CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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 #:	NDA208010
Drug Name:	Rayaldee
Indication(s):	For the (b)(4) treatment of secondary hyperparathyroidism (SHPT) in (b)(4) with chronic kidney disease (CKD) stages 3 or 4 and (b) (4)
Applicant:	OPKO Ireland Global Holdings Ltd.
Date(s):	Date submitted: June 02, 2015 PDUFA due date: March 29, 2016 Review due date: Feb 22, 2016
Review Priority:	Standard
Biometrics Division:	II
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Keywords: NDA review, clinical studies

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1. Executive summary

OPKO Ireland Global Holdings Ltd. proposes CTAP101 Capsules, under the conditionally approved propriety name "Rayaldee", for [redacted] treatment of secondary hyperparathyroidism (SHPT) in patients with stage 3 or 4 chronic kidney disease (CKD) and [redacted] Rayaldee contains the active pharmaceutical ingredient calcifediol which belongs to the established pharmacologic class of Vitamin D_3 Analogue. It was designed to release calcifediol over a prolonged period. The applicant claims Rayaldee is effective in suppressing the plasma intact parathyroid hormone (iPTH) in patients with SHPT. My review of the statistical evidence in efficacy suggests support for this claim. This NDA is approvable from statistical and efficacy point of view.

Two Phase 3 trials with identical study design were reviewed for this NDA submission: CTAP-CL-3001 and CTAP-CL-3002. Both were multicenter, randomized, placebo-controlled, double blind studies involving patients with SHPT, stage 3 or 4 CDK and vitamin D insufficiency.

The primary efficacy endpoint in the two pivotal studies was the number (n, %) of subjects in the intent-to-treat (ITT) population that attained a mean decrease in plasma iPTH of ≥ 30% from baseline in the efficacy assessment period (EAP). As shown in Table 1, the proportion of subjects that attained a mean decrease in plasma iPTH ≥ 30% from baseline in the EAP was significantly greater in the Rayaldee-treated group than the placebo group (p-value < 0.001). There was no evidence that the effect of Rayadee versus placebo on plasma iPTH reduction differs between CDK stages 3 and 4.

All patients missing at least 3 out of 4 measurements in the EAP were defined as non-responders in the primary analysis. The percentage of patients missing at least 3 out of 4 measurements in the EAP was 10-20% in both treatment groups. Considering that the placebo group had very low response rate, the sponsor's method of handling missing data appeared conservative and acceptable.

Table 1 Primary efficacy results (iPTH) for Rayaldee in patients with SHPT, stage 3 or 4 CDK and vitamin D insufficiency

Study	Treatment arm	N[1]	Change in plasma iPTH[2] Mean (SD)	Responders n (%)	p-value[3]
CTAP-CL-3001	Placebo	72	5.11 (29.56)	6 (8.3)	<0.001
	Rayaldee	141	-22.80 (26.41)	46 (32.6)	
CTAP-CL-3002	Placebo	72	3.70 (24.49)	5 (7.0)	<0.001
	Rayaldee	144	-21.33 (26.20)	49 (34.1)	
Pooled	Placebo	144	4.42 (27.10)	11 (7.6)	<0.001
	Rayaldee	285	-22.05 (26.26)	95 (33.3)	

1. ITT population, same as randomized
2. Among the subjects with 2 or more measurements in the EAP ("Nonmissing" in disposition tables Table 3 and Table 4)
3. Cochran-Mantel-Haenszel test controlling for CDK stage

Results from a key secondary endpoint showed that the proportion of subjects in the ITT population who achieved total 25-hydroxyvitamin D ≥ 30 ng/mL in the EAP was significantly greater in the Rayaldee-treated group than the placebo group ($p < 0.001$). The study-wise type I error was controlled by a fixed sequential method with pre-specified prioritization.

This review on efficacy supports the claim of using Rayaldee for (b)(4) treatment of SHPT in (b)(4) with stage 3 or 4 CKD and (b)(4)

2. Introduction

2.1 Overview

2.1.1 Class and indication

CTAP101 Capsules, under the conditionally approved propriety name "Rayaldee", contain the active pharmaceutical ingredient calcifediol which belongs to the established pharmacologic class of Vitamin D_3 Analogs. It was designed to release calcifediol over a prolonged period. The product is indicated for the (b)(4) treatment of SHPT in (b)(4) with stage 3 or 4 CKD and (b)(4)

2.1.2 History of drug development

Oral calcifediol was approved in the US in 1980 as Calderol for the treatment for metabolic bone disease in dialysis patients and was withdrawn from the market in 2002 for commercial reasons not associated with safety or efficacy. Calderol displayed pharmacokinetic (PK) characteristics consistent with an immediate-release formulation.

Development of Rayaldee (sustained release of calcifediol) was initiated in 2006 by Cytochroma Inc., which was acquired by OPKO Health Inc. in 2013. Subsequent development under IND 075162 was performed by two OPKO subsidiaries, OPKO IP Holdings II, Ltd. and OPKO Ireland Global Holdings Ltd (OPKO).

Cytochroma consulted the Division at a pre-IND meeting on 18 December 2006 and at a clinical End-of-Phase 2 meeting on 14 February 2012. The design of primary endpoint and analysis in this NDA submission followed the advice from FDA at End-of-Phase 2 meeting: "We are currently requiring as evidence of a clinically relevant response in CKD patients with SHPT a single primary endpoint based on iPTH response. An iPTH responder is defined (b)(4) a patient who has a mean decrease of 30% (or greater) in iPTH from baseline where the mean is calculated across all visits during a predetermined efficacy assessment phase. The choice of which responder definition to use would be made at the protocol stage. The primary statistical analysis would compare the proportion of responders between CTAP101 and placebo. Assessments of 25-hydroxyvitamin D levels are considered to be secondary endpoints." OPKO held a pre-NDA meeting with the Division on 08 October 2014.

2.1.3 Specific studies reviewed

Two pivotal phase 3 trials with identical study design were reviewed for this NDA submission. Both were multicenter, randomized, placebo-controlled, double blind studies involving patients with SHPT, stage 3 or 4 CDK and vitamin D insufficiency. Subjects were stratified by CDK stage and randomized in a 2: 1 ratio to receive once daily 30 mcg oral dose of Rayaldee (or placebo) at bedtime for 12 weeks followed by an additional 14 weeks of treatment with either 30 or 60 mcg of Rayaldee (or placebo). A total of 213 subjects were randomized in Study CTAP-CL-3001 (72 received placebo, and 141 received Rayaldee), and 216 subjects were randomized in Study CTAP-CL-3002 (72 received placebo and 144 received Rayaldee).

Subjects who completed either of the pivotal studies were eligible to enroll in a 6-month open-label extension study CTAP-CL-3003. A total of 354 subjects (83%) completed either one of the two pivotal phase 3 studies and 298 (69%) entered the extension study during which Rayaldee was administered daily at bedtime for another 26 weeks. The extension study is not the focus of this review.

2.2 Data sources

The data and final study report were submitted electronically. The submission was archived under the network path location <\\CDSESUB1\evsprod\NDA208010\208010.enx>. The information needed for this review was contained in Module 1 FDA Regional Information (cover letter, meeting correspondence, and labeling), Module 2.5 Clinical Overview, Module 2.7 Clinical Summary, and Module 5 Clinical Study Report. This review focuses on documents submitted to serial number 0000.

3. Statistical evaluation

3.1 Data and analysis quality

This submission is in electronic common technical document (eCTD) format with xml backbone. An information request was made regarding how missing data are dealt with for the derived endpoint across four measurements at EAP. With sponsor's response to the information request, all required materials that are necessary for statistical review were submitted.

Study datasets are provided as SAS XPORT transport files version 5. SAS code for primary and key secondary analyses was submitted. This review covered datasets from two Phase 3 studies and the integrated summary of efficacy which pooled data from the two studies.

For the individual trials, both tabulation and analysis datasets are provided. Tabulation datasets include the source data without any derivations or enrichments, whereas analysis datasets also include derived and enriched data (such as formatted variables, populations, derived endpoints). The tabulation and analysis datasets are joinable by the unique record identifier (USUBJID). This review mainly uses analyses datasets. The integrated summary of efficacy contains a pooled dataset from the two pivotal studies. It is mainly used for subgroup analysis in this review.

The datasets are in good organization. Variables in study datasets are consistently named and used across trials, with clear description in the Define.pdf file. The reported analysis results are in good quality. I was able to reproduce the results on the primary and key secondary efficacy endpoints in the Clinical Study Report (CSR).

3.2 Evaluation of efficacy

3.2.1 Study design and endpoints

The two pivotal phase 3 studies (CTAP-CL-3001 and CTAP-CL-3002) were multicenter, randomized, placebo-controlled, double blind studies involving patients with SHPT, stage 3 or 4 CKD and vitamin D insufficiency. **The primary objectives** were:

1. To evaluate the efficacy of Rayaldee versus placebo in reducing plasma iPTH by at least 30% from pre-treatment baseline,

2. To investigate the safety and tolerability of Rayaldee.

Subjects were stratified by CDK stage and randomized in a 2: 1 ratio to receive once daily 30 mcg oral dose of Rayaldee (or placebo) at bedtime for 12 weeks followed by an additional 14 weeks of treatment with either 30 or 60 mcg of Rayaldee (or placebo). The dose was increased to 60 mcg at the start of week 13 if plasma iPTH was > 70 pg/mL, serum total 25-hydroxyvitamin D was < 65 ng/mL and serum calcium was > 9.8 mg/dL. Plasma iPTH and serum calcium, phosphorus, calcifediol, total 25-hydroxyvitamin D were measured biweekly or monthly. The dose was reduced at any time during the treatment period for confirmed serum 25-hydroxyvitamin D > 100 ng/mL, serum calcium > 10.3 mg/dL, serum phosphorus > 5.5 ,g/dL or plasma iPTH < 30 pg/mL. Subjects who completed either of the pivotal studies were eligible to enroll in a 6-month open-label extension study CTAP-CL-3003.

This review only focuses on the efficacy results in the pivotal studies. **The efficacy analyses populations** include the intent-to-treat (ITT) and/or per protocol (PP) populations. The ITT population was defined as all randomized subjects who have taken at least 1 dose of study drug. The PP population was defined as all subjects who have at least 2 plasma iPTH determinations included in the calculated baseline value and in the EAP (weeks 20-26 or visits 10-13), and who do not have a major protocol deviation. A summary of data sets analyzed is provided in Table 2.

Table 2 Summary of data sets analyzed

	Study CTAP-CL-3001		**Study CTAP-CL-3002**	
	Placebo	**Rayaldee**	**Placebo**	**Rayaldee**
ITT population, n(%)[1]	72 100.0%	141 100.0%	72 100.0%	144 100.0%
PP population, n(%)	62 86.1%	115 81.6%	60 83.3%	119 82.6%

1.Percentage of randomized.

The primary efficacy endpoint was the number (n, %) of subjects in the ITT population that attained a mean decrease in plasma iPTH of >=30% from baseline in the EAP. **Two key secondary endpoints** were tested using a fixed sequential method and the following prioritization:

1. The number (n, %) of subjects in the ITT population attaining a mean serum total 25D of ≥30 ng/mL in the EAP,

2. The number (n, %) of subjects in the PP population attaining a mean decrease from baseline in plasma iPTH of ≥30% in the EAP.

The sample sizes were determined by the sponsor to ensure at least 80% power for a two-sided, alpha = 0.05 level test of equal proportions, assuming rates of 0.4 (Rayaldee) versus 0.1 (placebo) and using a 2: 1 ratio of Rayaldee: placebo subjects with a proposed 20% dropout rate.

3.2.2 Statistical methodologies

Primary efficacy was assessed in the ITT population by comparing the number (n, %) of subjects in each treatment group achieving a mean decrease from baseline in plasma iPTH of ≥ 30% in the EAP.

The calculation of the mean reduction in plasma iPTH from baseline in the EAP will be based on the following visits:

- If washout is required: baseline=average of visits 2, 3, 4
- If washout is not required: baseline=average of visits 1, 3, 4
- EAP=average of visits 10, 11, 12, 13

The primary analysis was pre-specified by the sponsor: the number (n, %) of subjects achieving ≥30% reduction from baseline in iPTH was compared between the treatment groups (active vs placebo) across the two stratification subgroups, stage 3 and stage 4 CKD, using the Cochran-Mantel-Haenszel (CMH) test statistic (alpha=0.05) for overall efficacy. The Chi-square test was used for reporting the results in each stratum.

According to the sponsor's response to our information request, subjects who terminated early were asked to complete a visit 13 schedule of activities. Therefore, the average iPTH value in the EAP was calculated using a minimum of 2 out of 4 measurements from visits 10-13 to exclude those subjects who terminated early. If 2 measurements were not available, the EAP value was set to "missing". These subjects were defined as non-responders in the ITT population and were excluded from the PP population. No imputation was performed for missing values. No sensitivity analysis was performed.

The key secondary endpoints are also binary variables. They were also analyzed using CMH method, stratified on CDK stages.

3.2.3 Patient disposition, demographic and baseline characteristics

Subject disposition for the two Phase 3 studies were summarized in Table 3 and Table 4. Non-missing refers to subjects who had 2 or more (out of 4) iPTH measurements in the EAP. PP are the subjects who are nonmissing and with no major protocol violation. Completers are the subjects who completed the study. The percentage of subjects who missed 3 or more iPTH measurements in the EAP was 11%-17% and was similar between the two treatment groups with slightly more missingness in the Rayaldee group.

Table 3 Summary of patient dispositions in Study CTAP-CL-3001

	CKD Stage 3		**CKD Stage 4**		**Total**	
	Placebo	**Rayaldee**	**Placebo**	**Rayaldee**	**Placebo**	**Rayaldee**
Randomized, n(%)	36 100.0%	71 100.0%	36 100.0%	70 100.0%	72 100.0%	141 100.0%
ITT, n(%)	36 100.0%	71 100.0%	36 100.0%	70 100.0%	72 100.0%	141 100.0%
Nonmissing, n(%)	33 91.7%	58 81.7%	31 86.1%	59 84.3%	64 88.9%	117 83.0%
PP, n(%)	33 91.7%	58 81.7%	29 80.6%	57 81.4%	62 86.1%	115 81.6%
Completer, n(%)	32 88.9%	56 78.9%	30 83.3%	57 81.4%	62 86.1%	113 80.1%
Early terminated, n(%)	4 11.1%	15 21.1%	6 16.7%	13 18.6%	10 13.9%	28 19.9%
Subject withdrew consent	2	6	0	4	2	10
Serious adverse event	0	1	1	5	1	6
lost to follow-up	1	2	2	0	3	2
Major protocol violation	0	3	0	0	0	3
Subject non-compliance	0	2	0	1	0	3
Others	1	1	3	3	4	4

Source: clinical study report CTAP101-CL-3001 Table 6

Table 4 Summary of patient dispositions in Study CTAP-CL-3002

	CKD Stage 3		**CKD Stage 4**		**Total**	
	Placebo	**Rayaldee**	**Placebo**	**Rayaldee**	**Placebo**	**Rayaldee**
Randomized, n(%)	35 100.0%	80 100.0%	37 100.0%	64 100.0%	72 100.0%	144 100.0%
ITT, n(%)	35 100.0%	80 100.0%	37 100.0%	64 100.0%	72 100.0%	144 100.0%
Nonmissing, n(%)	30 85.7%	69 86.3%	31 83.8%	55 85.9%	61 84.7%	124 86.1%
PP, n(%)	29 82.9%	65 81.3%	31 83.8%	54 84.4%	60 83.3%	119 82.6%
Completer, n(%)	28 80.0%	66 82.5%	30 81.1%	55 85.9%	58 80.6%	121 84.0%

Early terminated, n(%)	7 20.0%	14 17.5%	7 18.9%	9 14.1%	14 19.4%	23 16.0%
Subject withdrew consent	1	6	4	1	5	7
Serious adverse event	2	2	0	2	2	4
lost to follow-up	1	3	1	2	2	5
Major protocol violation	0	0	1	0	1	0
Subject non-compliance	2	1	0	2	2	3
Others	1	2	1	2	2	4

Source: clinical study report CTAP101-CL-3002 Table 6

Subject demographic information for the two Phase 3 studies was summarized in Table 5 and Table 6. All the patients are from USA. The two treatment groups were roughly balanced for all the demographic factors.

Table 5 Summary of patient demographic information in Study CTAP-CL-3001

	CKD Stage 3		**CKD Stage 4**		**Total**	
	Placebo	**Rayaldee**	**Placebo**	**Rayaldee**	**Placebo**	**Rayaldee**
Sex, n(%) males	21 (58.3%)	32 (45.1%)	18 (50.0%)	38 (54.3%)	39 (54.2%)	70 (49.6%)
Age, years Mean (SD) Range	 64.6 (13.0) 25-83	 65.3 (8.9) 40-83	 64.2 (12.7) 28-85	 64.8 (11.6) 30-83	 64.4 (12.7) 25-85	 65.1 (10.3) 30-85
Race, n (%) White African-American Other	 22 (61.1%) 12 (33.3%) 2 (5.6%)	 36 (50.7%) 31 (43.7%) 4 (5.6%)	 26 (72.2%) 10 (27.8%) 0 (0.0%)	 49 (70.0%) 19 (27.1%) 2 (2.9%)	 48 (66.7%) 22 (30.6%) 2 (2.8%)	 85 (60.3%) 50 (35.5%) 6 (4.3%)
Baseline iPTH, pg/mL Mean (SD)	127.3 (33.3)	125.1 (38.5)	157.1 (52.5)	168.9 (62.3)	142.2 (46.1)	146.8 (56.0)
Baseline 25D, ng/mL Mean (SD)	 19.5 (5.8)	 20.8 (5.0)	 18.9 (5.1)	 19.7 (5.1)	 19.2 (5.4)	 20.2 (5.1)

Source: modified from clinical study report CTAP101-CL-3001 Table 8 and 9

Table 6 Summary of patient demographic information in Study CTAP-CL-3002

	CKD Stage 3		**CKD Stage 4**		**Total**	
	Placebo	**Rayaldee**	**Placebo**	**Rayaldee**	**Placebo**	**Rayaldee**
Sex, n(%) males	13 (37.1%)	39 (48.8%)	20 (54.1%)	34 (53.1%)	33 (45.8%)	73 (50.7%)
Age, years Mean (SD) Range	 64.4 (10.7) 35-84	 67.4 (10.3) 40-85	 66.1 (9.5) 49-82	 66.0 (11.6) 29-84	 65.3 (10.1) 35-84	 66.8 (10.9) 29-85
Race, n (%) White African-American Other	 19 (54.3%) 15 (42.9%) 1 (2.9%)	 54 (67.5%) 26 (32.5%) 0 (0.0%)	 27 (73.0%) 8 (21.6%) 2 (5.4%)	 44 (68.8%) 17 (26.6%) 3 (4.7%)	 46 (63.9%) 23 (31.9%) 3 (4.2%)	 98 (68.1%) 43 (29.9%) 3 (2.1%)
Baseline iPTH, pg/mL Mean (SD)	141.1 (56.0)	132.1 (38.7)	169.2 (67.1)	167.0 (82.4)	155.6 (63.1)	147.6 (64.2)

Baseline 25D, ng/mL Mean (SD)	18.8 (5.4)	19.9 (5.6)	19.9 (5.6)	19.4 (5.5)	19.4 (5.5)	19.7 (5.6)

Source: modified from clinical study report CTAP101-CL-3002 Table 8 and 9

3.2.4 Results and conclusions

I verified the sponsor's results of primary endpoint (Table 7 and Table 8). The proportion of subjects in the ITT population who achieved at least 30% mean reduction in plasma iPTH from baseline in the EAP was significantly greater in the Rayaldee-treated group than the placebo group in both pivotal studies ($p < 0.001$). I tested the homogeneity of the odds ratios across CDK stages using the Breslow-Day test. There was no evidence that the effect of Rayadee versus placebo on plasma iPTH reduction differs between CDK stages 3 and 4 (p=0.501 for Study CTAP-CL-3001, p=0.603 for Study CTAP-CL-3002).

I also verified the sponsor's results of key secondary endpoints. The proportion of subjects in the PP population who achieved at least 30% mean reduction in plasma iPTH from baseline in the EAP was significantly greater in the Rayaldee-treated group than the placebo group in both pivotal studies ($p < 0.001$; Table 9 and Table 10). Response rates were higher in the PP population than in the ITT population, primarily because subjects who terminated prematurely were defined as non-responders in the ITT population, irrespective of observed changes in plasma iPTH, and were excluded in the PP population. The proportion of subjects in the ITT population who achieved total 25-hydroxyvitamin D >=30 ng/mL in the EAP was significantly greater in the Rayaldee-treated group than the placebo group in both pivotal studies ($p < 0.001$; Table 11 and Table 12).

Table 7 Number and percentage of patients with iPTH reduction >=30% at EAP in the ITT population in Study CTAP-CL-3001

	CDK Stage 3		**CDK Stage 4**		**Total**	
	Placebo	**Rayaldee**	**Placebo**	**Rayaldee**	**Placebo**	**Rayaldee**
	N=36	N=71	N=36	N=70	N=72	N=141
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Responder	4 (11.1)	24 (33.8)	2 (5.6)	22 (31.4)	6 (8.3)	46 (32.6)
Non-responder	32 (88.9)	47 (66.2)	34 (94.4)	48 (68.6)	66 (91.7)	95 (67.4)
p value[1]		0.012		0.003		<0.001

Source: clinical study report CTAP101-CL-3001 Table 14

1. Cochran-Mantel-Haenszel test controlling for CDK stage for the total, Chi-square test for CDK Stage 3 and 4

Table 8 Number and percentage of patients with iPTH reduction >=30% at EAP in the ITT population in Study CTAP-CL-3002

	CDK Stage 3		**CDK Stage 4**		**Total**	
	Placebo	**Rayaldee**	**Placebo**	**Rayaldee**	**Placebo**	**Rayaldee**
	N=35	N=80	N=37	N=64	N=72	N=144
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Responder	3 (8.6)	27 (33.8)	2 (5.4)	22 (34.4)	5 (7.0)	49 (34.1)
Non-responder	32 (91.4)	53 (66.3)	35 (94.6)	42 (65.6)	67 (93.0)	95 (65.9)
p value[1]		0.005		0.001		<0.001

Source: clinical study report CTAP101-CL-3002 Table 14
1. Cochran-Mantel-Haenszel test controlling for CDK stage for the total, Chi-square test for CDK Stage 3 and 4

Table 9 Number and percentage of patients with iPTH reduction >=30% at EAP in the PP population in Study CTAP-CL-3001

	CDK Stage 3		CDK Stage 4		Total	
	Placebo	**Rayaldee**	**Placebo**	**Rayaldee**	**Placebo**	**Rayaldee**
	N=33	N=58	N=29	N=57	N=62	N=115
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Responder	4 (12.1)	24 (41.4)	1 (3.4)	22 (38.6)	5 (7.8)	46 (40.0)
Non-responder	29 (87.9)	34 (58.6)	28 (96.6)	35 (61.4)	57 (92.2)	69 (60.0)
p value[1]		0.004		<0.001		<0.001

Source: clinical study report CTAP101-CL-3001 Table 15
1. Cochran-Mantel-Haenszel test controlling for CDK stage for the total, Chi-square test for CDK Stage 3 and 4

Table 10 Number and percentage of patients with iPTH reduction >=30% at EAP in the PP population in Study CTAP-CL-3002

	CDK Stage 3		CDK Stage 4		Total	
	Placebo	**Rayaldee**	**Placebo**	**Rayaldee**	**Placebo**	**Rayaldee**
	N=29	N=65	N=31	N=54	N=60	N=119
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Responder	3 (10.3)	25 (38.5)	2 (6.5)	22 (40.7)	5 (8.4)	47 (39.6)
Non-responder	26 (89.7)	40 (61.5)	29 (93.5)	32 (59.3)	55 (91.6)	72 (60.4)
p value[1]		0.006		<0.001		<0.001

Source: clinical study report CTAP101-CL-3002 Table 15
1. Cochran-Mantel-Haenszel test controlling for CDK stage for the total, Chi-square test for CDK Stage 3 and 4

Table 11 Number and percentage of patients with normal serum total 25-hydroxyvitamin >=30 ng/mL at EAP in the ITT population in Study CTAP-CL-3001

	CDK Stage 3		CDK Stage 4		Total	
	Placebo	**Rayaldee**	**Placebo**	**Rayaldee**	**Placebo**	**Rayaldee**
	N=36	N=71	N=36	N=70	N=72	N=141
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Responder	2 (5.6)	55 (77.5)	0 (0.0)	58 (82.9)	2 (2.8)	113 (80.2)
Non-responder	34 (94.4)	16 (22.5)	36 (100)	12 (17.1)	70 (97.2)	28 (19.8)
p value[1]		<0.001		<0.001		<0.001

Source: clinical study report CTAP101-CL-3001 Table 16
1. Cochran-Mantel-Haenszel test controlling for CDK stage for the total, Chi-square test for CDK Stage 3 and 4

Table 12 Number and percentage of patients with normal serum total 25-hydroxyvitamin >=30 ng/mL at EAP in the ITT population in Study CTAP-CL-3002

	CDK Stage 3		CDK Stage 4		Total	
	Placebo	**Rayaldee**	**Placebo**	**Rayaldee**	**Placebo**	**Rayaldee**
	N=35	N=80	N=37	N=64	N=72	N=144

	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Responder	1 (2.9)	67 (83.8)	4 (10.8)	53 (82.8)	5 (6.8)	120 (83.3)
Non-responder	34 (97.1)	13 (16.3)	33 (89.2)	11 (17.2)	67 (93.2)	24 (16.7)
p value[1]		<0.001		<0.001		<0.001

Source: clinical study report CTAP101-CL-3002 Table 16

1. Cochran-Mantel-Haenszel test controlling for CDK stage for the total, Chi-square test for CDK Stage 3 and 4

3.3 Evaluation of safety

Analyses on safety events were reviewed by Dr. William Lubas in the medical division.

3.4 Benefit: risk assessment (optional)

4. Findings in special/subgroup populations

4.1 Sex, Race, Age, and Geographic Region

Comparison of the treatment effect in the primary endpoint in subgroups was assessed by pooling data in the two Phase 3 efficacy trials. The factors considered for subgroup analyses include:

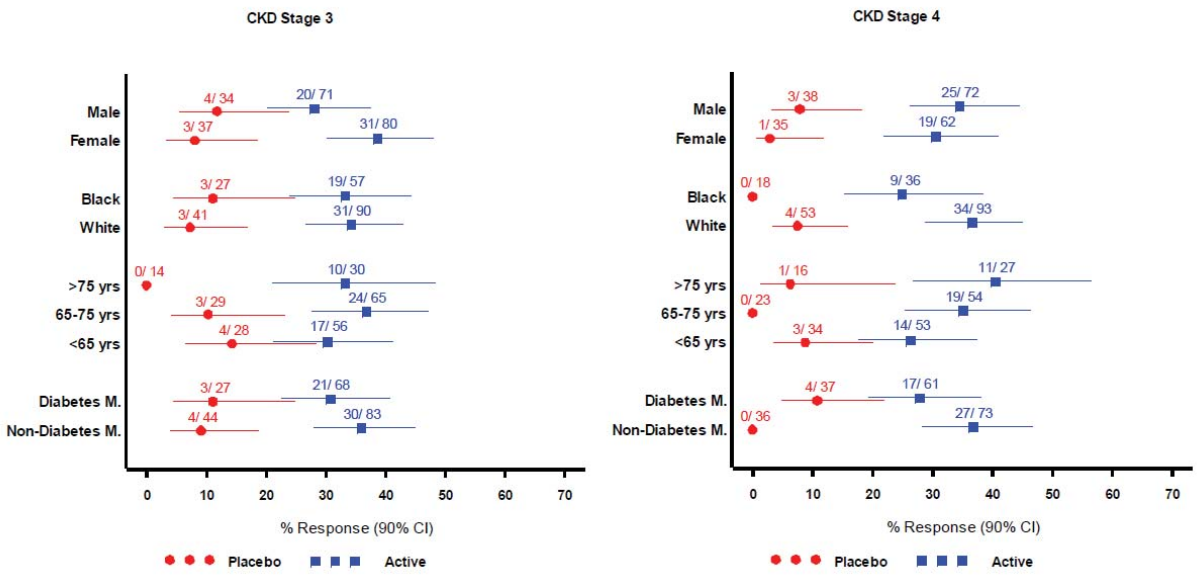
- Sex
- Race
- Age (>75 years, 65-75 years, <65 years)

All patients in the studies are from US. Therefore, subgroup analysis on geographic region is not applicable.

Figure 1 displays the proportion of subjects with mean plasma iPTH reduction of ≥ 30% from baseline by treatment group and CKD stage at EAP in ITT Population. Confidence intervals of 90% were determined using Wilson (score) confidence limits for a binomial proportion. The proportion of patients with iPTH reduction >=30% at EAP in the ITT population was higher in the Rayaldee versus placebo across all subgroups.

I conducted subgroup analyses using a logistic regression model, with CDK stage, treatment, subgroup, interaction between treatment and subgroup in the model. None of the treatment-by-subgroup interaction was statistically significant at alpha = 0.10 (p-value = 0.27 for sex, 0.47 for race, 0.18 for age group), suggesting the treatment effect on iPTH was similar across these subgroups.

Figure 1 Proportion of Subjects with Mean Plasma iPTH Reduction of ≥30% from Baseline in the EAP in ITT Population (Pooled Data from Studies CTAP101-CL-3001 and CTAP101-CL-3002)



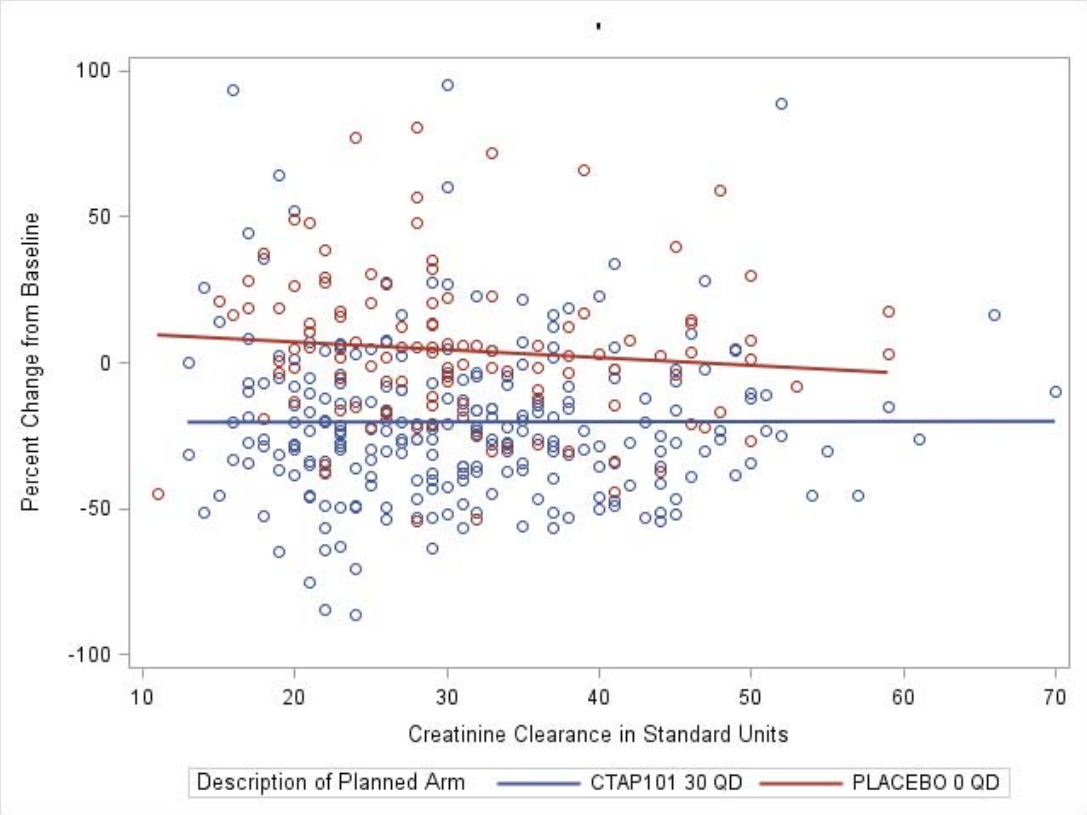
Source: sponsor's response to information request, 16 December 2015

4.2 Other Special/Subgroup Populations

The sponsor also did subgroup analyses for diabetes status using pooled data (Figure 1). I tested the treatment-by-subgroup interaction for diabetes status using the same logistic regression model. The treatment effect was larger among patients without diabetes than patients with diabetes at alpha = 0.10 (p-value = 0.09). The difference does not appear to be clinically meaningful.

I tested the interaction between treatment group and the continuous creatinine clearance values at the screening visit using the same logistic regression model. The interaction was not statistically significant at alpha = 0.10 (p-value = 0.69). Figure 2 further illustrated that creatinine clearance was not an effect modifier for the treatment effect on iPTH.

Figure 2 Percent Change in iPTH from baseline in the EAP versus Creatinine Clearance at Screening (Pooled Data)



5. Summary and Conclusions

5.1 Statistical Issues

No major statistical issue was identified in this submission.

Cochran-Mantel-Haenszel (CMH) test was used in the primary analysis for overall efficacy. The sponsor's method for primary analysis was acceptable.

All patients missing at least 3 out of 4 measurements in the EAP were defined as non-responders in the primary analysis. The percentage of patients missing at least 3 out of 4 measurements in the EAP was 10-20% in both treatment groups. Considering that the placebo group had very low response rate, the sponsor's method of handling missing data appeared conservative and acceptable.

The study-wise type I error was controlled by a fixed sequential method with pre-specified prioritization.

5.2 Collective Evidence

Both pivotal Phase 3 studies showed superiority of Rayaldee versus placebo in terms of reduction of plasma iPTH from baseline in patients with SHPT. The proportion of patients that attained a mean decrease in plasma iPTH ≥ 30% from baseline in the EAP was 32.6% in the Rayaldee group versus 8.3% in

the placebo group in Study CTAP-CL-3001 (p-value < 0.001), and 34.1% in the Rayaldee group versus 7.0% in the placebo group in Study CTAP-CL-3002 (p-value < 0.001).

Subgroup analyses of iPTH based on the pooled data showed that the treatment effect was similar across subgroups defined by sex, age and race. All patients in the studies are from US. The treatment effect appeared to be larger among patients without diabetes than patients with diabetes at alpha = 0.10 (p-value = 0.09), but the difference is not clinically meaningful.

5.3 Conclusions and Recommendations

This review on efficacy supports the claim of using Rayaldee for (b)(4) treatment of SHPT in patients with stage 3 or 4 CKD and (b)(4) This NDA is approvable from statistical point of view.

5.4 Labeling recommendations

1. (b) (4) It is recommended that results from individual studies be included in the label (b) (4), for showing the consistency of results across studies. (b) (4) . (b)(4)

2. The label included (b) (4) For example,

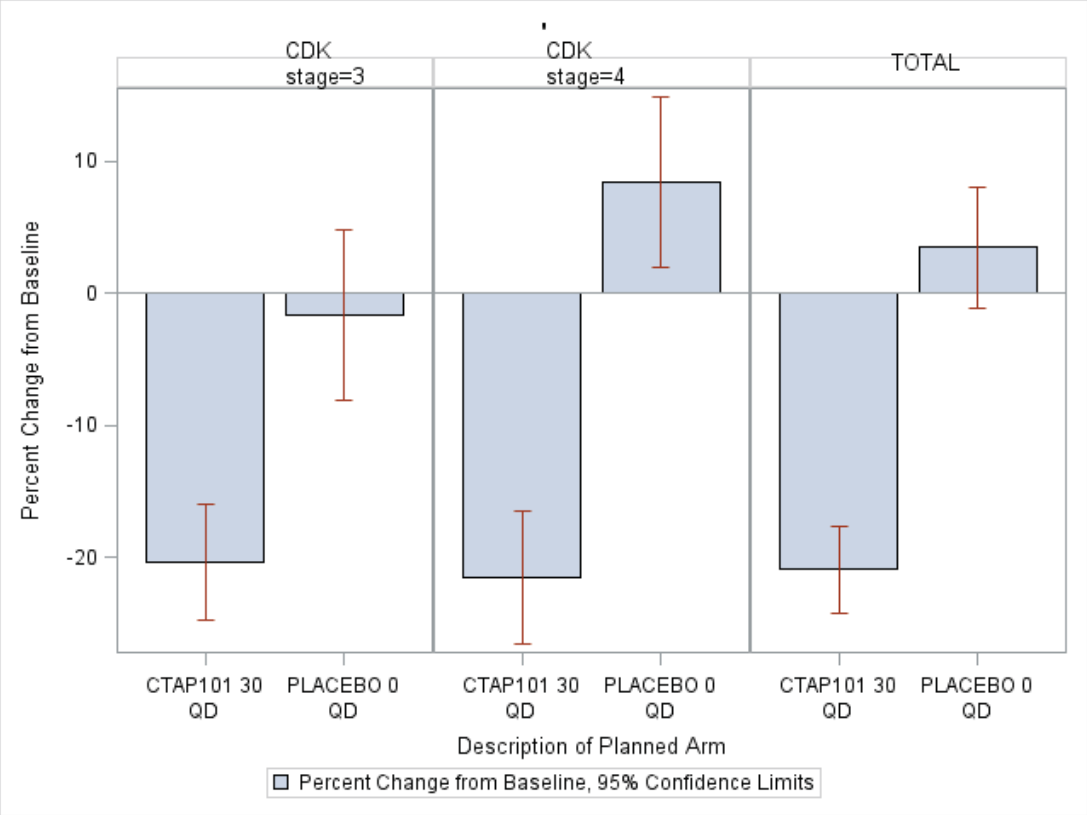
   (b)(4)

   The label should be revised to include results from the pre-specified primary and key secondary analyses only.

3. (b)(4)

Appendices

Figure 3 Mean Percent Change in iPTH from Baseline in Patients with 2 or More Measurements in the EAP (Pooled Data)



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

/s/

JIWEI HE
02/12/2016

MARK D ROTHMANN
02/12/2016
I concur

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

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 208-010
Drug Name:	Calcifediol
Study:	Six-Month Subcutaneous Injection Carcinogenicity Study in rasH2 Transgenic Mice
Applicant:	Sponsor: OPKO Canada, Inc. 100 Allstate Parkway, Suite 600 Markham, On L3R 6H3 Canada Testing Facility: (b)(4)
Documents Reviewed:	Electronic submission: Submitted on 5/29/2015 Electronic data: Submitted on 5/29/2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - VI
Statistical Reviewer:	Hepei Chen
Secondary Reviewer:	Mohammad Atiar Rahman, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products
Reviewing Pharmacologist:	Parvaneh Espandiari, Ph.D.
Date Submitted:	September 2, 2015
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included a carcinogenicity study report in transgenic mice. The study was to determine the potential carcinogenic toxicity of Calcifediol (25-hydroxyvitamin D3), a vitamin D prohormone, when given by daily subcutaneous injection for 26 weeks to mice. In addition, the toxicokinetic characteristics of Calcifediol was determined. Results of this review have been discussed with the reviewing toxicologist Dr. Espandiari.

In this review the phrase "dose response relationship" refers to the linear component (trend) of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Mouse Study

Two separate experiments, one in male and one in female, were conducted in this mouse study. As indicated in Table 1, one hundred and fifty Hemizygous rasH2 transgenic mice of each sex were assigned randomly to one of six treatments which included one saline group, one vehicle control group, one positive control group, and three Calcifediol treated groups. For each sex, the sample size was 25 in each group. The mice in all groups, except in the positive control group, (group 1, 2, 4, 5, and 6) were administered the drug or control by daily subcutaneous injection for a period of approximately 6 months.In this review the three treated groups with 3, 10, and 33 µg/kg/day of Calcifediol were referred to as the low, mid, and high dose groups, respectively. The mice in the saline, and vehicle control groups received the saline, and 2% Tween 80 in phosphate buffered saline plus 1% ethanol, respectively, in the same manner as the treated groups. The mice in the positive control received a single administration of N-Nitrosomethylurea (NMU) only on Day 1.

Table 1. Experimental Design in Mouse Study

Dose Group	Group Name	Test Material	No. of Toxicity Animals in Male and Female	Dose level (µg/kg/day) In Male and Female
Group 1	Saline	Saline	25	0
Group 2	Vehicle control	Reference Item	25	0
Group 3	Positive control	NMU	25	75[a]
Group 4	Low	Calcifediol	25	3
Group 5	Mid	Calcifediol	25	10
Group 6	High	Calcifediol	25	33

[a] mg/kg for Positive Control

Throughout the study, animals were observed for general health/mortality and morbidity twice daily, once in the morning and once in the afternoon. Animals were not removed from cage during observation, unless necessary for identification or confirmation of possible findings. The animals were removed from the cage, and a detailed clinical observation was performed weekly, beginning during Week -1. The presence of palpable masses was observed during the detailed examination. The site, size and appearance of these masses were recorded when first detected and, following this initial description, the presence or disappearance of these masses was monitored. Animals were weighed individually weekly, starting during Week 1. A fasted weight was recorded on the day of necropsy.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor applied the log-rank test to the saline group (group 1), the vehicle control group (group 2), and the three Calcifediol treated groups (group 4, 5, and 6) in order to assess the significance of the overall treatment effect on mortality data. If the log-rank test reveals significant differences among these five groups ($p \leq 0.05$), then the significance of an overall dose response relationship test in mortality across the vehicle control group and the three treated groups were evaluated using the method of Tarone. Using the Multtest procedure of the SAS/STAT module, Tarone's test was implemented as a Peto two-sided test, with all uncensored deaths coded as 2 and all censored deaths coded as 0. The arithmetic dose level scores 0, 3, 10 and 33 were used as score to perform this overall dose response relationship test. In addition to the overall dose response relationship test, the vehicle control group was compared to each of the other four groups using a Peto two-sided test. The dose response relationship test and each pairwise group comparison of interest were conducted at the 5% significance level.

Sponsor's findings:

The sponsor's results showed no statistically significant dose response relationship or increase/decrease in mortality across the vehicle control group/saline group and the three treated groups due to the test article in male or female mice.

2.1.2. Tumor data analysis

For each dataset of interest within each sex, the sponsor evaluated the significance of an overall dose response relationship in tumor incidence across the vehicle control group and the three treated groups, and across the saline group and the three treated groups using the Cochran-Armitage's one-sided exact test at the 5% significance level. Furthermore, in order to check if the tumor incidence treated groups was significantly higher than the tumor incidence in control groups, the vehicle control group and the saline group were each compared to each of the three treated groups using Fisher's exact one-sided test at the 5% significance level. The same test was also applied between the vehicle control group and the saline group to test if the tumor incidence in the vehicle control group was significantly higher than the tumor incidence in the saline group. The arithmetic dose level scores 0, 3, 10 and 33 were used to perform this overall dose response relationship test.

Sponsor's findings:

The sponsor's analysis showed a statistically significant positive dose response relationship across the saline group and the three treated groups for bronchioloalveolar adenoma combined with carcinoma in lung of male mice (p-value = 0.0269). No other statistically significant findings in tumor incidence were noted in the sponsor's analysis among the vehicle control group and the three treated groups.

Although statistically significant, given that there was no significant result for the trend test when compared to the vehicle control group, because of the absence of significance for the pairwise comparisons, the lack of a dose-related increase of precursor pre-neoplasic lesion (bronchioloalveolar hyperplasia), the statistical significance was only noted in males, the absence

of multiplicity of pulmonary adenoma, and the common nature of both tumor types in this strain of mouse the sponsor did not consider the lung neoplastic findings in male mice as treatment-related. The sponsor also pointed out that the lung tumors are the most prevalent tumor type in TgRasH2 mice and the incidence of lung bronchioloalveolar adenoma and carcinoma found in this study is comparable to historical data from the used test facility.

2.2. Reviewer's analyses

To verify the sponsor's analyses and perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically. The significance level for all statistical tests was set at 0.05.

2.2.1. Survival analysis

The reviewer used the Kaplan-Meier product limit method to evaluate the survival distributions of mice for the vehicle control group, the saline group, the positive control group, and the three Calcifediol treated groups. The dose response relationship was tested across the vehicle control group and the three treated groups, and between the saline group, the positive control group, the three treated groups, and the vehicle control group, using the likelihood ratio test; the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female mice, respectively. The intercurrent mortality data and the results of the tests for dose response relationship and homogeneity of survivals for the six dosing groups are given in Tables 1A and 1B in the appendix for male and female mice, respectively.

Reviewer's findings:

In the reviewer's analysis, the numbers of male mice surviving to their terminal necropsy were 24, 22, 3, 23, 25, and 25 in the saline group, the vehicle control group, the positive control group, the low, mid, and high dose groups, respectively. A statistically significant dose response relationship in mortality was noted for male mice ($p=0.0097$) with statistically significant increases in the mid and high groups when compared to the vehicle control group ($p=0.0384$ and 0.0384, respectively). For female, the numbers of mice surviving to their terminal necropsy were 23, 24, 5, 25, 25, and 24 in the saline group, the vehicle control group, the positive control group, the low, mid, and high dose groups, respectively. No statistically significant dose response relationship or pairwise group comparisons in mortality were noted in female mice. The reviewer's analysis also showed that the positive control group had a statistically significant ($p<0.0001$) increased unscheduled death compared with the vehicle control group in both male and female mice.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationship across the vehicle control group and the three Calcifediol treated groups, as well as pairwise comparisons of each of the three treated groups, the saline group, and the positive control group, with the vehicle control group, using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the ploy-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the *i*-th treatment group R^*_i is defined as $R^*_i = \sum w_{ij}$ where w_{ij} is the weight for the *j*-th animal in the *i*-th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w_{ij} as follows:

$w_{ij} = 1$ to animals dying with the tumor, and

$w_{ij} = (t_{ij} / t_{sacr})^3$ to animals dying without the tumor,

where t_{ij} is the time of death of the *j*-th animal in the *i*-th treatment group, and t_{sacr} is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date will also be assigned with $w_{ij}=1$ since $t_{ij} = t_{sacr}$.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the t_{sacr} should not be affected by the unplanned early terminations. The t_{sacr} should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than t_{sacr}, regardless their actual terminal sacrifice time, t_{sacr} was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. The present study is a 26 week study. For this kind of medium or short term study no such suggested value of k in the literature is known to this reviewer. Following the suggested value for long term studies, this reviewer analyzed the tumor data using k=3. Therefore, any significant finding form this analysis should be interpreted more carefully, including pathological consideration.

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female mice, respectively.

Multiple testing adjustment:

Following the FDA guidance for the carcinogenicity study design and data analysis for 26 week studies, all tests were performed at 0.05 level.

Reviewer's findings:

The tumor type with p-value less than 0.05 for dose response relationship across the vehicle control group / saline group and three treated groups is reported in the Text Table 2.

The reviewer's tumor analysis showed no statistically significant dose response relationship across the vehicle control group and the three treated groups; while a statistically significant dose response relationship was noted across the saline group and the three treated group (p=0.0281) for bronchioloalveolar adenoma combined with carcinoma in lung of male mice. No statistically

significant pairwise comparisons were noted when comparing the saline group and the three treated groups to the vehicle control group for both male and female mice. The analysis showed a statistically significant increased incidence of bronchioloalveolar adenoma/carcinoma in male mice positive control compared to their vehicle control (p=0.0387).

Table 2. Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons in Mice

Organ name	Tumor name	Saline (N)	Positive (P)	Vehicle (C) 0 mg	Low (L) 3 mg	Mid (M) 10 mg	High (H) 33 mg
Male - Lung	Bronchioloalveolar Adenoma/Carcinoma	0/25 (25)[&]	5/8(26)	2/22(25)	1/23 (25)	3/22 (25)	4/21 (25)
		P-C vs N	P-C vs P	P-Trend (C)	P-C vs L	P-C vs M	P-C vs H
		0.7653	0.0387 $	0.1202	0.5000	0.5200	0.3535
		P-Trend (N)	P-N vs P	P-N vs C	P-N vs L	P-N vs M	P-N vs H
		0.0281 $ [a]	0.0026 $	0.2347	0.4898	0.1173	0.0549
				P-Trend (N+C)	P-N+C vs L	P-N+C vs M	P-N+C vs H
				0.0405 $ [b]	0.7038	0.2097	0.0953

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted number of animals without tumor; ZZ=unweighted total number of animals observed;
$ = Significant at 5% level;
[a] Dose response relationship test across the saline group and the three treated groups.
[b] Dose response relationship test across the vehicle control + saline group and the three treated groups.

3. Summary

In this submission the sponsor included a carcinogenicity study report in transgenic mice. The study was to determine the potential carcinogenic toxicity of Calcifediol (25-hydroxyvitamin D_3), a vitamin D prohormone, when given by daily subcutaneous injection for 26 weeks to mice. In addition, the toxicokinetic characteristics of Calcifediol was determined.

Two separate experiments, one in male and one in female, were conducted in this mouse study. One hundred and fifty Hemizygous rasH2 transgenic mice of each sex were assigned randomly to one of six treatments which included one saline group, one vehicle control group, one positive control group, and three Calcifediol treated groups. For each sex, the sample size was 25 in each group. All groups except the positive group (group 1, 2, 4, 5, and 6) were administered by daily subcutaneous injection for a period of approximately 6 months; while the positive control received a single administration only on Day 1.

In the reviewer's analysis, the numbers of male mice surviving to their terminal necropsy were 24, 22, 3, 23, 25, and 25 in the saline group, the vehicle control group, the positive control group, the low, mid, and high dose groups, respectively. A statistically significant dose response relationship in mortality was noted for male mice (p=0.0097) with statistically significant increases in the mid and high groups when compared to the vehicle control group (p=0.0384 and 0.0384, respectively). For female, the numbers of mice surviving to their terminal necropsy were 23, 24, 5, 25, 25, and 24 in the saline group, the vehicle control group, the positive control group, the low, mid, and high dose groups, respectively. No statistically significant dose response relationship or pairwise group comparisons in mortality were noted in female mice. The reviewer's analysis also showed that the positive control group had a statistically significant (p<0.0001) increased unscheduled death compared with the vehicle control group in both male

and female mice.

The reviewer's tumor analysis showed no statistically significant dose response relationship across the vehicle control group and the three treated groups; while a statistically significant dose response relationship was noted across the saline group and the three treated group (p=0.0281) for bronchioloalveolar adenoma combined with carcinoma in lung of male mice. No statistically significant pairwise comparisons were noted when comparing the saline group and the three treated groups to the vehicle control group for both male and female mice.

Hepei Chen.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, DBVI

Cc: Archival NDA 208010

Dr. Parvaneh Espandiari
Dr. Lillian Patrician
Dr. Mohammad Atiar Rahman

4. Appendix

Table 1A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control (C)		Low (L) 3 mg		Mid (M) 10 mg		High (H) 33 mg		Saline (N)		Positive Control (P)	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13											8	32.00
14 - 26	3	12.00	2	8.00					1	4.00	14	88.00
Terminal sacrifice	22	88.00	23	92.00	25	100.00	25	100.00	24	96.00	3	12.00
Total	25		25		25		25		25		25	

Test	C, L, M, H	C vs. L	C vs. M	C vs. H	C vs. N	C vs. P
Dose-Response (Likelihood Ratio)	0.0097**	0.6471	0.0384*	0.0384*	0.2968	<.0001**
Homogeneity (Log-Rank)	0.1306	0.6467	0.0770	0.0770	0.3073	<.0001**

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

Table 1B: Intercurrent Mortality Rate in Female Mice

	Vehicle Control (C)		Low (L) 3 mg		Mid (M) 10 mg		High (H) 33 mg		Saline (N)		Positive Control (P)	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13			1	4.00							3	12.00
14 - 26	1	4.00	1	8.00			1	4.00	2	8.00	17	80.00
Terminal sacrifice	24	96.00	23	92.00	25	100.00	24	96.00	23	92.00	5	20.00
Total	25		25		25		25		25		25	

Test	C, L, M, H	C vs. L	C vs. M	C vs. H	C vs. N	C vs. P
Dose-Response (Likelihood Ratio)	0.7673	0.5521	0.2390	0.9885	0.5757	<.0001**
Homogeneity (Log-Rank)	0.5563	0.5557	0.3173	0.9885	0.5770	<.0001**

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
** = Significant at 1% level.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

Organ name	Tumor name	Saline (N) P-C vs N	Positive (P) P-C vs P	Vehicle (C) 0 mg P-Trend	Low (L) 3 mg P-C vs L	Mid (M) 10 mg P-C vs M	High (H) 33 mg P-C vs H
Gland, Harderian	Adenocarcinoma	0/25 (25) 0.5102	0/10(25) 0.2941	1/23(25) 0.4471	0/24 (25) 0.5000	0/25 (25) 0.5102	1/24 (25) 0.2551
	Adenoma	1/24 (25) 0.5102	0/10(25) NC	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Gland, Prostate	Carcinoma	0/25 (25) NC	1/10(24) 0.3235	0/23(24) NC	0/22 (23) NC	0/23 (23) NC	0/24 (24) NC
Gland, Thyroid	Follicular Cell Adenoma	0/25 (25) NC	0/10(25) NC	0/24(25) 0.2551	0/24 (25) NC	0/25 (25) NC	1/24 (25) 0.5102
Hemolymphoretic ular Tissue	Lymphoma, Malignant	0/25 (25) 0.5000	19/2(25) 0.0000 $	1/24(25) 0.7475	0/24 (25) 0.4898	0/25 (25) 0.5000	0/25 (25) 0.5000
Large Intestine, Cecum	Adenocarcinoma	0/25 (25) NC	2/8(25) 0.0802	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
	Leiomyoma	0/25 (25) NC	0/10(25) NC	0/24(25) 0.2551	0/24 (25) NC	0/25 (25) NC	1/24 (25) 0.5102
Liver	Hepatocellular Adenoma	1/24 (25) 0.5102	0/10(25) NC	0/24(25) 0.2551	0/24 (25) NC	1/24 (25) 0.5102	0/25 (25) NC
Lung	Bronchioloalveolar Adenoma	0/25 (25) 0.5102	4/8(25) 0.0336 $	1/23(25) 0.1500	1/23 (25) NC	3/22 (25) 0.3202	3/22 (25) 0.3202
	Bronchioloalveolar Carcinoma	0/25 (25) 0.5102	1/9(25) 0.5080	1/23(25) 0.4471	0/24 (25) 0.5000	0/25 (25) 0.5102	1/24 (25) 0.2551
	Bronchioloalveolar Adenoma/ Bronchioloalveolar Carcinoma	0/25 (25) 0.7653 0.0281 $ [a]	5/8(26) 0.0387 $	2/22(25) 0.1202	1/23 (25) 0.5000	3/22 (25) 0.5200	4/21 (25) 0.3535
	Hemangiosarcoma	0/25 (25) NC	0/10(25) NC	0/24(25) 0.2551	0/24 (25) NC	0/25 (25) NC	1/24 (25) 0.5102
Lymph Node, Mesenteric	Hemangiosarcoma	0/25 (25) NC	1/9(25) 0.3030	0/23(24) NC	0/22 (23) NC	0/25 (25) NC	0/25 (25) NC
Pancreas	Hemangiosarcoma	0/25 (25) NC	0/10(25) NC	0/24(25) 0.2551	0/24 (25) NC	1/24 (25) 0.5102	0/25 (25) NC
Site Injection, Scapular Left	Hemangiosarcoma	1/24 (25) 0.5102	0/0(1) NC	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Skin	Papilloma	0/25 (25) NC	1/9(25) 0.2941	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
	Squamous Cell Carcinoma	0/25 (25) NC	1/9(25) 0.2941	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable. $ = Significant at 5% level;
[a] Dose response relationship test across the saline group and the three treated groups.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice (Continued)

Organ name	Tumor name	Saline (N) P-C vs N	Positive (P) P-C vs P	Vehicle (C) 0 mg P-Trend	Low (L) 3 mg P-C vs L	Mid (M) 10 mg P-C vs M	High (H) 33 mg P-C vs H
Small Intestine, Duodenum	Adenocarcinoma	0/25 (25) NC	1/9(25) 0.2941	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Small Intestine, Ileum	Adenocarcinoma	0/25 (25) NC	1/9(25) 0.2941	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
	Leiomyosarcoma	0/25 (25) NC	0/10(25) NC	0/24(25) 0.2551	0/24 (25) NC	0/25 (25) NC	1/24 (25) 0.5102
Small Intestine, Jejunum	Adenocarcinoma	0/25 (25) NC	4/7(25) 0.0063 $	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
	Leiomyosarcoma	0/25 (25) NC	0/10(25) NC	0/24(25) 0.2551	0/24 (25) NC	0/25 (25) NC	1/24 (25) 0.5102
Spleen	Hemangiosarcoma	1/24 (25) 0.8384	1/9(24) 0.4654	4/20(25) 0.5093	0/24 (25) 0.9454	0/25 (25) 0.9498	2/23 (25) 0.6864
Stomach	Adenocarcinoma	0/25 (25) NC	1/9(25) 0.2941	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
	Papilloma	0/25 (25) NC	6/6(25) 0.0005 $	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
	Squamous Cell Carcinoma	0/25 (25) NC	6/8(25) 0.0011 $	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Whole body	Hemangiosarcoma	2/23 (25) 0.8084	2/8(25) 0.3299	5/19(25) 0.5120	1/24 (25) 0.9144	1/24 (25) 0.9144	3/22 (25) 0.6729

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable. $ = Significant at 5% level;

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	Saline (N) P-C vs N	Positive (P) P-C vs P	Vehicle (C) 0 mg P-Trend	Low (L) 3 mg P-C vs L	Mid (M) 10 mg P-C vs M	High (H) 33 mg P-C vs H
Gland, Harderian	Adenoma	1/24 (25) 0.5102	2/11(25) 0.1171	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Gland, Mammary	Adenocarcinoma	0/25 (25) NC	1/12(25) 0.3514	0/24(25) 0.5102	1/23 (25) 0.5000	0/25 (25) NC	0/25 (25) NC
Heart	Mesothelioma, Malignant	0/25 (25) NC	0/13(25) NC	0/24(25) 0.2551	0/24 (25) NC	0/25 (25) NC	1/24 (25) 0.5102
Hemolymphoretic ular Tissue	Lymphoma, Malignant	0/25 (25) NC	18/4(25) 0.0000 $	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Larynx	Papilloma	0/25 (25) NC	1/12(25) 0.3514	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Lung	Bronchioloalveolar Adenoma	1/24 (25) 0.5102	3/11(25) 0.0431 $	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Skin	Papilloma	0/25 (25) NC	3/11(25) 0.0431 $	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
	Squamous Cell Carcinoma	1/24 (25) 0.5102	4/10(25) 0.0136 $	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Small Intestine, Jejunum	Adenocarcinoma	0/25 (25) NC	3/10(24) 0.0368 $	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Spleen	Hemangiosarcoma	2/22 (24) 0.4844	2/12(25) 0.2888	1/24(25) 0.2639	1/23 (25) 0.7449	1/24 (25) NC	2/23 (25) 0.5000
Stomach	Papilloma	0/25 (25) NC	10/5(25) 0.0000 $	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
	Squamous Cell Carcinoma	0/25 (25) NC	2/11(25) 0.1171	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Thymus	Thymoma, Benign	0/25 (25) NC	0/13(25) NC	0/24(25) 0.2577	0/24 (25) NC	0/24 (24) NC	1/24 (25) 0.5102
Tongue	Papilloma	0/25 (25) NC	1/12(25) 0.3514	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Urinary Bladder	Mesenchymal Tumor, Malignant	1/23 (24) 0.5000	0/13(24) NC	0/24(25) NC	0/24 (25) NC	0/24 (24) NC	0/25 (25) NC
	Transitional Cell Carcinoma	0/24 (24) NC	0/13(24) NC	0/24(25) 0.5103	1/23 (25) 0.5000	1/23 (24) 0.5000	0/25 (25) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable. $ = Significant at 5% level;

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Saline (N) P-C vs N	Positive (P) P-C vs P	Vehicle (C) 0 mg P-Trend	Low (L) 3 mg P-C vs L	Mid (M) 10 mg P-C vs M	High (H) 33 mg P-C vs H
Uterus	Adenoma	0/25 (25) NC	1/12(25) 0.3514	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
	Endometrial Stromal Polyp	0/25 (25) NC	7/7(25) 0.0003 $	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
	Hemangiosarcoma	1/24 (25) 0.5102	0/13(25) NC	0/24(25) NC	0/24 (25) NC	0/25 (25) NC	0/25 (25) NC
Vagina	Papilloma	0/25 (25) NC	1/10(22) 0.3143	0/24(25) NC	0/24 (25) NC	0/24 (24) NC	0/25 (25) NC
Whole body	Hemangiosarcoma	4/21 (25) 0.1743	2/12(25) 0.2888	1/24(25) 0.1256	1/23 (25) 0.7449	2/23 (25) 0.5000	3/22 (25) 0.3046

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable. $ = Significant at 5% level;

Figure 1A: Kaplan-Meier Survival Functions for Male Mice

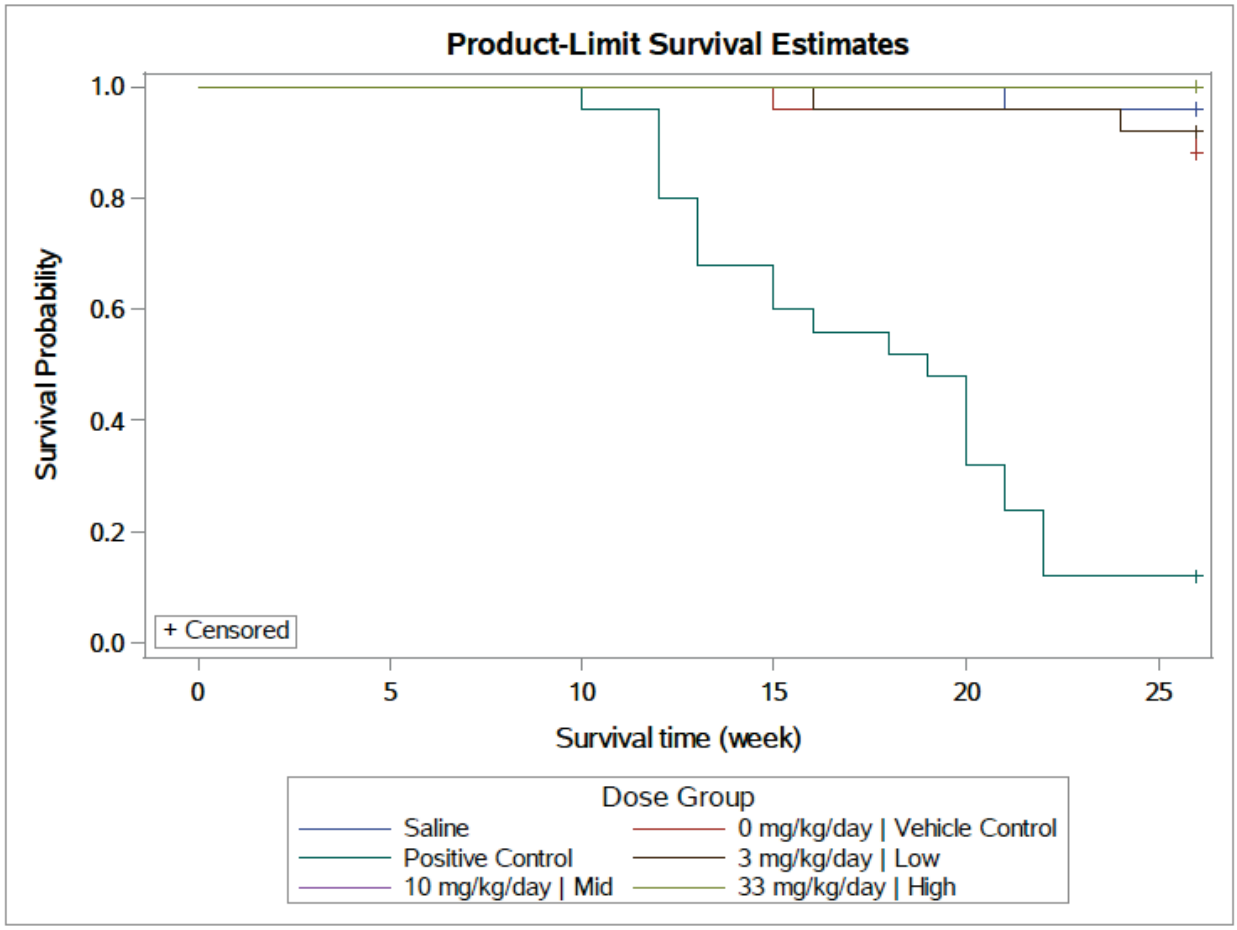
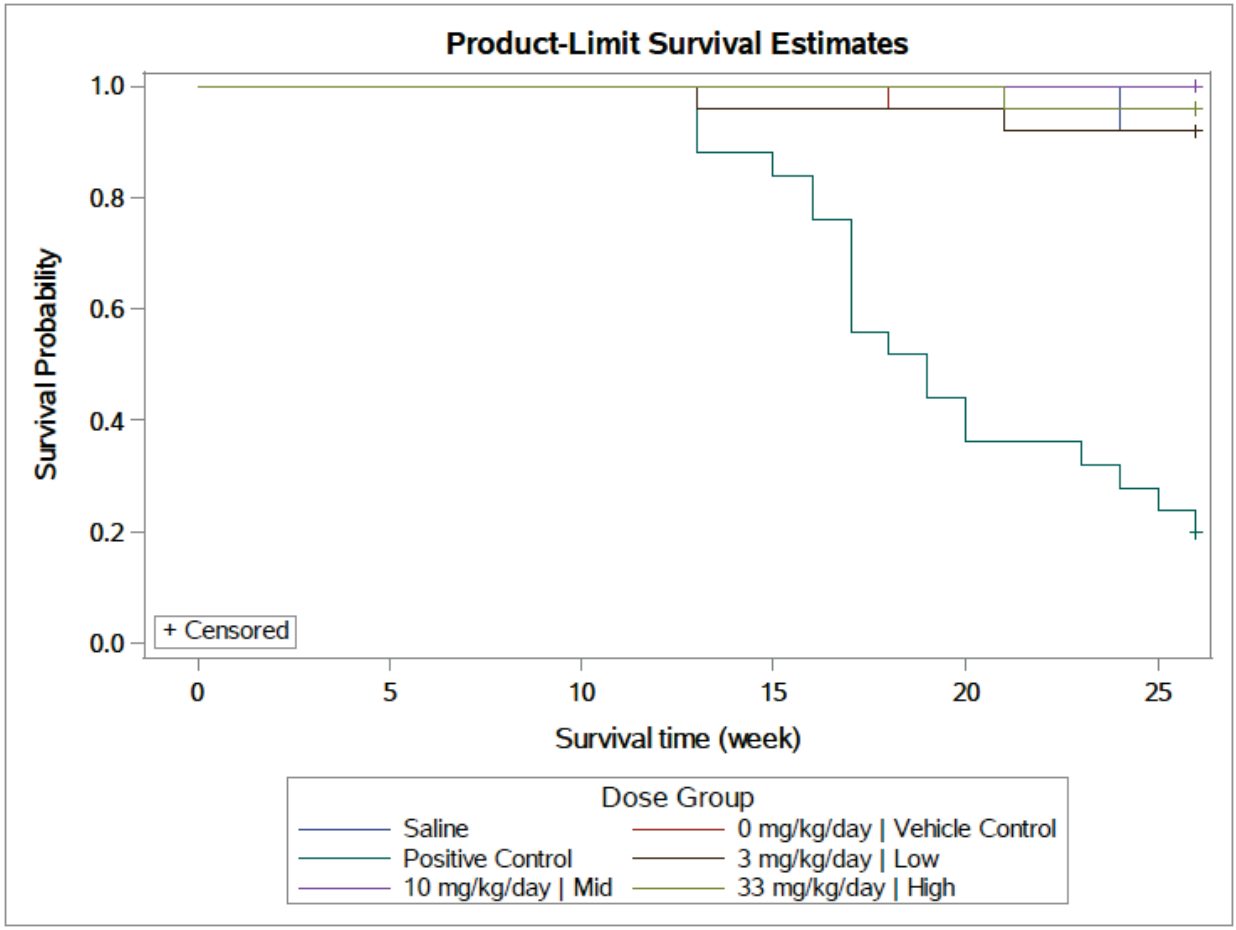


Figure 1B: Kaplan-Meier Survival Functions for Female Mice



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/s/

HEPEI CHEN
12/08/2015

KARL K LIN
12/10/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: NDA208010 Applicant: OPKO Stamp Date: May 29 2015

Drug Name: Rayaldee NDA/BLA Type: Standard Review

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	*			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	*			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	*			For subgroup analysis for efficacy, only pooled analysis on studies 3001 and 3002 was conducted.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	*			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?
Yes.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comments
Designs utilized are appropriate for the indications requested.	*			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	*			For the primary analysis, it is not clear how the endpoint will be calculated if there are some missing values in visits 10,11,12,13 of EAP and whether there is imputation.
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			*	
Appropriate references for novel statistical methodology (if present) are included.	*			In section 9.2 of SAP, details about multiple imputation methods should be provided.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Safety data organized to permit analyses across clinical trials in the NDA/BLA.	*			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		*		No sensitivity analysis (proposed in SAP) results can be found.

Comments:
We will make the following information request.

Please describe the exact rules that were used for calculating the change from baseline in iPTH to EAP in the primary analysis if there were missing values in baseline visits (1,2,3,4) and/or the EAP visits (10,11,12,13). Please describe under what circumstances, if any, imputation was carried out, as well as the models and assumptions used for the imputation. It states in the SAP that "Subjects without primary endpoint data during the entire efficacy assessment period will be classified as treatment failures". Explain whether this approach was implemented, as well as what approach was used for patients missing only some of the primary endpoint data during the efficacy assessment period.

In addition, Section 9.2 of the statistical analysis plan for study CTAP101-CL-3001 states that "The final selection of the imputation method will be made after reviewing the extent and pattern of missing values, but prior to unblinding treatment assignments". Please indicate whether the imputation approach was finalized prior to data unblinding and if so, where it is documented. In the same section, it states that "we will perform a sensitivity analysis to compare that analysis with the analysis that includes the data points collected following study drug discontinuation". Please describe where the sensitivity analysis results are documented or submit results from such an analysis.

Please provide SAS code for the primary and key secondary analyses as well as sensitivity analyses (preferably, just the code to carry out the analyses rather than to produce tables and figures).

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/s/

JIWEI HE
07/16/2015

GREGORY P LEVIN
07/16/2015