = bilateral lower extremity; ACE = angiotensin converting enzyme
 a. Numbers in parentheses represent number of days since last dose of study drug.
 b. Event led to premature termination.
 c. Subject died 14 days after the last documented dose of study drug.
 d. Subject died (cardiac arrest).
 e. Subject died (hepatic encephalopathy).

12 APPENDIX F.

Adverse Events reported in AERS Datamart for Zemplar post-marketing

Adverse Event	N	%
Dysgeusia	17	26
Dermatitis	9	14
Pruritus	8	13
Chest pain	4	6
Dyspnea/respiratory distress	4	6
Nausea	4	6
Skin disorder/ulcer/nodule	4	6
Hypercalcemia/blood calcium increased	4	6
Medication error	4	6
Vomiting	3	5
Hemolytic anemia	3	5
Hypersensitivity	3	5
Thrombocytopenia	3	5
Abdominal pain	2	3
Pyrexia	2	3
Anxiety/nervousness	2	3
Dizziness	2	3
Hemorrhage	2	3
Cardiac arrest	2	3
Rash scaly/maculopapular	2	3
Anorectal disorder/proctalgia	2	3
Paresthesia	2	3
Ecchymosis	2	3
Blood pressure increased/hypertension	2	3
Hemoglobin decreased	2	3
Headache	2	3
Leucopenia	2	3
Malaise	2	3
Pain	2	3
Haematochezia	1	2
Body temperature increased	1	2
Weight decreased	1	2

Adverse Event	N	%
URI	1	2
Agitation	1	2
Bacteremia	1	2
Medical device complication	1	2
Blood glucose increased	1	2
Diarrhea	1	2
Drug interaction	1	2
Erythema multiforme	1	2
Musculoskeletal pain	1	2
Ejection fraction decreased	1	2
Asthenia	1	2
Confusional state	1	2
Asthma	1	2
Blood parathyroid hormone increased	1	2
Bone pain	1	2
Calcinosis	1	2
Calcium metabolism disorder	1	2
Carcinoma	1	2
Coronary artery disease	1	2
Whole blood transfusion	1	2
Cardiac catheterization	1	2
Circulatory collapse	1	2
Atrial fibrillation	1	2
Heart rate increased	1	2
Aortic valve disease	1	2
Pulmonary edema	1	2
Syncope	1	2
Hemodialysis	1	2
Localized exfoliation	1	2
Stevens-Johnson syndrome	1	2
Vaginal disorder	1	2
Dry mouth	1	2
Injection site pain	1	2
Laryngeal edema	1	2
Face edema	1	2

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Adverse Event	N	%
Tongue edema	1	2
Flushing	1	2
Dysphagia	1	2
Insomnia	1	2
Loss of consciousness	1	2
Low turnover osteopathy	1	2
Blood parathyroid hormone decreased	1	2
Pharmaceutical product complaint	1	2
Myalgia	1	2
Arthralgia	1	2
Myocardial infarction	1	2
Palpitations	1	2
Anaphylactoid reaction	1	2
Rhinitis	1	2
Sepsis	1	2
Mental impairment	1	2
Convulsion	1	2

13 APPENDIX G.

Average Weekly Dose (mcg/week) of Paricalcitol Capsule by Week for TIW and QD Treatment Regimens (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)		
	Average Weekly Dose (mcg/week)	
	TIW	QD
Week 1	(N = 72)	(N = 35)
Mean (SD)	6.1 (1.45)	6.9 (1.35)
Week 2	(N = 71)	(N = 35)
Mean (SD)	6.2 (1.32)	6.8 (1.49)
Week 3	(N = 70)	(N = 35)
Mean (SD)	6.4 (1.44)	6.7 (1.92)
Week 4	(N = 69)	(N = 34)
Mean (SD)	6.3 (1.60)	6.8 (2.25)
Week 5	(N = 68)	(N = 33)
Mean (SD)	8.8 (3.39)	9.6 (4.42)
Week 6	(N = 68)	(N = 33)
Mean (SD)	8.9 (3.58)	10.4 (4.46)
Week 7	(N = 68)	(N = 33)
Mean (SD)	9.9 (3.49)	11.1 (4.23)
Week 8	(N = 68)	(N = 33)
Mean (SD)	10.0 (3.52)	11.1 (4.39)
Week 9	(N = 68)	(N = 33)
Mean (SD)	11.9 (4.73)	12.5 (6.12)
Week 10	(N = 68)	(N = 33)
Mean (SD)	12.1 (5.20)	12.3 (6.53)
Week 11	(N = 65)	(N = 33)
Mean (SD)	12.1 (4.98)	11.8 (6.62)
Week 12	(N = 63)	(N = 31)
Mean (SD)	11.5 (5.41)	11.9 (6.87)
Week 13	(N = 62)	(N = 31)
Mean (SD)	12.5 (6.09)	11.7 (7.54)
Week 14	(N = 61)	(N = 31)
Mean (SD)	12.2 (6.36)	11.5 (7.67)
Week 15	(N = 61)	(N = 31)
Mean (SD)	11.3 (6.33)	11.6 (8.17)
Week 16	(N = 61)	(N = 30)
Mean (SD)	11.2 (7.02)	10.1 (7.84)
Week 17	(N = 61)	(N = 28)
Mean (SD)	11.2 (6.91)	10.4 (7.73)
Week 18	(N = 61)	(N = 27)
Mean (SD)	11.2 (6.96)	10.7 (7.57)
Week 19	(N = 61)	(N = 27)
Mean (SD)	10.1 (6.86)	10.4 (7.53)
Week 20	(N = 59)	(N = 27)
Mean (SD)	9.7 (6.94)	9.8 (7.46)

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 Paricalcitol capsules, Zemplar®

Average Weekly Dose (mcg/week) of Paricalcitol Capsule by Week for TIW and QD Treatment Regimens (Double-Blind, Placebo-Controlled, Pivotal Phase 3 CKD Stage 3 and 4 Studies; All Treated Subjects)		
	Average Weekly Dose (mcg/week)	
	TIW	QD
Week 21	(N = 58)	(N = 25)
Mean (SD)	9.1 (6.65)	9.3 (6.62)
Week 22	(N = 57)	(N = 25)
Mean (SD)	9.0 (6.82)	9.2 (6.44)
Week 23	(N = 57)	(N = 25)
Mean (SD)	9.6 (7.17)	9.2 (7.27)
Week 24	(N = 57)	(N = 25)
Mean (SD)	9.2 (7.00)	8.3 (7.91)
Week 25	(N = 9)	(N = 9)
Mean (SD)	5.0 (6.75)	5.8 (8.68)
Week 26	(N = 1)	(N = 1)
Mean (SD)	15.0 (0.00)	6.0 (0.00)

TIW = 3 times a week, no more often than every other day; QD = every day

14 APPENDIX H. LITERATURE

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