CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-606

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-606	Submission Date(s): July 28, 2004
Brand Name	Zemplar capsules
Generic Name	paricalcitol
Reviewer	Wei Qiu, Ph.D.
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OCPB Division	DPEII
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Abbott Laboratories
Relevant NDA(s)	20-819
Submission Type	Original NDA
Formulation; Strength(s)	Capsules; 1, 2, and 4 ug
Indication	Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 3 and 4.

Table of Contents

1 Executive Summary 1
1.1 Recommendation 1
1.2 Phase IV Commitments 2
1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings 2
2 Question Based Review 3
2.1 General Attributes of the Drug 3
2.2 General Clinical Pharmacology 4
2.3 Intrinsic Factors 10
2.4 Extrinsic Factors 11
2.5 General Biopharmaceutics 14
2.6 Analytical Section 20
3 Detailed Labeling Recommendations 20
4 Appendix 23
4.1 Cover Sheet and OCPB Filing/Review Form 23
4.2 Individual Study Synopsis 27

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-606 submitted on July 28, 2004 and finds it acceptable. Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

Reviewer's Comments:

1. Based on the sponsor's provided dissolution data, the dissolution specification of not less than — (Q= —, at 45 minutes is recommended.

2. The sponsor proposed that dissolution would be monitored for the first three lots of marketed product for each strength while concurrently monitoring disintegration per USP <701>. The sponsor will propose an appropriate disintegration specification in lieu of dissolution testing. The proposal is acceptable, however, the disintegration specification needs to be concurred by the agency.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics

Absolute Bioavailability

The absolute bioavailability (F) of paricalcitol capsule ranged from 72% to 86% for healthy volunteers, CKD Stage 5 patients on hemodialyis (HD) and CKD Stage 5 patients on continuous peritoneal dialysis (CPD) (**Table 1**).

Table 1. Mean (95% Confidence Interval (CI)) Paricalcitol Absolute Bioavailability

	Healthy	CKD Stage 5 on HD	CKD Stage 5 on CPD
F (95% CI)	72.1% (63.5 – 81.7)	78.8% (66.9 – 92.9)	86.1% (66.5 – 111.5)

Single Dose vs. Multiple Dose

In healthy subjects, the extent of absorption (AUC) following 11 day QD dosing was 18% lower than that obtained after a single dose. Similarly, significant lower (not more than 18%) extent of absorption following 6 day QD dosing than single dose was found in both CKD Stage 3 and 4 patients.
The Cmax, Tmax, and T1/2 values were not found significantly different between single dose and multiple dose administrations in healthy subjects and CKD Stage 3 and 4 patients.

Healthy Subjects vs. Target Patient Populations

Cross study comparison suggested that the oral clearance of paricalcitol capsules in CKD Stage 3 or 4 patients were approximately 55 to 61% lower than that in healthy subjects.

Dose Proportionality

Dose proportionality was established over the dose range of 0.06 to 0.48 ug/kg paricalcitol capsule in terms of AUC values. However, the Cmax values were not found to be strictly proportional to dose.

Excretion

After IV and oral administration of ^{3}H-paricalcitol, about 19% and 18% of the dose (total radioactivity) was excreted in urine and about 63% and 70% of the dose was excreted in feces, respectively. No parent drug was excreted in urine following IV or oral administration. Approximately 2% of dose were unchanged parent in the feces following IV and oral administration.

Drug Interaction

Omeprazole
The 40 mg omeprazole oral capsule administered 2 hour prior to four 4 ug paricalcitol capsules had no effect on the pharmacokinetics of paricalcitol capsule.

Ketoconazole
Co-administration of multiple dose of ketoconazole 200 mg BID increased AUC of paricalcitol capsule approximately 2-fold with little change (~10%) in Cmax of paricalcitol capsule.

Special population

Renal impairment
Cross study comparison showed that the clearance of paricalcitol in CKD 3, 4, and 5 on HD or CPD was comparable. The mean oral clearance values were 1.5 to 1.8 L/h.

Biopharmaceutics

Dosage form equivalence
The to-be-marketed capsule strengths 1 ug SEC#2, 2 ug SEC#3, and 4 ug SEC#3 capsules in a total dose of 8 ug were bioequivalent.

Food Effect
The high fat meal had no significant effect on Cmax and AUC of 4 ug SEC#3 paricalcitol capsule.

Clinical Lot vs. Commercial Lot
The 4 ug SEC#3 capsule from the commercial lot was bioequivalent to the clinical lot.

2 Question Based Review

2.1 General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Paricalcitol is a third generation of Vitamin D2 analog and it is currently marketed as Zemplar injection for intravenous administration. Zemplar injection is indicated for the prevention and treatment of the secondary hyperparathyroidism associated with chronic renal failure (CKD Stage 5 or ESRD). Zemplar injection is administered three times a week during every dialysis session.

This NDA introduced a paricalcitol soft elastic oral capsule dosage form with 1, 2, and 4 ug dose strengths. The proposed indication is the prevention and treatment of secondary hyperparathyroidism in CKD Stage 3 and 4. The various stages of chronic kidney disease are summarized in **Table 2**.

Table 2. Stages of Chronic Kidney Disease

CKD Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Mild ↓ GFR	60 – 89
3	Moderate ↓ GFR	30 – 59
4	Severe ↓ GFR	15 – 29
5	Kidney failure	< 15 (or dialysis)

2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Paricalcitol is insoluble in water. The structure of paricalcitol is shown in **Figure 1**. Paricalcitol is formulated in [redacted] as a soft elastic-capsule.

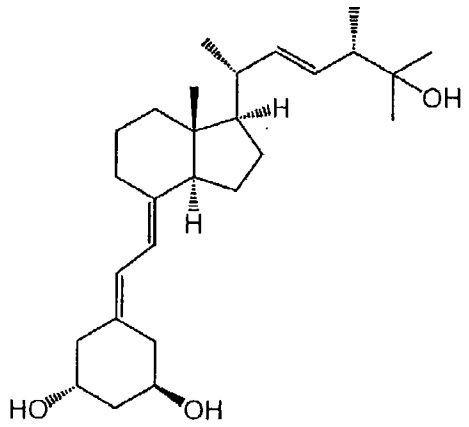

Figure 1. Chemical Structure of Paricalcitol

2.2 General Clinical Pharmacology

1. What are the PK characteristics of paricalcitol capsule?

1) What are the single dose and multiple dose PK parameters?

The single dose and multiple dose pharmacokinetics of paricalcitol capsule in healthy subjects following a single 4 ug dose and 4 ug daily (QD) dosing for 11 days, a single 8 ug dose and 8 ug three-times a week (TIW) dosing for 5 doses were assessed in a crossover study (Study 2001025) (**Table 3**). The single dose and multiple dose pharmacokinetics of parcicalcitol capsule in CKD Stage 3 patients following a single 4 ug dose and 4 ug once daily dose for 6 days, and in CKD Stage 4 patients following a single 3 ug dose and 3 ug once daily dose for 6 days were evaluated in study M03-633 (**Table 4**).

In healthy subjects, the extent of absorption after 11 day QD dosing was significant lower (18%) than single dose administration. The Cmax, Tmax, or T1/2 values were not significantly different between multiple dose and single dose administration. With TIW dosing regiment, no significant difference was found between single dose and multiple dose for AUC, Cmax, Tmax, or T1/2 values.

Table 3. Mean ± SD of Pharmacokinetic Parameters of Paricalcitol capsule (Study 2001025)

	Regimen A@			Regimen B@	
	Study Day 1	Study Day 12	Study Day 13	Study Day 1	Study Day 12 and 13
N	19	19	19	19	19
C_{max} (ng/mL)	0.100 ± 0.033	0.112 ± 0.031	0.105 ± 0.035	0.200 ± 0.062	0.217 ± 0.077
C_{max}/Dose	0.025 ± 0.008	0.028 ± 0.008	0.026 ± 0.009	0.025 ± 0.008	0.027 ± 0.010
C_{min} (ng/mL)&	ND	0.005 ± 0.010	0.001 ± 0.005	ND	0.000 ± 0.000
T_{max} (h)	4.8 ± 2.8	4.4 ± 2.6	4.5 ± 1.6	4.4 ± 1.4	4.3 ± 2.6
$AUC_{0\text{-last}}$	0.701 ± 0.339	ND	ND	2.047 ± 0.881	ND
$AUC_{0\text{-inf}}$	1.107 ± 0.342$^{\alpha}$	ND	ND	2.551 ± 1.079	ND
$AUC_{0\text{-}\tau}$*	ND	1.074 ± 0.359	0.904 ± 0.196#	ND	2.257 ± 0.566
AUC/Dose†	0.277 ± 0.086	0.268 ± 0.090	0.226 ± 0.049%	0.319 ± 0.135	0.282 ± 0.071
$t_{1/2}$ (h)§	6.2 ± 2.1$^{\alpha}$	6.8 ± 3.1$^{\varepsilon}$	5.8 ± 2.5$^{\varepsilon}$	7.3 ± 3.2	6.8 ± 2.2$^{\delta}$
CL/F (L/h)&	3.95 ± 1.19$^{\alpha}$	4.33 ± 2.08	4.65 ± 1.16	3.65 ± 1.61	3.79 ± 1.07
Vd_{β}/F (L)&	38.9 ± 18.7$^{\alpha}$	44.9 ± 23.0$^{\varepsilon}$	43.7± 17.9$^{\varepsilon}$	41.0 ± 12.7	42.1 ± 28.7$^{\delta}$
AI	ND	1.759 ± 1.829	1.483 ± 1.442	ND	1.000 ± 0.312
DFL	ND	2.584 ± 0.889‡	2.761 ± 0.761‡	ND	4.637 ± 1.397

AUC units: (ng•h/mL), C_{max} units: (ng/mL). α: N=14, δ: N=18, ε: N=17; ND: Not Determined.

* $AUC_{0\text{-}24}$ in Regimen A and $AUC_{0\text{-}48}$ in Regimen B after multiple doses.

#: Statistically significantly different ($P < 0.05$) from Regimen A Study Day 1, $AUC_{0\text{-inf}}$.

$: Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests on β.

&: Parameter was not tested statistically.

†: Regimen A and B Study Day 1: $AUC_{0\text{-inf}}$/Dose; Regimen A Study Day 12 and 13: $AUC_{0\text{-}24}$/Dose; Regimen B Study Day12: $AUC_{0\text{-}48}$/Dose.

@: Regimen A: 4 µg QD and Regimen B: 8 µg TIW.

%: Statistically significantly different ($P < 0.05$) from Regimen B, Study Day 12 and 13 dose-normalized $AUC_{0\text{-}48}$.

‡: Statistically significantly different from Regimen B, Study Day 12 and 13 DFL.

In CKD Stage 3 and 4 patients, the extent of absorption following multiple dose administration was 8% and 18% lower than single dose administration, respectively. The Cmax values were significant higher after multiple dose than single dose administration. The Tmax and T1/2 values were not significant different.

Table 4 Mean ± SD of Pharmacokinetic Parameters of Parcalcitol Capsules (Study M03-633)

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Pharmacokinetic Parameters (units)		Moderate Renal Impairment		Severe Renal Impairment	
		Study Day 1	Study Day 8	Study Day 1	Study Day 8
N		15	15	14*	13
f_u	(%)	0.08 ± 0.05		0.08 ± 0.02	
C_{max}	(ng/mL)	0.113 ± 0.036	0.155 ± 0.057¥	0.065 ± 0.012‡	0.097 ± 0.023¥
C_{max}/Dose	(ng/mL/µg)	0.028 ± 0.009	0.039 ± 0.014	0.022 ± 0.004	0.032 ± 0.008
C_{min}	(ng/mL)	--	0.047 ± 0.018	--	0.049 ± 0.010
T_{max}	(h)	4.7 ± 2.5	4.2 ± 1.9	5.9 ± 3.6	9.1 ± 5.5
AUC_{0-24}	(ng•h/mL)	1.454 ± 0.407	2.220 ± 0.701§	1.020 ± 0.230	1.754 ± 0.421§
$AUC_{0-\infty}$	(ng•h/mL)	2.424 ± 0.614	--	2.127 ± 0.733	--
β	(h^{-1})	0.041 ± 0.007	0.045 ± 0.009	0.035 ± 0.013	0.030 ± 0.007‡
$t_{1/2}$	(h)	16.76 ± 2.65	15.53 ± 3.21	19.70 ± 7.19	22.95 ± 5.63
CL/F†	(L/h)	1.766 ± 0.505	2.014 ± 0.774	1.517 ± 0.359	1.751 ± 0.388
Vdβ/F	(L)	43.72 ± 14.45	46.76 ± 19.35	46.40 ± 12.45	61.61 ± 20.34¥
AI£		--	1.54 ± 0.31	--	1.75 ± 0.39
DFL£	(%)	--	116.77 ± 35.24	--	64.86 ± 17.79

* N = 14 for C_{max} and T_{max} only. N = 13 for rest of the pharmacokinetic parameters on Study Day 1 in severe renal impairment group.

§ Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β.

† No statistical evaluations performed to compare Study Day 1 CL/F and Study Day 8 CL/F only.

£ No statistical evaluations performed.

‡ Statistically significantly different between groups on the corresponding Study Day.

¥ Statistically significantly different from Study Day 1 within group.

§ Statistically significantly different from Study Day 1 $AUC_{0-\infty}$ within group.

2) How does the PK of paricalcitol capsules in healthy volunteers compare to that in targeted populations of CKD Stage 3 and 4 patients?

Cross study comparison of single dose paricalcitol clearance of paricalcitol capsules in healthy subjects, CKD Stage 3 and 4 patients suggested that the oral clearance of paricalcitol capsules in CKD Stage 3 or 4 patients were approximately 55 to 61% lower than that in healthy subjects (**Table 5**).

Table 5. Mean ± SD paricalcitol apparent clearance (CL/F) following single oral dose for different populations (Studies 2001025 and M03-633)

	CL/F (L/h)	Study Number
Healthy (QD dose)	3.95 ± 1.19	2001025
Healthy (TIW dose)	3.65 ± 1.61	2001025
CKD Stage 3	1.77 ± 0.50	M03-633
CKD Stage 4	1.52 ± 0.36	M03-633

3) What are the characteristics of drug absorption?

Paricalcitol capsules were rapidly and well absorbed in healthy subjects and CKD Stage 5 patients on hemodialyis (HD) and CKD Stage 5 patients on continuous peritoneal dialysis (CPD). The absolute bioavailability (F) ranged from 72% to 86% in these populations. The F was not assessed in the targeted populations of CKD Stage 3 and 4 patients, but it is expected to be between 72 to 86% based upon available data in healthy and CKD Stage 5 patients (**Table 1**).

The absolute bioavailability of paricalcitol in healthy subjects, was evaluated under fasting and low-fat fed conditions (Study 2000007). All subjects were given the following three regimens in a randomized crossover fashion: Regimen A, 0.24 ug/kg paricalcitol capsule oral dose under low-fat fed conditions; Regimen B, 0.24 ug/kg paricalcitol capsule oral dose under fasting condition;

and Regimen C, 0.24 ug/kg paricalcitol injection intravenous dose under low-fat fed conditions. The mean plasma paricalcitol concentration-time profiles are presented in **Figure 2**. Pharmacokinetic parameters are summarized in **Table 6**. Based on log-transformed mean AUC0-inf ratios, the absolute bioavailability (F) of paricalcitol capsule administered orally was 66.4% and 72.1% in healthy subjects under fasting and low-fat fed conditions, respectively.

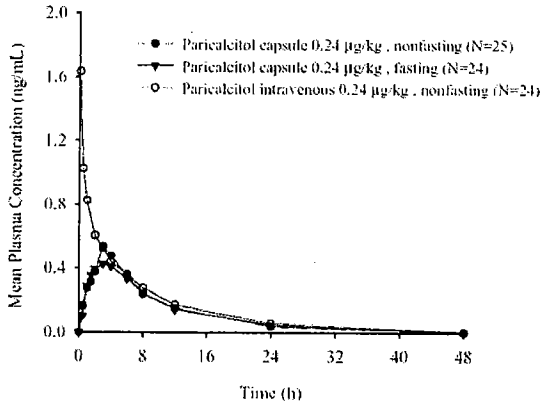

Figure 2. Mean plasma paricalcitol concentration-time profiles after a 0.24 ug/kg dose in healthy subjects (Study 2000007)

Table 6. Mean ± SD pharmacokinetic parameters (Study 2000007)

Part I, Bioavailability	Regimens		
Pharmacokinetic Parameters	A (N = 25)	B (N = 24)	C (N = 24)
C_{max} (ng/mL)	0.630 ± 0.262*	0.493 ± 0.125*	1.670 ± 0.529
C_{max}/Dose	2.62 ± 1.09	NA	6.96 ± 2.20
T_{max} (h)	3.0 ± 1.1	2.9 ± 1.4	NA
$AUC_{0\text{-last}}$ (ng•h/mL)	4.70 ± 1.13*	4.67 ± 1.60*	6.66 ± 2.19
$AUC_{0\text{-inf}}$ (ng•h/mL)	5.25 ± 1.25*	5.16 ± 1.72*	7.77 ± 2.73
$AUC_{0\text{-inf}}$/Dose	21.87 ± 5.20	NA	32.38 ± 11.39
β (1/h)	0.118 ± 0.054	0.134 ± 0.127	0.103 ± 0.046
$t_{1/2}$ (h) $	5.9 ± 2.8	5.2 ± 5.7	6.7 ± 3.1
CL (L/h) †φ	3.6 ± 1.0	4.2 ± 2.7	2.6 ± 1.1
Vd_β (L) †φ	33.5 ± 11.4	35.5 ± 11.9	29.9 ± 17.9

Regimen A: Paricalcitol capsule formulation, 0.24 µg/kg, administered orally under nonfasting conditions (test).
Regimen B: Paricalcitol capsule formulation, 0.24 µg/kg, administered orally under fasting conditions (test).
Regimen C: Paricalcitol intravenous formulation, 0.24 µg/kg, administered intravenously under nonfasting conditions (reference).
* Statistically significantly different from Regimen C ($p < 0.05$).
$ Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β.
† Parameter was not tested statistically.
φ CL for Regimen C and CL/F for Regimens A and B; Vd_β for Regimen C and Vd_β/F for Regimens A and B.

The absolute bioavailability of paricalcitol in CKD Stage 5 patients on HD was evaluated under low-fat fed conditions (Study 2000005) (**Figure 3**). All patients were given the following two regimens in a randomized crossover fashion: Regimen A, 0.24 ug/kg paricalcitol capsule oral dose and Regimen B, 0.24 ug/kg paricalcitol injection intravenous dose. The mean paricalcitol plasma concentration-time profiles are presented in **Figure 3**. Based on log-transformed mean AUC0-inf ratios, the absolute bioavailability (F) of paricalcitol capsule was 78.8% in CKD Stage 5 patients on HD under low-fat fed conditions.

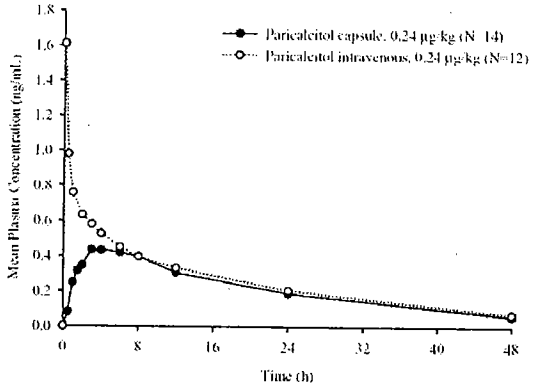

Figure 3. Mean plasma paricalcitol concentration-time profiles after a 0.24 ug/kg dose in CKD Stage 5 patients on HD (Study 2000005)

The absolute bioavailability of paricalcitol in CKD Stage 5 patients on CPD was evaluated under low-fat fed conditions (Study 2000006) (**Figure 4**). All patients were given the following two regimens in a randomized crossover fashion: Regimen A, 0.24 ug/kg paricalcitol capsule oral dose, and Regimen B, 0.24 ug/kg paricalcitol injection intravenous dose. The mean paricalcitol plasma concentration-time profiles are presented in **Figure 4**. Based on log-transformed mean AUC0-inf ratios, the absolute bioavailability of paricalcitol capsule was 86.1% in CKD Stage 5 patients on CPD under low-fat fed conditions.

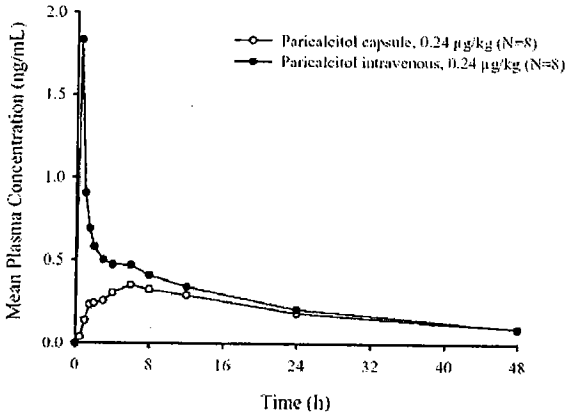

Figure 4. Mean plasma paricalcitol concentration-time profiles in CKD Stage 5 patients on CPD (Study 2000006)

4) What are the characteristics of drug distribution?

Paricalcitol was extensively bound (>99.9%) to plasma proteins. The average apparent volume of distribution of paricalcitol capsule in the target populations, CKD Stage 3 and 4, was approximately 44 to 46 L (Study M03-633). The CKD Stage 5 patients on HD or CPD had similar

range of volume of distribution compared to CKD Stage 3 or 4 patients. Healthy subjects had slightly lower values (**Table 7**).

Table 7. Mean ± SD paricalcitol apparent volume of distribution following single oral dose of paricalcitol capsule in healthy subjects and patients with different stages of CKD

	Vd/F (L)	Study
Healthy Subjects	33.5 ± 11.4	2000007
CKD Stage 3	43.7 ± 14.4	M03-633
CKD Stage 4	46.4 ± 12.4	M03-633
CKD Stage 5 on HD	38.0 ± 16.4	2000005
CKD Stage 5 on CPD	48.7 ± 15.6	2000006

5) What are the characteristics of drug excretion?

After IV and oral administration (0.48 ug/kg) ^{3}H-paricalcitol, the majority of the circulating radioactivity was due to parent drug. Two circulating metabolites M18 and M24 were found in plasma. M18 was 24®-hydroxy paricalcitol and the structure of M24 was not identified.

Approximately 19% and 18% of the dose (total radioactivity) was excreted in urine and 63% and 70% of the dose was excreted in feces over the 336-hour sampling interval, respectively, for IV and oral dose administrations. Greater than 80% of administered radioactivity was accounted for following IV and oral administration.

No parent drug was excreted in urine following IV or oral administrations, implying very limited renal clearance. Six metabolites were found in urine and represented about 40% of total urinary radioactivity.

Approximately 2% of dose radioactivity were unchanged parent in the feces following IV and oral administration. Eight fecal metabolites represented about 40% of total fecal radioactivity. Four metabolites corresponding to about 20% of the fecal radioactivity have retention times consistent with M11 (25-O-paricalcitol glucuronide), M13 (24(R),26-dihydroxyparicalitol), M14 (24(S),28-dihydroxyparicalcitol) and M18 (24(R)-hydroxyparicalcitol), all of which have been identified from in vitro metabolism studies.

6) Based on PK parameters, is dose proportionality established?

Dose proportionality over the dose range of 0.06 to 0.48 ug/kg following a single oral dose administration under low-fat fed conditions was assessed in healthy subjects (Study 2000007) (**Table 8**). The dose-normalized AUC and Cmax were assessed for dose proportionality. Statistical analysis demonstrated that dose proportionality was established in terms of AUC but not Cmax.

Table 8. Mean ± SD of Pharmacokinetic Parameters of paricalcitol capsules in healthy subjects (Study 2000007)

Pharmacokinetic Parameter (units)	Doses			
	0.06 µg/kg (N=8)	0.12 µg/kg (N=8)	0.24 µg/kg (N=25)	0.48 µg/kg (N=7)
C_{max} (ng/mL)	0.141 ± 0.031	0.244 ± 0.03	0.630 ± 0.262	0.972 ± 0.172
C_{max}/Dose (ng/mL/µg/kg)	2.35 ± 0.51	2.04 ± 0.25	2.62 ± 1.09	2.02 ± 0.36
T_{max} (h)	2.4 ± 0.7	3.6 ± 1.3	3.0 ± 1.1	2.6 ± 0.6
$AUC_{0\text{-last}}$ (ng•h/mL)	1.04 ± 0.46	2.36 ± 0.46	4.70 ± 1.13	8.17 ± 2.71
$AUC_{0\text{-}\infty}$ (ng•h/mL)	1.29 ± 0.56	2.75 ± 0.49	5.25 ± 1.25	8.77 ± 2.85
$AUC_{0\text{-}\infty}$/Dose (ng•h/mL/µg/kg)	21.51 ± 9.28	22.92 ± 4.08	21.87 ± 5.20	18.26 ± 5.94
β (1/h)	0.153 ± 0.082	0.113 ± 0.037	0.118 ± 0.054	0.121 ± 0.045
$t_{½}$ (h)$^{\$,\dagger}$	4.5 ± 2.7	6.2 ± 2.1	5.9 ± 2.8	5.7 ± 2.3
CL/F (L/h)†	4.0 ± 2.0	3.6 ± 0.8	3.6 ± 1.0	4.5 ± 1.5
Vdβ/F (L)†	27.4 ± 6.0	32.8 ± 7.7	33.5 ± 11.4	38.0 ± 6.4

$ Harmonic mean ± pseudo-standard deviation; evaluations of $t_{½}$ were based on statistical tests for β.

† Parameter was not tested statistically.

2.3 Intrinsic Factors

1. Special population

1) Renal impairment

The target populations of paricalcitol capsule are CKD Stage 3 and 4 patients. The single dose PK of paricalcitol in CKD Stage 5 patients (0.24 ug/kg) on HD and CPD were evaluated in Studies 2000005 and 2000006. For comparison, the pharmacokinetics from healthy subjects (0.24 ug/kg) obtained from study 2000007 were also included (**Table 9**).

Table 9. Comparison of pharmacokinetic parameters (Mean ± SD) among healthy, CKD Stage 3, CKD Stage 4, and CKD Stage 5 on HD and CPD patients following a single oral dose of paricalcitol capsule

Pharmacokinetic Parameters (units)		Study 2000007 Healthy Subjects	Study M03-633 CKD Stage 3 Subjects	Study M03-633 CKD Stage 4 Subjects	Study 2000005 CKD Stage 5 Subjects on Hemodialysis	Study 2000006 CKD Stage 5 Subjects on Peritoneal Dialysis
Dose	(µg/kg)	0.24	0.047*	0.036#	0.24	0.24
N		25	15	14†	14	8
C_{max}	(ng/mL)	0.630 ± 0.262	0.113 ± 0.036	0.065 ± 0.012	0.575 ± 0.172	0.413 ± 0.064
T_{max}	(h)	3.0 ± 1.1	4.7 ± 2.5	5.9 ± 3.6	4.0 ± 3.3	6.0 ± 3.3
$AUC_{0\text{-}\infty}$	(ng•h/mL)	5.25 ± 1.25	2.424 ± 0.614	2.127 ± 0.733	11.67 ± 3.23	13.41 ± 5.48
β	(h^{-1})	0.118 ± 0.054	0.041 ± 0.007	0.035 ± 0.013	0.050 ± 0.017	0.039 ± 0.02
$t_{½}$$^{\$}$	(h)	5.9 ± 2.8	16.76 ± 2.65	19.70 ± 7.19	13.9 ± 5.1	17.7 ± 9.6
CL/F	(L/h)	3.6 ± 1.0	1.766 ± 0.505	1.517 ± 0.359	1.82 ± 0.75	1.76 ± 0.77
Vdβ/F	(L)	33.5 ± 11.4	43.72 ± 14.45	46.40 ± 12.45	38.0 ± 16.4	48.7 ± 15.6
F	(%)	72.1	NS	NS	78.8	86.1
f_u	(%)	0.06 ± 0.01&	0.06 ± 0.01&	0.07 ± 0.02&	0.09 ± 0.04&	0.09 ± 0.04&

* A flat dose of 4 µg was used; the per-kg dose has been calculated based on a mean body weight of 83.4 kg.

\# A flat dose of 3 µg was used; the per-kg dose has been calculated based on a mean body weight of 83.3 kg.

† N = 14 for C_{max} and T_{max} only. N = 13 for rest of the pharmacokinetic parameters on Study Day 1 in CKD Stage 4 subjects.

$ Harmonic mean and pseudo standard deviation.

& Measured at 15 nM paricalcitol concentration.

NS = Not studied.

Cross study comparison suggested that the apparent clearance of paricalcitol capsules in CKD 3, 4, and 5 on HD or CPD was comparable. The apparent clearance in healthy subject was 2 fold of the values in patients with CKD Stage 3, 4 or 5.

2.4 Extrinsic Factors

1. Drug-drug interactions

1) Is the drug an inhibitor and/or an inducer of CYP enzymes?

The effects of paricalcitol on cytochrome P450 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A activities were evaluated in human liver microsomal fractions (Drug Metabolism Report NO. 51 (R&D/04/276)). Up to 50 nM (21 ng/mL), paricalcitol had no effect on activities of all nine P450s (**Table 10**).

In all assays, substrate concentrations were approximately equal to their respective Km values. The anticipated clinical plasma concentrations of zemplar should not exceed 1 ng/mL (2.5 nM) after an oral dose and thus this compound was less likely to be a source of clinical drug-drug interaction through inhibition of these tested P450 enzymes.

Table 10. Effect of paricalcitol on CYP450 enzyme activities (Percentage of Control Activity)

		A-122358	
Enzyme	Activity	5 nM	50 nM
CYP1A2	Phenacetin *O*-deethylation	104.0 ± 1.8	102.4 ± 3.1
CYP2A6	Coumarin 7-hydroxylation	98.3 ± 2.7	98.6 ± 3.9
CYP2B6	*S*-mephenytoin *N*-demethylation	102.1 ± 12.7	98.6 ± 7.7
CYP2C8	Taxol 6α-hydroxlation	88.9 ± 5.0	92.2 ± 4.7
CYP2C9	Tolbutamide 4-hydroxylation	102.4 ± 7.9	99.0 ± 2.0
CYP2C19	*S*-mephenytoin 4'-hydroxylation	97.5 ± 6.8	100.2 ± 2.4
CYP2D6	Dextromethorphan *O*-demethylation	99.8 ± 6.4	94.0 ± 1.0
CYP2E1	Chlorzoxazone 6-hydroxylation	97.4 ± 7.4	88.6 ± 16.6
CYP3A	Terfenadine hydroxylation/carboxylation	104.7 ± 14.9	101.1 ± 12.3

Induction study (Drug metabolism Report 53) was submitted to NDA 20-819 and was reviewed by Dr. Shinja Kim. The following was copied from her review.

***In vitro* induction study (Drug Metabolism Report 53):** This study investigated potential of A-122358 (paricalcitol) to induce the human hepatic cytochrome P450 3A4, 2B6 and 2C9 using fresh primary cultured human hepatocytes obtained from 3 donors. Paricalcitol is not considered an inducer *in vitro* for CYP3A4, 2B6 and 2C9 based on the results because percent potency indexes were less than 40%, although concentrations used as positive inducers for CYP2B6 (Phenobarbital 2 mM) and CYP2C9 (rifampin 20 μM) were 2 times higher than those FDA guidance recommended (20 μM Rifampin for CYP3A4 is within the recommended concentration) (**Table 11**).

Table 11 . Effect of a 3-Day Co - Incubation of A-122358 or Positive Control Inducers on CYP2B6, 2C9 and 3A-Dependent Activities in Freshly Isolated Human Hepatocytes (Fold Increase in Activity; n=3±SD)

Enzyme	Activity	Positive Control	A-122358				Potency Index (%)[a]
			0.5 nM	5 nM	50 nM	100 nM	
CYP2B6	S-mephenytoin N-demethylation	16.7±7[b]	1.3±0.3	1.3±0.4	1.3±0.1	1.6±0.2	4
CYP2C9	Diclofenac 4'-hydroxylation	6.2±0.7[c]	1.2±0.1	1.1±0.1	1.2±0.1	1.5±0	10
CYP3A4	Testosterone 6β-hydroxylation	19.3±2[c]	1.1±0.3	1.3±0.5	1.8±0.7	2.0±1.0	6

[a]mean (n=3) at 100 nM A-122358, [b]2 mM Phenobarbital, [c]20 µM Rifampicin
Potency Index (%) = (Fold induction, test compound -1)/(Fold induction, positive control-1)

2) What is the effect of CYP3A inhibitor, ketoconazole, on pharmacokinetics of paricalcitol capsule?

Drug-drug interaction with ketoconazole was submitted to NDA 20-819 and was reviewed by Dr. Shinja Kim. The following is from her review.

Drug interaction study (Study M04-062): The effect of a 3A4 inhibitor on paricalcitol exposure was assessed using ketoconazole on pharmacokinetics of paricalcitol. Paricalcitol 4 µg capsule was administered on Day 1 and Day 8, and ketoconazole 200mg BID (q12h) was administered from Day 4 to Day 8 in healthy subjects under fasting conditions. Results were summarized in **Tables 12-13**. The study showed that ketoconazole increased AUC_{0-t} and $AUC_{0-\infty}$ of paricalcitol approximately 2-fold, while minimal (~10% increase) change in Cmax of paricalcitol when both were orally co-administered (Tables 1-2). The mean half-life of paricalcitol was 17.0 hours (with 50% reduction in clearance) in the presence of ketoconazole as compared to 9.8 hours, when paricalcitol was administered alone.

Table 12. Mean ± SD Pharmacokinetic Parameters of Paricalcitol

Pharmacokinetic Parameters (units)		Treatments£	
		Paricalcitol Alone (Study Day 1) (N = 14)	Paricalcitol + Ketoconazole (Study Day 8) (N = 14)
T_{max}	(h)	4.4 ± 2.8	5.2 ± 2.5
C_{max}	(ng/mL)	0.114 ± 0.024	0.127 ± 0.037
AUC_{0-last}	(ng•h/mL)	1.360 ± 0.390	2.681 ± 0.975*
$AUC_{0-\infty}$	(ng•h/mL)	1.597 ± 0.449	3.175 ± 1.315*
β	(h^{-1})	0.071 ± 0.031	0.041 ± 0.014*
$t_{½}$¢,†	(h)	9.80 ± 4.46	17.0 ± 6.12
CL/F†	(L/h)	2.76 ± 1.02	1.41 ± 0.46
$Vd_β/F$†	(L)	40.9 ± 9.4	36.0 ± 10.2

£ Paricalcitol alone = 4 µg paricalcitol capsule dose (Study Day 1);
Paricalcitol + ketoconazole = 4 µg paricalcitol capsule dose on Study Day 8 + 200 mg BID ketoconazole tablets on Study Days 4 through 10.

* Statistically significantly different than that from paricalcitol alone (ANOVA, $p < 0.05$).

¢ Harmonic mean ± pseudo-standard deviation; evaluations of $t_{½}$ were based on statistical tests for β.

† Parameter was not tested statistically.

Table 13. Extent of Paricalcitol – Ketoconazole Interaction

Regimens	Pharmacokinetic	Central Values*		Relative Bioavailability	
				Point	90% Confidence
Test vs. Reference	Parameter	Test	Reference	Estimate+	Interval
Paricalcitol + ketoconazole (Study Day 8) vs. Paricalcitol alone (Study Day 1)	C_{max}	0.122	0.112	1.091	0.950 – 1.253
	$AUC_{0\text{-last}}$	2.543	1.301	1.955	1.759 – 2.172
	$AUC_{0\text{-}\infty}$	2.983	1.528	1.952	1.735 – 2.196

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

3) What is the effect of omeprazole on pharmacokinetics of paricalcitol capsule?

The effect of omeprazole on paricalcitol bioavailability was evaluated in a single-dose, fasting, randomized, two-period, crossover study (M02-436). Subjects were given two regimens under fasting conditions: Regimen A, four 4 ug paricalcitol capsules and Regimen B, one omeprazole 40 mg capsule administered approximately 2 hours prior to four 4 ug paricalcitol capsules. The mean plasma concentration-time profiles for paricalcitol alone and paricalcitol with omeprazole are shown in **Figure 5** and pharmacokinetic parameters are summarized in **Table 14.**

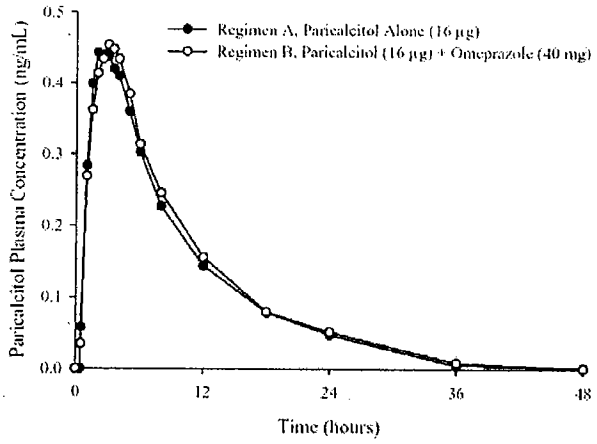

Figure 5. Mean plasma paricalcitol concentration-time profiles following administration of paricalcitol alone vs. Omeprazole and paricalcitol (Study M02-436)

Table 14. Effect of Omeprazole on paricalcitol bioavailability

Regimens Test *vs.* Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Omeprazole with Paricalcitol (B)	Paricalcitol Alone (A)	Point Estimate†	90% Confidence Interval
Omeprazole + Paricalcitol *vs.* Paricalcitol Alone	C_{max}	0.525	0.509	1.032	0.920 – 1.158
	$AUC_{0\text{-last}}$	4.559	4.267	1.068	0.968 – 1.180
	$AUC_{0\text{-}\infty}$	5.028	4.832	1.041	0.951 – 1.139

* Antilogarithm of the least squares means for logarithms.

† Antilogarithm of the difference (Regimen B minus Regimen A) of the least squares means for logarithms.

Data from the 25 subjects who received both regimens were included in the statistical analyses of the pharmacokinetic parameters. Results showed that omeprazole had no effect on paricalcitol pharmacokinetics because the 90% confidence intervals for Cmax and AUC were within the 0.80 and 1.25 range.

2.5 General Biopharmaceutics

1. Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The aqueous solubility of paricalcitol was low. Since the highest dosage strength 4 ug of paricalcitol was not completely soluble in 250 mL of water, it would be considered a low soluble drug according to the BCS system.

In vitro Caco-2 cell permeability measurements showed that the absorptive (A to B) apparent permeability (Papp) value at 5 or 50 uM concentration of paricalcitol ranged from 3.76 to 12.02 x 10-6 cm/sec at pH of 6.8 to 7.4. The secretory apparent permeability (B to A) was in the same range suggesting paricalcitol net absorption was characterized by passive diffusion and not affected by active transporters. The in vivo absolute bioavailability of 72 to 86% suggested that paricalcitol was a medium permeability drug. According to the agency's guidance, a drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose. Thus, paricalcitol may be reasonable to be classified as a BCS Class 4 drug.

2. What is the quantitative composition of the to-be-marketed capsules?

The quantitative compositions of the to-be-marketed paricalcitol capsules are shown in **Table 15**. The 2 ug and 4 ug capsules (SEC#3) have the same amount of inactive ingredients but different amount of active ingredient, paricalcitol. The 1 ug SEC#2 capsule has the exact half of the amount of 2 ug SEC#3 capsule.

Table 15. Premix Quantitative Composition of Paricalcitol Capsule Content, 1 ug (SEC#2), 2 ug (SEC#3), and 4 ug (SEC#3) Formulations

Component	Amount	
	1 ug SEC#2	2 and 4 ug SEC#3
Paricalcitol	1 ug	2 or 4 ug
— alcohol, USP, EP		
Butylated Hydroxytoluene (BHT), NF	/	/

q.s. = quantity sufficient

The 2 ug SEC#3 formulation was used in Phase 3 clinical trials. The 1 ug SEC#2 and 4 ug SEC#4 formulations were shown to be dosage form equivalent to the 2 ug SEC#3 formulation in a crossover study.

3. What is the relative bioavailability of the paricalcitol capsule from the commercial lot to the clinical lot?

The commercial lot has the same formulation as the clinical lot. The only difference was the lot sizes. The relative bioavailability of the to-be-marketed capsule 4 ug SEC#3 formulation (Regimen B) from the commercial lot relative to the clinical lot (Regimen A) was evaluated in a crossover study under fasting conditions in 48 healthy subjects (Study M02-437). The mean plasma concentration-time profiles are shown in **Figure 6**. The pharmacokinetic parameters are summarized in **Table 16**.

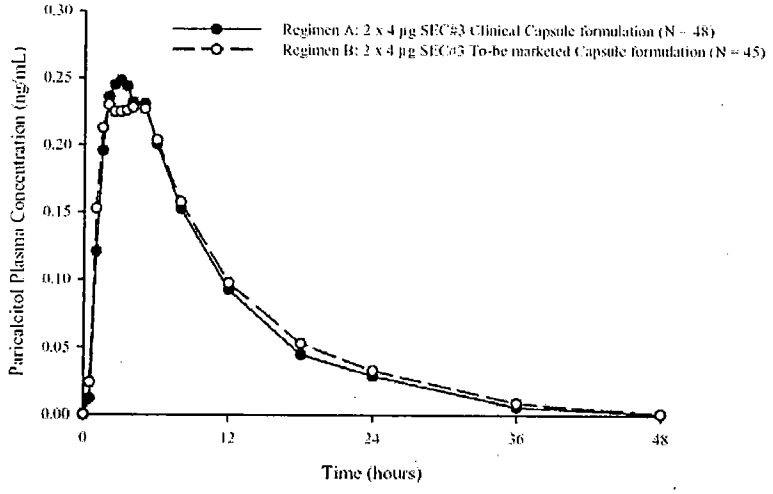

Figure 6 Mean paricalcitol plasma concentration-time profiles

Table 16. Mean ± SD pharmacokinetic parameters of paricalcitol capsules (Study M02-437)

Pharmacokinetic Parameters (units)		Regimens£ A (N = 47)	B (N = 45)	C (N = 47)
T_{max}	(h)	3.1 ± 1.9	3.1 ± 2.0	5.4 ± 2.9*
C_{max}	(ng/mL)	0.301 ± 0.066	0.302 ± 0.071	0.266 ± 0.076*
AUC_{0-t}	(ng•h/mL)	2.658 ± 0.861	2.854 ± 1.101	2.930 ± 0.962
AUC_{0-inf}‡	(ng•h/mL)	3.152 ± 1.076	3.320 ± 1.214	3.521 ± 1.102
β‡	(h^{-1})	0.109 ± 0.053	0.099 ± 0.038	0.081 ± 0.029*
$t_{1/2}$$,‡	(h)	6.38 ± 3.13	6.97 ± 2.64	8.51 ± 3.03
CL/F†,‡	(L/h)	2.83 ± 0.94	2.76 ± 1.09	2.52 ± 0.89
$Vd_β/F$†,‡	(L)	30.0 ± 12.4	29.0 ± 8.7	32.5 ± 8.9

* Statistically significantly different ($P < 0.05$) from that of Regimen B.

£ All three regimens were administered as 8 µg (2 x 4µg) of paricalcitol.

Regimen A: 2 x 4 µg paricalcitol capsules, clinical formulation, administered under fasting conditions.

Regimen B: 2 x 4 µg paricalcitol capsules, to-be marketed formulation, administered under fasting conditions.

Regimen C: 2 x 4 µg paricalcitol capsules, to-be marketed formulation, administered under nonfasting conditions.

$ Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β.

† Parameter was not tested statistically.

‡ N = 45 for Regimen A, N = 44 for Regimen B, and N = 47 for Regimen C.

Statistical analysis results showed that the 4 ug capsule from the commercial lot was bioequivalent to the clinical lot because the 90% confidence interval for the Cmax and AUC ratios were within the 0.80 and 1.25 range (**Table 17**).

Table 17. Bioequivalence assessment between the 4 ug SEC#3 from commercial log and clinical lot

Regimens Test *vs.* Reference	Pharmacokinetic Parameter	Central Value* Test Regimen B	Central Value* Reference Regimen A	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
B *vs* A	C_{max}	0.296	0.294	1.006	0.938 – 1.080
	AUC_{0-last}	2.666	2.507	1.063	0.982 – 1.151
	$AUC_{0-\infty}$	3.121	2.944	1.060	0.982 – 1.144

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Regimen A: 2 x 4 µg SEC#3 clinical capsule formulation.

Regimen B: 2 x 4 µg SEC#3 to-be marketed capsule formulation.

4. What is the effect of food on the bioavailability of paricalcitol capsule?

The effect of high-fat meal on the to-be-marketed 4 ug SEC#3 formulation, the highest strength, was evaluated in 48 healthy subjects in a crossover Study M02-437. A total dose of 8 ug was

used for each regimen. The mean plasma concentration-time profiles for the fasting (Regimen B) and high-fat fed conditions (Regimen C) are presented in **Figure 7**. Pharmacokinetic parameters are summarized **in Table 16**.

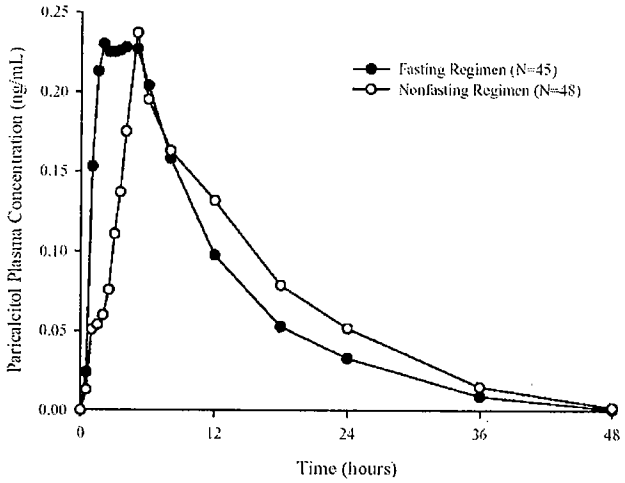

Figure 7. Mean plasma paricalcitol concentration-time profiles following administration of two 4 ug to-be-marketed capsule under fasting and high-fat fed conditions (Study M02-437)

Food significantly increased Tmax values from 3.1 to 5.4 hours. The ratios of the Cmax, AUC0-last, and AUC0-inf parameters for high-fat fed and fasting conditions were 0.860, 1.032, and 1.067, respectively. The high fat meal had no significant effect on Cmax and AUC of paricalcitol capsule because the 90% confidence intervals were within the 0.80 and 1.25 range (**Table 18**).

Table 18. Effect of Food on the 4 ug to-be-marketed capsule (Study M02-437)

		Central Value*			
		Test	Reference	Food Effect	
Regimens Test *vs.* Reference	Pharmacokinetic Parameter	Nonfasting Regimen	Fasting Regimen	Point Estimate+	90% Confidence Interval
Nonfasting *vs.* Fasting	C_{max}	0.254	0.296	0.860	0.801 – 0.923
	$AUC_{0\text{-last}}$	2.750	2.666	1.032	0.953 – 1.117
	$AUC_{0\text{-}\infty}$	3.330	3.121	1.067	0.990 – 1.150

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

5. How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The sponsor proposed dissolution method is as follows:

Apparatus: USP Apparatus 1 (baskets)
Speed: 100 RPM
Volume: 500 mL
Medium: ——

During method development, the sponsor evaluated , and found it not acceptable. The dissolution data in showed no detectable release of paricalcitol in these media after 60 minutes. Since paricalcitol is insoluble in water and it is formulated the gelatin capsule, the sponsor added , in the dissolution medium. The comparison of the release profiles in concentrations of showed that the mg/mL level was the most appropriate.

The in vitro dissolution results for the capsule lots examined in all the clinical studies are shown in **Table 19**. With the limited data, the specification of not less than (Q= , in 45 minutes is recommended.

Table 19. Drug product dissolution testing results

Dosage Form	Lot Number	Manufacturing Site/Date	Lot Size	No. Units Tested	Dissolution Statistics	% Dissolved (minutes) 20	30	45	60
1 µg Capsule (#3 SEC)	77-124-DH	05/2001	capsules	6	Mean	58.7	82.5	87.4	92.7
					Low				
					High				
					CV%	5.8	2.1	5.8	1.4
1 µg Capsule (#2 SEC)	86-133-DH	12/2001	capsules	6	Mean	57.5	89.1	99.2	100.7
					Low				
					High				
					CV%	13.6	3.1	1.2	1.0
2 µg Capsule (#3 SEC)	77-125-DH	05/2001	capsules	6	Mean	60.4	88.6	97.3	99.1
					Low				
					High				
					CV%	6.3	2.3	0.5	2.8
4 µg Capsule (#3 SEC)	77-126-DH	05/2001	capsules	6*	Mean	52.8	80.9	93.9	95.9
					Low				
					High				
					CV%	9.6	4.7	1.2	2.6
4 µg Capsule (#3 SEC)	90-139-DH+	02/2002	capsules	6**	Mean	52.4	79.9	94.5	98.3
					Low				
					High				
					CV%	10.3	4.5	2.4	1.6

SEC = Soft Elastic Capsule. + Lot 87-051-C5-22 for the analytical data.

* System suitability failure resulted in an incomplete profile. Repeat of assay resulted in 12 data points being reported for the 20, 30 and 45 minute samplings.

** System suitability failure resulted in an incomplete profile. Repeat of assay resulted in 12 data points being reported for the 20 and 30 minute samplings.

The sponsor compared the mean fraction absorbed in vivo and the mean fraction dissolved in vitro. A linear relationship was found between fraction absorbed in vivo and fraction dissolved in vitro by adding a time-scaling factor of 5. However, the predictive power of this relationship is unknown because the in vitro-in vivo relationship has not been validated.

6. Is dosage form equivalence established?

The dosage form equivalence between the to-be-marketed strengths 1 ug SEC#2, 2 ug SEC#3, and 4 ug SEC#3 formulations were evaluated in a single dose crossover study (Study M02-435). The mean plasma concentration-time profiles are presented in **Figure 8**. The mean ± SD pharmacokinetic parameters of paricalcitol are presented in **Table 20**.

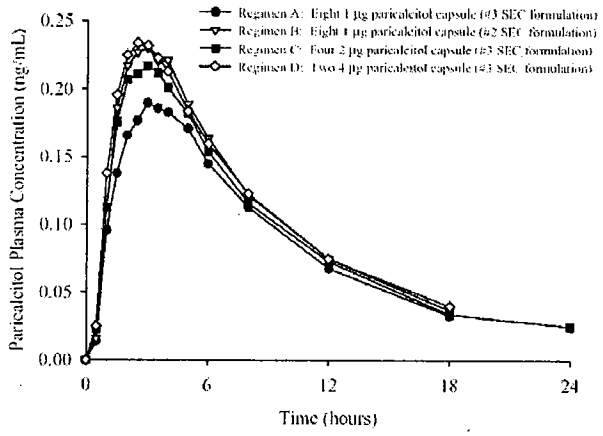

Figure 9 Mean Paricalcitol Plasma Concentration vs. Time

Table 20. Mean ± SD Pharmacokinetic Parameters of Paricalcitol capsules (M02-435)

	Regimen[£]			
	A	B	C	D
Pharmacokinetic Parameters (units)	**1 µg Capsules (#3 SEC)**	**1 µg Capsules (#2 SEC)**	**2 µg Capsules (#3 SEC)**	**4 µg Capsules (#3 SEC)**
N	82[‡]	82[‡]	80	80[‡]
C_{max} (ng/mL)	0.228 ± 0.080	0.277 ± 0.116*	0.262 ± 0.070*	0.284 ± 0.092*
T_{max} (h)	3.2 ± 1.4	3.0 ± 1.5	2.9 ± 1.6	2.5 ± 1.1*[†]
$AUC_{0\text{-last}}$ (ng•h/mL)	1.95 ± 0.92	2.21 ± 0.90*	2.16 ± 0.95*	2.28 ± 1.00*
$AUC_{0\text{-}\infty}$ (ng•h/mL)	2.42 ± 1.34	2.57 ± 1.00*	2.65 ± 1.28*	2.67 ± 1.11*
$\beta^{\S}$ (1/h)	0.112 ± 0.050	0.120 ± 0.050	0.118 ± 0.053	0.111 ± 0.045
$t_{1/2}^{\S,\&}$ (h)	6.2 ± 2.8	5.8 ± 2.4	5.9 ± 2.7	6.2 ± 2.6
$CL/F^{\&}$ (L/h)	4.17 ± 2.50	3.84 ± 2.67	3.68 ± 1.67	3.56 ± 1.85
$V_d\beta/F^{\&}$ (L)	39.16 ± 18.20	31.29 ± 10.32	33.52 ± 10.99	33.00 ± 12.31

£ Regimen A: Eight 1 µg paricalcitol capsules (#3 SEC formulation).
Regimen B: Eight 1 µg paricalcitol capsules (#2 SEC formulation).
Regimen C: Four 2 µg paricalcitol capsules (#3 SEC formulation).
Regimen D: Two 4 µg paricalcitol capsules (#3 SEC formulation).
All regimens were administered as a single 8 µg dose under fasting conditions.

* Statistically significantly different from Regimen A (ANOVA, $p < 0.05$).

† Statistically significantly different from Regimen B (ANOVA, $p < 0.05$).

§ Harmonic mean ± pseudo-standard deviation; evaluations of $t_{½}$ were based on statistical tests for β.

‡ N = 80 for β, $t_{½}$, and $V_d\beta/F$ for Regimen A. N = 81 for β, $t_{½}$, and $V_d\beta/F$ for Regimen B and N = 79 for T_{max}, β, $t_{½}$, CL/F and $V_d\beta/F$ for Regimen D.

§ β was not estimable for two subjects, one subject, and one subject for Regimens A, B and D, respectively.

& Parameter was not tested statistically.

Results showed that Regimen B (8 x 1 ug SEC#2 capsules), C (4 x 2 ug SEC#3 capsules), and D (2 x 4 ug SEC#3 capsules) were bioequivalent because the 90% confidence intervals for both Cmax and AUC fell within the 0.80 to 1.25 range (**Table 21**). Thus, dosage form equivalent was established for all to-be-marketed strengths.

The 1 ug SEC#3 capsules, which have the same amount of inactive ingredients with 2 ug and 4 ug SEC#3 capsules except active compound, were shown to be not dosage form equivalent to the 2 ug and 4 ug SEC#3 capsules.

Table 21. Bioequivalence and Relative Bioavailability

Regimens Test *vs.* Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate+	90% Confidence Interval
A *vs.* B	C_{max}	0.215	0.256	0.839	0.789 – 0.891
	$AUC_{0\text{-last}}$	1.787	2.020	0.885	0.821 – 0.953
	$AUC_{0\text{-}\infty}$	2.209	2.397	0.922	0.862 – 0.985
A *vs.* C	C_{max}	0.215	0.253	0.848	0.798 – 0.902
	$AUC_{0\text{-last}}$	1.787	1.990	0.898	0.834 – 0.968
	$AUC_{0\text{-}\infty}$	2.209	2.416	0.915	0.855 – 0.978
A *vs.* D	C_{max}	0.215	0.271	0.793	0.745 – 0.843
	$AUC_{0\text{-last}}$	1.787	2.057	0.868	0.806 – 0.936
	$AUC_{0\text{-}\infty}$	2.209	2.457	0.899	0.841 – 0.962
B *vs.* C	C_{max}	0.256	0.253	1.012	0.952 – 1.075
	$AUC_{0\text{-last}}$	2.020	1.990	1.015	0.942 – 1.094
	$AUC_{0\text{-}\infty}$	2.397	2.416	0.992	0.928 – 1.061
B *vs.* D	C_{max}	0.256	0.271	0.945	0.889 – 1.005
	$AUC_{0\text{-last}}$	2.020	2.057	0.982	0.911 – 1.059
	$AUC_{0\text{-}\infty}$	2.397	2.457	0.975	0.912 – 1.044
C *vs.* D	C_{max}	0.253	0.271	0.934	0.878 – 0.994
	$AUC_{0\text{-last}}$	1.990	2.057	0.967	0.897 – 1.043
	$AUC_{0\text{-}\infty}$	2.416	2.457	0.983	0.919 – 1.052

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

2.6 Analytical Section

1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Two LC-MS/MS methods (Method A and B) were validated for the determination of paricalcitol concentration in plasma. The lower limit of quantitation (LLOQ) for Method A and B was 0.02 ng/mL and 0.01 ng/mL of paricalcitol, respectively. The precision (%CV) ranged from 9.5% to 11.9% and from 4.6% to 6.6% for Method A and B, respectively. The accuracy ranged from 92.9 to 99.4% and from 95.7% to 101.0% of the target concentration for Method A and B, respectively.

3 Detailed Labeling Recommendations

Under **CLINICAL PHARMACOLOGY** section:

2 Page(s) Withheld

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

_ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

4 Appendix

4.1 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	**21-606**	**Brand Name**	**Zemplar capsule**
OCPB Division (I, II, III)	**II**	**Generic Name**	**paricalcitol**
Medical Division	**510**	**Drug Class**	**Metabolism**
OCPB Reviewer	**Wei Qiu, Ph.D.**	**Indication(s)**	**Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 3 and 4**
OCPB Team Leader	**Hae-Young Ahn**	**Dosage Form**	**Soft gelatin capsules**
		Dosing Regimen	**1 mcg, 2 mcg, and 4 mcg**
Date of Submission	**July 28, 2004**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review		**Sponsor**	**Abbott laboratories**
PDUFA Due Date		**Priority Classification**	**Standard**
Division Due Date		**Type of submission: paper or electronic**	**Paper and electronic**

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**

STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	X	1		**Single iv and oral doses.**
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x			
multiple dose:	x	1		
Patients-				
single dose:	x	2		**These studies also evaluated absolute F.**
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		**Same study evaluate absolute F.**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1		Omeprazole. Ketoconazole study will be submitted within 3 months of NDA submission.
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	x	1		
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	x			Data pooled from 9 phase 1 studies
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	x			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	3		1. To-be-marketed Vs clinical capsules 2. Two Dosage form equivalence studies (one pilot).
replicate design; single / multi dose:				
Food-drug interaction studies:	x			
Dissolution:	x			
(IVIVC):	x			
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				

Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		10		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	x	Because the only difference between clinical lot and to-be-marketed lot was the lot scale, DSI inspection is not requested. The clinical lot was 20% of the to-be-marketed lot.
Comments sent to firm ?		
QBR questions (key issues to be considered)	1. What is the absolute bioavailability of Zemplar capsules in healthy subjects and patients? 2. How is paricalcitol eliminated in humans? 3. How does paricalcitol accumulate after multiple dosing? 4. Is dose proportionality established? 5. Is dosage form equivalence established? 6. How does omeprazole affect PK of Zemplar capsules? 7. How does ketoconazole affect PK of Zemplar capsules? 8. What is the PK in renal impaired patients? 9. How does food affect the bioavailability of Zemplar capsules? 10. Is the IVIVC established?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

The following studies were submitted:

BA and BE study reports

1. **Study 2001-004**: Assessment of the Bioequivalence of Zemplar (Paricalcitol) Capsules at Three Dosage Strengths (1, 2, and 4 ug)---This was a pilot phase 1 study.

2. **Study M02-435**: Assessment of the Bioequivalence of Zemplar (paricalcitol) capsules at Dosage Strengths 1 ug (#3 SEC), 1 ug (#2 SEC), 2 ug (#3 SEC), and 4 ug (#3 SEC). This was a Phase 1, single-dose, open-label, randomized, fasting study conducted with 88 subjects according to a three-cohort, four-period, crossover dose strength linking design. Each regimen was administered as a single 8 ug dose. It was concluded that Regimens B (8 x 1ug SEC#2), C (4 x 2 ug SEC#3), and D (2 x 4 ug SEC#3) was BE. Regimen A (8 x 1 ug SEC#3) was equivalent to Regimens B, C, and D with respect to AUC0-t and AUC0-inf; however, equivalence could not be concluded for Cmax.

3. **Study M02-437**: Assessment of the bioavailability of Zemplar (paricalcitol) Commercial capsule relative to Zemplar (paricalcitol) Clinical Capsule and Assessment of the Effect of

Food on the Bioavailability of Zemplar (paricalcitol) Commercial Capsule. The purpose of the study was to evaluate BE between the 4 ug SEC#3 formulation manufactured at the clinical lot scale and the 4 ug SEC#3 formulation manufactured at the to-be-marketed lot scale. This phase 1, single dose, open-label randomized study was conducted according to a three-period, complete-crossover design. Sixty subjects received one of three sequences of the following regimens: Regimen A (two 4 ug paricalcitol capsules, clinical formulation, fasting); Regimen B (two 4 ug paricalcitol capsules, to-be-marketed formulation, fasting); Regimen C (two 4 ug paricalcitol capsules, to-be-marketed formulation, high fat fed condition). It was concluded that the 4 ug to-be-marketed capsule were BE to the 4 ug clinical capsule. The high fat meal has no significant effect on the bioavailability of the to-be-marketed capsule. However, the high fat meal caused a significant increase in mean paricalcitol Tmax.

Human PK studies

4. **Study 2000-007**: An assessment of the safety, bioavailability and dose proportionality of a Zemplar capsule formulation in volunteers in general good health. This was a phase 1, single dose, four period, partial-crossover (part I: Periods 1, 2, and 3, complete crossover followed by Part II: Period 4), fasting and nonfasting, open-label, randomized study. The objectives were the bioavailability of a paricalcitol capsule formulation relative to that of a paricalcitol intravenous formulation, the effect of food on the bioavailability of the paricalcitol capsule formulation, and whether there was pharmacokinetic dose-proportionality with the paricalcitol capsule formulation. The mean absolute bioavailability of the paricalcitol capsule administered as a single oral dose under fasting and nonfasting conditions was 66.4% and 72.1%, respectively. Administration of the paricalcitol capsule following a low fat moderate calories breakfast had no effect on paricalcitol AUC; however, there was about a 21% increase in Cmax. Following oral administration, paricalcitol pharmacokinetics was dose-proportional over the 0.06 ug/kg to 0.48 ug/kg dose range. Paricalcitol pharmacokinetics was not influenced by gender.

5. **Study 2001-025**: Single and multiple dose safety and pharmacokinetic assessment of a Zemplar (paricalcitol) capsule following daily and three-times a week dosing in volunteers in general good health. No unexpected paricalcitol accumulation following multiple-dose administration was observed. Paricalcitol administered orally either as 4 ug QD or 8 ug TIW resulted in similar steady-sate exposure.

6. **Study 2000-005**: An assessment of the safety and bioavailability of a paricalcitol (Zemplar) capsule formulation in subjects with End-Stage Renal Disease, Undergoing hemodialysis. The estimated absolute bioavailability of paricalcitol administered as a single oral dose under nonfasting conditions in subjects with end-stage renal disease who were undergoing hemodialysis was 78.8%.

7. **Study 2000-006**: An assessment of the safety and bioavailability of a Zemplar (paricalcitol) capsule formulation in subjects with End-Stage Renal Disease, undergoing continuous peritoneal dialysis. The absolute bioavailability of paricalcitol administered as a single oral dose of capsule formulation was estimated to be 86.1%.

8. **Study M03-633**: A Phase 1 single and multiple dose study to determine the safety, pharmacokinetics and pharmacodynamics of Zemplar (paricalcitol) capsule in subjects with moderate to severe renal impairment. The pharmacokinetics of paricalcitol in subjects with moderate (CKD stage 3) and severe (CKD Stage 4) renal impairment were similar to those in subjects with ESRD (CKD Stage 5).

9. Study 2001-030: Absorption and disposition of [3H]-paricalcitol in man following either a single intravenous administration or a single oral administration. Total radioactivity was eliminated primarily in the feces (approximately 63-70% of the administered dose), with

approximately 52% excreted by 96 hours postdose. Mean total recovery accounted for 82.7% and 87.4% of the administered dose following IV and oral administration, respectively.

10. **Study M02-436**: Assessment of the Single-Dose Pharmacokinetics and Safety of the Coadministration of Paricalcitol and Omeprazole. This was a Phase 1, single-dose, open-label, fasting, randomized, drug interaction, and crossover study in 26 subjects. The objective of this study was to assess the effect of omeprazole on the pharmacokinetics of paricalcitol. There were no statistically significant differences in any of the pharmacokinetic parameters between the two regimens.

Results from a drug-drug interaction study with ketoconazole and in vitro study examining the metabolic enzyme induction potential of paricalcitol with primary cultured human liver cells will be submitted during the first three months of the review cycle. Datasets for all clin pharma studies were included except study 2001-030. Population PK analysis and IVIVC were included.

4.2 Individual Study Synopsis

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/s/

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5/18/05 10:07:18 AM
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