CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205917Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	205917
Supporting document/s:	1
Applicant's letter date:	06/07/2013
CDER stamp date:	06/10/2013
Product:	Paricalcitol Injection
Indication:	Prevention/treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5
Applicant:	Hikma Pharmaceuticals Co. Ltd
Review Division:	DMEP
Reviewer:	Parvaneh Espandiari, Ph.D.
Supervisor/Team Leader:	Karen Davis-Bruno, Ph.D.
Division Director:	Jean-Marc Guettier, M.D.
Project Manager:	Meghna M Jairath, Pharm.D.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of [NDA 205917] are owned by [Hikma Pharmaceuticals Co] or are data for which [Hikma Pharmaceuticals Co] has obtained a written right of reference.

Any information or data necessary for approval of [NDA 205917] that [Hikma Pharmaceuticals Co. Ltd] does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of [NDA 205917].

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

The Sponsor proposed a new drug application under section 505(b)(2) for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 5. The listed drug (LD) is Zemplar™ (NDA 020819) for the same indication and for the same patient population. The safety profile of the Zemplar has been well established; therefore, nonclinical (pharmacology, pharmacokinetics and toxicology) studies for the new formulation are relying on the previous findings of the safety and efficacy for Zemplar.
The new formulation has the same active ingredient (Paricalcitol) of the LD; however, it has different levels of alcohol (35% v/v vs. 20% v/v in Zemplar) and different inactive ingredient of sorbitol (7% v/v vs. 30% v/v propylene glycol in Zemplar). The levels of alcohol and sorbitol are within Inactive Ingredients Guidance (IIG) limits for other marketed i.v. products and additional toxicity/safety studies are not required for qualification of the inactive ingredient for the new formulation.
The Sponsor conducted a 4-week repeat-dose toxicity study in rats with a 2-week recovery period to assess the potential toxicity of the new formulation to the approved Zemplar.

1.2 Brief Discussion of Nonclinical Findings

Results of the nonclinical study suggested similar TK and/or toxicity profile between the new formulations of Paricalcitol to the approved LD of Zemplar.
TK data were similar for both compounds at 1µg/kg/day (for both time points of Day 1 and 27) and at 3µg/kg/day on Day 1. On Day 27, for new formulation, at 3µg/kg/day, C_{max} vales were lower (~2.2X for males and 1.6X for females) and T_{max} values were higher (males 3X and females 2X) with the new paricalcitol formulation compared to Zemplar. These differences at higher dose level did not affect the potential toxicity of the new formulation based on the histopathology incidences provided.

1.3 Recommendations

None

1.3.1 Approvability

Yes

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Section 8.1 Pregnancy

Same as the LD (Zemplar)

Section 8.3 Nursing Mothers

Same as the LD (Zemplar)

Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Same as the LD (Zemplar)

2 Drug Information

2.1 Drug

CAS Registry Number: 131918-61

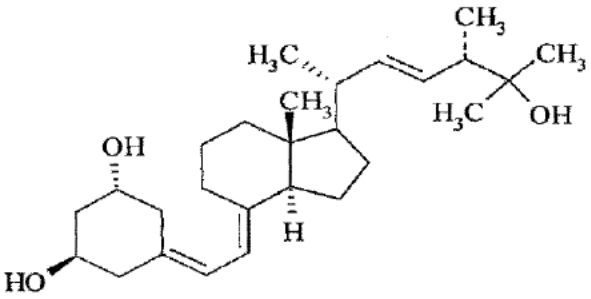
Generic Name: Analog of calcitriol, the metabolically active form of vitamin D

Code Name: NA

Chemical Name: (1α,3β,7E,22E)-19-Nor-9,10-Secoergosta-5,7,22-triene-1,3,25-triol; or, (7E,22E)-19-Nor-9,10- Secoergosta- 5,7,22- triene-1α, 3ß, 25-triol

Molecular Formula/Molecular Weight: $C_{27}H_{44}O_3$/416.64 g/mol

Structure or Biochemical Description



Pharmacologic Class: Vitamin D analogue of calcitriol, the metabolically active form of vitamin D

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 20819 (Zemplar™); DMF (b) (4) (Paricalcitol); ANDA 090,829, ANDA (b) (4), ANDA (b) (4) DA 018,044; NDA 018,874; NDA 020,862 and IND (b) (4)

2.3 Drug Formulation

The proposed new formulation has an active ingredient of Paricalcitol (same as LD) and two inactive ingredients of alcohol (35% vs, 20% in RD) and sorbitol alcohol (vs. propylene glycol alcohol in the LD). Alcohol is approved for use in concentrations up to (b) (4)% in i.v. infusion and injection dosage forms (FDA database, for Inactive Ingredient Search for Approved Drug Products). Sorbitol is recognized as safe (GRAS) and is used as excipient in approved drugs (FDA database, for Inactive Ingredient Search for Approved Drug Products). Sponsor's Tables:

	ZEMPLAR (paricalcitol) Injection (RLD)	Exela's Paricalcitol Injection
Strength(s)	2 µg/mL and 5 µg/mL	2 µg/mL and 5 µg/mL
Configurations/ Label Claim	2 µg / 1 mL 5 µg / 1 mL 5 µg / 2 mL	2 µg / 1 mL 5 µg / 1 mL 5 µg / 2 mL
Active Ingredient	Paricalcitol, USP	Paricalcitol, USP
(b) (4)	Propylene Glycol Alcohol	Sorbitol Alcohol
	Water for Injection	Water for Injection
Dosage Form	Injection, solution	Injection, solution
Route of Administration	Intravenous	Intravenous

IIG Levels of the Excipients in Paricalcitol Injection

Ingredients	IIG Levels[1]	Concentration % v/v
Sorbitol Solution, USP	Intravenous (Infusion); Injection (b) (4)%	7%
Alcohol, USP	Intravenous (Infusion); Injection (b) (4)%	35%
Water for Injection, USP	N/A	q.s. to 100.0%

Comparison of Exela's Paricalcitol Injection Drug Product with Abbott Laboratories Zemplar® (paricalcitol) Injection.

Ingredients	Exela's Formulation	Abbott's Formulation[1]
Paricalcitol	2 µg/mL or 5 µg/mL	2 µg/mL or 5 µg/mL
Alcohol, 190 proof, USP	35% v/v	20% v/v
Propylene Glycol, USP		30% v/v
Sorbitol Solution, 70%, USP	7% v/v	
Water for Injection, USP	q.s.	q.s.

[1] Information regarding Abbott Laboratories Zemplar ® (paricalcitol) Injection formulation was obtained from the current package insert, vial label, and carton.

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

The Sponsor refers to the DMF (b) (4) for Paricalcitol.

2.6 Proposed Clinical Population and Dosing Regimen

The recommended initial dose of Paricalcitol is 0.04mcg/kg to 0.1mcg/kg (2.8 – 7 mcg) as a bolus dose no more frequently than every other day at any time during dialysis.

2.7 Regulatory Background

- On October 19, 2010, Exela Pharma Sciences submitted the PIND (b) (4) for Paricalcitol Injection (2 and 5mcg/mL).
- On January 3, 2011, Pre-NDA meeting was requested to discuss the drug development of Paricalcitol injection (2 and 5 mcg/mL) under 505(b)(2) with the LD of Zemplar (NDA 20-819). The letter of authorization for DMF (b) (4) (Paricalcitol) was also submitted. Currently, for this NDA, Exela Pharma Sciences, LLC ("Exela") acts as agent for the NDA applicant, Hikma Pharmaceutical Co. Ltd.
- On July 11, 2012, the Sponsor requested a meeting with the Agency to discuss the new formulation development under 505(b)(2) application. The Agency denied the request for a meeting and responded to the submitted questions in the meeting request package as follows:

Pharm/Tox Response to Sponsor's Questions in PIND (Repeated in IND (b) (4))

Question 1: Does the Agency concur that for Exela's Paricalcitol Injection, the appropriate Reference Listed Drug (RLD) is ZEMPLAR (NDA #020819) injection?

* ZEMPLAR contains, as per labeling, paricalcitol, 2 mcg or 5 mcg; propylene glycol. 30% (v/v); and alcohol. 20% (v/v) per I mL in sterile water for injection?

* Exela's Paricalcitol injection will contain paricalcitol, 2 mcg or 5 mcg; alcohol. 35% (v/v); and sorbitol solution 7% (v/v) per 1 mL in water for injection.

Pharm/Tox Response: Yes.

Question 2: Is the Agency in agreement with the 505(b)(2) regulatory pathway for Exela's Paricalcitol injection?

* Exela proposes to rely on data in the public domain to satisfy non-clinical requirements and to provide information about the clinical pharmacology efficacy and safety of paricalcitol Injection for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5. Specifically, Exela' intends to use ZEMPLAR as the Reference Listed Drug. Exela believes that the distinct formulation differences between ZEMPLAR and Exela's Paricalcitol Injection identified above will make Exela's filing ineligible for an ANDA submission under 505(j).

Pharm/Tox Response: Yes.
The Agency is in agreement with the 505(b)(2) regulatory pathway for Exela's Paricalcitol injection.

Question 3: Does the FDA agree that the pharmacokinetics, efficacy, and safety data in the public domain and from the approved labeling of ZEMPLAR (NDA #020819) support the efficacy and safety of Exela's Paricalcitol Injection for the same indications?

* Exela 's Paricalcitol Injection contain/¡ the same amount of active drug substance (Paricalcitol) as ZEMPLAR. Exela 's Paricalcitol Injection distinctly differs in the (b) (4) used to dissolve paricalcitol. From the available literature, Exela is unable to find any data or report that indicate that these differences in formulation between ZEMPLAR and Exela's Paricalcitol Injection .will affect safety or efficacy of Exela 's Paricalcitol Injection. Exela therefore requests that the FDA determine that no pharmacokinetic studies or clinical studies are needed to demonstrate efficacy and safety of Exela's Paricalcitol injection.

Pharm/Tox Response: Please see section 2.6.1.3.

Question 4: Does the FDA agree that the pediatric studies will be required and that PREA has been addressed?

* Abbott Laboratories has conducted studies in patients aged 5-19 years, with end-stage renal disease on hemodialysis. Exela requests that the FDA determine that no clinical studies in the pediatric population are needed to demonstrate efficacy and safety of Exela's Paricalcitol Injection for pediatric use.

Pharm/Tox Response: It is premature to comment on the proposed pediatric plan at this time. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Please provide your request and rationale for any waiver or deferral at the time of the NDA submission. If you plan to ask for a deferral of the pediatric trial for a certain age group, please provide a brief description of the proposed trial at the time of BLA submission, focusing on the collection of adequate information on dose, safety and efficacy, as well as the protocol submission date, the study completion date, and the final report submission date.

- On October 11, 2012, the Sponsor acknowledged the receipt of the communication dated 08/30/2012 and requested clarification on the Agency's requirements for the bridging nonclinical 28-day repeat-dose toxicology study with toxicokinetics, local tolerance, and the recovery period in a relevant species. The following are the questions and the reviewer's responses to the questions.

Exela's Additional Questions:

Exela requests clarification on the Agency's requirements of the bridging nonclinical 28-day repeat-dose toxicology study with toxicokinetics, local tolerance, and the recovery period in a relevant species.

o *What species(s) should be used in the completion of this study that would satisfy the bridging data requirement as well as provide sufficient data to support a biowaiver?*

Crl: CD (SD) rats from [redacted] (b) (4) *are indicated as the species selected in your Draft Protocol 11-Oct-12. for the 28-day repeat dose toxicity study This species is acceptable for the proposed study. The adequacy of data to support a biowaiver is a review issue.*

o *Does the Agency agree that the bridging study requirement to support the NDA filing, for both the 0.2 µg/mL and 0.5 µg/mL drug products, is satisfied with only the 0.2 µg/mL drug product as this represents the largest formulation volume (highest exposure to the formulation excipients)?*

You plan to submit a 505(b)(2) application for your drug products containing two different formulations (2 mcg/mL and 5mcg/mL) based on their comparability to the two approved formulations of the labeled drug (2 mcg/mL and 5mcg/mL Zemplar (paricalcitol) Injection. Based on the information you provided, the concentrations of the drug substance vary but the excipients concentrations (b) (4) in your two formulations. The agency suggest that you test your formulation with higher concentration of the drug substance (5mcg/mL) along with a comparable concentration of agency approved LD, Zemplar in your bridging nonclinical toxicity study

- *Does the FDA agree that the studies outlined in the attached draft protocol satisfies the bridging data requirement as well as provides sufficient data to support a biowaiver?*

The study design outlined in your draft protocol for the bridging study is acceptable. However, the adequacy of data to support a biowaiver is a review issue.

- On Jun 10, 2013, The Sponsor submitted NDA205917 application under section 505(b)(2) for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5.

3 Studies Submitted

A 4-week repeat dose toxicity studies in rats

3.1 Studies Reviewed

A 4-week repeat dose toxicity studies in rats

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

P/T reviews for IND (b) (4)

4 Pharmacology

4.1 Primary Pharmacology

No new information.

Paricalcitol, a synthetically manufactured analog of calcitriol, is the active form of vitamin D. Its biological actions are mediated through binding of the vitamin D receptor (VDR), which results in the selective activation of vitamin D responsive pathways. Vitamin D and Paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion.

4.2 Secondary Pharmacology

No new information.

4.3 Safety Pharmacology

No new information.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No new information.

5.2 Toxicokinetics

TK data is included in the toxicity study.

6 General Toxicology

A 4-week repeat dose toxicity study in rats with a 2-week recovery period was conducted to assess the potential toxicity and TK of the new Paricalcitol formulation to the approved Zemplar. Findings of this study showed consistency between the pharmacological and toxicity profiles of the new formulation to the LD.

6.2 Repeat-Dose Toxicity

Study title: Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period	
Study no.:	030508
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	23-Jan-2013
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	Paricalcitol (Lot XLNM1109); 103.5% Zemplar (Lot 20-569-DK); 99.4%

Key Study Findings:

Toxicity profiles were similar for both new formulations and the LD.

Methods	
Doses:	0 (vehicle), 1, or 3µg/kg/day Paricalcitol or Zemplar
Frequency of dosing:	3 days/week for 4 consecutive weeks
Route of administration:	Intravenous (tail vein)
Dose volume:	0.2 or 0.6mL/kg
Formulation/Vehicle:	30% propylene glycol (v/v) and 20% (b) (4) (v/v) in Sterile Water for Injection
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	15/sex/group

Age:	8.7 to 9 weeks of age
Weight:	268.6 to 364.3g (male) and 173.3 to 246.1g (female)
Satellite groups:	Control: 3/sex/group; Paricalcitol or Zemplar 9/sex/group
Unique study design:	Recovery groups= 5/sex/group
Deviation from study protocol:	None

Sponsor's Table:

Group Assignment and Dose Levels

Dose Group	Number of Animals (M/F)	Test Article	Dose Level (µg/kg)	Dose Concentration (µg/mL)	Dose Volume (mL/kg)	Number of Animals for Necropsy (M/F)	
						Terminal (Day 28*)	Recovery (Day 42*)
1	15/15	Vehicle	0	0	0.6	10/10	5/5
2	15/15	Paricalcitol	1	5	0.2	10/10	5/5
3	15/15	Paricalcitol	3	5	0.6	10/10	5/5
4	15/15	Zemplar	1	5	0.2	10/10	5/5
5	15/15	Zemplar	3	5	0.6	10/10	5/5
6 (TK)	3/3	Vehicle	0	0	0.6	0/0	0/0
7 (TK)	9/9	Paricalcitol	1	5	0.2	0/0	0/0
8 (TK)	9/9	Paricalcitol	3	5	0.6	0/0	0/0
9 (TK)	9/9	Zemplar	1	5	0.2	0/0	0/0
10 (TK)	9/9	Zemplar	3	5	0.6	0/0	0/0

TK = toxicokinetics
**Terminal necropsy was one day following the final dose. Recovery necropsy was 14 days following the terminal necropsy.*

Observations and Results

Mortality

None

Clinical Signs

Unremarkable

Body Weights

Unremarkable

Feed Consumption

Unremarkable

Ophthalmoscopy

Unremarkable

ECG

Unremarkable

Hematology

Unremarkable

Clinical Chemistry

Unremarkable

Changes were reported with the lack of a dose response relationship and large individual animal variation.

Urinalysis

Unremarkable

Gross Pathology

Unremarkable

Organ Weights

Unremarkable

Histopathology

Adequate Battery: Yes, histopathological evaluation was performed only for tissues of animals that were treated with control or 3µg/kg/day of Paricalcitol or Zemplar.

Peer Review: Yes

Histopathological findings:

- Kidney: Calcification was reported in both new formulations for both Main and Recovery studies; however, these findings in the kidneys are less concerning because of the patient population not having normal renal function.
- Thyroid: Focal cyst (minimal unilateral) was higher in males treated with the new formulation compared to males treated with Zemplar (4/10vs. 2/10). This incidence was not related to the treatment (embryonic) and was not reported after the Recovery study.
- Uterus: At the end of the Recovery study, dilation; lumen; bilateral/unilateral was higher for the new formulation (4/5) compared to the control (2/5) or Zemplar (1/5) treated animals; however, this finding was not related to the treatment.

See Table below for significant histopathological changes:

		Males			Females		
		Control	P*	Z**	Control	P	Z
Kidney							
Fibrosis; subcapsular; unilateral; focal (minimal)	Main Recovery	0/10 0/5	0/10 0/5	2/10 1/5	0/10 0/5	1/10 0/5	0/10 0/5
Basophilia; tubular; cortex; unilateral; focal	Main Recovery	0/10 0/5	1/10 0/5	0/10 0/5	0/10 0/5	0/10 0/5	0/10 0/5
Nephrocalcinosis; proximal tubule; unilateral, focal,	Main Recovery	0/10 0/5	1/10 3/5	0/10 1/5	0/10 0/5	1/10 1/5	1/10 2/5
Nephrocalcinosis; proximal tubule; unilateral, multifocal,	Main Recovery	0/10 0/5	2/10 0/5	2/10 2/5	0/10 0/5	1/10 0/5	1/10 0/5
Nephrocalcinosis; proximal tubule; bilateral, multifocal,	Main Recovery	0/10 0/5	0/10 2/5	1/10 0/5	0/10 0/5	1/10 0/5	0/10 1/5
Mineralization; corticomedullary junction;	Main Recovery	0/10 0/5	0/10 0/5	0/10 0/5	0/10 0/5	0/10 1/5	0/10 0/5

bilateral; multifocal							
Thyroid Gland							
Cyst(s), embryonic remnants; unilateral; focal	Main Recovery	1/10 0/5	4/10 0/5	2/10 1/5	3/10 0/5	3/10 0/5	2/10 1/5
Cyst(s), embryonic remnants; bilateral; multifocal	Main Recovery	0/10 0/5	0/10 0/5	1/10 0/5	0/10 0/5	0/10 1/5	2/10 1/5
Uterus							
Dilation; lumen; bilateral/unilateral	Main Recovery	NA	NA	NA	5/10 2/5	4/10 4/5	1/10 1/5

*P=Paricalcitol; **Z=Zemplar (LD); Main Study (n=10); Recovery (n=5)

See Tables below from the Sponsor:

Table 40: Summary Histopathology Data

	MALES			FEMALES		
Dose (µg/kg)	0 µg/kg	3 µg/kg	3 µg/kg	0 µg/kg	3 µg/kg	3 µg/kg
Number of Animals on Study :	10	10	10	10	10	10
	Vehicle	Paricalcitol	Zemplar	Vehicle	Paricalcitol	Zemplar
KIDNEYS;						
Examined	(10)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	4	2	3	6	3	5
fibrosis; subcapsular; unilateral; focal	(0)	(0)	(2)	(0)	(1)	(0)
minimal	0	0	2	0	1	0
infarction; unilateral; focal	(0)	(0)	(0)	(0)	(2)	(0)
minimal	0	0	0	0	2	0
basophilia; tubular; cortex; unilateral; focal	(0)	(1)	(0)	(0)	(0)	(0)
minimal	0	1	0	0	0	0
basophilia; tubular; cortex; unilateral; multifocal	(4)	(3)	(3)	(2)	(3)	(3)
minimal	4	3	3	2	3	3
basophilia; tubular; cortex; bilateral; multifocal	(1)	(3)	(3)	(0)	(1)	(1)
minimal	1	3	3	0	1	1
nephrocalcinosis; proximal tubule; unilateral; focal	(0)	(1)	(0)	(0)	(1)	(1)
minimal	0	1	0	0	1	1
nephrocalcinosis; proximal tubule; unilateral; multifocal	(0)	(2)	(2)	(0)	(0)	(0)
minimal	0	2	2	0	0	0
nephrocalcinosis; proximal tubule; bilateral; multifocal	(0)	(0)	(1)	(0)	(1)	(0)
minimal	0	0	1	0	1	0

Test Article-Related Kidney Findings: Terminal Necropsy (Day 28)

	MALES			FEMALES		
	Grp 1	Grp 3	Grp 5	Grp 1	Grp 3	Grp 5
Dose (ug/kg):	0	3	3	0	3	3
Number of Animals on Study :	10	10	10	10	10	10
KIDNEYS;						
Examined	(10)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	4	2	3	6	3	5
nephrocalcinosis; proximal tubule; unilateral; focal, minimal	0	1	0	0	1	1
nephrocalcinosis; proximal tubule; unilateral; multifocal, minimal	0	2	2	0	0	0
nephrocalcinosis; proximal tubule; bilateral; multifocal, minimal	0	0	1	0	1	0

Test Article-Related Kidney Findings: Recovery Necropsy (Day 42)

	MALES			FEMALES		
	Grp 1	Grp 3	Grp 5	Grp 1	Grp 3	Grp 5
Dose (ug/kg):	0	3	3	0	3	3
Number of Animals on Study :	5	5	5	5	5	5
KIDNEYS;						
Examined	(5)	(5)	(5)	(5)	(5)	(5)
Within Normal Limits	3	0	1	2	2	1
nephrocalcinosis; proximal tubule; unilateral; focal, minimal	0	3	1	0	1	2
nephrocalcinosis; proximal tubule; unilateral; multifocal, minimal	0	0	2	0	0	0
nephrocalcinosis; proximal tubule; bilateral; multifocal, minimal	0	2	0	0	0	1

Table 40: Summary Histopathology Data – Terminal / Died During or Following Blood Collection

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

Removal Reason: Killed Terminal/Died During or Following Blood Collection	MALES					FEMALES				
Test Article	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5
Dose (ug/kg)	0 ug/kg	1 ug/kg	3 ug/kg	1 ug/kg	3 ug/kg	0 ug/kg	1 ug/kg	3 ug/kg	1 ug/kg	3 ug/kg
Number of Animals on Study :	10	10	10	10	10	10	10	10	10	10
ADRENAL GLANDS;										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
AORTA;										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
BONE MARROW, FEMUR;										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
BONE MARROW, STERNUM;										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
BONE, FEMUR;										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
BONE, STERNUM;										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
BRAIN;										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
CERVIX;										
Examined	(-)	(-)	(-)	(-)	(-)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	-	-	-	-	-	10	0	10	0	10
EPIDIDYMIDES;										
Examined	(10)	(0)	(10)	(0)	(10)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	9	0	10	0	9	-	-	-	-	-
infiltration, mononuclear cells; interstitial; unilateral; focal	(1)	(0)	(0)	(0)	(0)	(-)	(-)	(-)	(-)	(-)
minimal	1	0	0	0	0	-	-	-	-	-
hypospermia; unilateral	(0)	(0)	(0)	(0)	(1)	(-)	(-)	(-)	(-)	(-)
moderate	0	0	0	0	1	-	-	-	-	-

Table 40: Summary Histopathology Data – Terminal / Died During or Following Blood Collection (continued)

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

Removal Reason: Killed Terminal/Died During or Following Blood Collection	MALES					FEMALES				
Test Article	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	10	10	10	10	10	10	10	10	10	10
ESOPHAGUS:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
EYES:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
HEART:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	6	0	5	0	5	9	0	9	0	6
cardiomyopathy; focal	(4)	(0)	(3)	(0)	(3)	(1)	(0)	(1)	(0)	(1)
minimal	4	0	3	0	3	1	0	0	0	1
mild	0	0	0	0	0	0	0	1	0	0
cardiomyopathy; multifocal	(0)	(0)	(2)	(0)	(2)	(0)	(0)	(0)	(0)	(3)
minimal	0	0	2	0	2	0	0	0	0	3
INJECTION SITE:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	8	0	10	0	10	9	0	9	0	9
inflammation; chronic-active; locally extensive	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(1)	(0)	(1)
mild	0	0	0	0	0	1	0	1	0	1
inflammation, acute; perivascular; diffuse	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	2	0	0	0	0	0	0	0	0	0
INTESTINE, CECUM:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
INTESTINE, COLON:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
INTESTINE, DUODENUM:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
INTESTINE, ILEUM:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10

Table 40: Summary Histopathology Data – Terminal / Died During or Following Blood Collection (continued)

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

Removal Reason: Killed Terminal/Died During or Following Blood Collection	MALES					FEMALES				
Test Article	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	10	10	10	10	10	10	10	10	10	10
INTESTINE, JEJUNUM:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
INTESTINE, RECTUM:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
KIDNEYS:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	4	0	2	0	3	6	0	3	0	5
fibrosis; subcapsular; unilateral; focal	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(1)	(0)	(0)
minimal	0	0	0	0	2	0	0	1	0	0
infarction; unilateral; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
minimal	0	0	0	0	0	0	0	2	0	0
mineralization; papilla; unilateral; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	0	0	1	0	0	0	0	0
mineralization; cortex; unilateral; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
minimal	0	0	0	0	0	0	0	0	0	1
mineralization; corticomedullary junction; unilateral; focal	(0)	(0)	(1)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
minimal	0	0	1	0	0	1	0	0	0	0
mineralization; corticomedullary junction; bilateral; multifocal	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(1)
minimal	0	0	0	0	0	1	0	0	0	1
basophilia; tubular; cortex; unilateral; focal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	1	0	0	0	0	0	0	0
basophilia; tubular; cortex; unilateral; multifocal	(4)	(0)	(2)	(0)	(3)	(2)	(0)	(3)	(0)	(3)
minimal	4	0	2	0	3	2	0	3	0	3
basophilia; tubular; cortex; bilateral; multifocal	(1)	(0)	(3)	(0)	(3)	(0)	(0)	(1)	(0)	(1)
minimal	1	0	3	0	3	0	0	1	0	1
infiltration, mononuclear cells; cortex; unilateral; multifocal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0	0	0
infiltration, mononuclear cells; cortex; bilateral; multifocal	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	2	0	0	0	0	0	0	0	0	0

Table 40: Summary Histopathology Data – Terminal / Died During or Following Blood Collection (continued)

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

Removal Reason: Killed Terminal/Died During or Following Blood Collection	MALES					FEMALES				
Test Article	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar ----	Group 5
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	10	10	10	10	10	10	10	10	10	10
KIDNEYS: (continued)										
cyst(s), embryonic remnants; corticomedullary junction; unilateral; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0	0	0
nephrocalcinosis; proximal tubule; unilateral; focal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(1)	(0)	(1)
minimal	0	0	1	0	0	0	0	1	0	1
nephrocalcinosis; proximal tubule; unilateral; multifocal	(0)	(0)	(2)	(0)	(2)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	2	0	2	0	0	0	0	0
nephrocalcinosis; proximal tubule; bilateral; multifocal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(1)	(0)	(0)
minimal	0	0	0	0	1	0	0	1	0	0
LIVER:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	3	0	1	0	2	3	0	2	0	3
infiltration, mononuclear cells; multifocal	(7)	(0)	(9)	(0)	(8)	(7)	(0)	(8)	(0)	(7)
minimal	7	0	9	0	8	7	0	8	0	7
hyperplasia; biliary; focal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	1	0	0	0	0	0	0	0
LUNGS:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	8	9	0	10	0	9
hemorrhage; acute; alveolus; locally extensive	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(1)
mild	0	0	0	0	1	0	0	0	0	1
mineralization; muscularis; artery; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	0	0	1	0	0	0	0	0
granuloma; interstitium; focal	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
minimal	0	0	0	0	0	1	0	0	0	0
LYMPH NODE, CERVICAL:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	9	0	10	0	9	10	0	10	0	10
congestion; subcapsular sinus; multifocal	(1)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	1	0	0	0	0	0
LYMPH NODE, MESENTERIC:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10

Table 40: Summary Histopathology Data – Terminal / Died During or Following Blood Collection (continued)

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

Removal Reason: Killed Terminal/Died During or Following Blood Collection	MALES					FEMALES				
Test Article	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	10	10	10	10	10	10	10	10	10	10
MAMMARY GLANDS:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
NERVE, OPTIC:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
NERVE, SCIATIC:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
OVARIES:										
Examined	(-)	(-)	(-)	(-)	(-)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	-	-	-	-	-	10	0	10	0	10
PANCREAS:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
PARATHYROID GLANDS:										
Examined	(10)	(0)	(8)	(0)	(10)	(10)	(0)	(9)	(0)	(10)
Within Normal Limits	10	0	8	0	10	10	0	9	0	10
Not Examined: NOT PRESENT	0	0	2	0	0	0	0	1	0	0
PITUITARY GLAND:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
PROSTATE GLAND:										
Examined	(10)	(0)	(10)	(0)	(10)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	5	0	5	0	5	-	-	-	-	-
infiltration, mononuclear cells; interstitial; multifocal	(5)	(0)	(5)	(0)	(5)	(-)	(-)	(-)	(-)	(-)
minimal	5	0	5	0	5	-	-	-	-	-
SALIVARY GLAND, MANDIBULAR:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10

Table 40: Summary Histopathology Data – Terminal / Died During or Following Blood Collection (continued)

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

Removal Reason: Killed Terminal/Died During or Following Blood Collection	MALES					FEMALES				
Test Article	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	10	10	10	10	10	10	10	10	10	10
SEMINAL VESICLES:										
Examined	(10)	(0)	(10)	(0)	(10)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	10	0	10	0	10	-	-	-	-	-
SKELETAL MUSCLE, BICEPS FEMORIS:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
SKIN:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
SPINAL CORD, CERVICAL:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
SPINAL CORD, LUMBAR:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
SPINAL CORD, THORACIC:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
SPLEEN:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
STOMACH:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
TESTES:										
Examined	(10)	(0)	(10)	(0)	(10)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	9	0	9	0	8	-	-	-	-	-
degeneration; seminiferous tubule; unilateral; multifocal	(0)	(0)	(0)	(0)	(1)	(-)	(-)	(-)	(-)	(-)
mild	0	0	0	0	1	-	-	-	-	-
degeneration; seminiferous tubule; bilateral; multifocal	(1)	(0)	(1)	(0)	(1)	(-)	(-)	(-)	(-)	(-)
mild	1	0	1	0	1	-	-	-	-	-

Table 40: Summary Histopathology Data – Terminal / Died During or Following Blood Collection (continued)

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

Removal Reason: Killed Terminal/Died During or Following Blood Collection	MALES					FEMALES				
Test Article	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	10	10	10	10	10	10	10	10	10	10
THYMUS:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	9	0	9	9	0	8	0	9
congestion; multifocal	(0)	(0)	(1)	(0)	(1)	(1)	(0)	(2)	(0)	(1)
mild	0	0	1	0	1	1	0	2	0	1
THYROID GLANDS:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	9	0	4	0	7	7	0	7	0	3
cyst(s), embryonic remnants; unilateral; focal	(1)	(0)	(4)	(0)	(2)	(3)	(0)	(3)	(0)	(2)
minimal	1	0	4	0	2	3	0	3	0	2
cyst(s), embryonic remnants; unilateral; multifocal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(2)
minimal	0	0	0	0	1	0	0	0	0	2
cyst(s), embryonic remnants; bilateral; multifocal	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(3)
minimal	0	0	2	0	0	0	0	0	0	3
TONGUE:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
TRACHEA:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
URINARY BLADDER:										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	9	0	10	0	10	10	0	10	0	10
infiltration, mononuclear cells; mucosa; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0	0	0
UTERUS:										
Examined	(-)	(-)	(-)	(-)	(-)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	-	-	-	-	-	8	0	6	0	9
dilation; lumen; bilateral	-	-	-	-	-	8	0	4	0	1
VAGINA:										
Examined	(-)	(-)	(-)	(-)	(-)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	-	-	-	-	-	10	0	10	0	10

Table 41: Summary Histopathology Data – Recovery

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

Removal Reason: Killed Recovery	MALES					FEMALES				
Test Article	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	5	5	5	5	5	5	5	5	5	5
ADRENAL GLANDS:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
AORTA:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
BONE MARROW, FEMUR:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
BONE MARROW, STERNUM:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
BONE, FEMUR:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
BONE, STERNUM:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
BRAIN:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
CERVIX:										
Examined	(-)	(-)	(-)	(-)	(-)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	-	-	-	-	-	5	0	5	0	5
EPIDIDYMIDES:										
Examined	(5)	(0)	(5)	(0)	(5)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	5	0	5	0	5	-	-	-	-	-
ESOPHAGUS:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5

Table 41: Summary Histopathology Data – Recovery (continued)

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

Removal Reason: Killed Recovery	MALES					FEMALES				
Test Article	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	5	5	5	5	5	5	5	5	5	5
EYES:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
HEART:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	1	0	5	0	4	5	0	5	0	3
cardiomyopathy: focal	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0	0	0
mild	1	0	0	0	0	0	0	0	0	0
cardiomyopathy: multifocal	(2)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(2)
minimal	2	0	0	0	1	0	0	0	0	2
INJECTION SITE:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	4	0	5	5	0	5	0	5
inflammation: chronic-active: locally extensive	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	1	0	0	0	0	0	0	0
ulceration: locally extensive	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	1	0	0	0	0	0	0	0
INTESTINE, CECUM:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
INTESTINE, COLON:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
INTESTINE, DUODENUM:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
INTESTINE, ILEUM:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
INTESTINE, JEJUNUM:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5

Table 41: Summary Histopathology Data – Recovery (continued)

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

	MALES					FEMALES				
Removal Reason: Killed Recovery	Group 1	Group 2	Group 3	Group 4	Group 5	Group 1	Group 2	Group 3	Group 4	Group 5
Test Article	Vehicle	--- Paricalcitol ---		----- Zemplar -----		Vehicle	--- Paricalcitol ---		----- Zemplar -----	
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	5	5	5	5	5	5	5	5	5	5
INTESTINE, RECTUM:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
KIDNEYS:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	3	0	0	0	1	2	0	2	0	1
fibrosis; subcapsular; unilateral; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	0	0	1	0	0	0	0	0
infarction; unilateral; focal	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)
minimal	0	0	0	0	0	2	0	0	0	0
mineralization; corticomedullary junction; unilateral; focal	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
minimal	0	0	0	0	0	1	0	0	0	0
mineralization; corticomedullary junction; unilateral; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
minimal	0	0	0	0	0	0	0	1	0	0
mineralization; corticomedullary junction; bilateral; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
minimal	0	0	0	0	0	0	0	1	0	0
basophilia; tubular; cortex; unilateral; multifocal	(2)	(0)	(2)	(0)	(4)	(1)	(0)	(0)	(0)	(1)
minimal	2	0	2	0	4	1	0	0	0	1
basophilia; tubular; cortex; bilateral; multifocal	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	2	0	0	0	0	0	0	0
cyst(s), embryonic remnants; corticomedullary junction; unilateral; focal	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
mild	0	0	0	0	0	1	0	0	0	0
nephrocalcinosis; proximal tubule; unilateral; focal	(0)	(0)	(3)	(0)	(1)	(0)	(0)	(1)	(0)	(2)
minimal	0	0	3	0	1	0	0	1	0	2
nephrocalcinosis; proximal tubule; unilateral; multifocal	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	0	0	2	0	0	0	0	0
nephrocalcinosis; proximal tubule; bilateral; multifocal	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
minimal	0	0	2	0	0	0	0	0	0	1

Table 41: Summary Histopathology Data – Recovery (continued)

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

	MALES					FEMALES				
Removal Reason: Killed Recovery	Group 1	Group 2	Group 3	Group 4	Group 5	Group 1	Group 2	Group 3	Group 4	Group 5
Test Article	Vehicle	--- Paricalcitol ---		----- Zemplar -----		Vehicle	--- Paricalcitol ---		----- Zemplar -----	
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	5	5	5	5	5	5	5	5	5	5
LIVER:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	1	0	0	0	1	2	0	1	0	1
necrosis; coagulative; centrilobular; multifocal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0	0	0
infiltration, mononuclear cells; multifocal	(4)	(0)	(5)	(0)	(4)	(3)	(0)	(4)	(0)	(4)
minimal	4	0	5	0	4	3	0	4	0	4
inflammation, subacute; centrilobular; multifocal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0	0	0
telangiectasis; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
minimal	0	0	0	0	0	0	0	0	0	1
LUNGS:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	4	0	5	0	5	5	0	5	0	5
mineralization; interstitium; artery; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0	0	0
LYMPH NODE, CERVICAL:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
LYMPH NODE, MESENTERIC:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
MAMMARY GLANDS:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
NERVE, OPTIC:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
NERVE, SCIATIC:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5

Table 41: Summary Histopathology Data – Recovery (continued)

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

Removal Reason: Killed Recovery	MALES					FEMALES				
Test Article	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	5	5	5	5	5	5	5	5	5	5
OVARIES:										
Examined	(-)	(-)	(-)	(-)	(-)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	-	-	-	-	-	5	0	5	0	5
PANCREAS:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
PARATHYROID GLANDS:										
Examined	(5)	(0)	(4)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	4	0	5	5	0	5	0	5
Not Examined: NOT PRESENT	0	0	1	0	0	0	0	0	0	0
PITUITARY GLAND:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
PROSTATE GLAND:										
Examined	(5)	(0)	(5)	(0)	(5)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	4	0	4	0	3	-	-	-	-	-
infiltration, mononuclear cells: interstitial:										
multifocal	(1)	(0)	(1)	(0)	(2)	(-)	(-)	(-)	(-)	(-)
minimal	1	0	1	0	2	-	-	-	-	-
SALIVARY GLAND, MANDIBULAR:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
SEMINAL VESICLES:										
Examined	(5)	(0)	(5)	(0)	(5)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	5	0	5	0	5	-	-	-	-	-
SKELETAL MUSCLE, BICEPS FEMORIS:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
SKIN:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	4	0	5	5	0	5	0	5
inflammation: chronic-active: locally extensive	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
moderate	0	0	1	0	0	0	0	0	0	0
ulceration: locally extensive	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
marked	0	0	1	0	0	0	0	0	0	0

Table 41: Summary Histopathology Data – Recovery (continued)

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

Removal Reason: Killed Recovery	MALES					FEMALES				
Test Article	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	5	5	5	5	5	5	5	5	5	5
SPINAL CORD, CERVICAL:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
SPINAL CORD, LUMBAR:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
SPINAL CORD, THORACIC:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
SPLEEN:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
STOMACH:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
TESTES:										
Examined	(5)	(0)	(5)	(0)	(5)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	5	0	5	0	5	-	-	-	-	-
THYMUS:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
THYROID GLANDS:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	4	5	0	4	0	3
cyst(s), embryonic remnants: unilateral:										
focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(1)
minimal	0	0	0	0	1	0	0	0	0	1
cyst(s), embryonic remnants: bilateral:										
multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(1)
minimal	0	0	0	0	0	0	0	1	0	1

Table 41: Summary Histopathology Data – Recovery (continued)

030508 - Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period

Removal Reason: Killed Recovery	MALES					FEMALES				
Test Article	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5	Group 1 Vehicle	Group 2 --- Paricalcitol ---	Group 3	Group 4 ----- Zemplar -----	Group 5
Dose (µg/kg)	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg	0 µg/kg	1 µg/kg	3 µg/kg	1 µg/kg	3 µg/kg
Number of Animals on Study :	5	5	5	5	5	5	5	5	5	5
TONGUE:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
TRACHEA:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
URINARY BLADDER:										
Examined	(5)	(0)	(5)	(0)	(5)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	5	0	5	0	5	5	0	5	0	5
UTERUS:										
Examined	(-)	(-)	(-)	(-)	(-)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	-	-	-	-	-	3	0	1	0	4
dilation; lumen; unilateral	-	-	-	-	-	1	0	0	0	0
dilation; lumen; bilateral	-	-	-	-	-	1	0	4	0	1
VAGINA:										
Examined	(-)	(-)	(-)	(-)	(-)	(5)	(0)	(5)	(0)	(5)
Within Normal Limits	-	-	-	-	-	5	0	5	0	5

Toxicokinetics

- At 1ug/kg/day, for both time points (Day 1&27), the TK data were similar for animals that were treated with both formulations.
- At 3ug/kg/day, on Day 27, for animals that were treated with the new formulation, values of C_{max} were lower (2.2X for males and 1.6X for females) and values of T_{max} were higher (males 3X and females 2X). In addition, based on AUC values for both compounds, there was no accumulation of Paricalcitol by multiple dosing (Sponsor Table):

Day	Test Article	Group	Dose (µg/kg)	Sex	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)
1	Paricalcitol	7	1	Male	0.250	2.63	16.2	34.8	53.8
				Female	0.083	1.49	18.9	25.9	30.3
	Paricalcitol	8	3	Male	0.083	2.44	49.7	92.7	133
				Female	0.083	1.28	53.1	68.6	76.6
	Zemplar	9	1	Male	0.083	2.57	15.3	27.6	41.2
				Female	0.083	1.59	18.2	23.6	28.6
	Zemplar	10	3	Male	0.083	2.00	55.7	90.4	116
				Female	0.083	1.36	62.0	69.6	79.1
27	Paricalcitol	7	1	Male	0.083	3.13	14.5	27.4	48.5
				Female	0.083	2.67	14.7	22.1	34.0
	Paricalcitol	8	3	Male	0.250	NR[1]	30.1	69.8	NR
				Female	0.500	NR	16.2	44.9	NR
	Zemplar	9	1	Male	0.083	3.28	28.8	28.1	48.2
				Female	0.083	1.48	17.3	21.6	25.1
	Zemplar	10	3	Male	0.083	1.84	67.1	88.8	115
				Female	0.250	2.33	26.3	44.9	65.0

[1] *NR = Not reportable, due to poor goodness-of-fit (R^2<0.8) for the elimination phase.*

Dosing Solution Analysis

According to the Sponsor, “The dosing formulations for both the test article and comparator test article had been shown to be solutions, and homogeneity testing was not performed. Stability information for the formulated Paricalcitol was provided to the Study Director for retention in the study file.”

7 Genetic Toxicology

No genotoxicity studies were submitted

8 Carcinogenicity

No carcinogenicity studies were submitted

9 Reproductive and Developmental Toxicology

No reproductive studies were conducted

9.2 Prenatal and Postnatal Development

11 Integrated Summary and Safety Evaluation

Paricalcitol, a synthetically manufactured analog of calcitriol, is the active form of vitamin D. Its biological actions are mediated through binding of the vitamin D receptor, which results in the selective activation of vitamin D responsive pathways. Vitamin D and Paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion.

The Sponsor proposed a new drug application under section 505(b)(2) for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5. The approval listed drug for this NDA is Zemplar™ (NDA 020819) for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5. The new formulation is different from the LD in levels of alcohol (35% v/v vs. 20% v/v in Zemplar), and in inactive ingredient of sorbitol (7% v/v vs. 30% v/v propylene glycol in Zemplar). The safety profile of the Zemplar has been well established. Therefore, the Sponsor conducted a 4-week repeat dose toxicity study in rats with a 2-week recovery period to assess the potential toxicity of the new formulation to the approved Zemplar.

Results of this study showed no mortality, clinical signs, or treatment-related effects on body weight, food consumption, ophthalmologic parameters, clinical pathology (hematology, coagulation, serum chemistry, and urine parameters), organ weights, or necropsy findings.

Histopathological findings were noted mostly for the kidney tissues in animals that were treated at 3µg/kg/day Paricalcitol or Zemplar (tissues from animals treated at 1µg/kg/day were not evaluated). These findings were minimal, focal or multifocal, unilateral or bilateral calcification in the proximal tubules. However, these findings are less concerning because of the patient population not having normal renal function.

TK data were similar for animals that were treated with both compounds at 1µg/kg/day and for both time points (Day 1 and 27); also, in animals that were treated at 3µg/kg/day on Day 1. However, on Day 27, treated animals with 3µg/kg/day of the new formulation animals showed

lower C_{max} values (2.2X for males and 1.6X for females) and higher T_{max} values (3X males and 2X females). These differences did not affect the potential toxicity of the new formulation.

Findings of this study suggested no significant TK or toxicity profile difference between the new formulations of Paricalcitol to the approved LD of Zemplar.

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

/s/

PARVANEH ESPANDIARI
03/07/2014

KAREN L DAVIS BRUNO
03/07/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205917 **Applicant:** Hikma Pharmaceuticals Co. Ltd **Stamp Date:** 10 June 2013

Drug Name: Paricalcitol injection 2 mcg/mL and 5 mcg/mL **NDA Type:** 505(b)(2)

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The submission is in CTD format.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Based on the Pre-IND meeting, a 28-day bridging toxicity study in rats was conducted to establish “bridge” data between the Sponsor’s formulation and the approved Zemplar. Paricalcitol has been tested in genetic (*in vitro* and *in vivo*) and carcinogenicity (mice/rats) studies.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		The bridge toxicity study was conducted with the same formulation and the route of the administration that are planned to be marketed.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		There is information regarding the human dose multiples in mg/m2 in: Drug Interactions (7), Pregnancy (8.1), and Nonclinical Toxicology (13) sections.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	According to the Sponsor, total impurities are not more than (b) (4) %. Based on DMF (b) (4), the total impurities for paricalcitol are not more than (b) (4) %.
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____

The original submission contained a 28-day comparative, bridging toxicity study that was a draft, unaudited report. The sponsor was contacted to request a final, GLP, audited (QA/QC), and signed report submission prior to the filing deadline (8/9/13). The sponsor has provided this final report as requested.

There are no potential review issues to be forwarded to the Applicant for the 74-day letter.

Parvaneh Espandiari, Ph.D
Reviewing Pharmacologist

Karen Davis Bruno, Ph.D
Team Leader/Supervisor

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

/s/

PARVANEH ESPANDIARI
07/31/2013

KAREN L DAVIS BRUNO
07/31/2013