U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 21606/S-016
Supplement #:	
Drug Name:	Zemplar (paricalcitol) capsules
Indication(s):	Zemplar is a vitamin D analog indicated for the prevention and treatment of secondary hyperparathyroidism associated with • Chronic kidney disease (CKD) Stages 3 and 4 • CKD Stage 5 in patients on hemodialysis (HD) or peritoneal dialysis (PD)
Applicant:	Abbvie
Date(s):	Submitted: 12/18/15 Review due: 9/12/16
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Roberto C. Crackel, PhD
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Keywords: Missing data, multiple imputation, Bayesian analysis

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Brief introduction

Zemplar capsules were originally FDA approved on May 26th 2005 for patients with secondary hyperparathyroidism. Abbvie submitted an efficacy supplement on December 18th 2015 as part of post marketing requirements and labeling updates. Included in this submission are results from the pediatric study M10-149 and study M11-612 that were established under the Pediatric Research Equity Act (PREA). The focus of this review will be on study M10-149. Study M10-149 is the first study to examine Zemplar capsules in pediatric CKD stage 3 and stage 4 patients. The study consisted of two parts; part 1 was an open-label pharmacokinetic study, while part 2 was a 12-week randomized, double-blind, placebo-controlled, multi-center study to evaluate the safety and efficacy of Zemplar capsules on serum intact parathyroid hormone (iPTH) reduction. Patients who completed the 12-week double-blind period of part 2 were eligible to participate in an open-label period wherein all patients received paricalcitol capsules.

1.2 Conclusions and recommendation

The results of the protocol specified analysis demonstrated a difference in proportions of responders between Zemplar and placebo, however, patients who were unconfirmed responders or had an unknown status were imputed as non-responders. I performed two analyses to address these missing data (i.e., not assuming missing data as non-responders). When addressing missing data we chose methods that were easy in its implementation. These methods, however, produced smaller p-values than Fisher's exact test. For a given method, the p-value increased when addressing missing data. While the missing data are cause for concern, however, since the results from both our analyses and the sponsors analysis were statistically significant (albeit borderline), and in addition to the results of the PK/PD analysis, there remains evidence that Zemplar lowers iPTH in a pediatric setting.

The results of this study (M10-149) will be used for pediatric dosing information in the Dosage and Administration section of the product label. The results apply to the indication of pre-dialysis patients (Stage 3 and 4 CKD) to support efficacy and safety in pre-dialysis patients.

1.3 Primary endpoint results

Based on the protocol specified analysis, the primary results are summarized as follows:

- Five known responders on Zemplar capsules and zero known responders on placebo

- There were three unknown responders (two of which are unconfirmed) on Zemplar and one unconfirmed responder for placebo

- The sponsor imputed each unknown responder as a non-responder

- Under the sponsor's imputation, there was a significantly greater proportion of patients on Zemplar capsules who achieved two consecutive ≥ 30% reductions from baseline in iPTH levels than patients on placebo. Fisher's exact test was used and the p-value was calculated to be 0.045

We performed two analyses to address missing data. We chose methods that were easy in its implementation. The first analysis used Bayesian methods while the second analysis was a multiple imputation that used the Agresti-Caffo method. See table below:

	P-value (All failures)	P-value (Addressing missing data)
Bayesian (Jeffrey's prior)	0.009	0.017
Agresti-Caffo (Unrestricted variance)	0.028	0.0335
Agresti-Caffo (Restricted variance)	0.037	0.0441
Fisher's exact	0.045	N/A

We see that the p-values increased for each method when missing data was addressed.

1.4 Statistical issues and findings

- Missing Data: The number of known responders on Zemplar was five compared to zero on placebo, resulting in a p-value of 0.045 (assuming each unknown responder is a non-responder). However, there were two unconfirmed responders and an additional patient with an unknown response status on Zemplar (who dropped out from the study) and one unconfirmed responder on placebo. A summary of these patients are as follows:

Zemplar:

Subject ID	Status	Baseline	Week 2	Week 4	Week 8	Week 12
3360602	Unconfirmed responder	268	280	147	--	--
3883201	Unknown responder	88	124	--	--	--
4031405	Unconfirmed responder	155	99	--	--	--

Placebo:

Subject ID	Status	Baseline	Week 2	Week 4	Week 8	Week 12
4054701	Unconfirmed responder	175	--	118	198	269

The highlighted numbers indicate a measurement that was a > 30% reduction from baseline. For the two unconfirmed responders on Zemplar, the following measurement is missing while for the unconfirmed responder on placebo, the prior measurement is missing.

The sponsor considered each of these patients as non-responders; however, this may not be appropriate. To evaluate the impact of missing data, if the placebo patient is a responder, it will take at least 2 of the 3 unknown responders on Zemplar to maintain a significant result (if the Fisher's exact test is used).

- Subgroup analysis: No subgroup analysis was performed on age, sex, and race. Demographic and baseline characteristics, however, were summarized. Analysis describing the treatment effect for age was not necessary since this was a pediatric study. An analysis describing the treatment effect for sex and race was not performed and no justification was given. An analysis by stratum (CKD Stage 3 / Stage 4) was performed and did not yield a statistically significant result.

- A small sample 95% confidence interval for the difference in proportions was calculated by the sponsor to be (0.075, 0.528). The method used was based on the standardized statistic and inverting a 2-sided test (see Agresti A, Min Y. (2001). On small-sample confidence intervals for parameters in discrete distributions. Biometrics 57: 963-971 or StatXact 10 documentation: p.517-527).

- An exact confidence interval for the proportion of responders on Zemplar is: (0.097 , 0.535). Thus, we can see that the assumed response rate for Zemplar in the sample size calculation was overestimated (assuming the three unknown responders are non-responders) .

- There was one patient who was randomized to Zemplar who withdrew prior to receiving study drug or trial activities because of travel and would be unable to attend planned visits. Therefore, another patient was enrolled and assigned to Zemplar to maintain equal sample sizes in the treatment arms. However, the new patient used the same patient ID as the patient who withdrew.

2 INTRODUCTION

2.1 Overview

On December 18th 2015, Abbvie submitted an efficacy supplement for Zemplar capsules (NDA 21606) as part of post marketing requirements and labeling updates for the pediatric study M10-149 and study M11-612 that were established under the Pediatric Research Equity Act (PREA). The focus of this review will be on study M10-149. Study M10-149 consisted of two parts. Part 1 was an open-label pharmacokinetic study, while part 2 was a 12-week randomized, double-blind, placebo-controlled, multi-center study to evaluate the safety and efficacy of Zemplar capsules on serum intact parathyroid hormone (iPTH) reduction. This report will summarize the statistical review of the sponsor's methods for the primary endpoint as well as the results of the FDA's analysis in addressing missing data.

2.1.1 Class and Indication

Zemplar capsules may be administered once daily in adults with CKD stages 3, 4, or 5 and is available in daily doses of 1 mcg or 2 mcg or three times a week in doses of 2 mcg or 4 mcg (depending on baseline iPTH levels). Currently, the indication does not distinguish between adults and children. No change to the indication is proposed.

2.1.2 Specific Study Reviewed

One randomized clinical trial was reviewed. Study M10-149 consisted of two parts. Part 1 was an open-label pharmacokinetic study, while part 2 was a 12-week randomized, double-blind, placebo-controlled, multi-center study to evaluate the safety and efficacy of Zemplar capsules on iPTH reduction.

At screening, patients were to be between the ages of 10 and 16 (inclusive), have CKD stage 3 or 4 as determined be eGFR (15 to 59 mL/min/1.73 m^2). For patients who were currently on VDRA and had CKD stage 3, an iPTH measurement ≥ 60 pg/mL was required and ≥ 90 pg/mL for stage 4 patients. For VDRA naïve patients and had CKD stage 3, an iPTH measurement ≥ 75 pg/mL was required and ≥ 110 pg/mL for stage 4 patients.

2.2 Data Sources

The data and final study report were submitted electronically as an eCTD submission. The submission can be accessed at the following link:

\\CDSESUB1\evsprod\NDA021606\021606.enx

The following documents were used to support this review.

Document
Clinical study report
Statistical analysis plan

All results presented in this review were derived from the submitted datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There were no issues concerning the submission of data sets and files.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study design: Part 2 of study M10-14 was a 12-week randomized, double-blind, placebo-controlled, multi-center study to evaluate the safety and efficacy of Zemplar capsules on iPTH reduction. A total of 36 patients were randomized in a 1:1 fashion to either Zemplar or placebo. Landmark visits with respect to iPTH measurements and which were included in the primary efficacy analysis were baseline, weeks 2, 4, 8, and 12.

Sample size: It was assumed that 66% of patients on Zemplar would achieve two consecutive ≥ 30% decreases from baseline and 17% of patients on placebo. Under these assumptions, a sample size of 18 subjects per arm is needed to provide 82% power to detect a significant difference.

Primary efficacy endpoint: Two consecutive ≥ 30% decreases in iPTH levels from baseline

Secondary efficacy endpoints: Selected secondary endpoints include:

- Comparison between the treatment groups in the proportion of patients who achieved a final iPTH level within KDOQI target range by CKD stage

- Comparisons between treatment groups in the mean change from baseline in iPTH to each post baseline visit (weeks 2, 4, 8, and 12)

3.2.2 Statistical Methodologies

Protocol specified primary efficacy analysis: Fisher's exact test was used to test if there is a difference of proportion of patients who achieved two consecutive ≥ 30% reductions from baseline in iPTH levels between patients who received Zemplar and patients who received placebo.

Protocol specified primary analysis population: All randomized patients who took at least one dose of study drug.

Estimands: The intention-to-treat (ITT) estimand was used in the primary analysis, i.e., all randomized patients who took at least one dose of study drug and all observed measurements were used in the analysis.

FDA sensitivity analysis of the primary efficacy endpoint:

To address the impact of missing measurements for the three patients on Zemplar and the one patient on placebo, we performed two separate analyses. The first analysis is a Bayesian analysis that considers Jeffrey's prior while the second analysis is a multiple imputation analysis that uses the Agresti-Caffo procedure and Rubin's rule to combine the results. Both these procedures tend to be less conservative than Fisher's exact test and will result in smaller p-values. To set the stage for both analyses, we perform a multiple imputation on the missing measurements (continuous) for each of the 4 patients to obtain estimates for the proportion of additional responders on each arm as follows:

Step 1:

To address the missing measurements for the two unconfirmed responders and unknown responder on the experimental arm, we assume a "wash out" of any Zemplar effect. We used the completers from the placebo arm to build a series of regression models to impute missing measurements. For the imputation (see section 1.4), in regards to patient #3360602, there is only need to impute a measurement at week 8. For patient #3883201 and patient #4031405, we will impute a measurement at week 4 and conditioned on this value, impute a measurement at week 8, and conditioned on this value, impute a measurement at week 12.

For the placebo patient we used data from the placebo completers from all landmark visits to impute the week 2 measurement. We imputed 100,000 data sets and obtained estimates for 0 and 1 additional responders on placebo. Likewise, we obtained estimates for 0, 1, 2, and 3 additional responders on Zemplar.

Bayesian analysis:

Using the results from step 1, we used Jeffrey's prior to estimate the probability that the proportion of responders on Zemplar is greater than the proportion of responders on placebo and to obtain a 95% credible interval for the difference in these proportions. See appendix for details of the procedure.

Agresti-Caffo method: The Agresti-Caffo method adds one known responder and one known non-responder to both the placebo and Zemplar groups and then uses the normalized test statistic. For small sample sizes, the Agresti-Caffo method generally does better on probability coverage for confidence intervals and maintaining the desired type I error rate than Wald's procedure. Further, we used the results from step 1 to perform a multiple imputation by

simulating the proportion of total responders for placebo and Zemplar. We generated 100,000 data sets to obtain a multiple imputation point estimate and standard error.
Protocol specified control of type-I error: No correction for multiplicity was made for testing of secondary endpoints. Secondary endpoints only provided supportive evidence.

Protocol specified analysis of secondary efficacy endpoints:

1. The comparison between the treatment groups in the proportion of patients who achieved a final iPTH level within KDOQI target range by CKD stage was analyzed using a Fisher's exact test.
2. The comparisons between treatment groups in the mean change from baseline in iPTH to each post baseline visit (Weeks 2, 4, 8, and 12) was analyzed using the MMRM.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition at week 12 / missing data:

Patient disposition at week 12

Study	Group	Randomized	Treated / ITT
M10-149	Zemplar	18	18 (100%)
	Placebo	19	18 (94.7%)

One subject (number 3360602) withdrew consent prior to starting trial activities. Because screening was ongoing at the time the subject ended participation, another subject was enrolled to ensure that each treatment group had 18 subjects, for a total of 36 subjects in the ITT Dataset

Missing data at week 12

	Known Responders	Known Non-Responders	Unknown	Total
Zemplar	5	10	3	18
Placebo	0	17	1	18

	Non-responder and no missing measurements	Non-responder and missing measurements	Unknown	Responder and no missing measurements	Responder and missing measurements	Total
Zemplar	7	3	3	3	2	18
Placebo	12	5	1	0	0	18

Demographic and baseline characteristics: The amount of male patients was double or more in each of the placebo and Zemplar groups. Whites made up 94.4% and 77.8% of the patients in the placebo and Zemplar groups, respectively. There were 61.1% and 55.6% of CKD stage 3 patients on placebo and Zemplar, respectively. See table 2 below.

Table 2: Demographics and baseline characteristics

		Treatment Group, n (%)		
Characteristic		**Placebo N=18**	**Zemplar N=18**	**Total N=18**
Sex, n (%)	Female	5 (27.8)	6 (33.3)	11 (30.6)
	Male	13 (72.2)	12 (66.7)	25 (69.4)
Race, n(%)	White	17 (94.4)	14 (77.8)	31 (86.1)
	Asian	0 (0)	3 (16.7)	3 (8.3)
	Other	1 (5.6)	1 (5.6)	2 (5.6)
Ethnicity	Hispanic or Latino	5 (27.8)	4 (22.2)	9 (25.0)
	No ethnicity	13 (72.2)	14 (77.8)	27 (75.0)
Age, years	Mean +/- SD	13.3 (1.75)	13.9 (1.81)	13.6 (1.78)
	Median (Min-Max)	14.0 (10 - 16)	14.0 (10 - 17)	14.0 (10 - 17)
CKD Stage	Stage 3	11 (61.1)	10 (55.6)	21 (58.3)
	Stage 4	7 (38.9)	8 (44.4)	15 (41.7)
Weight, kg	Mean +/- SD	48.2 (12.25)	46.7 (10.22)	47.4 (11.15)
	Median (Min-Max)	45.0 (29 - 78)	46.0 (31 - 66)	45.5 (29 - 78)
Weight, kg (females)	Mean +/- SD	42.8 (3.35)	47.7 (14.35)	45.5 (10.67)
	Median (Min-Max)	44.0 (37 - 45)	40.5 (36 - 66)	43.0 (36 - 66)
Weight, kg (males)	Mean +/- SD	50.3 (13.85)	46.2 (8.19)	48.3 (11.45)
	Median (Min-Max)	52 (29 - 78)	46.0 (31 - 62)	47.0 (29 - 78)
Height, cm	Mean +/- SD	152.8 (13.35)	155.3 (11.72)	154.0 (12.44)
	Median (Min-Max)	152.5 (128 - 178)	157.0 (134 - 174)	155.5 (128 - 178)

Height, cm (females)	Mean +/- SD	147.6 (4.83)	153.2 (6.11)	150.6 (6.04)
	Median (Min-Max)	146.0 (144 - 156)	154 (144 - 161)	149.0 (144 - 161)
Height, cm (males)	Mean +/- SD	154.8 (15.14)	156.3 (13.84)	155.5 (14.25)
	Median (Min-Max)	155.0 (128 - 178)	158.0 (134 - 174)	157.0 (128 - 178)

3.2.4 Results and Conclusions

Protocol specified primary and FDA's sensitivity analysis of primary endpoint:

Under the sponsor's imputation, there was a significantly greater proportion of patients on Zemplar capsules who achieved two consecutive ≥ 30% reductions from baseline in iPTH levels than patients on placebo. The p-value was calculated to be 0.045

Results from FDA's sensitivity analysis addressing missing data:

Step 1 (obtaining estimates for the proportion of additional responders):

Results: 100,000 simulations were ran and the estimated probability for each possibility of the number of additional responders are provided below:

Placebo:

0 additional responders ≈ 0.76948
1 additional responder ≈ 0.23052

Zemplar:

0 additional responders ≈ 0.60011
1 additional responder ≈ 0.33881
2 additional responders ≈ 0.05781
3 additional responders ≈ 0.00327

For the results of the study to be statistically non-significant (using Fisher's exact test), there would need to be 1 additional responder on placebo with 0 or 1 additional responders on Zemplar. Using the above results, the proportion of times the p-value was greater than 0.05 was 0.216440.

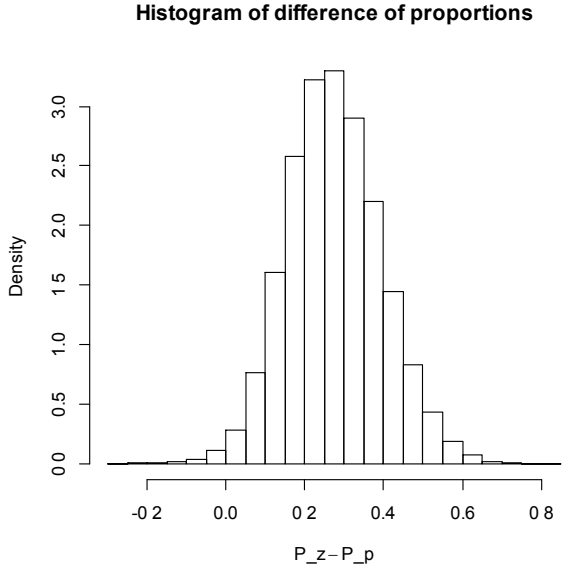
Bayesian analysis: 100,000 draws were made to obtain Monte-Carlo estimates. The results are:

- 95% credible interval: (0.0544 , 0.5196)

- P ($P_z > P_p$) =0.9915, where P_z and P_p are the proportion of responders on Zemplar and Placebo, respectively. In other words, there is a 99.15% chance that the proportion of responders on Zemplar is greater than the proportion of responders on Placebo.

- 2-sided p-value (posterior probability) = 0.017

- The figure below is a histogram of the differences between the proportion of responders on Zemplar and the proportion of responders on Placebo:



Agresti-Caffo (Multiple Imputation): 100,000 data sets were generated. Using Rubin's rule we have:

Null-restricted variance: $\hat{p}_{MI} = 0.2617$

where $\hat{p}_{MI}$ is the multiple imputation point estimate for the difference in the proportion of responders between Zemplar and Placebo,

$\sqrt{\hat{V}_{MI}} = 0.1300$

where $\sqrt{\hat{V}_{MI}}$ is the standard error of $\hat{p}_{MI}$, and

2-sided p-value = 0.0441

Unrestricted variance:

$\hat{p}_{MI} = 0.2617$

$\sqrt{\hat{V}_{MI}} = 0.1231$

$95\%\ C.I. = 0.2617 \pm 1.96 * 0.1231 = (0.0204, 0.5030)$

2-sided p-value = 0.0335

Secondary endpoints:

1. **Comparison between the treatment groups in the proportion of patients who achieved a final iPTH level within KDOQI target range by CKD stage:** Below are the results for the comparison between the treatment groups in the proportion of patients who achieved a final iPTH level within KDOQI target range by CKD stage

Table 3:

Proportion of patients achieved a final iPTH level within KDOQI target range

Response	Paricalcitol n/N (%)	Placebo n/N (%)	p-value
		All	
Yes	6/18 (33.3)	2/18 (11.1)	0.128
No	12/18 (66.7)	16/18 (88.9)	
		CKD Stage 3	
Yes	3/10 (30)	0/11 (0)	0.090
No	7/10 (70)	11/11 (100)	
		CKD Stage 4	
Yes	3/8 (37.5)	2/7 (28.6)	1.000
No	5/8 (62.5)	5/7 (71.4)	

a. Cochran-Mantel_Haenszel (CMH) test, adjusting for CKD Stage
b. Fisher's exact test was used to calculate p-values

None of the results were statistically significant

2. **Change from baseline to each post baseline visit:** Below is the sponsor's result for the secondary endpoint of mean change from baseline in iPTH to each post baseline visit. There was a significant difference from Zemplar to placebo at each post baseline visit. However, the analysis that was run was the MMRM. The MMRM assumes that patients who discontinue therapy will have outcomes in similar fashion to those who continue therapy. In addition, the reported p-values have not been adjusted for multiplicity.

Table 4:
Mean change from baseline in iPTH to each post baseline visit (Weeks 2, 4, 8, and 12)

		Visit			Change from Baseline			Between Group Comparison	
Visit	Treatment Group	N	Mean	(SD)	LS Mean	SE	p-value	Difference (95% C.I.)	p-value
Overall								-72.40 (-108.05, -36.75)	<0.001
Baseline	Paricalcitol	18	144.28	-64.86					
	Placebo	18	155.44	-97.26					
Week 2	Paricalcitol	16	133.63	-93.8	-12.16	14.695	0.414	-62.55 (-105.60, -19.49)	0.006

	Placebo	15	183.07	-121.6	50.39	15.186	0.002		
Week 4	Paricalcitol	16	135.31	-88.24	-11.27	22.117	0.614	-68.43 (-130.39, -6.47)	0.032
	Placebo	18	214.28	-168.9	57.16	20.813	0.01		
Week 8	Paricalcitol	13	131.15	-70.38	-12.79	24.814	0.61	-70.09 (-137.82, -2.37)	0.043
	Placebo	18	213.67	-161.9	57.31	22.099	0.015		
Week 12	Paricalcitol	12	111.25	-50.84	-17.05	19.186	0.381	-88.52 (-142.04, -35.01)	0.002
	Placebo	15	230.47	-173.7	71.47	17.61	<0.001		

Since this secondary endpoint was pre-specified and corrected for multiplicity, it is unlikely that it would be allowed to be put in the product label. Thus, there was no need to address missing data and no further analyses were conducted.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No subgroup analysis was performed on age, sex, and race. Demographic and baseline characteristics however, were summarized. Analysis describing the treatment effect for age was not necessary since this was a pediatric study. An analysis describing the treatment effect for sex and race was not performed and no justification was given. A summary of known responders by sex and race is given as follows:

Number of patients in sex and race categories. The number of known responders is given in parentheses

	Males	Female	White	Non-White
Zemplar	12 (2)	6 (3)	14 (4)	4 (1)
Placebo	13 (0)	5 (0)	17 (0)	1 (0)

4.1 Analysis by CKD stratum

Proportion of patients achieving two consecutive ≥ 30% reductions from baseline in iPTH levels stratified by CKD stage

Response	**Paricalcitol n/N (%)**	**Placebo n/N (%)**	**Difference**	**95% C.I.**	**p-value**
		CKD Stage 3			
Yes	3/10 (30)	0/11 (0)	30.0	(-2.3 , 62)	0.09
No	7/10 (70)	11/11 (100)			
		CKD Stage 4			
Yes	2/8 (25)	0/7 (0)	25.0	(-16.4 , 60.1)	0.467
No	6/8 (75)	7/7 (100)			

The analysis by stratum (CKD Stage 3 / Stage 4) was not statistically significant.

5 SUMMARY AND CONCLUSIONS

5.1 Collective Evidence

Based off the protocol specified analysis, there were a significantly greater proportion of patients on Zemplar capsules who achieved two consecutive ≥ 30% reductions from baseline in iPTH levels than patients on placebo. There were five known responders on Zemplar capsules and zero known responders on placebo. However, there were three patients with an unknown response status on Zemplar and one unconfirmed responder on placebo. For the analysis, the sponsor imputed each of these patients as a non-responder. Fisher's exact test was used and the p-value was calculated to be 0.045.

To address the impact of missing data, we performed two analyses. The methods chosen were easy to implement. The methods did, however, produce smaller p-values than Fisher's exact test. The first analysis was a Bayesian approach that utilized a Jeffrey's prior to obtain a credible interval for the difference in proportions. The 95% credible interval was computed to be (0.0544, 0.5196) in favor of the drug, and the 2-sided p-value (posterior probability) was computed to be 0.017.

The second analysis was a multiple imputation that used the Agresti-Caffo method and Rubin's rule to obtain a point estimate of the difference in proportions and a standard error of this estimate. For the unrestricted variance, the resulting 95% confidence interval was calculated to be (0.0204,0.5030) and the 2-sided p-value to be 0.0335. For the null-restricted variance, the 2-sided p-value was calculated to be 0.0441.

For each method, the p-values increased when addressing missing data compared to imputing unknown responders as non-responders. While the missing data are cause for concern, however, since the results from both our analyses and the sponsors analysis were statistically significant (albeit borderline), and in addition to the results of the PK/PD analysis, there remains evidence that Zemplar lowers iPTH in a pediatric setting.

The only subgroup analysis that was performed was across CKD stratum, which did not yield a statistically significant result. An analysis was not performed for age since this was a pediatric population. Further, no justification was given for why an analysis was not performed for sex and gender.

Another issue was that there was one patient who was randomized to Zemplar who withdrew prior to receiving study drug or trial activities because of travel and would be unable to attend planned visits. Therefore, another patient was enrolled and assigned to Zemplar to maintain equal sample sizes in the treatment arms, however the new patient used the same patient ID as the patient who withdrew. However, this issue was not pursued.

5.2 Labeling Recommendation

With respect to the blinded phase of the study, since patients who were unconfirmed responders or with an unknown response status were imputed as non-responders, there is concern this may not be appropriate. We are recommending inserting the sponsor's table (excluding the proportion of patients who achieved a final iPTH level within KDOQI target range) in describing the results of the primary analysis with a footnote detailing the amount of missing data and that each of the patients were treated as a non-responder. The sponsors original table and our proposed table are shown below:

Table that the sponsor proposes inserting in the label

Table 7. Changes in iPTH from Baseline in the CKD Stages 3 and 4 Pediatric Study	
Phase/Treatment	**Two Consecutive ≥ 30% Reductions From Baseline in iPTH Levels** (b) (4)
Blinded Phase	
Placebo	0/18 (0%)
Paricalcitol	5/18 (2(b)(4)8%)*
* p < 0.05 compared to placebo	

(b) (4)

Table that the FDA is proposing to insert in the label

Table 7. Changes in iPTH from Baseline in the CKD Stages 3 and 4 Pediatric Study	
Phase/Treatment	**Two Consecutive ≥ 30% Reductions From Baseline in iPTH Levels[a]**
Blinded Phase	
Placebo	0/18 (0%)
Paricalcitol	5/18 (2(b)(4)8%)*
* p < 0.05 compared to placebo	

(b) (4)

a 3 patients on Paricalcitol and 1 patient on Placebo had unknown response data. The primary analysis treated these subjects as failures.

(b) (4)

(b) (4)

[redacted]

6 APPENDIX

Impact of missing data:

Since there is one patient on placebo and three patients on Zemplar whose status is unknown, there are 8 potential outcomes with respect to the number of additional responders. We use Fisher's exact test to compute the p-value for each potential outcome as shown below (the highlighted numbers show a non-significant result):

Table 1: Impact of missing data

# **of additional responders**		
Placebo	Zemplar	p
0	0	
0	1	
0	2	
0	3	
1	0	
1	1	
1	2	
1	3	

Thus, there are three possible scenarios:

1. Placebo patient is not a responder => p-value < 0.05
2. Placebo patient is a responder and 0 or 1 additional responders on Zemplar => p-value > 0.05
3. Placebo patient is a responder and 2 or 3 additional responders on Zemplar => p-value < 0.05

Here, we see that if the placebo patient is a responder, it will take at least 2 of the 3 unknown responders on Zemplar to maintain a significant result.

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

/s/

ROBERTO C CRACKEL
09/08/2016

MARK D ROTHMANN
09/09/2016
I concur