

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-606

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21606/N_000

Drug Name: Zemplar (paricalcitol) 1 mcg, 2 mcg, & 4 mcg capsules

Indication(s): Prevention and Treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 3 & 4

Applicant: Abbott Laboratories

Date(s): Submitted 7-28-04
User Fee Goal Date: 5-30-05

Review Priority: Standard

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Keywords: Clinical studies, NDA review

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1. EXECUTIVE SUMMARY

The drug product, subject to this NDA, is in 1 mcg, 2 mcg and 4 mcg soft gelatin capsule (SGC) dosage forms [also referred to in this NDA as soft elastic capsule (SEC)]. The active ingredient is identical to that approved (17 April 1998) and marketed in the United States under NDA 20-819, Zemplar ® (paricalcitol) Injection, as well as 25 non-U.S. countries. The subject drug is a prescription drug and is currently being developed outside the United States.

The primary objective of the clinical investigations included in this NDA, was to demonstrate that paricalcitol capsule is safe and effective in the prevention and treatment of secondary hyperparathyroidism (2° HPT) associated with chronic kidney disease (CKD) Stage 3 and 4.

Three pivotal Phase 3, double-blind, placebo-controlled, multi-center studies (Study 2001019, Study 2001020, and Study 2001021) were conducted in CKD Stage 3 and 4 subjects with 2° HPT (iPTH levels of ≥ 150 pg/mL). In these studies, a total of 107 subjects were dosed with paricalcitol capsule and 113 were dosed with placebo. Two (Study 2001019 and Study 2001020) of the 3 studies were conducted using a TIW regimen, three times a week (no more often than every other day) and 1 (Study 2001021) study was conducted using a QD regimen. The studies were 24 weeks in duration.

The remaining information on the EXECUTIVE SUMMARY is distributed in the following three sub-sections.

Note: New Drug Application is abbreviated by NDA. Except where specifically mentioned otherwise (in italics, as notes, reviewer's comments, conclusions, etc.) or clear from the context, all other results and statements in this document are the sponsor's. Sometimes, the sponsor's statements may be slightly changed for brevity or for clarity.

1.1 Conclusions and Recommendations

The Reviewing Medical Officer reported that the Medical Team deem the primary efficacy variable to be appropriate.

This reviewer's statistical tests based on the "Analysis Datasets" supplied to the FDA Electronic Document Room (EDR) by the sponsor provided statistically highly significant evidence in favor of the efficacy of paricalcitol. These are consistent with the sponsor's many analyses. Even the worst-case analyses provided statistically highly significant evidence in favor of the efficacy of paricalcitol. This reviewer does not see any statistical concerns that may reverse the conclusion about the efficacy of the drug.

Apparently, the Zemplar response rates were almost the same in all three studies. However, in the alternate day dose studies ...19 and ...20, the mean IPTH (pg/ml) slightly increased starting from Week 19 and Week 17 in the Zemplar group. However, in the daily dose Study ...21, the

mean IPTH (pg/ml) in the Zemplar group maintained a downward trend up to the end of the study.

The labeling states,

However, the treatment groups were highly statistically significantly different with respect to percent of patients having visit calcium value >10.5. This percent was 18.7 for the Zemplar group and 0.9 for the placebo group.

For a safety variable, it should not be stated (as has been done in the labeling) that

The confidence intervals are given in Section 3.2. Evaluation of Safety.

1.2 Brief Overview of Clinical Studies

A brief overview of the three pivotal clinical studies is presented here first in a tabular form and then in a short write-up. More details are in Section 2.1 Overview.

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

Study ID	No. of Investigators/ Locations/ Status/ Completion Date	Design Control Type	Study Objective	Study Drug Dose and Regimen	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Age (Range)	Major Inclusion Criteria	Primary Endpoint
2001019	13 investigators/ US 1 investigator/ Poland/complete 15 January 2004	Prospective, randomized, placebo-controlled, double-blind, 24-week, multi-center study	To determine the safety and efficacy of paricalcitol capsules as compared to placebo in reducing elevated serum PTH levels in subjects with CKD	Group 1: Paricalcitol Capsule Group 2: Placebo Capsule The initial dose was based on average iPTH from PTV1 and PTV2: ≤ 500 pg/mL: 2 mcg TIW > 500 pg/mL: 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.	Paricalcitol: 39 subjects randomized and dosed, 36 were included in the ITT population Placebo: 36 subjects randomized and dosed, 34 were included in the ITT population	24 weeks	Paricalcitol: 27 Males (69%), 12 Females (31%) Age range: 22 - 89 Placebo: 25 Males (69%), 11 Females (31%) Age range: 46 - 90	Subjects ≥ 18 years of age with CKD Stage 3 & 4 Average of 2 consecutive iPTH values of ≥ 150 pg/mL 2 consecutive serum calcium levels of ≥ 8.0 to ≤ 10.0 mg/dL 2 consecutive serum phosphorus levels of ≤ 5.2 mg/dL	The achievement of 2 consecutive ≥ 50% decreases from baseline in iPTH

M = males; F = females; US = United States; iPTH = intact parathyroid hormone; TIW = 3-times-a-week; PTH = parathyroid hormone; CKD = chronic kidney disease; ITT = intent-to-treat; QD = every day; PTV1 = Pre-Treatment Visit 1; PTV2 = Pre-Treatment Visit 2

Study ID	No. of Investigators/ Locations/ Status/ Completion Date	Design Control Type	Study Objective	Study Drug Dose and Regimen	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Age (Range)	Major Inclusion Criteria	Primary Endpoint
2001020	14 investigators/ US 1 investigator/ Poland/ complete 26 February 2004	Prospective, randomized, placebo-controlled, double-blind, 24-week, multi-center study	To determine the safety and efficacy of paricalcitol capsules as compared to placebo in reducing elevated serum PTH levels in subjects with CKD	Group 1: Paricalcitol Capsule Group 2: Placebo Capsule The initial dose was based on average iPTH from PTV1 and PTV2: ≤ 500 pg/mL: 2 mcg TIW > 500 pg/mL: 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.	Paricalcitol: 33 subjects randomized and dosed, 32 were included in the ITT population Placebo: 37 subjects randomized and dosed, 36 were included in the ITT population	24 weeks	Paricalcitol: 21 Males (64%), 12 Females (36%) Age range: 30 - 91 Placebo: 24 Males (65%), 13 Females (35%) Age range: 37 - 79	Subjects ≥ 18 years of age with CKD Stage 3 & 4 Average of 2 consecutive iPTH values of ≥ 150 pg/mL 2 consecutive serum calcium levels of ≥ 8.0 to ≤ 10.0 mg/dL 2 consecutive serum phosphorus levels of ≤ 5.2 mg/dL	The achievement of 2 consecutive ≥ 30% decreases from baseline in iPTH

Study ID	No. of Investigators/ Locations/ Status/ Completion Date	Design Control Type	Study Objective	Study Drug Dose and Regimen	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Age (Range)	Major Inclusion Criteria	Primary Endpoint
2001021	12 investigators/ US 2 investigators/ Poland/ complete 05 March 2004	Prospective, randomized, placebo-controlled, double-blind, 24-week, multi-center study	To determine the safety and efficacy of paricalcitol capsules as compared to placebo in reducing elevated serum PTH levels in subjects with CKD	Group 1: Paricalcitol Capsule Group 2: Placebo Capsule The initial dose was based on average iPTH from PTV1 and PTV2: ≤ 500 pg/mL: 1 mcg QD > 500 pg/mL: 2 mcg QD 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.	Paricalcitol: 35 subjects randomized and dosed, 33 were included in the ITT population Placebo: 40 subjects randomized and dosed, 38 were included in the ITT population	24 weeks	Paricalcitol: 25 Males (71%), 10 Females (29%) Age range: 42 - 84 Placebo: 27 Males (68%), 13 Females (32%) Age range: 32 - 93	Subjects ≥ 18 years of age with CKD Stage 3 & 4 Average of 2 consecutive iPTH values of ≥ 150 pg/mL 2 consecutive serum calcium levels of ≥ 8.0 to ≤ 10.0 mg/dL 2 consecutive serum phosphorus levels of ≤ 5.2 mg/dL	The achievement of 2 consecutive ≥ 30% decreases from baseline in iPTH

The initial dose of the study drug in the 3 pivotal Phase 3 studies was based on baseline iPTH levels. Two of the studies (Study 2001019 and Study 2001020) initiated dosing at 2 mcg TIW for subjects with a baseline iPTH level ≤ 500 pg/mL or 4 mcg TIW for subjects with a baseline iPTH level > 500 pg/mL. Thereafter, dosing was titrated in 2 mcg increments based on serum calcium, phosphorus, and iPTH levels. If a subject was receiving 2 mcg TIW and a dose reduction was needed, the dose was to be reduced to 2 mcg twice weekly and subsequently to 2 mcg once weekly. If a subject required a dose reduction below 2 mcg once weekly, he/she was to be discontinued from the study.

The third study (Study 2001021) initiated dosing at 1 mcg QD for subjects with a baseline iPTH level \leq 500 pg/ mL or 2 mcg QD for subjects with a baseline iPTH level $>$ 500 pg/ mL. Thereafter, dosing was titrated in 1 mcg increments based on serum calcium, phosphorus, and iPTH levels. If a subject was receiving 1 mcg QD and a dose reduction was needed, the dose was to be reduced to 1 mcg TIW. If a subject required a dose reduction below 1 mcg TIW, he/she was to be discontinued from the study.

The primary efficacy endpoint for each study was 2 consecutive \geq 30% decreases in iPTH from baseline.

1.3 Statistical Issues and Findings

This reviewer's statistical tests based on the "Analysis Datasets" supplied to the FDA Electronic Document Room (EDR) by the sponsor provided statistically highly significant evidence in favor of the efficacy of paricalcitol. These are consistent with the sponsor's many analyses. Even the worst-case analyses provided statistically highly significant evidence in favor of the efficacy of paricalcitol. This reviewer does not see any statistical concerns that may reverse the conclusion about the efficacy of the drug.

In Study 2001020, a statistically significant difference ($p = 0.031$) was observed between treatment groups for time since CKD diagnosis, with placebo subjects (mean = 7.76 years) having CKD longer than Zemplar subjects (mean = 4.17 years). This difference between the treatment groups in time since CKD diagnosis (in Study 2001020 only) is related to 3 placebo subjects (705, 706, and 1302) who had been diagnosed with CKD more than 20 years (26, 33, and 39 years, respectively). The distribution in years since CKD diagnosis was compared using a Wilcoxon rank-sum test (Appendix 16.1__ 9 of the NDA Study Report) and was not statistically significant ($p = 0.223$). The median time since CKD diagnosis was 3.50 years in the Zemplar group and 4.60 years in the placebo group.

When the years since CKD diagnosis is >10 years, 3 out of 12 patients did not achieve 2 consecutive $\geq 30\%$ decreases from baseline in iPTH. This failure rate is more than those in other subgroups of "years since CKD diagnosis." However, without further evidence, this should not be taken as a fact.

Apparently, the Zemplar response rates were almost the same in all three studies. However, in the alternate day dose studies ...19 and ...20, the mean iPTH (pg/ml) slightly increased starting from Week 19 and Week 17 in the Zemplar group. However, in the daily dose Study ...21, the mean iPTH (pg/ml) in the Zemplar group maintained a downward trend up to the end of the study.

The labeling states, ' _____
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However, the treatment groups were highly statistically significantly different with respect to percent of patients having visit calcium value >10.5. This percent was 18.7 for the Zemplar group and 0.9 for the placebo group.

For a safety variable, it should not be stated (as has been done in the labeling) that

The confidence intervals are given in

Section 3.2. Evaluation of safety.

2. INTRODUCTION

2.1 Overview

INDICATIONS AND USAGE

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

Three pivotal Phase 3, double-blind, placebo-controlled, multi-center studies (Study 2001019, Study 2001020, and Study 2001021) were conducted in CKD Stage 3 and 4 subjects with 2° HPT (iPTH levels of ≥ 150 pg/mL).

Study 2001019

Study 2001019 was a Phase 3, prospective, randomized, placebo-controlled, double-blind, multi-center trial to evaluate the safety and efficacy of paricalcitol capsule in reducing elevated serum iPTH levels (≥ 150 pg/mL) in CKD Stage 3 and 4 subjects. Approximately 68 subjects aged ≥ 18 years were to be randomly assigned in an equal ratio (1: 1) to 1 of 2 treatment groups: Group 1 - paricalcitol capsule; Group 2 - placebo capsule.

The study was divided into 4 phases: Screening Phase, Pre-treatment Phase, Treatment Phase, and Follow-Up Phase. During the Treatment Phase, subjects were to self-administer 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). Doses may have been increased in 2 mcg increments every 4 weeks. Dose reductions were to occur according to a protocol-specified algorithm. However, dosing could have been adjusted any time if, in the judgment of the Investigator, a risk

to subject safety existed. Safety and efficacy were determined through adverse event monitoring and clinical laboratory evaluations during the 24-week Treatment Phase through the Follow-Up Visit.

Seventy-four (74) subjects were randomized at 13 investigative sites in the US and 1 subject was randomized at 1 investigative site in Poland. All 75 subjects received at least 1 dose of study drug; 39 received paricalcitol capsule and 36 received placebo.

Studied Period (Years): Initiation Date (First Subject Dosed): 15 April 2002

Completion Date (Last Subject Completed Dosing): 12 January 2004

Number of Subjects (Planned and Analyzed):

Planned: 68 subjects (34 per treatment group) Enrolled: 75 subjects (39 Zemplar, 36 Placebo)

Analyzed:	Zemplar	Placebo
Randomized and Treated:	39	36
Evaluated for Primary Efficacy (Intent to Treat)	36	34
Evaluated for Safety and Secondary Efficacy (All Treated)	39	36

Diagnosis and Main Criteria for Inclusion:

Male or female subjects ≥ 18 years of age who had been in the care of a physician ≥ 2 months for CKD prior to entry into the study and had not been on active vitamin D therapy for at least 4 weeks prior to the Screening Visit were eligible. Prior to entry into the Pre-Treatment Phase, subjects had to have iPTH ≥ 120 pg/mL and an eGFR of 15 to 60 mL/min (and not expected to begin dialysis for at least 6 months). Prior to treatment, subjects had to have an average of 2 consecutive iPTH values of ≥ 150 pg/mL, taken at least 1 day apart (all values must have been ≥ 120 pg/mL), 2 consecutive serum calcium levels of ≥ 8.0 to ≤ 10.0 mg/dL, and 2 consecutive serum phosphorus levels of ≤ 5.2 mg/dL. Female subjects of childbearing potential had to have a negative pregnancy test prior to treatment, had to use a protocol-specified birth control method throughout the study, and could not be nursing. Subjects who had been taking a phosphate binder were to have been on a stable regimen at least 4 weeks prior to the Screening Visit.

Efficacy:

The Intent-To-Treat population (Full Analysis Set) was defined as all randomized subjects with a baseline iPTH and at least 2 on-treatment iPTH measurements. This population was used in the primary efficacy analysis.

The primary efficacy analysis was a comparison between the Zemplar and placebo treatment groups of the proportion of subjects achieving 2 consecutive decreases from baseline in iPTH of at least 30%. This comparison was performed using a Fisher's exact test.

All randomized subjects who received at least 1 dose of study drug were used in secondary efficacy analyses.

Secondary efficacy analyses were performed comparing changes/percent change from baseline between the Zemplar and placebo treatment groups using a one-way analysis of variance (ANOVA) with treatment group as the factor for the following variables: iPTH and biochemical bone activity markers.

Efficacy Results:

A statistically significantly ($p < 0.001$) greater proportion of subjects treated with Zemplar (initially dosed according to baseline iPTH values) had 2 consecutive $\geq 30\%$ decreases from baseline in iPTH compared with subjects who received placebo (33/36, 92% versus 4/34, 12%). Additionally, in an exploratory analysis to evaluate the robustness of the primary efficacy analysis, a statistically significantly ($p < 0.001$) greater proportion of Zemplar subjects had 4 consecutive $\geq 30\%$ decreases from baseline in iPTH compared with placebo subjects (26/36, 72% versus 0/34, 0%).

There was a statistically significant difference between the Zemplar and placebo treatment groups in mean change from baseline to Final Visit in iPTH using ANOVA with treatment as the factor. Zemplar-treated subjects had a mean decrease (- 58.1 pg/mL, representing a 19.2% decrease) in iPTH at the Final Visit compared with a mean increase (50.4 pg/mL, representing a 16.9% increase) among placebo-treated subjects. Similarly, Zemplar-treated subjects had a statistically significant mean decrease (- 95.7 pg/ mL, representing a 33.0% decrease) in iPTH at the Last On-Treatment Visit compared with a mean increase (32.5 pg/ mL, representing an 11.2% increase) among placebo-treated subjects. The larger mean decrease and mean percent decrease using the Last On-Treatment Visit may be more representative of a treatment effect.

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. In Zemplar-treated subjects, decreases in iPTH were observed as early as Week 3 (the first time iPTH was measured after the first dose) and continued throughout the Treatment Phase. A 30% mean reduction in iPTH occurred by Week 9 and the maximum decrease (- 46.0%) from baseline in iPTH was observed at Week 19.

Using a one-way ANOVA, statistically significant differences were observed between the Zemplar and placebo treatment groups in mean changes from baseline to Final Visit for all of the biochemical bone activity marker variables. Zemplar-treated subjects had mean decreases in urinary deoxypyridinoline, urinary pyridinoline, serum osteocalcin, and serum bone-specific alkaline phosphatase while placebo subjects experienced mean increases in urinary deoxypyridinoline, urinary pyridinoline, and serum osteocalcin and a small mean decrease in serum bone-specific alkaline phosphatase. The one-way ANOVA for urinary pyridinoline yielded a statistically significant difference in change from baseline between the Zemplar and placebo treatment groups ($p = 0.043$) while the Wilcoxon rank-sum test yielded a non-significant difference for changes from baseline between the 2 treatment groups ($p = 0.138$). The results of the Wilcoxon rank-sum tests for the other bone activity markers were consistent with the results

using the one-way ANOVA. The favorable result observed in the Zemplar group suggests correction of high-turnover bone disease associated with 2° HPT.

Study 2001020

Study 2001020 was similar in design and other aspects to the previous study “Study 2001019”. Some specifics which are different are presented below.

Investigator(s): Multi-center; 15 Investigators

Study Site(s): 14 study sites in the U.S. and 1 study site in Poland

Studied Period (Years):

Initiation Date (First Subject Dosed): 3 April 2002

Completion Date (Last Subject Completed Dosing): 23 February 2004

Number of Subjects (Planned and Analyzed):

Planned: 68 subjects (34 per treatment group)

Enrolled: 70 subjects (33 Zemplar, 37 Placebo)

Analyzed:

Randomized and Treated

	Zemplar	Placebo
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	33	37
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Evaluated for Primary Efficacy (Intent-to-Treat)

	32	36
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Evaluated for Safety and Secondary Efficacy (All Treated)

	33	37
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Efficacy Results:

A statistically significantly ($p < 0.001$) greater proportion of subjects treated with Zemplar (initially dosed according to baseline iPTH values) had 2 consecutive $\geq 30\%$ decreases from baseline in iPTH compared with subjects who received placebo (29/32, 91% versus 6/36, 17%). Additionally, in an exploratory analysis to evaluate the robustness of the primary efficacy analysis, a statistically significantly ($p < 0.001$) greater proportion of Zemplar-subjects had 4 consecutive $\geq 30\%$ decreases from baseline in iPTH compared with placebo subjects (26/32, 81% versus 0/36, 0%).

There was a statistically significant difference between the Zemplar and placebo treatment groups in mean change from baseline to Final Visit in iPTH using ANOVA with treatment as the factor. Zemplar-treated subjects had a mean decrease (- 80.7 pg/ mL, representing a 30.3% decrease) in iPTH at the Final Visit compared with a mean increase (12.2 pg/ mL, representing a 9.4% increase) among placebo-treated subjects. Similarly, Zemplar-treated subjects had a statistically significant mean decrease (- 83.1 pg/ mL, representing a 33.4% decrease) in iPTH at the Last On-Treatment Visit compared with a mean increase (10.1 pg/ mL, representing a 2.9% increase) among placebo-treated subjects.

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. In Zemplar-treated subjects, decreases in iPTH were observed as early as Week 3 (the first time iPTH was measured after the first dose) and continued throughout the Treatment Phase. A 30% mean reduction in iPTH occurred by Week 9 and the maximum decrease (- 48.2%) from baseline in iPTH was observed at Week 17.

Statistically significant differences were observed between the Zemplar and placebo treatment groups in mean changes from baseline to Final Visit for the serum biochemical bone activity markers of serum osteocalcin and serum bone-specific alkaline phosphatase. Zemplar-treated subjects had mean decreases in serum osteocalcin and serum bone-specific alkaline phosphatase while placebo subjects experienced a mean increase in serum osteocalcin and a small mean decrease in serum bone-specific alkaline phosphatase. Serum bone-specific alkaline phosphorus and osteocalcin are currently considered more sensitive and specific bone markers to evaluate the degree of bone remodeling in the setting of CKD than urine bone markers.

Study 2001021

Study 2001021 was similar in design and other aspects previous two studies, except that the dosing was different as mentioned before. Some specifics which are different are presented below.

Investigator(s): Multi-center; 14 Investigators
Study Site(s): 12 study sites in the U.S. and 2 study sites in Poland
Publications: None
Studied Period (Years):
 Initiation Date (First Subject Dosed): 11 April 2002
 Completion Date (Last Subject Completed Dosing): 03 March 2004.

Number of Subjects (Planned and Analyzed):
Planned: 68 subjects (34 per treatment group)
Enrolled: 75 subjects (35 Zemplar, 40 Placebo)

Analyzed:	Zemplar	Placebo
Randomized and Treated	35	40
Evaluated for Primary Efficacy (Intent-to-Treat)	33	38
Evaluated for Safety and Secondary Efficacy (All Treated)	35	40

Efficacy Results:

A statistically significantly ($p < 0.001$) greater proportion of subjects treated with Zemplar (initially dosed according to baseline iPTH values) had 2 consecutive $\geq 30\%$ decreases from baseline in iPTH compared with subjects who received placebo (30/33, 91% versus 4/38, 11%). Additionally, in an exploratory analysis to evaluate the robustness of the primary efficacy analysis, a statistically significantly ($p < 0.001$) greater proportion of Zemplar-subjects had 4

consecutive $\geq 30\%$ decreases from baseline in iPTH compared with placebo subjects (23/33, 70% versus 0/38, 0%).

There was a statistically significant difference between the Zemplar and placebo treatment groups in mean change from baseline to Final Visit in iPTH using ANOVA with treatment as the factor. Zemplar-treated subjects had a mean decrease (- 46.9 pg/ mL, representing a 15.2% decrease) in iPTH at the Final Visit compared with a mean increase (52.6 pg/ mL, representing a 19.1% increase) among placebo-treated subjects. Similarly, Zemplar-treated subjects had a statistically significant mean decrease (- 130.8 pg/mL, representing a 50.0% decrease) in iPTH at the Last On-Treatment Visit compared with a mean increase (61.1 pg/mL, representing a 21.4% increase) among placebo-treated subjects. The larger mean decrease and mean percent decrease using the Last On-Treatment Visit may be more representative of a treatment effect.

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. In Zemplar-treated subjects, decreases in iPTH were observed as early as Week 3 (the first time iPTH was measured after the first dose) and continued throughout the Treatment Phase. A 30% mean reduction in iPTH occurred by Week 7 and the maximum decrease (- 52.4%) from baseline in iPTH was observed at Week 23.

Major statistical issues and findings have been discussed in Section 1.3 above.

2.2 Data Sources

Location of the NDA in EDR (electronic documents room): \\CDSESUB1\21-606\2004-07-28

Related data provided are in the electronic document room: \\CDSESUB1\21-606\2004-07-28\crt

Statistical Amendments:

\\CDSESUB1\21-606\2004-11-24

\\CDSESUB1\21-606\2004-12-10

\\CDSESUB1\21-606\2004-12-15

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The subsections under each study below are: **Study Design and Endpoints; Patient Disposition, Demographic and Baseline Characteristics; Statistical Methodologies; Results and Conclusions.**

A list of abbreviation and definition of terms has been provided in the NDA and is reproduced in this document as Appendix I.

In the submission of 12-10-04, the sponsor stated,

“The purpose of this amendment is to provide information requested by Dr. Japo Choudhury at FDA. He requested a copy of the finalized statistical plan, which was not provided in the original NDA, but was submitted as part of the Pre-NDA Meeting Package for January 23, 2004 (IND 60,672, serial #065). The final statistical plan is attached.

In addition, Dr. Choudhury requested the specific dates for the blind break for the three pivotal clinical studies. They are as follows:

Study number: 2001019 - January 29, 2004
2001020 - March 16, 2004
2001021 - March 24, 2004”

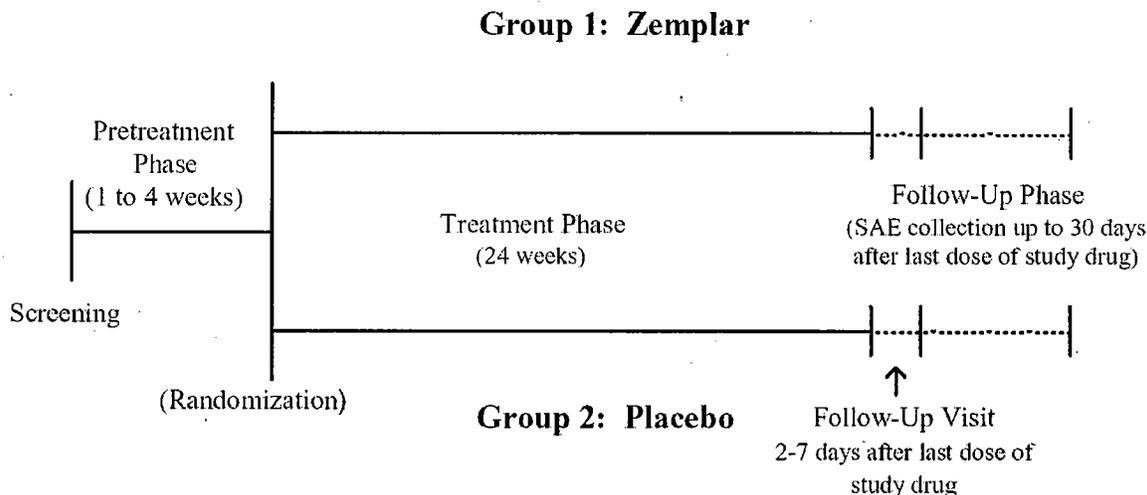
3.1.1 Study 2001019

Study Design and Endpoints

Study 2001019 was a Phase 3, prospective, randomized, placebo-controlled, double-blind, 24-week Treatment Phase, multi-center study in CKD (Stages 3 and 4) subjects with elevated iPTH levels (≥ 150 pg/mL). Potential subjects with an eGFR of 15 - 60 mL/min underwent procedures to determine their baseline intact parathyroid hormone (iPTH), calcium, and phosphorus levels for eligibility to receive treatment. Approximately 68 qualified subjects were to be randomized in an equal ratio (1: 1) to 1 of 2 treatment groups: Zemplar Capsule (Group 1) and placebo (Group 2).

The study was performed in 4 parts - a Screening Visit, a Pre-Treatment Phase, a Treatment Phase, and a Follow-Up Phase. The study design schematic is depicted in Figure below.

Study Design Schematic



At the Screening Visit, subjects reviewed and signed the informed consent form prior to the conduct of any study-specific Screening procedures. A blood sample was drawn for iPTH, blood urea nitrogen (BUN), albumin, and serum creatinine levels. A spot urine sample was used to calculate the calcium/creatinine ratio. 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 using a formula derived from the "Modification of Diet in Renal Disease" (MDRD) study. Subjects with an eGFR of 15 to 60 mL/min were eligible to undergo Pre-Treatment Phase procedures. Subjects must not have been expected (in the opinion of the Investigator) to begin dialysis for at least 6 months in order to enter the Pre-Treatment Phase. Subjects were to enter the Pre-Treatment Phase within 14 days of undergoing Screening procedures.

The Pre-Treatment Phase was 1 to 4 weeks. During this phase, subjects had 2 scheduled office visits. The office visits could have occurred at any time during a 4-week period, but must have been at least 1 day apart. During these visits, 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. If the subject was unable to meet these criteria, he/she could have been re-screened once after 4 weeks. Study procedures performed during Pre-Treatment Visit 1 included a medical history, physical examination, vital signs, complete chemistry, hematology, concurrent medications, and a serum pregnancy test (if female of childbearing potential). A 24-hour urine collection for calcium, phosphorus, and creatinine clearance (Ccr) was to be done at either Pre-Treatment Visit 1 or 2. Subjects who satisfied inclusion and exclusion criteria after a minimum of 1 week in the Pre-Treatment Phase were eligible to enter the Treatment Phase.

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). Procedures to be performed during the Treatment Phase included vital signs, chemistry and hematology, urinary pyridinoline, urinary deoxypyridinoline, serum bone-specific alkaline phosphatase, serum osteocalcin, urinalysis, spot urine for calcium/creatinine ratio, and recording of adverse events and concurrent medications. 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 chemistry results for iPTH, calcium, and phosphorus. Doses may have been increased in 2 mcg increments every 4 weeks. Dose reductions were to occur according to the algorithm presented in Figure 2. However, dosing could have been adjusted any time if, in the judgment of the Investigator, a risk to subject safety existed. Subjects who achieved any of the following criteria were considered to have completed or were discontinued from the study:

- completed 24 weeks of treatment
- required dialysis
- iPTH increased by 3-fold from baseline after 4 weeks of treatment for 2 consecutive measurements
- iPTH increased to > 1000 pg/mL after 4 weeks of treatment for 2 consecutive measurements

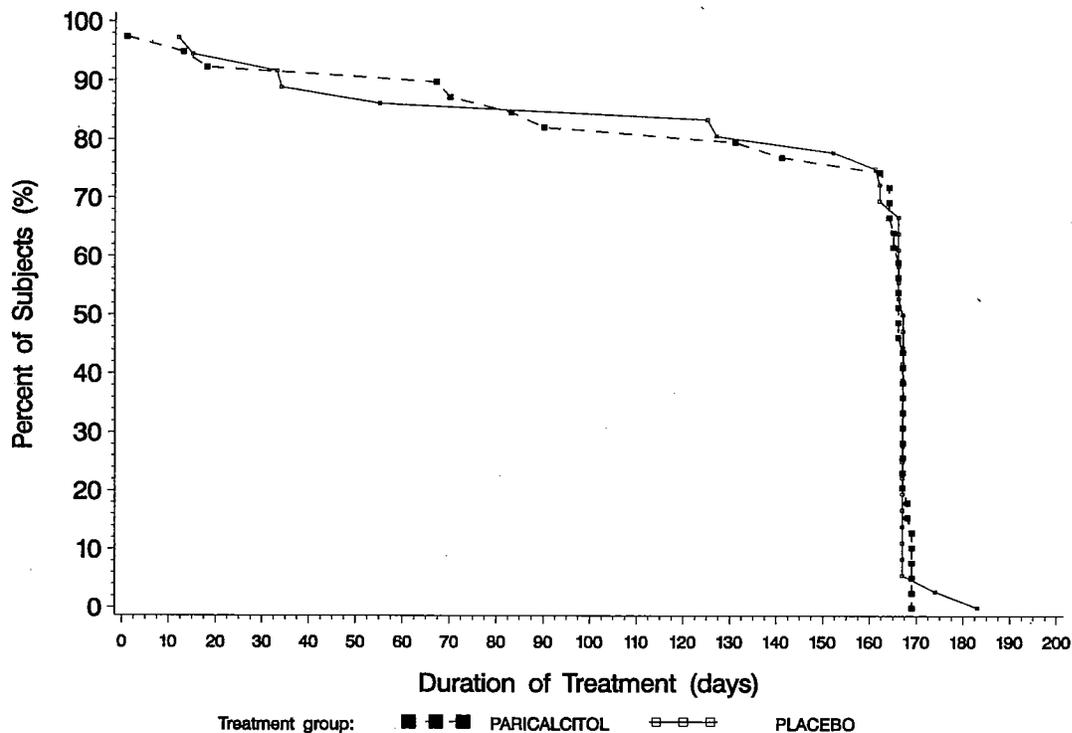
After Treatment Week 24 (or following premature termination), subjects entered the Follow-Up Phase. Subjects were to return for study procedures at the Follow-Up Visit 2 to 7 days after their last dose of study drug, and must not have re-started any vitamin D treatment until after the Follow-Up Visit was complete. Procedures at the Follow-Up Visit included a complete physical examination, vital signs, a complete chemistry and hematology evaluation, urinary pyridinoline, urinary deoxypyridinoline, serum bone-specific alkaline phosphatase, serum osteocalcin, eGFR, spot urine for calcium/creatinine ratio, a 24-hour urine collection for calcium, phosphorus and Ccr, urinalysis, and recording of adverse events and concurrent medications.

Through the course of the study, safety was evaluated through the changes observed in renal function, adverse events, laboratory assessments, and vital signs.

The primary efficacy endpoint was the achievement of 2 consecutive $\geq 30\%$ decreases from baseline iPTH levels. Safety was assessed through an evaluation of clinically meaningful hypercalcemia (2 consecutive calcium results > 10.5 mg/dL), the incidence of adverse events, the change from baseline in chemistry, hematology and urinalysis laboratory variables, the change from baseline in subject vital signs, and progressive changes in kidney function observed via changes in eGFR.

Patient Disposition

Percent of Subjects in Study over Time – Study H01–019



Seventy-four (74) subjects were randomized in the study by 13 Investigators at 13 sites in the U.S. and 1 subject was randomized at 1 investigative site in Poland. All 75 subjects received at least 1 dose of study drug; 39 received Zemplar and 36 received placebo. Subject disposition is presented below.

Reasons for Premature Termination from the Study (All Treated Subjects)

	Zemplar (n = 39)	Placebo (n = 36)
Reason for Premature Termination^a		
Adverse event ^b	1 (3%)	2 (6%)
Withdrew consent	1 (3%)	1 (3%)
Lost to follow-up	2 (5%)	1 (3%)
Other ^c	5 (13%)	5 (14%)
Total Terminated Prematurely	9 (23%)	9 (25%)
Total Completed 24 Weeks of Treatment	30 (77%)	27 (75%)

- a. Only 1 reason for termination is provided per subject in Table 7. Two subjects terminated prematurely for 2 reasons: Zemplar (1101) for lost to follow-up (counted in table) and other [subject hospitalized but continued to take supply of drug]; Placebo (902) for withdrew consent (counted in table) and noncompliance.
- b. Zemplar: 1 subject (502) with liver function tests abnormal. Placebo: 1 subject (501) with confusion, dehydration, hyperglycemia, and acute kidney failure and 1 subject (705) with hypervolemia. (Complete adverse event descriptions are presented in Table 26 for subjects who terminated prematurely.)
- c. Zemplar: 2 subjects (801 and 809) required dose reduction to 0 mcg, 2 subjects (101 and 404) had a history of kidney stones, and 1 subject (507) died. Placebo: 1 subject (1502) required dose reduction to 0 mcg, 1 subject (901) did not have study drug dispensed in error, 1 subject (704) was withdrawn due to Investigator decision, 1 subject (506) was dispensed study drug that was assigned to another subject, and 1 subject (1201) was withdrawn due to coordinator miscalculation of study drug dose.

Cross Reference: Table 14.1__1.2 and Table 14.1__1.3 and Appendix 16.2__1.1 and Appendix 16.2__7.1.1

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 (5) 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 (5) 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.

Numbers of Subjects Included in the Safety and Efficacy Evaluations

Analysis	Zemplar	Placebo
Primary Analysis of Efficacy (Intent-to-Treat Population)	36 (92%)	34 (94%)
Safety and Secondary Efficacy (All Treated Subject Population)	39 (100%)	36 (100%)

Cross Reference: Table 14.1__1.1

The primary efficacy analysis was performed using the Intent-to-Treat set of subjects defined as all randomized subjects with a baseline iPTH measurement and at least 2 on-treatment iPTH measurements. All other analyses were performed using the all treated set of subjects defined as all randomized subjects who received at least 1 dose of study drug. A summary of the numbers

of subjects included in the safety and efficacy evaluations is presented by treatment group in Table above.

Three (3) Zemplar subjects (101, 404, and 1202) and 2 placebo subjects (902 and 1502) were randomized and were treated, but were not included in the Intent-to-Treat population because they did not have at least two on-treatment values of iPTH. The iPTH data for these subjects is presented in Appendix 16.2__ 3 of the NDA Study Report.

Demographic and Baseline Characteristics

No statistically significant differences were observed between the treatment groups in baseline demographic characteristics for all treated subjects. The majority of the subjects in both treatment groups were male (69% in both treatment groups) and most were white (64% Zemplar and 72% placebo). Age ranged from 22 to 90 years, with a mean age of 63.5 years in the Zemplar group and 64.7 years in the placebo group. Both treatment groups had more smokers than nonsmokers and more drinkers than nondrinkers. The time since CKD diagnosis ranged from 0.5 to 26.0 years, with a mean time of 4.86 years in the Zemplar group and 5.11 years in the placebo group. Subject demographic data are summarized for all treated subjects by treatment group in the following Table.

Demographics (All Treated Subjects)

	Zemplar (N = 39)	Placebo (N = 36)	P-value ^a
Gender			1.000
Female	12 (31%)	11 (31%)	
Male	27 (69%)	25 (69%)	
Race			0.596
Asian	2 (5%)	0 (0%)	
Black	12 (31%)	10 (28%)	
White	25 (64%)	26 (72%)	
Tobacco Use			0.815
Nonsmoker	17 (44%)	14 (39%)	
Smoker (includes ex-smokers)	22 (56%)	22 (61%)	
Alcohol Use			1.000
Nondrinker	14 (36%)	13 (36%)	
Drinker (includes ex-drinkers)	25 (64%)	23 (64%)	
Age Group			0.819
< 65 years	17 (44%)	17 (47%)	
≥ 65 years	22 (56%)	19 (53%)	
Age (years)			0.699

Mean (SE)	63.5 (2.41)	64.7 (1.81)	
Median	66.0	65.0	
Range	22-89	46-90	
Time Since CKD Diagnosis (years)^b			0.850
Mean (SE)	4.86 (0.807)	5.11 (1.065)	
Median	3.50	2.50	
Range	0.5-22.8	0.6-26.0	

CKD = chronic kidney disease

a. P-values for race, gender, tobacco use, alcohol use, and age group are derived from Fisher's exact test. P-values for mean age and time since first CKD diagnosis are from F-test testing equality of means between treatment groups.

b. Zemplar: n = 38; Placebo: n = 35

Cross Reference: Table 14.1__ 2.1 and Appendix 16.2__ 4.1 and Appendix 16.2__ 4.3

There were no statistically significant differences between the treatment groups in pre-treatment values of vital sign variables, including height, weight, temperature, systolic and diastolic blood pressures, and pulse rate.

Medical History

The proportions of subjects within each medical history category with an abnormal history were generally similar between treatment groups except that conditions associated with the pulmonary system were reported by a greater proportion of Zemplar subjects (67%) compared with placebo subjects (47%). Conditions associated with the genitourinary (100% in both groups), cardiovascular (100% Zemplar and 97% placebo), metabolic (100% Zemplar and 92% placebo), and musculoskeletal (90% Zemplar and 94% placebo) systems were the most commonly reported abnormal histories in both treatment groups. All serum pregnancy tests performed on female subjects prior to treatment were negative.

Physical Examination

The proportions of subjects within each physical examination category with an abnormality were generally similar between the treatment groups, except that a greater proportion of placebo subjects (64%) reported abnormalities associated with the extremities compared with Zemplar subjects (49%).

Pre-Treatment Medications

The most commonly used pre-treatment medications in both groups were ACE inhibitors and/ or angiotensin II receptor blockers (79% Zemplar and 75% placebo) cholesterol and triglyceride reducers (77% Zemplar and 53% placebo), high-ceiling diuretics (69% Zemplar and 78%

placebo), antithrombotic agents (51% Zemplar and 58% placebo), and beta-blocking agents (46% Zemplar and 53% placebo).

Compliance

Two of 39 (5%) Zemplar subjects and none of the placebo subjects indicated < 60% compliance with the dosing regimen greater than 10% of the time.

Statistical Methodologies

Prior to the randomization schedule being released, a final statistical analysis plan was written, signed, and dated. This document provided clarification to the analyses discussed in Section 8.0 of the 2001019 protocol and also described additional analyses to be performed. These clarifications and additional analyses are summarized in the following paragraphs. Also indicated in this section are additional analyses and summarizations performed that were not defined prior to the release of the schedule. A complete description of the statistical methods used in this study is given in Appendix 16.1__ 9 of the Study report.

The primary analysis of efficacy was performed using the Intent-to-Treat Population. Secondary efficacy analyses and analyses of safety were performed using the All Subject Population.

Primary Efficacy Analysis

The primary efficacy analysis was a comparison between the Zemplar and placebo treatment groups of the proportion of subjects achieving 2 consecutive decreases from baseline in iPTH of at least 30%. This comparison was performed using the Fisher's exact test. All non-missing iPTH measurements following the first dose of study drug were included in this analysis. If more than 1 iPTH measurement existed for a subject a particular day, the largest of these iPTH measurements was considered to be that subject's iPTH measurement for that day.

Baseline for iPTH was defined as the average of the last 2 iPTH measurements collected during the Pre-Treatment Phase of the study (rounded to 1 decimal place). This baseline was calculated for each subject by averaging the last 2 iPTH measurements collected on visits prior to the day that the first dose of study drug was taken.

Percent change from baseline in iPTH was calculated and, for the primary efficacy analysis, this calculated percent change from baseline was rounded to 2 decimal places.

Secondary Efficacy Analyses

Change and Percent Change from Baseline Analyses in iPTH

Final Visit Analyses

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 Final Visit analyses.

Longitudinal Analyses

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 1 measurement following the first dose of study drug were not included in these analyses.

For Final Visit and longitudinal analyses, the change and percent change from baseline in iPTH was compared between Zemplar and placebo using a one-way analysis of variance (ANOVA) with treatment as the factor. Also at a given visit, the change and percent change from baseline was compared between Zemplar and placebo using an analysis of covariance (ANCOVA) with baseline as the second factor.

Both “observed value” and “last observation carried forward (LOCF)” methods were used for analyses at scheduled post-baseline visits. First, for the “observed value” method, a subject's measurement for a visit was the measurement on a day closest to the scheduled visit, for which the possible measurements to choose from were those collected within a given interval of days prior to and after the scheduled visit. Second, for the “LOCF” method, a subject's measurement was the measurement on a day closest to the scheduled visit, for which the possible measurements to choose from were all those collected after the first dose of study drug and prior to a given interval of days beyond the scheduled visit. For either method, if 2 values were equidistant from the scheduled visit, one being before and 1 after the scheduled visit, then the earlier measurement was considered the measurement for that visit. Dosing day intervals that were used to select data that corresponded to the visits at which iPTH was measured is defined in Appendix 16.1 __ 9 of the NDA Study Report.

Results and Conclusions

Primary Efficacy Analysis (Intent-to-Treat Population)

The primary efficacy endpoint was 2 consecutive $\geq 30\%$ decreases from baseline in iPTH. In the Intent-to-Treat population, 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 (Table 14.2__ 1.1 of the NDA Study Report).

A statistically significantly greater proportion of subjects in the Zemplar group (92%) had 2 consecutive $\geq 30\%$ decreases from baseline in iPTH compared with subjects in the placebo group (12%). A summary of the primary efficacy analysis results is presented by treatment group in the Table below.

	Zemplar (N = 36)	Placebo (N = 34)	P-value ^a
Subject achieved 2 consecutive $\geq 30\%$ decreases from baseline in iPTH	33 (92%)	4 (12%)	< 0.001

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

Cross Reference: Table 14.2__ 1.2.1 and Appendix 16.2__ 6.1.1

§ In the worst-case analyses presented below, placebo subjects not included in the primary efficacy analysis are considered to have achieved the primary efficacy endpoint and paricalcitol capsule subjects not included in the primary efficacy analysis are considered to have failed to achieve the primary efficacy endpoint. The analyses presented below include results based on all randomized and treated subjects.

**Proportion of Subjects Who Achieved 2 Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Treatment Group for H01-019
(All Treated Subjects)**

	Paricalcitol Capsule (N = 39)	Placebo (N = 36)	p-value ^a
Subject achieved 2 consecutive $\geq 30\%$ decreases from baseline in iPTH	33 (85%)	6 (17%)	< 0.001

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

Secondary Efficacy Analysis (All Treated Subject Population)

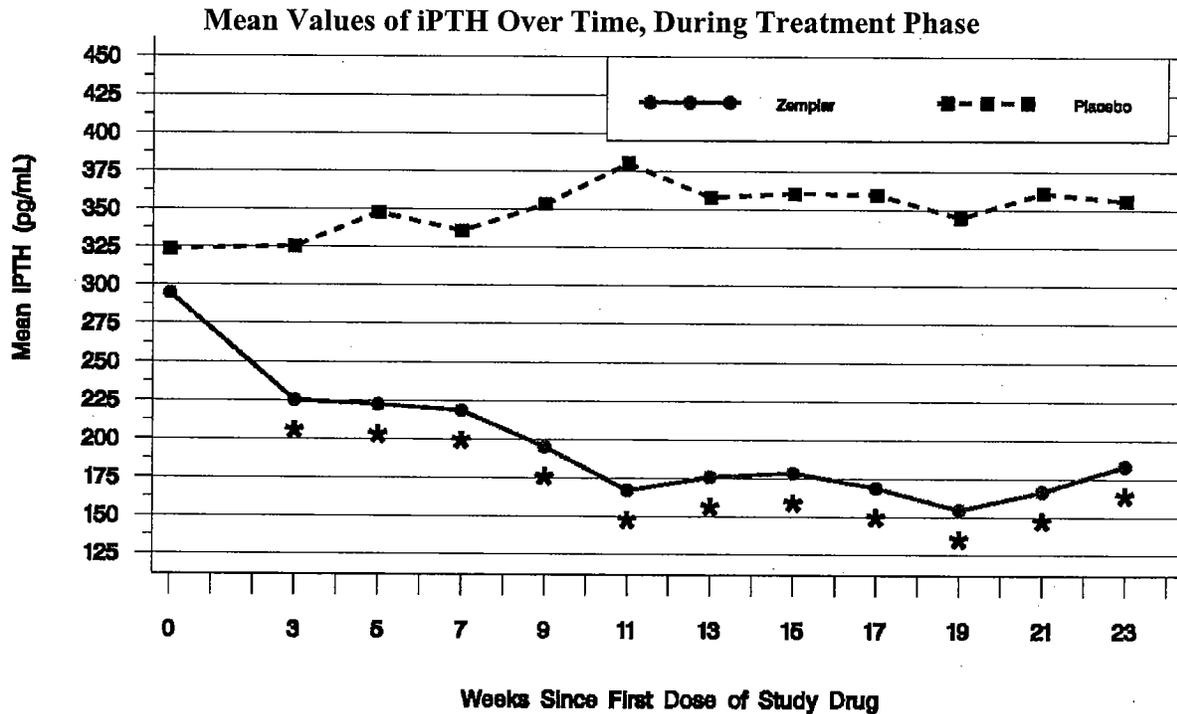
Mean Change and Percent Change from Baseline to Final Visit in iPTH (All Treated Subjects)

iPTH (pg/mL)	Zemplar (N = 37) ^a	Placebo (N = 35) ^b	ANOVA P-value ^c
Mean Baseline Value (Baseline Range)	285.9 (151.0-701.0)	324.8 (147.0-697.5)	0.214
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.

Cross Reference: Table 14.2__ 1.1, Table 14.2__ 2.1.1 and Table 14.2__ 2.4.1 and Appendix 16.2__ 6.1.1

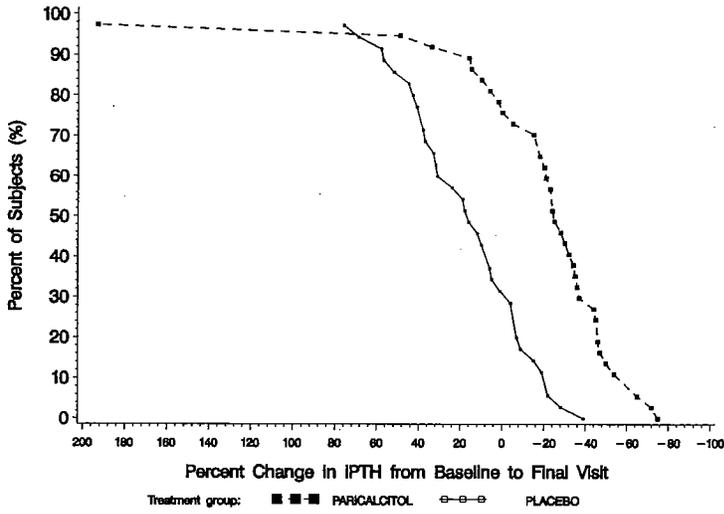


Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	39	35	36	35	35	34	32	33	31	32	31	29
Placebo N	36	32	34	33	29	32	29	30	30	28	28	29

* 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.

Following is the graph for the cumulative distribution function for percent change in iPTH at final visit. From this, percent of patients (y-axis value) with a value of Percent Change in iPTH at final visit, smaller than or equal to a value on the x-axis can be read.

Percent of Subjects with Specified (or Lower) Percent Change in IPTH at Final Visit
Study H01-019



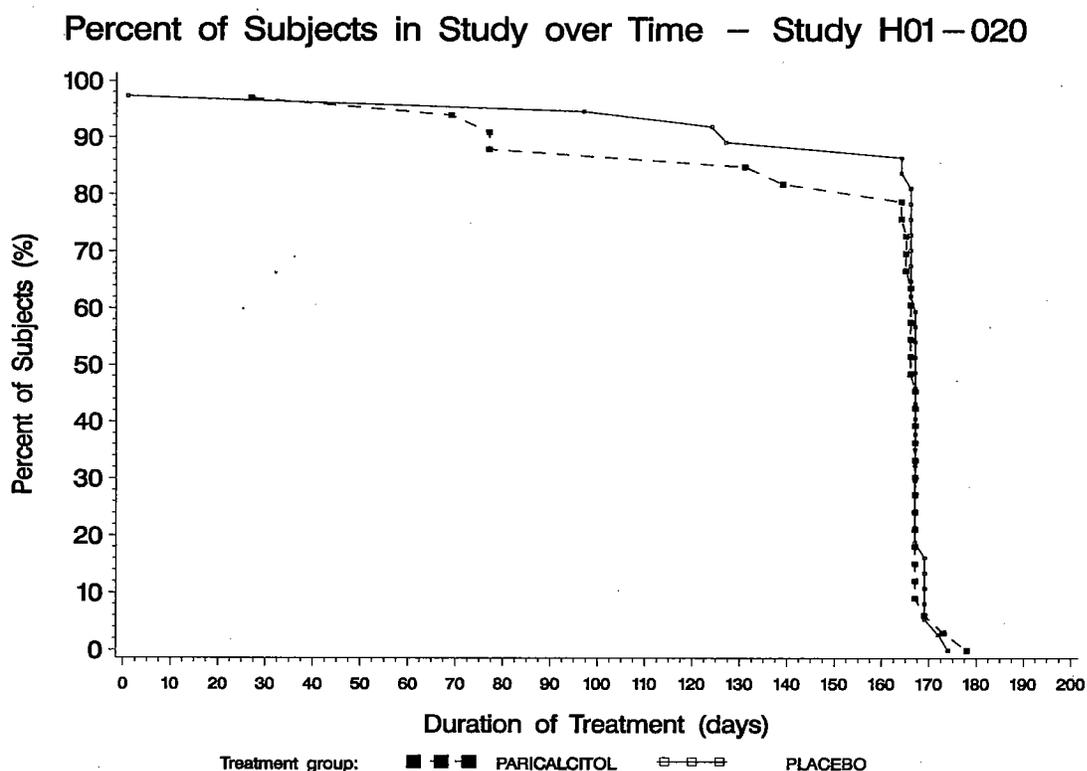
This reviewer's statistical tests based on the "Analysis Datasets" supplied to the FDA Electronic Document Room (EDR) by the sponsor provided statistically highly significant evidence in favor of the efficacy of Zemplar. These are consistent with the sponsor's many analyses. Even the worst-case analyses presented above provided statistically highly significant evidence in favor of the efficacy of Zemplar.

**APPEARS THIS WAY
ON ORIGINAL**

3.1.2 Study 2001020

Study Design and Endpoints were similar to that of the previous study.

Patient Disposition



Sixty-seven (67) subjects were randomized in the study by 14 Investigators at 14 sites in the U. S and 3 subjects were randomized at 1 investigative site in Poland. All 70 subjects received at least 1 dose of study drug; 33 received Zemplar and 37 received placebo.

Of the 33 subjects randomized into the study and treated with Zemplar, 27 (82%) completed treatment and 6 (18%) were terminated prematurely from the study. Three (3) of the subjects terminated prematurely due to "other" reasons (i.e., required dose reduction to 0 mcg [2 subjects], history of kidney stones which violated exclusion criteria [1 subject]), 1 terminated prematurely due to adverse events, 1 was lost to follow-up, and 1 was noncompliant.

Of the 37 subjects randomized into the study and treated with placebo, 33 (89%) completed treatment and 4 (11%) were terminated prematurely from the study. Two (2) of the subjects

terminated prematurely due to noncompliance, 1 terminated prematurely due to adverse events, and 1 subject terminated prematurely due to " other" reasons (i.e., history of nephrolithiasis which violated exclusion criteria).

A summary of the reasons subjects terminated prematurely from the study is presented in Table below.

	Zemplar	Placebo
	(n = 33)	(n = 37)
Reason for Premature Termination^a		
Adverse event ^b	1(3%)	1(3%)
Lost to follow-up	1(3%)	0(0%)
Noncompliance	1(3%)	2(5%)
Other ^c	3(9%)	1(3%)
Total Terminated Prematurely	6(18%)	4(11%)
Total Completed 24 Weeks of Treatment	27 (82%)	33 (89%)
a.	Only 1 reason for termination is provided per subject in Table 7. One subject terminated prematurely for 2 reasons: Zemplar (1206) for noncompliance (counted in table) and other [subject missed 2 appointments.]	
b.	Zemplar: 1 subject (1403) with uremia. Placebo: 1 subject (705) with uremia. (Complete adverse event descriptions are presented in Table 26 for subjects who terminated prematurely.)	
c.	Zemplar: 2 subjects (708 and 1303) required dose reduction to 0 mcg, and 1 subject (1405) had a history of kidney stones. Placebo: 1 subject (1407) had a history of nephrolithiasis.	
Cross Reference: Table 14.1__1.2 and Table 14.1__1.3 and Appendix 16.2__1.1 and Appendix 16.2__7.1.1		

Numbers of Subjects Included in the Safety and Efficacy Evaluations

Analysis	Zemplar	Placebo
Primary Analysis of Efficacy (Intent-to-Treat Population)	32(97%)	36(97%)
Safety and Secondary Efficacy (All Treated Subject Population)	33 (100%)	37 (100%)
Cross Reference: Table 14.1__1.1		

The primary efficacy analysis was identical to the previous study.

One (1) Zemplar subject (402) and 1 placebo subject (1407) were randomized and treated, but were not included in the Intent-to-Treat population because they did not have at least 2 on-treatment values of iPTH. The iPTH data for these subjects are presented in Appendix 16.2__3 of the Study Report in the NDA.

Demographic and Baseline Characteristics

No statistically significant differences were observed between the treatment groups for gender, race, tobacco use, alcohol use, age, or age group for all treated subjects. The majority of the subjects in both treatment groups were male (64% in the Zemplar group and 65% in the placebo group) and most were white (64% in the Zemplar group and 68% in the placebo group). Age ranged from 30 to 91 years, with a mean age of 62.5 years in the Zemplar group and 57.9 years in the placebo group. Both treatment groups had more smokers than nonsmokers and more drinkers than nondrinkers. A statistically significant difference ($p = 0.031$) was observed between treatment groups for time since CKD diagnosis, with placebo subjects (mean = 7.76 years) having CKD longer than Zemplar subjects (mean = 4.17 years). The difference between the treatment groups in time since CKD diagnosis is related to 3 placebo subjects (705, 706, and 1302) who had been diagnosed with CKD more than 20 years (26, 33, and 39 years, respectively). The distribution in years since CKD diagnosis was compared using a Wilcoxon rank-sum test (Appendix 16.1__ 9 of the NDA Study Report) and was not statistically significant ($p = 0.223$). The median time since CKD diagnosis was 3.50 years in the Zemplar group and 4.60 years in the placebo group. Subject demographic data are summarized for all treated subjects by treatment group in Table below.

Demographics (All Treated Subjects)

	Zemplar (N = 33)	Placebo (N = 37)	P-value ^a
Gender			1.000
Female	12 (36%)	13 (35%)	
Male	21 (64%)	24 (65%)	
Race			0.800
Asian	1 (3%)	0 (0%)	
Black	11 (33%)	12 (32%)	
White	21 (64%)	25 (68%)	
Tobacco Use			0.131
Nonsmoker	8 (24%)	16 (43%)	
Smoker (includes ex-smokers)	25 (76%)	21 (57%)	
Alcohol Use			0.810
Nondrinker	15 (45%)	15 (41%)	
Drinker (includes ex-drinkers)	18 (55%)	22 (59%)	
Age Group			0.455
< 65 years	20 (61%)	26 (70%)	
≥ 65 years	13 (39%)	11 (30%)	
Age (years)			0.123
Mean (SE)	62.5 (2.36)	57.9 (1.85)	
Median	59.0	61.0	
Range	30-91	37-79	

Time Since CKD Diagnosis (years)

0.031

Mean (SE)	4.17 (0.490)	7.76 (1.477)
Median	3.50	4.60
Range	0.2-11.0	0.2-38.7

CKD = chronic kidney disease

- a. P-values for race, gender, tobacco use, alcohol use, and age group are derived from Fisher's exact test. P-values for mean age and time since first CKD diagnosis are from F-test testing equality of means between treatment groups.

Cross Reference: Table 14.1__2.1 and Appendix 16.2__4.1 and Appendix 16.2__4.3

Medical History

The proportions of subjects within each medical history category with an abnormal history were generally similar between treatment groups. Conditions associated with the genitourinary (100% in both groups), cardiovascular (100% in both groups), and metabolic (94% Zemplar and 100% placebo) systems were the most commonly reported abnormal histories in both treatment groups. All serum pregnancy tests performed on female subjects prior to treatment were negative.

Physical Examination

The proportions of subjects within each physical examination category with an abnormality were generally similar between the treatment groups.

Pre-Treatment Medications

Greater proportions of Zemplar subjects received high-ceiling diuretics, beta-blocking agents, and ACE inhibitors and/ or angiotensin II receptor blockers compared to placebo subjects. The most commonly used pre-treatment medications in both groups were high-ceiling diuretics (85% Zemplar and 57% placebo), ACE inhibitors and/ or angiotensin II receptor blockers (70% Zemplar and 62% placebo), cholesterol and triglyceride reducers (58% Zemplar and 65% placebo), beta-blocking agents (58% Zemplar and 46% placebo), and antithrombotic agents (55% Zemplar and 49% placebo).

Treatment Compliance

Two (2) of 33 (6%) Zemplar subjects and 1 of 37 (3%) placebo subjects indicated < 60% compliance with the dosing regimen greater than 10% of the time.

Statistical Methodologies

Prior to the randomization schedule being released, a final statistical analysis plan was written, signed, and dated. This document provided clarification to the analyses discussed in Section 8.0 of the 2001020 protocol, and also described additional analyses to be performed. These clarifications and additional analyses are summarized in the following paragraphs. Also indicated in this section are additional analyses and summarizations performed that were not defined prior to the release of the randomization schedule. A complete description of the statistical methods used in this study is given in Appendix 16.1__ 9 of the NDA Study Report.

The primary, secondary, and longitudinal analyses of efficacy were identical to the previous study.

Results and Conclusions

Primary Efficacy Analysis (Intent-to-Treat Population)

The primary efficacy endpoint was 2 consecutive $\geq 30\%$ decreases from baseline in iPTH. In the Intent-to-Treat population, mean baseline levels of iPTH were 248.8 pg/mL (range: 152.5 to 442.0 pg/ mL) in the Zemplar group and 263.1 pg/ mL (range: 150.0 to 625.0 pg/ mL) in the placebo group. The difference between the treatment groups in baseline iPTH was not statistically significant (Table 14.2__ 1.1 of the Study Report in the NDA).

A statistically significantly greater proportion of subjects in the Zemplar group (91%) had 2 consecutive $\geq 30\%$ decreases from baseline in iPTH compared with subjects in the placebo group (17%). A summary of the primary efficacy analysis results is presented by treatment group in the Table below.

	Zemplar	Placebo	P-value^a
Subject achieved 2 consecutive $\geq 30\%$ decreases from baseline in iPTH	(N = 32) 29 (91%)	(N = 36) 6 (17%)	< 0.001

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

Cross Reference: Table 14.2__ 1.2.1 and Appendix 16.2__ 6.1.1

§ In the (worst case) analyses presented below, placebo subjects not included in the primary efficacy analysis are considered to have achieved the primary efficacy endpoint and paricalcitol capsule subjects not included in the primary efficacy analysis are considered to have failed to achieve the primary efficacy endpoint. The analyses presented below include results based on all randomized and treated subjects.

Proportion of Subjects Who Achieved 2 Consecutive \geq 30% Decreases from Baseline in iPTH by Treatment Group for H01-020

(All Treated Subjects)

	Paricalcitol Capsule (N = 33)	Placebo (N = 37)	p-value^a
Subject achieved 2 consecutive \geq 30% decreases from baseline in iPTH	29 (88%)	7 (19%)	< 0.001

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

Secondary Efficacy Analysis (All Treated Subject Population)

Mean Change and Percent Change from Baseline to Final Visit in iPTH (All Treated Subjects)

iPTH (pg/mL)	Zemplar (N = 33)	Placebo (N = 36)^a	ANOVA P-value^b
Mean Baseline Value (Baseline Range)	248.9 (152.5-442.0)	263.1 (150.0-625.0)	0.552
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

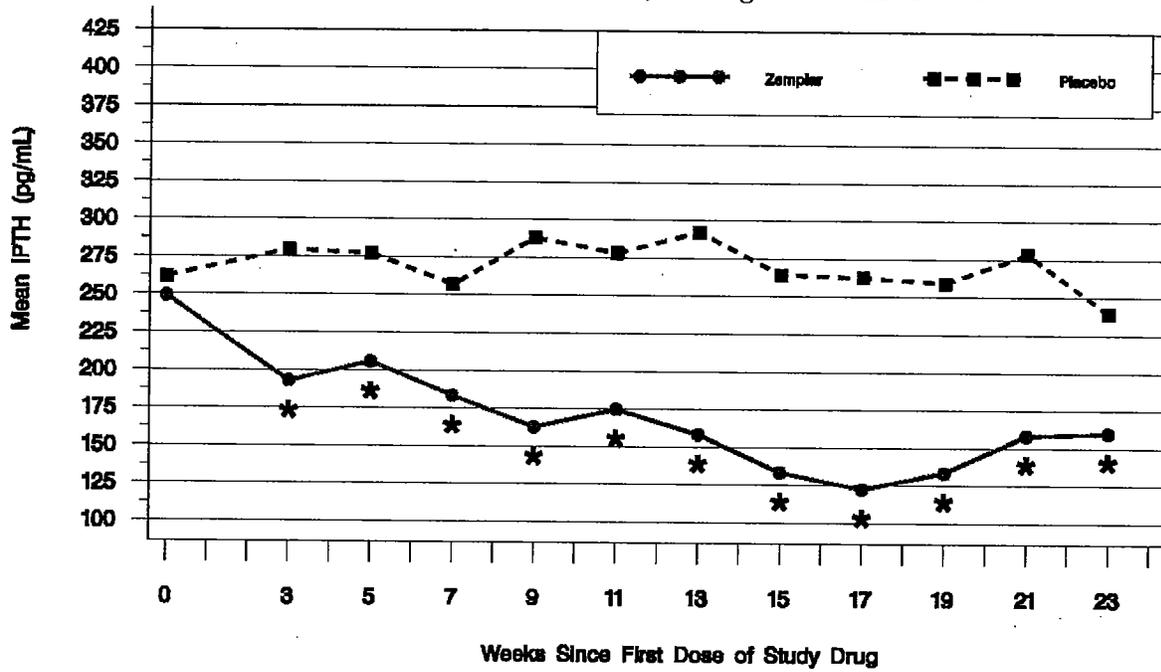
a. Placebo Subject 1407 had no iPTH measurements following the first dose of study medication; therefore, only 36 subjects (versus 37) are included in this analysis.

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

Cross Reference: Table 14.2__1.1, Table 14.2__2.1.1 and Table 14.2__2.4.1 and Appendix 16.2__6.1.1

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Mean Values of iPTH Over Time, During Treatment Phase



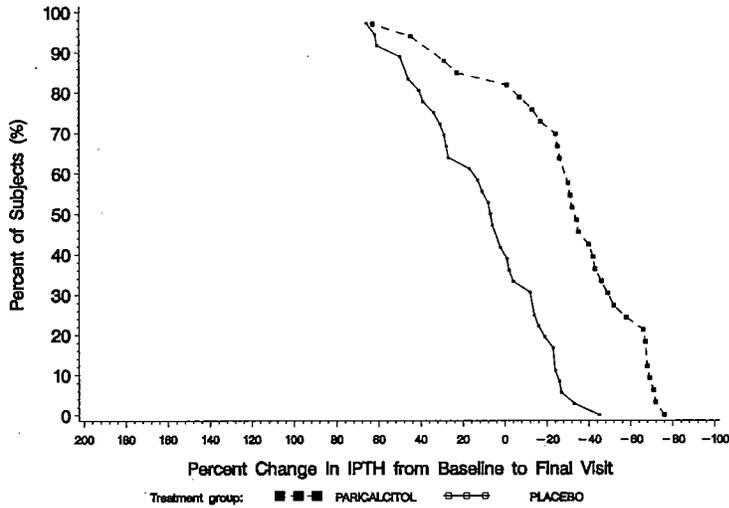
Week	0	3	5	7	9	11	13	15	17	19	21	23
Zemplar N	33	33	33	32	32	29	32	29	29	27	30	26
Placebo N	37	36	35	35	34	36	36	35	30	33	33	32

* 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.

Following is the graph for the cumulative distribution function for percent change from baseline in iPTH at final visit. From this, percent of patients (y-axis value) with a value of Percent Change in iPTH at final visit, smaller than or equal to a value on the x-axis can be read.

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Percent of Subjects with Specified (or Lower) Percent Change in IPTH at Final Visit
Study H01-020



This reviewer’s statistical tests based on the “Analysis Datasets” supplied to the FDA Electronic Document Room (EDR) by the sponsor provided statistically highly significant evidence in favor of the efficacy of paricalcitol. These are consistent with the sponsor’s many analyses. Even the worst-case analyses presented above provided statistically highly significant evidence in favor of the efficacy of paricalcitol.

3.1.3 Study 2001021

Study Design and Endpoints were similar to that of the previous study except for the dosing.

During the Treatment Phase, subjects were to self-administer study drug once daily for a total of 24 weeks. The initial dose was 1 or 2 mcg (depending on baseline iPTH levels). Dose adjustments were to be made according to these chemistry results for iPTH, calcium, and phosphorus. Doses may have been increased in 1 mcg increments every 4 weeks. Dose reductions were to occur according to a protocol-specified algorithm. However, dosing could have been adjusted any time if, in the judgment of the Investigator, a risk to subject safety existed.

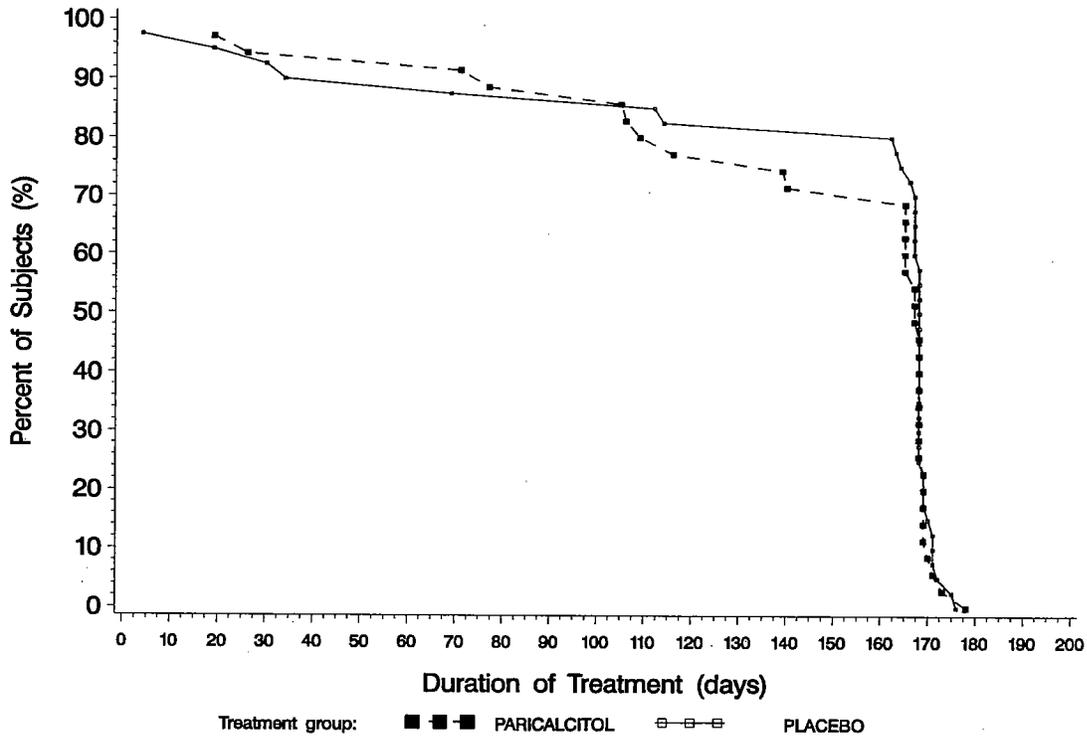
Number of Subjects (Planned and Analyzed):

Planned: 68 subjects (34 per treatment group) Enrolled: 75 subjects (35 Zemplar, 40 Placebo)

Analyzed:	<u>Zemplar</u>	<u>Placebo</u>
Randomized and Treated	35	40
Evaluated for Primary Efficacy (Intent-to-Treat)	33	38
Evaluated for Safety and Secondary Efficacy (All Treated)	35	40

Patient Disposition

Percent of Subjects in Study over Time – Study H01–021



Fifty-nine (59) subjects were randomized in the study by 12 Investigators at 12 sites in the U. S. and 16 subjects were randomized at 2 investigative sites in Poland. All 75 subjects received at least 1 dose of study drug; 35 received Zemplar and 40 received placebo. Subject disposition is presented below.

Of the 35 subjects randomized into the study and treated with Zemplar, 25 (71%) completed treatment and 10 (29%) were terminated prematurely from the study. Five (5) of the subjects terminated prematurely due to “other” reasons (i.e., required dose reduction to 0 mcg [2 subjects], history of kidney stones and had a Pre-Treatment calcium value > 10.0 mg/dL which violated inclusion/exclusion criteria [1 subject], concurrently used an exclusionary drug (Advair) during the study [1 subject], and received prednisone during the study and had increased calcium values [1 subject]), 4 terminated prematurely due to adverse events, and 1 withdrew consent.

Of the 40 subjects randomized into the study and treated with placebo, 33 (82%) completed treatment and 7 (18%) were terminated prematurely from the study. Three (3) of the subjects withdrew consent, 2 terminated prematurely due to adverse events, and 2 subjects terminated prematurely due to “other” reasons (i.e., required dose reduction to 0 mcg [1 subject], and terminated early due to not meeting inclusion/ exclusion criteria [1 subject]).

A summary of the reasons subjects terminated prematurely from the study is presented in Table below.

Reasons for Premature Termination from the Study (All Treated Subjects)

	Zemplar (n = 35)	Placebo (n = 40)
Reason for Premature Termination^a		
Adverse event ^b	4 (11%)	2 (5%)
Withdrew consent	1 (3%)	3 (8%)
Other ^c	5 (14%)	2 (5%)
Total Terminated Prematurely	10	7
Total Completed 24 Weeks of Treatment	25 (71%)	33 (82%)

a. Only 1 reason for termination is provided per subject in Table 7. One subject terminated prematurely for 2 reasons: Placebo (1403) for adverse event (counted in table) and withdrew consent.

b. Zemplar: 1 subject (102) with uremia, 1 subject (202) with back pain, hematuria, and contusion to renal cyst, 1 subject (401) with hepatic encephalopathy, and 1 subject (604) with allergic reaction. Placebo: 1 subject (1003) with chest pain and hypervolemia, and 1 subject (1403) with anorexia and asthenia. (Complete adverse event descriptions are presented in Table 26 for subjects who terminated prematurely.)

c. Zemplar: 2 subjects (503 and 1404) required dose reduction to 0 mcg, 1 subject (504) had a history of kidney stones and a Pre-Treatment calcium value of > 10.0 mg/dL, 1 subject (801) received prednisone and had increased calcium values, and 1 subject (1402) used an exclusionary drug (Advair) during the study. Placebo: 1 subject (904) required dose reduction to 0 mcg, and 1 subject (803) did not meet inclusion/exclusion criteria.

Cross Reference: Table 14.1__1.2 and Table 14.1__1.3 and Appendix 16.2__1.1 and Appendix 16.2__7.1.1

Numbers of Subjects Included in the Safety and Efficacy Evaluations

Analysis	Zemplar	Placebo
Primary Analysis of Efficacy (Intent-to-Treat Population)	33 (94%)	38 (95%)
Safety and Secondary Efficacy (All Treated Subject Population)	35 (100%)	40 (100%)
Cross Reference:	Table 14.1__1.1	

The primary efficacy analysis was performed using the Intent-to-Treat set of subjects defined as all randomized subjects with a baseline iPTH measurement and at least 2 on-treatment iPTH measurements. All other analyses were performed using the all treated set of subjects defined as all randomized subjects who received at least 1 dose of study drug. A summary of the numbers

of subjects included in the safety and efficacy evaluations are presented by treatment group in Table above.

Two (2) Zemplar subjects (504 and 604) and 2 placebo subjects (803 and 1403) were randomized and were treated, but were not included in the Intent-to-Treat population because they did not have at least 2 on-treatment values of iPTH. The iPTH data for these subjects are presented in Appendix 16.2__ 3 of the NDA Study Report.

Demographic and Baseline Characteristics

No statistically significant differences were observed between the treatment groups in baseline demographic characteristics for all treated subjects. The majority of the subjects in both treatment groups were male (71% in the Zemplar group and 68% in the placebo group) and most were white (80% in both the Zemplar and placebo groups). Age ranged from 32 to 93 years, with a mean age of 64.6 years in the Zemplar group and 62.9 years in the placebo group. Both treatment groups had more smokers than nonsmokers and more drinkers than nondrinkers. The time since CKD diagnosis ranged from 0.3 to 51.4 years, with a mean time of 7.05 years in the Zemplar group and 5.39 years in the placebo group. Subject demographic data are summarized for all treated subjects by treatment group in Table below.

Demographics (All Treated Subjects)			
	Zemplar	Placebo	
Gender			0.804
Female	10 (29%)	13 (32%)	
Male	25 (71%)	27 (68%)	
Race			0.468
Asian	0 (0%)	1 (2%)	
Black	5 (14%)	7 (18%)	
American Indian-Alaska Native	2 (6%)	0 (0%)	
White	28 (80%)	32 (80%)	
Tobacco Use			1.000
Nonsmoker	16 (46%)	18 (45%)	
Smoker (includes ex-smokers)	19 (54%)	22 (55%)	
Alcohol Use			0.624
Nondrinker	10 (29%)	14 (35%)	
Drinker (includes ex-drinkers)	25 (71%)	26 (65%)	
Age Group			0.642
< 65 years	14 (40%)	19 (48%)	
≥ 65 years	21 (60%)	21 (52%)	
Age (years)			0.552
Mean (SE)	64.6 (1.79)	62.9 (2.20)	
Median	67.0	66.5	
Range	42-84	32-93	
Time Since CKD Diagnosis (years)			0.388

Mean (SE)	7.05 (1.617)	5.39 (1.088)
Median	3.80	3.30
Range	0.3-51.4	0.4-31.5

CKD = chronic kidney disease

- a. P-values for race, gender, tobacco use, alcohol use, and age group are derived from Fisher's exact test.
P-values for mean age and time since first CKD diagnosis are from F-test testing equality of means between treatment groups.

Cross Reference: Table 14.1__2.1 and Appendix 16.2__4.1 and Appendix 16.2__4.3

Medical History

The proportions of subjects within each medical history category with an abnormal history were generally similar between treatment groups. Conditions associated with the genitourinary (100% in both groups), cardiovascular (100% in both groups), and metabolic (100% Zemplar and 95% placebo) systems were the most commonly reported abnormal histories in both treatment groups. All serum pregnancy tests performed on female subjects prior to treatment were negative.

Physical Examination

The proportions of subjects within each physical examination category with an abnormality were generally similar between the treatment groups.

Pre-Treatment Medications

The most commonly used pre-treatment medications in both groups were high-ceiling diuretics (69% Zemplar and 68% placebo), antithrombotic agents (66% Zemplar and 62% placebo), beta-blocking agents (57% Zemplar and 65% placebo), cholesterol and triglyceride reducers (54% Zemplar and 55% placebo), and ACE inhibitors and/ or angiotensin II receptor blockers (57% Zemplar and 70% placebo).

Treatment Compliance

Two (2) of 35 (6%) Zemplar subjects and 1 of 40 (2%) placebo subjects indicated < 60% compliance with the dosing regimen greater than 10% of the time.

Statistical Methodologies

A complete description of the statistical methods used in this study is given in Appendix 16.1__9 of the NDA Study Report.

The primary, secondary, and longitudinal analyses of efficacy were identical to the previous studies.

Results and Conclusions

Primary Efficacy Analysis (Intent-to-Treat Population)

The primary efficacy endpoint was 2 consecutive $\geq 30\%$ decreases from baseline in iPTH. In the Intent-to-Treat population, mean baseline levels of iPTH were 260.7 pg/mL (range: 145.0 to 856.0 pg/mL) in the Zemplar group and 250.0 pg/mL (range: 149.5 to 594.0 pg/mL) in the placebo group. The difference between the treatment groups in baseline iPTH was not statistically significant (Table 14.2__ 1.1) of the NDA Study Report.

A statistically significantly greater proportion of subjects in the Zemplar group (91%) had 2 consecutive $\geq 30\%$ decreases from baseline in iPTH compared with subjects in the placebo group (11%).

A summary of the primary efficacy analysis results is presented by treatment group in the Table below.

	Zemplar (N = 33)	Placebo (N = 38)	P-value ^a
Subject achieved 2 consecutive $\geq 30\%$ decreases from baseline in iPTH	30 (91%)	4 (11%)	< 0.001

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

Cross Reference: Table 14.2__1.2.1 and Appendix 16.2__6.1.1

§ In the (worst case) analyses presented below, placebo subjects not included in the primary efficacy analysis are considered to have achieved the primary efficacy endpoint and paricalcitol capsule subjects not included in the primary efficacy analysis are considered to have failed to achieve the primary efficacy endpoint. The analyses presented below include results based on all randomized and treated subjects.

Proportion of Subjects Who Achieved 2 Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Treatment Group for H01-021

(All Treated Subjects)

	Paricalcitol Capsule (N = 35)	Placebo (N = 40)	p-value ^a
Subject achieved 2 consecutive $\geq 30\%$ decreases from baseline in iPTH	30 (86%)	6 (15%)	< 0.001

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

Secondary Efficacy Analysis (All Treated Subject Population)

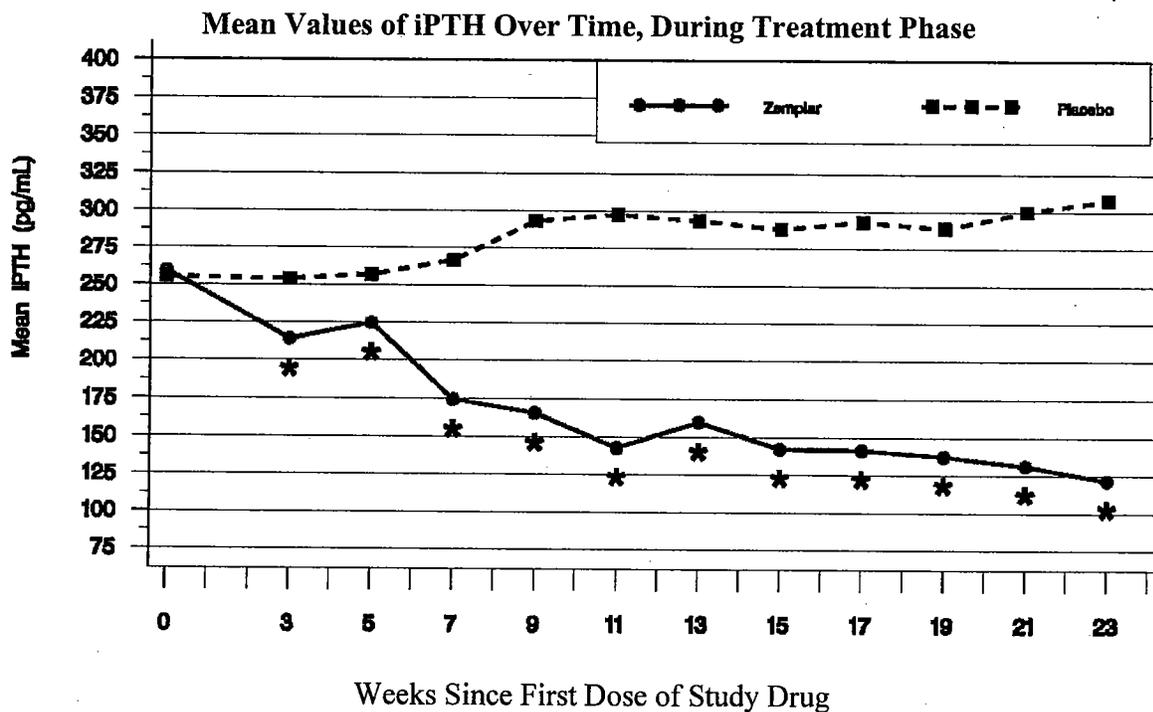
Mean Change and Percent Change from Baseline to Final Visit in iPTH (All Treated Subjects)

iPTH (pg/mL)	Zemplar (N = 35)	Placebo (N = 40)	ANOVA P-value ^a
Mean Baseline Value	259.1	255.1	0.879
(Baseline Range)	(145.0-856.0)	(149.5-594.0)	
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.

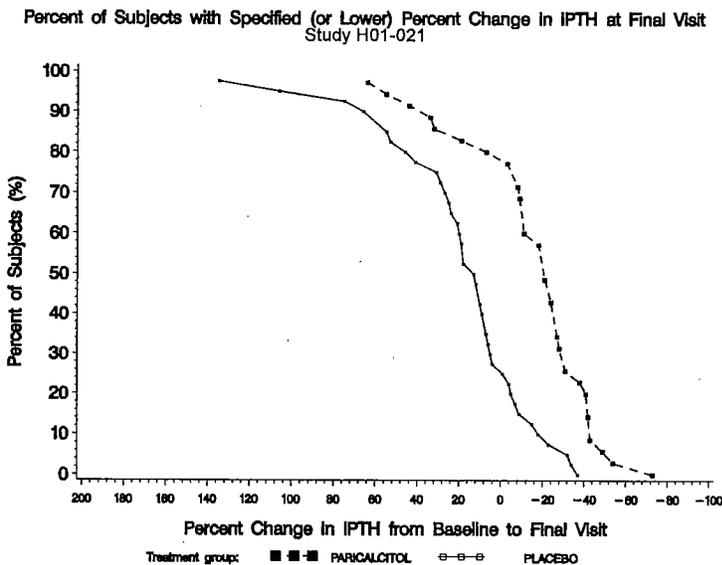
Cross Reference: Table 14.2__1.1, Table 14.2__2.1.1 and Table 14.2__2.4.1 and Appendix 16.2__6.1.1



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 time-point.

Following is the graph for the cumulative distribution function for percent change from baseline in IPTH at final visit. From this, percent of patients (y-axis value) with a value of Percent Change in IPTH at final visit, smaller than or equal to a value on the x-axis can be read.



This reviewer’s statistical tests based on the “Analysis Datasets” supplied to the FDA Electronic Document Room (EDR) by the sponsor provided statistically highly significant evidence in favor of the efficacy of paricalcitol. These are consistent with the sponsor’s many analyses. Even the worst-case analyses presented above provided statistically highly significant evidence in favor of the efficacy of paricalcitol.

3.2 Evaluation of Safety

I have not performed a complete evaluation of safety. I requested the Medical Officer to consult me whenever there are statistical issues.

The treatment group were highly statistically significantly different with respect to percent of patients having visit calcium value >10.5. This percent was 18.7 for the Zemplar group and 0.9 for the placebo group.

For a safety variable, it should not be stated (e.g. in labeling) _____

The confidence intervals for the difference between the treatment groups with respect to percent of patients having visit CAxP product value >55 was (-.015 to .165) for 90% confidence and (-.032 to .182) for 95% confidence. The percent was 24.3 for the Zemplar group and 16.1 for the placebo group.

The confidence intervals for the difference between the treatment groups with respect to percent of patients having visit phosphorus value >5.5 was (-.047 to .149) for 90% confidence and (-.066 to .168) for 95% confidence. The percent was 29.0 for the Zemplar group and 16.9 for the placebo group.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

These studies were not powered for detecting treatment by subgroup interactions. In this section, results are provided for data obtained by combining all three studies. Homogeneity test is performed to check the consistency among different subgroups or treatment by subgroup interaction. However, the power of such tests is, generally, low.

4.1 Gender, Race, and Age

Differences between the treatment groups in the proportion of subjects who achieved 2 consecutive $\geq 30\%$ decreases from baseline in iPTH were statistically significant within the male and female subpopulations. Additionally, a non-significant p-value for the homogeneity test demonstrated the homogeneity of the treatment group differences in iPTH when analyzed by gender. A summary of the primary efficacy analysis results by gender is presented in Table below.

	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 $\geq 30\%$ 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.

Cross Reference: Table 10.2__1.

Results for the other subgroups are provided below similarly.

Proportion of Subjects Who Achieved 2 Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Age Group (< 65 years and ≥ 65 years) in the 3 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.
 Cross Reference: Table 10.2__2.

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Proportion of Subjects Who Achieved 2 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		p-value ^a	Paricalcitol		p-value ^a	
	Capsule (N = 79)	Placebo (N = 94)		Capsule (N = 22)	Placebo (N = 14)		
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.
Cross Reference: Table 10.2_10.

Proportion of Subjects Who Achieved 2 Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Race in the 3 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 ^b	
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.
Cross Reference: Table 10.2_3.

4.2 Other Special/Subgroup Populations

Differences between the treatment groups in the proportion of subjects who achieved 2 consecutive $\geq 30\%$ decreases from baseline in iPTH were statistically significant within the various baseline weight (< 50 kg, ≥ 50 kg to < 100 kg and ≥ 100 kg) subpopulations. Additionally, homogeneity of the treatment group differences was demonstrated in iPTH when analyzed by baseline body weight (< 50 kg, ≥ 50 to < 100 kg, and ≥ 100 kg).

Within the < 50 kg subpopulation, the difference between the treatment groups was not statistically significant likely due to the small sample size (n = 6); however, each of the subjects

who weighed < 50 kg and who received paricalcitol capsule, achieved 2 consecutive $\geq 30\%$ decreases from baseline in iPTH compared to the 3 subjects who received placebo and did not achieve the primary efficacy endpoint. A summary of the primary efficacy analysis results by baseline body weight is presented in Table below.

Proportion of Subjects Who Achieved 2 Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Baseline Body Weight in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)

	< 50 kg (N = 6)			≥ 50 to < 100 kg (N = 135)			≥ 100 kg (N = 67)			Homogeneity p-value ^b
	Paricalcitol Capsule (N = 3)	Placebo (N = 3)	p-value ^a	Paricalcitol Capsule (N = 64)	Placebo (N = 71)	p-value ^a	Paricalcitol Capsule (N = 34)	Placebo (N = 33)	p-value ^a	
2 consecutive $\geq 30\%$ decreases from Baseline in iPTH	3 (100%)	0 (0%)	0.100	56 (88%)	11 (16%)	< 0.001	33 (97%)	3 (9%)	< 0.001	0.143

- a. p-value derived from Fisher's exact test.
 - b. p-value for the Breslow-Day test of odds ratio homogeneity.
- Cross Reference: Table 10.2__4.

Results for the other subgroups are provided below similarly.

Proportion of Subjects Who Achieved 2 Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Geographic Region in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)

	US (N = 189)			Non-US (Poland) (N = 20)			Homogeneity p-value ^b
	Paricalcitol Capsule (N = 91)	Placebo (N = 98)	p-value ^a	Paricalcitol Capsule (N = 10)	Placebo (N = 10)	p-value ^a	
2 consecutive $\geq 30\%$ decreases from Baseline in iPTH	83 (91%)	13 (13%)	< 0.001	9 (90%)	1 (10%)	0.001	0.910

- a. p-value derived from Fisher's exact test.
 - b. p-value for the Breslow-Day test of odds ratio homogeneity.
- Cross Reference: Table 10.2__5.

Proportion of Subjects Who Achieved 2 Consecutive \geq 30% Decreases from Baseline in iPTH by Alcohol Use in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)

	Alcohol User (N = 132)		p-value ^a	Alcohol Non-User (N = 77)		p-value ^a	Homogeneity p-value ^b
	Paricalcitol Capsule (N = 65)	Placebo (N = 67)		Paricalcitol Capsule (N = 36)	Placebo (N = 41)		
2 consecutive \geq 30% decreases from Baseline in iPTH	58 (89%)	9 (13%)	< 0.001	34 (94%)	5 (12%)	< 0.001	0.415

- a. p-value derived from Fisher's exact test.
b. p-value for the Breslow-Day test of odds ratio homogeneity.
Cross Reference: Table 10.2__6.

Proportion of Subjects Who Achieved 2 Consecutive \geq 30% Decreases from Baseline in iPTH by Tobacco Use in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)

	Tobacco User (N = 122)		p-value ^a	Tobacco Non-User (N = 87)		p-value ^a	Homogeneity p-value ^b
	Paricalcitol Capsule (N = 61)	Placebo (N = 61)		Paricalcitol Capsule (N = 40)	Placebo (N = 47)		
2 consecutive \geq 30% decreases from Baseline in iPTH	56 (92%)	8 (13%)	< 0.001	36 (90%)	6 (13%)	< 0.001	0.837

- a. p-value derived from Fisher's exact test.
b. p-value for the Breslow-Day test of odds ratio homogeneity.
Cross Reference: Table 10.2__7.

Proportion of Subjects Who Achieved 2 Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Years Since CKD Diagnosis at Baseline in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)

	≤ 5 Years (N = 134)			> 5 to ≤ 10 Years (N = 43)			> 10 Years (N = 30)			Homogeneity p-value ^b
	Paricalcitol Capsule (N = 64)	Placebo (N = 70)	p-value ^a	Paricalcitol Capsule (N = 24)	Placebo (N = 19)	p-value ^a	Paricalcitol Capsule (N = 12)	Placebo (N = 18)	p-value ^a	
2 consecutive $\geq 30\%$ decreases from Baseline in iPTH	58 (91%)	10 (14%)	< 0.001	24 (100%)	2 (11%)	< 0.001	9 (75%)	2 (11%)	0.001	0.178

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

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

Cross Reference: Table 10.2__9.

In Study ...20, a statistically significant difference ($p = 0.031$) was observed between treatment groups for time since CKD diagnosis, with placebo subjects (mean = 7.76 years) having CKD longer than Zemplar subjects (mean = 4.17 years). This difference between the treatment groups in time since CKD diagnosis (in Study ...20 only) is related to 3 placebo subjects (705, 706, and 1302) who had been diagnosed with CKD more than 20 years (26, 33, and 39 years, respectively). The distribution in years since CKD diagnosis was compared using a Wilcoxon rank-sum test (Appendix 16.1__9 of the NDA Study Report) and was not statistically significant ($p = 0.223$). The median time since CKD diagnosis was 3.50 years in the Zemplar group and 4.60 years in the placebo group.

When the years since CKD diagnosis is >10 years, 3 out of 12 patients did not achieve 2 consecutive $\geq 30\%$ decreases from baseline in iPTH. This failure rate is more than those in other subgroups of "years since CKD diagnosis." However, without further evidence, this should not be taken as a fact.

Proportion of Subjects Who Achieved 2 Consecutive $\geq 30\%$ Decreases from Baseline in iPTH by Disease Severity at Baseline in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)

	iPTH $\geq 150 - \leq 300$ pg/mL (N = 153)			iPTH $> 300 - \leq 500$ pg/mL (N = 43)			iPTH > 500 pg/mL (N = 13)			Homogeneity p-value ^b
	Paricalcitol Capsule (N=77)	Placebo (N=76)	p-value ^a	Paricalcitol Capsule (N=21)	Placebo (N=22)	p-value ^a	Paricalcitol Capsule (N=3)	Placebo (N=10)	p-value ^a	
2 consecutive $\geq 30\%$ decreases from Baseline in iPTH	71 (92%)	8 (11%)	< 0.001	18 (86%)	4 (18%)	< 0.001	3 (100%)	2 (20%)	0.035	0.385

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

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

Cross Reference: Table 10.2__11.

Mean Change and Percent Change from Baseline to the Final Visit in iPTH in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies by Baseline Disease Severity (All Treated Subjects)

	≥ 150 – ≤ 300 pg/ml.			> 300 – ≤ 500 pg/ml.			> 500 pg/ml.		
	Paricalcitol Capsule (N = 80)	Placebo (N = 77)	ANOVA p-value ^a	Paricalcitol Capsule (N = 22)	Placebo (N = 24)	ANOVA p-value ^a	Paricalcitol Capsule (N = 3)	Placebo (N = 10)	ANOVA p-value ^a
Mean Baseline Value	222.2	211.5	-	357.1	377.5	-	742.0	570.2	-
Mean Final Visit Value	179.2	247.4	-	251.6	430.4	-	511.7	597.9	-
Mean Change from Baseline (SE)	-43.0 (9.16)	35.9 (9.33)	< 0.001	-105.5 (29.67)	52.8 (28.40)	< 0.001	-230.3 (53.92)	27.8 (29.54)	0.001
Mean Percent Change from Baseline (SE)	-18.6% (3.93)	16.7% (4.00)	< 0.001	-30.0% (8.21)	13.1% (7.86)	< 0.001	-31.4% (9.29)	4.6% (5.09)	0.006

a. One-way ANOVA with treatment as a factor.
 Cross Reference: Table 10.1__3.1.1.1.8 and Table 10.1__3.4.1.1.8.

Proportion of Subjects Who Achieved 2 Consecutive ≥ 30% Decreases from Baseline in iPTH by Diabetic Status at Baseline in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)

	Diabetic (N = 122)			Non-Diabetic (N = 87)			Homogeneity p-value ^b
	Paricalcitol Capsule (N = 61)	Placebo (N = 61)	p-value ^a	Paricalcitol Capsule (N = 40)	Placebo (N = 47)	p-value ^a	
2 consecutive ≥ 30% decreases from Baseline in iPTH	55 (90%)	10 (16%)	< 0.001	37 (93%)	4 (9%)	< 0.001	0.280

a. p-value derived from Fisher's exact test.
 b. p-value for the Breslow-Day test of odds ratio homogeneity.
 Cross Reference: Table 10.2__8.

**APPEARS THIS WAY
ON ORIGINAL**

Proportion of Subjects Who Achieved 2 Consecutive \geq 30% Decreases from Baseline in iPTH by Concomitant Calcium-Based Phosphate Binder Usage in the 3 Double-Blind, Placebo-Controlled, Pivotal Phase 3 Studies Combined (Intent-to-Treat Population)

	Concomitant Calcium-Based Binder Use (N = 52)		p-value ^a	Non-Calcium-Based Binder Use or Non-User (N = 157)		p-value ^a	Homogeneity p-value ^b
	Paricalcitol Capsule (N = 30)	Placebo (N = 22)		Paricalcitol Capsule (N = 71)	Placebo (N = 86)		
2 consecutive \geq 30% decreases from Baseline in iPTH	25 (83%)	3 (14%)	< 0.001	67 (94%)	11 (13%)	< 0.001	0.195

- a. p-value derived from Fisher's exact test.
b. p-value for the Breslow-Day test of odds ratio homogeneity.
Cross Reference: Table 10.2__12.

Paricalcitol treatment effects difference between these two subgroups are not statistically significant (2-sided p-value = .1208).

5. SUMMARY AND CONCLUSIONS

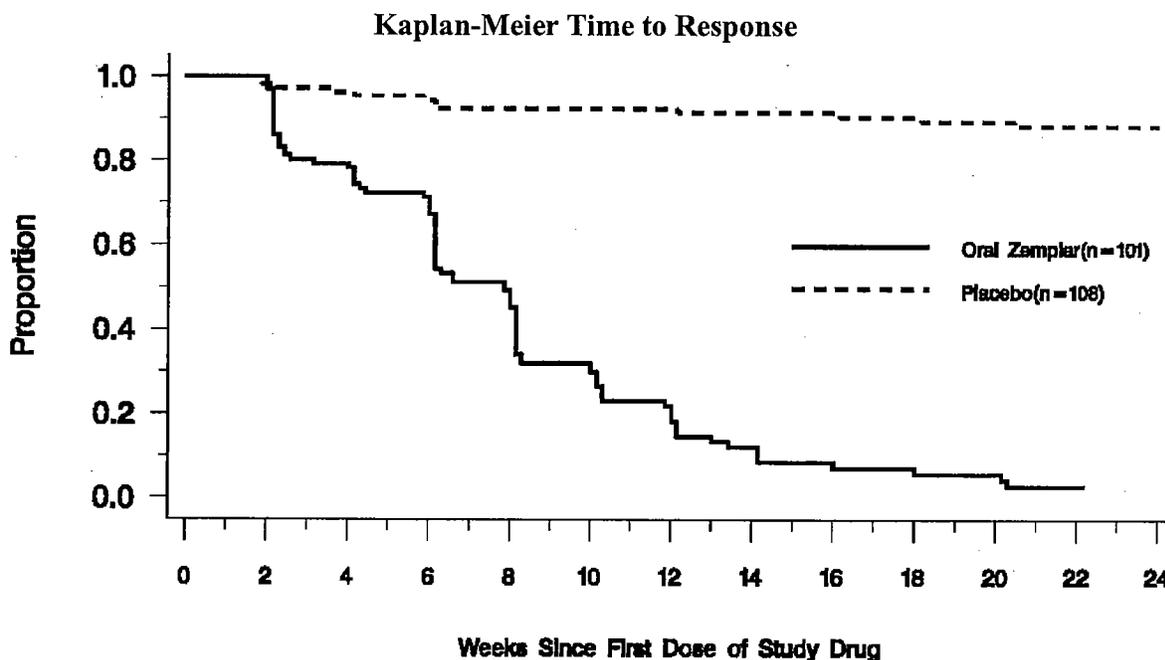
5.1 Statistical Issues and Collective Evidence

	Zemplar	Placebo	P-value ^a
	Study 2001019		
Subject achieved 2 consecutive \geq 30% decreases from baseline in iPTH	(N = 36) 33 (92%)	(N = 34) 4 (12%)	< 0.001
	Study 2001020		
Subject achieved 2 consecutive \geq 30% decreases from baseline in iPTH	(N = 32) 29 (91%)	(N = 36) 6 (17%)	< 0.001
	Study 2001021		
Subject achieved 2 consecutive \geq 30% decreases from baseline in iPTH	(N = 33) 30 (91%)	(N = 38) 4 (11%)	< 0.001

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

Apparently, the Zemplar response rates were almost the same in all three studies. However, in the alternate day dose studies ...19 and ...20, the mean IPTH (pg/ml) slightly increased starting from Week 19 and Week 17 in the Zemplar group. However, in the daily dose Study ...21, the mean IPTH (pg/ml) in the Zemplar group maintained a downward trend up to the end of the study.

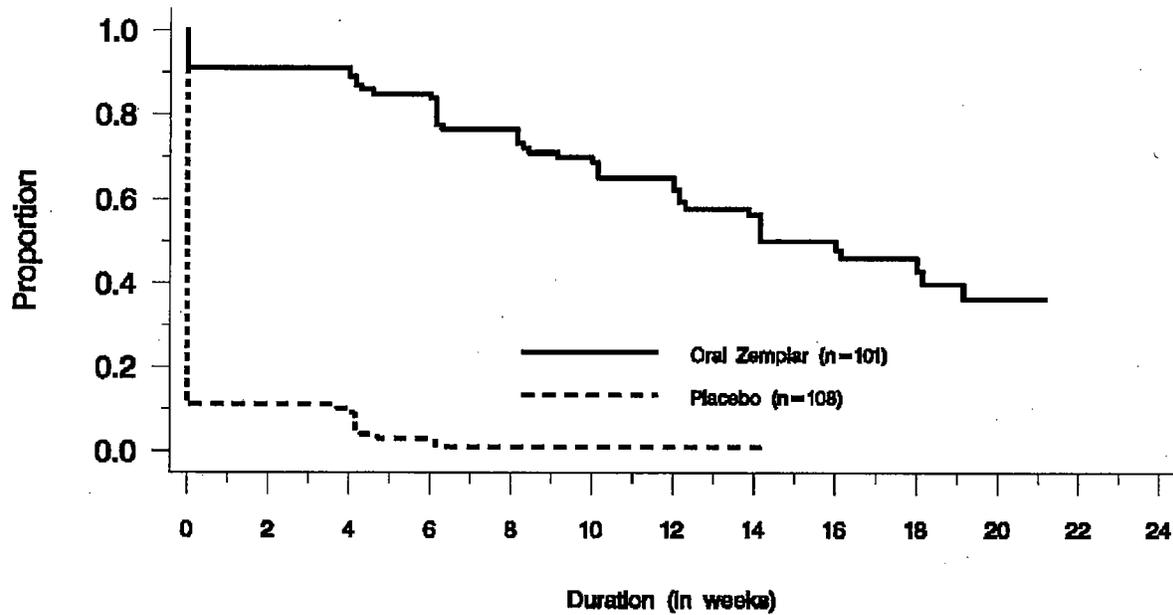
The sponsor provided analyses of the primary efficacy variable for the three studies separately, performed using “worst case” scenarios (e.g., scenarios such that placebo subjects, who dropped out, are considered to have met the endpoint and the active subjects, who dropped out, are considered to have failed to meet the endpoint). All the results were highly significant. Some of the analyses combining data from all three studies, are provided below.



Analyses were performed to assess time to and duration of response. 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. These results are presented graphically in the Figure above.

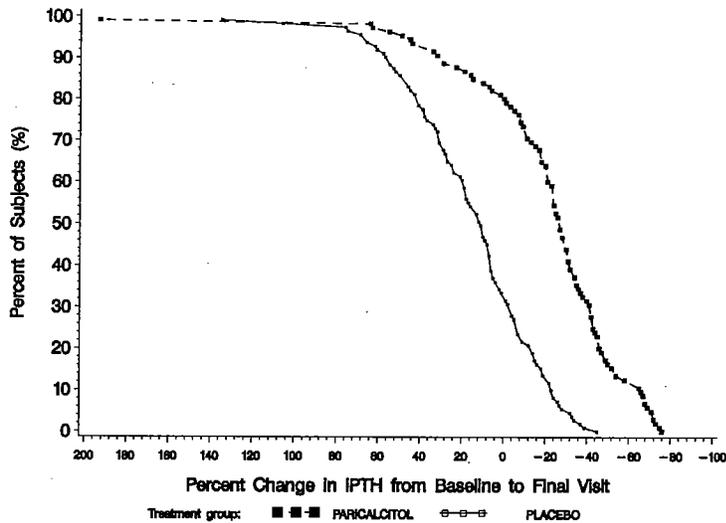
Kaplan-Meier estimates demonstrated that 69% of paricalcitol capsule-treated subjects maintained $\geq 30\%$ decreases in iPTH for at least 10 weeks (70 days). These results are presented graphically in the Figure below.

Kaplan-Meier Duration to Response



Following is the graph for the cumulative distribution function for change from baseline in IPTH at final visit. From this, percent of patients (y-axis value) with a value of Absolute Change in IPTH at final visit, smaller than or equal to a value on the x-axis can be read.

Percent of Subjects with Specified (or Lower) Percent Change in IPTH at Final Visit



This reviewer does not see any statistical concerns that may affect the conclusion about the efficacy of the drug.

For a safety variable, it should not be stated (e.g. in labeling) _____

When the years since CKD diagnosis is >10 years, 3 out of 12 patients did not achieve 2 consecutive $\geq 30\%$ decreases from baseline in iPTH. This failure rate is more than those in other subgroups of "years since CKD diagnosis." However, without further evidence, this should not be taken as a fact.

5.2 Conclusions and Recommendations

This reviewer's statistical tests based on the "Analysis Datasets" supplied to the FDA Electronic Document Room (EDR) by the sponsor provided statistically highly significant evidence in favor of the efficacy of Zemplar. These are consistent with the sponsor's many analyses. Even the worst-case analysis provided statistically highly significant evidence in favor of the efficacy of Zemplar. This reviewer does not see any statistical concerns that may affect the conclusion about the efficacy of the drug.

Apparently, the Zemplar response rates were almost the same in all three studies. However, in the alternate day dose studies ...19 and ...20, the mean IPTH (pg/ml) slightly increased starting from Week 19 and Week 17 in the Zemplar group. Whereas, in the daily dose Study ...21, the mean IPTH (pg/ml) in the Zemplar group maintained a downward trend up to the end of the study.

The labeling states, _____

However, the treatment groups were highly statistically significantly different with respect to percent of patients having visit calcium value >10.5. This percent was 18.7 for the Zemplar group and 0.9 for the placebo group.

For a safety variable, it should not be stated (as has been done in the labeling) that _____

Section 3.2. Evaluation of safety.

... the confidence intervals are given in

APPENDICES

Appendix I

List of Abbreviations and Definitions of Terms:

Abbreviations

2° HPT	secondary hyperparathyroidism
ALT (SGPT)	serum alanine aminotransaminase (serum glutamic pyruvic transaminase)
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST (SGOT)	serum aspartate aminotransaminase (serum glutamic oxaloacetic transaminase)
BID	twice daily
BLE	bilateral lower extremity
pro-BNP	pro-B-type natriuretic peptide
BUN	blood urea nitrogen
CAD	coronary artery disease
Ccr	creatinine clearance
CAPD	continuous ambulatory peritoneal dialysis
CKD	chronic kidney disease
CHF	congestive heart failure
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CT	computerized tomography
EKG	electrocardiogram
ER	emergency room
ESRD	end-stage renal disease
DE	Death
FDA	Food and Drug Administration
GCP	Good Clinical Practice
eGFR	estimated glomerular filtration rate
HD	hemodialysis
HIV	Human immunodeficiency virus
HPT	hyperparathyroidism
HS	hospitalization
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
iPTH	intact parathyroid hormone (used interchangeably with "PTH")
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
K/DOQI	Kidney Disease Outcome Quality Initiative

LDH	lactate dehydrogenase
LOCF	last observation carried forward
MDRD	Modification of Diet in Renal Disease
MPO	myeloperoxidase
PD	peritoneal dialysis
PH	prolonged hospitalization
PTH	parathyroid hormone
QD	once daily
RBC	red blood cells
SD	Standard deviation
SE	Standard error
SEC	soft elastic capsule
SOB	shortness of breath
SOP	Standard operating procedure
TIW	three times a week
WBC	white blood cells

Definition of Terms

Baseline iPTH	The average of the last 2 consecutive iPTH values obtained during the Pre-Treatment Phase. This value was compared to iPTH levels measured during the Treatment Phase.
Calcium	All serum calcium results were reported as corrected total serum calcium results using the following formula (for albumin levels < 4.0 g/dL): $\text{calcium (corrected)} = [(4.0 - \text{albumin}) \times 0.8 \text{ mg/dL}] + \text{calcium (measured)}$
Causally related adverse events	Adverse events considered by the Investigator to be possibly or probably related to study drug.
Chronic kidney disease (CKD) stages	Stage 1: Kidney damage with normal or increased GFR ($\geq 90 \text{ mL/min/1.73 m}^2$) Stage 2: Kidney damage with mild decreased GFR (60 to $89 \text{ mL/min/1.73 m}^2$) Stage 3: Moderate decrease GFR (30 to $59 \text{ mL/min/1.73 m}^2$) Stage 4: Severe decrease GFR (15 to $29 \text{ mL/min/1.73 m}^2$) Stage 5: Kidney failure GFR < $15 \text{ mL/min/1.73 m}^2$ (or dialysis)
Clinically meaningful hypercalcemia	Two consecutive serum calcium results > 10.5 mg/dL.

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