Tissues collected: 23 tissues, plus blood and plasma
4,8,24,72,168h post single oral dose
24h post 1st, 3rd, 5th, 7th dose, and at 68h post 7th dose

Assays: Radioactivity (plasma and tissues); parent drug and active metabolite by [redacted] or [redacted] (plasma, urine, feces)

Results: **(Table 1)**

- Bioavailability: 30% (^{3}H-AUC ratio oral:i.v.)
- Components in 0-120h plasma: 1a,25-OH2-D2 (38%), 1a-OH-D2 (7%), rest unidentified
- 1a,25-OH2-D2: Tmax 8h, $T_{1/2}$ 23h
- Tissue radioactivity (8-24 post dose) highest in: intestine, liver, stomach, adrenal gland
- Liver tissue levels of radioactivity at 8, 24, 72h post single oral dose: 3.54, 2.03, 0.26 ng equiv/g
- Components in 0-96h urine: no 1a-OH-D2 or 1,a,25OH2D2 detectable by [redacted]
- Radioactivity content of 0-24h bile and urine, after intraduodenal dose: 1.9% and 0.5% of dose
- In vitro protein binding of metabolite 1a,25OH2D2 in rat plasma: 98.5-99.1% at 0.1, 1, 10 ng/ml
- In vitro distribution to erythrocytes of 1a,25OH2D2: 0.9% (0.1 ng/ml) - 2.5% (10 ng/ml)

Study R1

TABLE 1. ADME of [^{3}H]-1a-OH-D2 in rats

Dose (route, number of doses)	2.5 µg/kg (oral, single)	2.5 µg/kg/day (oral, 7 days)	2.5 µg/kg (IV, single)
Absorption and Pharmacokinetics - Total ^{3}H			
C_{max} (ng/mL)[a]	0.519	0.84 (Day 1) 1.03 (Day 7)	19.26
t_{max}	8 hr	8 hr	5 min
AUC (ng-hr/mL)	22.4 (0-∞)	13.5 (Day 1, 0-24 hr) 19.1 (Day 7, 0-24 hr)	74.8 (0-∞)
Bioavailability (%)	30.0	NA	NA
Major components in 0-120 hr pooled plasma (% of radioactivity)	1α,25(OH)$_2$D$_3$ (37.5%) 1α-OH-D$_3$ (7.0%) unidentified (55.5%)	NA	NA
Tissue Distribution - Total ^{3}H			
Tissues with highest ^{3}H levels at 8 hr postdose, and plasma level (concentration, ng/g)[a]	small intestine (4.35) liver (3.54) stomach (2.15) adrenal gland (0.85) large intestine (0.61) [plasma = 0.34]	NA	NA
Tissues with highest ^{3}H levels at 24 hr postdose, and plasma level (concentration, ng/g)	liver (2.03) small intestine (0.75) adrenal gland (0.61) large intestine (0.41) Harder's gland (0.39) [plasma = 0.28]	liver (3.56)[b] adrenal gland (1.32) small intestine (1.13) epididymal fat (1.00) Harder's gland (0.80) [plasma = 0.39]	NA
Excretion Pattern			
Radioactivity in feces (% of total dose)	89.6% (0-168 hr)	95.2% (0-120 hr)[c]	NA
Major components in 0-72 hr feces (% of dose)	1α-OH-D$_3$ (29.3%) 1α,25(OH)$_2$D$_3$ (2.1%) unidentified (55.7%)	NA	NA
Radioactivity in urine (% of total dose)	4.7% (0-168 hr)	2.8% (0-120 hr)[c]	NA

NA Not applicable/Not determined
a Concentrations are ng equivalents of 1α,25(OH)$_2$D$_3$/g or mL of sample
b 24 hr after the last (7th) dose
c Cumulative from first day through 120 hr after the last (7th) dose

Additional data from single oral dose (2.5 ug/kg) study:

Drug/Metabolite	Cmax (pg/ml)	Tmax (h)	AUC (ng*h/ml)	T1/2 (h)
1a-OH-D2	64	8	ca. 1.6	10 and 29 (biphasic)
1a,25(OH)2D2	169	8	ca. 8.4	23

(B) Pharmacokinetic data from non-radiolabeled single dose, 7-day, 14-day and 52-week studies in rats

R2. Pharmacokinetics of BC-101 in Rats [redacted] 849-BCI-001-91)

Methods

Rats:	Female SD rats (5-7 wks, 120 g)
Doses:	0, 0.39 ug/kg, single oral dose
Plasma samples:	0, 2, 4, 6, 9, 12, 24, 48h postdose
Assay:	1a,25OH_2D2 and 1,24OH_2D2

Results: **(Table 2)**

- Control animals: no measurable 1a,25-metabolite plasma levels
- Dosed animals: C_{pl} of 1a,25-metabolite similar at 4,6,9h postdose; average T_{max} 6h
- Dosed animals: no measurable plasma levels of 1,24-metabolite

R3. Pharmacokinetics of BC-101 in Rats [redacted] 849-BCI-002-91)

Methods

Rats:	Female SD rats (120-150 g)
Doses:	0, 0.39, 2.5 ug/kg/day, for 7 days
Plasma samples:	9h postdose
Assay:	1a,25OH_2D2 and 1,24OH_2D2

Results: **(Table 2)**

- Control animals: 1a,25-metabolite plasma levels: < 5 pg/ml
- Plasma levels of 1a,25OH_2D2 increase, but less than proportional, with dose
- Endogenous calcitriol levels:

control	40 pg/ml
0.39 ug/kg	16.6 pg/ml
2.5 ug/kg	12.4 pg/ml

R4. Effect of BC-101 on Serum Biochemistry in Rats [redacted] 464-BCI-001-91)

Methods

Rats:	Male and female SD rats (6-7 wks, 165-265g)
Doses:	0, 6, 20, 100 ug/kg/day, for 14 days
Plasma samples:	24h after last 14th dose
Assay:	1a,25OH_2D2 and 1,24OH_2D2

Results: **(Table 2)**

- Control animals: 1a,25-metabolite plasma levels: ca. 10 pg/ml
- Plasma levels increase, but less than proportional, with dose
- Plasma levels of main 1a,25-metabolite: males >> females (ca. 2x)

R5. Analysis of 1a,25-dihydroxyvitamin D2 in serum samples from [redacted] Study No. 295-136 (One-year oral toxicity study in rats with [redacted]-870) (Continental Assays Corporation Study BCI Report No. T-105)

Note: These are data from Study VI of Animal Toxicity Studies; this Review, p.19; NDA Vol.1.8, p.007)

Methods

Rats:	Male and female SD rats (6-7 wks, 165-265g)
Doses:	0, 0.02, 0.06, 0.55, 5 ug/kg/day, for 52 weeks
Plasma samples:	4, 8, 24h after last dose in wks 26, 52
Assay:	1a,25OH_2D2

Results: **(Table 2)**

(Note: Data given are from Wk26, due to extensive mortality in HD group at Wk52)

BEST POSSIBLE COPY

- Control animals: 1a,25-metabolite plasma levels: <5 pg/ml
- Tmax: 4-8h postdose
- Plasma levels increase, but less than proportional, with dose
- Plasma levels males >> females (ca. 2x)
- Results suggest that 24h post dose levels measured in Study R4 are underestimates of "C_{max}"

TABLE 2. Concentrations of Active Metabolites in Rat Serum/Plasma After Oral Administration of 1α-OH-D_2

Study	Study	Sex	Dose (μg/kg)	Dosing Duration	Serum/Plasma 1α,25$(OH)_2D_2$ Concentration (pg/mL)(at time)	Serum/Plasma 1α,24-$(OH)_2D_2$ Concentration (pg/mL)(at time)
R2	[redacted]849-BCI-001-91	Female	0.39	Single	38.8 (6 h)	<10 (6 h)
R3	[redacted]849-BCI-002-91	Female	0.39	7 days	44.9 (9 h)	< 15 (9 h)
			2.5		90.6	105
R4	[redacted]464-BCI-001-91	Male	6	14 days	201 (24 h)	16.5 (24 h)
			20		355	36.6
			100		598	113
		Female	6		117	32.5
			20		134	42.8
			100		358	135
R5	[redacted]C 295-136	Male	0	26 weeks	< 5.0	ND
			0.02		15.8 (8 h)	ND
			0.06		44.7	ND
			0.55		140.7	ND
			5.0		NA	ND
		Female	0	26 weeks	< 5.0	ND
			0.02		6.7 (8 h)	ND
			0.06		20.7	ND
			0.55		71.0	ND
			5.0		234.3	ND

ND Not determined
NA Not applicable (no surviving animals)

R6. Four Week Oral Comparative Toxicity Study of 1-OH-D2 and 1-OH-D3 in rats [redacted]-14-90)

Note: These are data from Study IV of Animal Toxicity Studies; this Review, p. 12; NDA Vol. 1.6, p.112)

Methods

Animals: Crj:CD rats (6 wks, 192-236g)

Dose groups: control (0), 0.1, 0.5, 2.5, 12.5 ug/kg/day 1-a-OHD2 or 1-a-OHD3 (9 groups)

Assay: Plasma levels of 1a-OH-D2, 1a,25-OH_2-D2 and 1,25-OH_2-D3, in 0, 0.5, 2.5 ug/kg/day groups, on Day 1 and Day 15

Results: (Table 3)

- Plasma levels of both D2 and D3 metabolites were dose-dependently related to dose of 1a-OH-D2 or 1a-OH-D3 administered.
- After 15 days there is no production of 1α,25-$(OH)_2$-D_2 in the group given the D3 analog and there is no production of 1α,25-$(OH)_2$-D_3 in the group given the D2 analog.
- The AUCs for the total active metabolites for each dose of each drug do not change from Day 1 to Day 15, even though endogenous active metabolite production is completely suppressed. Apparently, suppression of endogenous production is parallelled by formation of exogenous 1a-OH-D metabolites.

BEST POSSIBLE COPY

TABLE 3. Active metabolite concentrations upon 1-OH-D2 and 1-OH-D3 dosing in rats

Study R6

DAY 1:

Compound & Dose	AUC (0-24), pg°h/ml		
	1α,25-(OH)$_2$-D$_2$	1α,25-(OH)$_2$-D$_3$	Total
Control	863	1458	2321
0.5 ug TSA-870	1772	1007	2779
2.5 ug TSA-870	4291	1095	5385
0.5 ug 1α-OH-D$_3$	774	3841	4615
2.5 ug 1α-OH-D$_3$	421	6215	6636

DAY 15:

Compound & Dose	AUC (0-24), pg°h/ml		
	1α,25-(OH)$_2$-D$_2$	1α,25-(OH)$_2$-D$_3$	Total
Control	787	1317	2103
0.5 ug TSA-870	2733	0	2733
2.5 ug TSA-870	5236	0	5236
0.5 ug 1α-OH-D$_3$	0	3626	3626
2.5 ug 1α-OH-D$_3$	0	6857	6857

R7. Pharmacokinetics of BCI-2-125, BCI-3-125 and [redacted]-103 following Single Oral Dose Administration to Rats ([redacted] 849-BCI-001-92)

Methods

Animals: Female SD rats (136-200g)

Doses: 0, 0.15, 0.39 ug/kg, single oral

Plasma samples: 1,2,3,4,6,9,15,24h after dose

Assay: BCI-2-125 = 1a,25(OH)$_2$D2
BCI-3-125 = 1a,25(OH)$_2$D3
LR-103 = 1a,24(OH)$_2$D2

Results: **(Table 4)**
See next page

Results: **(Table 4)**

- T_{max}: 1-3h postdose
- Plasma levels 1a,25(OH)$_2$D3 > 1a,25(OH)$_2$D2 >> 1a,24(OH)$_2$D2
- AUC increases less than proportional to dose at 0.39 ug/kg as compared to 0.15 ug/kg, for all three compounds. This is probably due to nonlinear metabolism and/or absorption.

TABLE 4. PK parameters after single dose of BCI-2-125, BCI-3-125, and [redacted]103

Study R7

		Endogenous dosed compound (pg/ml)	Endogenous BCI-3-125 (pg/ml)	Exogenous + endogenous dosed compound			
	Dose (ug/kg)			Cmax (pg/ml)	Tmax (h)	T1/2 (h)	AUC (pg*h/ml)
BCI-2-125 1a,25(OH)2D2	0.15	<10	67	155	2	6.9	1278
	0.39	<10	67	364	1	5.1	2555
BCI-3-125 1a,25(OH)2D3	0.15	67	(67)	233	1	7.7	2235
	0.39	67	(67)	492	1	5.8	3423
LR-103 1a,24(OH)2D2	0.15	<10	67	53	3	6.4	403
	0.39	<10	67	89	1	4.9	625

MONKEY STUDIES

(A) Pharmacokinetic data from radiolabeled single dose studies in monkeys

M1. Pharmacokinetics of [redacted]-870 in Rats and Monkeys [redacted]-14-107)

Methods

Animals:	Male crab-eating monkeys (3.3-4 kg)
Dose:	^{3}H-1a-OH-D2 (single oral or i.v)
Plasma collected :	12 time points between 1-168h post oral dose
	12 time points between 0.1-48h post iv dose
Excreta collected:	For 168h post single oral dose
Assays:	Sample radioactivity, [redacted]

Results **(Table 5)**

See next page

Results: (Table 5)

- Bioavailability: 27% (^{3}H-AUC ratio oral:i.v.)
- Components in (0-120h)-plasma: 1a,25-OH_2-D2 (23%), 1a-OH-D2 (2.5%), rest unidentified
- 1a,25-OH2-D2: T_{max} 24h, $T_{1/2}$ 22h
- Components in 0-96h urine: no 1a-OH-D2 or 1,a,25OH_2D2 detectable by [redacted]
- In vitro protein binding of metabolite 1a,25OH_2D2 in monkey plasma: 99.1% at 0.1, 1, 10 ng/ml
- In vitro distribution to erythrocytes of 1a,25OH_2D2: 6.4% (0.1 ng/ml), 4% (1ng/ml), 3.9% (10 ng/ml)

Study M1

TABLE 5. ADME of [^{3}H]-1a-OH-D2 in monkeys

Dose (route)	2.5 µg/kg (oral)	2.5 µg/kg (IV)
Absorption and Pharmacokinetics - Total ^{3}H		
C_{max} (ng/mL)[a]	0.289	26.7
t_{max}	48 hr	5 min
AUC (ng-hr/mL)	24.2 (0-∞)	89.2 (0-∞)
Bioavailability (%)	27.0	NA
Major components in 0-120 hr pooled plasma (% of radioactivity)	1α,25$(OH)_2D_3$ (22.9%) 1α-OH-D_3 (2.5%) unidentified (74.6%)	NA
Pharmacokinetics - 1α-OH-D_3		
C_{max} (ng/mL)	0.012	NA
t_{max} (hr)	24	NA
$t_{1/2}$	14 hr	NA
AUC (ng-hr/mL)	0.53	NA
Pharmacokinetics - 1α,25$(OH)_2D_3$		
C_{max} (ng/mL)	0.093	NA
t_{max} (hr)	24	NA
$t_{1/2}$ (hr)	22 hr	NA
AUC (ng-hr/mL)	4.60	NA
Excretion Pattern		
Radioactivity in feces (% of total dose)	89.9% (0-168 hr)	NA
Major components in 0-96 hr feces (% of dose)	1α-OH-D_3 (41.9%) 1α,25$(OH)_2D_3$ (5.4%) unidentified (37.7%)	NA
Radioactivity in urine (% of total dose)	3.9% (0-168 hr)	NA

NA Not applicable/Not determined
a Concentrations are ng equivalents of 1α,25$(OH)_2D_3$/mL

Additional data from single oral dose (2.5 ug/kg) study:

Drug/Metabolite	Cmax (pg/ml)	Tmax (h)	AUC (ng*h/ml)	T1/2 (h)
1a-OH-D2	12	24	ca. 5.5	14
1a,25(OH)2D2	93	24	ca. 8.4	22

(B). Pharmacokinetic data from non-radiolabeled single dose, 8-day and 52-week studies in monkeys

M2. Single-Dose Pharmacokinetic Study in Cynomolgus Monkeys ([redacted] Report 053).

Methods

Monkeys: Adult female cynomolgus monkeys

Doses: 0.39 ug/kg, single oral dose, or 0.39ug/kg, for 8 days

Plasma samples: 0,2,4,6,9,12,15,18,24,30,48h post single dose, or 9h after 8th dose
Assay: 1a,25OH_2D2
Results: **(Table 6)**

- Single dose study: plasma levels of 1a,25-metabolite maximal at ca. 6h postdose (range 48-124 pg/ml)
- Repeated dose study: plasma levels of 1a,25-metabolite at 9h postdose (range 15-79 pg/ml)
- Results appear inaccurate

M3. Analysis of 1a,25-dihydroxvitamin D2 in serum samples from [redacted] No.295-135 (One Year Oral Toxicity Study In Cynomolgus Monkeys) (Continental Assays Corporation BCI Report No. T-106).

Note: These are data from Study IX of Animal Toxicity Studies; this Review, p.28)

Methods
Monkeys: Male and female cynomolgus monkeys
Doses: 0, 0.06, 0.6, 6, 20 ug/kg/day, for 52 weeks
Plasma samples: at 4, 8, 24h after last dose in Wk 29, and at 0, 2, 4, 6, 8, 12, 24h after last dose in Wk 52
Assay: 1a,25OH_2D2
Results: **(Table 6)** *(Note: Data from both Wk29 and Wk52 are given)*

- Control animals: 1a,25-metabolite plasma levels: <18 pg/ml
- Time-plasma concentration relationship for 1a,25OH_2D2 inconsistent between dose groups
- Plasma levels increase less than proportionally with dose
- Plasma levels in Wk 29 on average somewhat lower than levels in Wk 52 (some accumulation)
- Plasma levels in males similar to females

TABLE 6

Concentrations of $1\alpha,25(OH)_2D_2$ in Monkey Serum After Oral Administration of 1α-OH-D_2

Study	Study	Sex	Dose (µg/kg)	Dosing Duration	$1\alpha,25(OH)_2D_2$ Concentration (pg/mL)	Time[a] (hr)
M2	[redacted]053	Female	0.39	Single	90.0	6
				8 days	42.4	9
M3	[redacted]295-135	Male	0	29 weeks	9.6	8
			0.06		20.0	4
			0.60		80.3	4
			6.0		239	4
			20.0		527	4
		Female	0	29 weeks	< 6.7	8
			0.06		19.0	8
			0.60		85.4	4
			6.0		276	8
			20.0		748	4
		Male	0	52 weeks	17.2	8
			0.06		31.9	0 (24)
			0.60		59.1	4
			6.0		361	0 (24)
			20.0		556	12
		Female	0	52 weeks	10.2	8
			0.06		25.9	0 (24)
			0.60		162	0 (24)
			6.0		311	8
			20.0		644	12

[a] Time after last dose at which maximum concentration shown occurs; 0 (24) indicates predose sample (collected 24 hours after previous day's dose).

BEST POSSIBLE COPY

METABOLITES

The main active 1a-OH-D2 metabolite in rats and monkeys is 1,25(OH)2D2. The activity of 1,25(OH)2D2 is generally assumed to be similar to 1,25(OH)2D3 (calcitriol). Additional information on the activity of metabolites was inferred from published literature comparing D2 and D3 metabolites.
For example, the receptor affinity of 1,24,25(OH)3-D2, which is formed by C-24 hydroxylation of 1,25(OH)2D2 in the kidney, is usually similar to the affinity of 1,24,25-(OH)3-D3, while both are less than the affinity of calcitriol. The pharmacological activity of 1,24,25(OH)3-D2 appears to be much less than of 1,25(OH)2-D2 (0.1x), and in rats the tri(OH) metabolite is rapidly cleared from plasma. The kidney also transforms 1a,24,25(OH)3D2 into tetra-hydroxylated metabolites (1a,24,25,26 or 28(OH)4D2). Their activity is unknown.
The other active liver metabolite is 1a,24(OH)2D2. This compound was identified in rat plasma. In vitro, this compound can be further modified in the side chain (OH-lation or truncation) to products with 0.1-0.2x the activity of the 1a,25(OH)D2-compound or calcitriol.

Thus, 1a-OH-D2 is metabolized in the liver to 1a,25- or 1a,24-(OH)2-D2, which is further hydroxylated or modified to relatively less active products in kidney or other tissues. Metabolite excretion appears to be mainly biliary, based on high fecal and low urine content of radioactivity after radioactive dose administration

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

Overall Summary and Conclusions of ADME Studies:

ANIMAL PK AND METABOLISM

ADME was studied in rats and monkeys using radiolabeled [^{3}H]-1α-OH-D2 dose administration, and a radioreceptor assay for the active metabolite 1a,25(OH)$_2$D2, and using [redacted] assays for non-radioactive labeled 1a-OH-D2 and its metabolites.

In rats and monkeys, 1a-OH-D2 is absorbed slowly, 25-30% bioavailable (as parent + metabolites), and extensively metabolized. 1a-OH-D2 is converted for a large part to 1a,25(OH)2D2. The plasma levels of the main circulating metabolite 1a,25(OH)2D2 are higher than those of the parent 1a-OH-D2. In rats, there was a sex difference in levels of 1-alpha,25(OH)$_2$VitD2 (male levels ca. 2x female levels), possibly related to higher hepatic vitaminD-25-hydroxylase activity in the male rat.

Plasma levels of 1,25(OH)2D2 are related dose-dependently to the administered dose of 1a-OH-D2. Tmax in plasma is 6-12h in rats, and 12-24h in monkeys. Pharmacokinetics in both rat and monkey are non-linear. In rat plasma, the 1,24 (OH)2-D2 metabolite is also generated, with levels related dose-dependently to administered dose. The level of this metabolite is the same in m and f. In both single and repeated dose studies the plasma levels of 1,25(OH)2D2 in the rat were relatively high as compared to the monkey, when doses were compared on the basis of ug/m2 body surface area. This will be discussed further below.

In vitro studies with human hepatoma cells show that both 1,24-D2 and 1,25-D2 can be formed in human liver cells. In vitro studies with bovine kidney homogenate and human epidermal cells showed that both of these compounds are further hydroxylated in the side chain (at C-24, 25, 26, or 28) to metabolites with lower activity. In rats, the t1/2 of these compounds is a few hours.

In rats and monkeys, urinary excretion of radiolabeled compound was <5% of dose, while fecal excretion varied between 89 and 95%.

In vitro protein binding is concentration-independent, and amounts to ca. 99% in rat, monkey, human plasma or serum. Binding of radiolabeled compound to rat, monkey or human erythrocytes in blood was <5%.

HUMAN PK AND METABOLISM

Intended human dose:

a. Initial dose 10 ug/day (3x/wk), or 30 ug/week = 0.07 ug/kg/day
b. Adjust dose to control HPT
c. Maximal dose (used in trials) 60 ug/week = 0.14 ug/kg/day

Administration of 1a-OH-D2 to human leads to the appearance of 1a,25(OH)2D2 in blood, in dose-dependent but not dose-proportional manner
Tmax is 10-12h after p.o. dosing, and of ca. 8h after i.v.dosing. Thus, rate of metabolic conversion and not absorption is the main limiting factor for Tmax of the active D2 metabolite.
Css is attained after 8 days, ie, after four once/2days doses.
Apparent terminal $T_{1/2}$ in humans is 32-37h (oral dose)
Bioavailability of orally administered 1a-OH-D2 is approximately 40%.
Protein binding is ca. 99%, erythrocyte binding <5%.
It is not clear whether 1,24(OH)2D2 is formed in humans.

Human PK of main 1a-OH-D2 metabolite, 1a,25(OH)2D2 (Data Vol. 1.1)

Study	Dose			#Doses (treatment duration)	Cplasma (pg/ml)	AUC (pg*ml/h)	T1/2 (h)	Urinary excretion
[redacted]117	5 ug/ 2days	2.5 ug/ day	0.042 ug/ kg/day	5 (10 days)	30	957	32	nd
	15 ug/ 2days	7.5 ug/ day	0.13 ug/ kg/day	5 (10 days)	67	2168	37	nd
[redacted]108	5-7.5 ug/2days (3x/wk)	2-2.9 ug/day	0.036-0.048 ug/kg/day	(10-16 weeks)	20-30	-	-	nd

nd = not determined

Comparison Animal-Human PK

The following table lists the animal dose and exposure multiples attained in 1-year oral toxicity studies in rat and monkey, for male animals. The multiples are based either on comparison of dose per m^2 body surface area (human dose multiple, HDM), or on actual data on plasma levels of 1,25(OH)2D2, the main active metabolite of the test compound (human exposure multiple, HEM). Multiples are based on a 30 ug/week clinical dose:

Dose/exposure comparison between species

	Study	Dose			HED* (ug/m2 basis)	Cpl,ss**	T1/2	Human Dose Multiple (HDM) based on dose (ug/m2 basis) comparison	Human Exposure Multiple (HEM) based on Cpl,ss* comparison
		ug/wk	ug/d	ug/kg/d	ug/kg/d	(pg/ml)	h	Factor	Factor
Rat	1-year oral tox								
				0.02	0.0033	15.8 (M)	23	0.048x	0.42x
				(0.04)	(0.0067)	(30)			
				0.06	0.01	44.7 (M)		0.14x	1.2x
				0.55	0.092	141 (M)		1.3x	3.8x
				5	0.9	234 (F) (465, M)[a]		12x	6x (F) (12x, M)[a]
Monkey	1-year oral tox								
				0.06	0.02	31.9	22	0.29x	0.8x
				0.6	0.2	59		2.9x	1.6x
				6	2	361		29x	9.4x
				20	6.67	556		96x	14.6x
Human									
	H-108	20	2.86	0.048	0.048	30	37	0.66x	0.79x
	H-117	53	7.5	0.13	0.13	67			
		60[a]	8.6[a]	0.14[a]	0.14[a]	76[a]		2x	2x

* HED = human equivalent dose in ug/kg/day units, based on comparison of dose per body surface area (ug/m2)
** Cpl,ss = steady state plasma concentration
[a] data are extrapolated

With a maximum clinical dose of 60ug/week, the highest multiple attained in the 1-year rat study (5 ug/kg/day) was a HDM of 6x (in males and females), corresponding to a HEM of 3.1x (in females). For the monkey (20 ug/kg/day) the highest HDM was 48x, corresponding to a HEM of 7.3x.

BEST POSSIBLE COPY

The fact that the HEM/HDM ratio decreases with increasing dose indicates overtly non-linear pharmacokinetics. This means that the exposure range that can be attained is much smaller than the dose range, in animals and probably also in humans.

The larger HEM/HDM ratio in the rat than in the monkey indicates that the plasma levels in the rat, as compared to the monkey, are relatively high. This is in agreement with the findings from toxicity studies that the rat is relatively more sensitive to toxicity of Hectorol than the monkey, ie, that NOAEL's in the rat are smaller than in the monkey, when expressed as doses on the basis of m^2 body surface area. However, the difference in plasma levels is not sufficient to explain the difference in NOAEL's. The reason for the relatively large rat plasma levels is unclear, since $T_{1/2}$ in monkey and rat are similar. Possibly, it reflects a species difference in hepatic 1a-OH-D_2-hydroxylation activity.

Comparison of monkey and human doses and plasma levels indicates that monkey plasma levels are approximately as expected from dose comparison on the basis of body surface area.

APPEARS THIS WAY ON ORIGINAL

3 PAGES
TRADE SECRET/
CONFIDENTIAL
COMMERCIAL

SUMMARY AND EVALUATION

Animal Toxicity Studies

Acute Toxicity

Acute effects of 1α-OH-D_2 were remarkably consistent in rats and mice, including the fact that in both species the sensitivity to 1α-OH-D_2 was 10-fold lower p.o. than i.p. Common dose dependent findings were; reduced motility, dyspnea, hyporeactivity, ataxia, abdominal position, diarrhea (in rats) reduced defecation (in mice) and body weight, congestion of the stomach mucosa (p.o. studies), tan foci on the hearts and tan or red foci on the kidneys of surviving animals. Renal discoloration, congestion of the lungs and staining around the mouth and anus and small spleens were noted in deceased animals. These toxicities reflect agonal changes and the pharmacological effect of the drug to cause hypercalcemia as well as effects secondary to hypercalcemia.

MICE Route:	Minimum lethal dose (ug/kg)	Human equivalent dose, HED* (ug/kg)	LD_{50} (ug/kg)	Human equivalent dose, HED* (ug/kg)	Human dose multiple, HDM**
P. O. males	320	26	449	37	222 x
P. O. females	630	52	495	41	246 x
I. P. males	30	2.5	35	3	-
I. P. females	60	5	30-60	2.5-5	-

RATS Route:	Minimum lethal dose (ug/kg)	Human equivalent dose, HED* (ug/kg)	LD_{50} (ug/kg)	Human equivalent dose, HED* (ug/kg)	Human dose multiple, HDM**
P. O. males	1250	208	1700	283	1700 x
P. O. females	2500	416	1800	300	1800 x
I. P. males	33	6	25	4	-
I. P. females	65	10	70	12	-

* HED in units of ug/kg by comparison of doses on a mg/m^2 basis

** HDM on basis of single oral human 10 ug dose (0.167 ug/kg/day, human weight 60 kg)

Males appear to be slightly more sensitive to the drug in both rat and mouse species. In this regard, male rats have been shown to metabolize vitamin D differently from females, resulting in higher plasma levels of the active main metabolite, 1,25-OH_2-D2. Another consistent finding was that the minimum lethal dose and the LD_{50} are very close indicating a very steep toxicity curve. When doses are compared on a mg/m^2 basis, the oral LD_{50} is approximately 200-2000 times the proposed human oral dose. However, it is likely that the oral LD_{50} is a smaller factor when expressed in terms of human exposure multiples, since ADME results have shown that plasma levels increase less than proportional to dose.

Repeated dose (<6-month) toxicity:

Four repeated dose toxicity studies were conducted with 1α-OH-D_2 in rats (4- and 13-weeks) and monkeys (2- and 13 weeks) however, the longer term (13-week) monkey study was conducted at too low a dose and the shorter term rat study was conducted only in males. The results of these studies show the

time and dose dependence of the effects of 1α-OH-D_2. All of these effects reflect the pharmacological actions of vitamin D and are consistent with results from other toxicity tests: diminished weight gain, hypercalcemia with calciuria and phosphaturia, pale kidneys with white foci, calcification of myocardium, selected blood vessels, gastric mucosa and muscle, and mineralization of kidney with accompanying tubular degeneration. Dose-dependent, increased proliferation of cancellous bone was a common finding in rats and, when severe, may affect bone marrow function resulting in hematological changes. The most sensitive indicator of toxicity of oral 1α-OH-D_2 was hypercalcemia. The following table lists the NOAEL levels in rats and monkeys expressed as doses, human dose multiples, and human exposure multiples. The latter are based on steady state plasma levels of 1a,25$(OH)_2$D2measured after repeated dosing for 26 weeks in the rat and 52 weeks in the monkey.

Study:	NOAEL (ug/kg)	HED* (ug/kg)*	Human dose multiple (HDM)*, **	Human exposure multiple (HEM)**
4-Wk Rat	0.1	0.017	0.24 x	2 x
13-Wk Rat	0.06	0.01	0.14 x	1.2 x
2-Wk Monkey	6	2	29x	9.4 x
13-wk Monkey	>2.5	>0.8	>11x	>3.8 x

* HED and HDM on a mg/m^2 basis.
** HDM and HEM based on a human dose of 30 ug/week = 0.07 ug/kg/day

Monkeys appeared to be 100 fold less sensitive than rats to the actions of the drug, i.e., when doses were compared on the basis of mg/m^2 body surface area. On the basis of exposure to the active compound, 1a,25$(OH)_2$D2, monkeys still appeared about 10 fold less sensitive to toxicity than rats. The reason for this difference is unclear. There were no significant sex-related differences in sensitivity to the pharmacological or toxicological action of 1a-OH-D2 in rats or monkeys.

As shown in the table above, the human dose multiples of the rat NOAEL levels were significant (ca. 10x) underestimates of the human exposure multiples, while the dose multiples in the monkey overestimated the exposure multiples (ca. 3x). However, even when expressed in terms of plasma exposure, the NOAEL in the rat is only 1-2 times the human proposed therapeutic exposure level. It should be noted that the multiples were derived from 1-year animal exposure data, and since some accumulation appeared to take place (p. 59), the exposure multiples may in fact be even smaller. The low NOAEL levels especially in the rat do not necessarily cause concern about the proposed clinical dose, since the toxicities observed in the rat studies all appeared to result from the desired pharmacological actions of the drug to increase plasma calcium levels and related tissue and physiopathology. Nevertheless, these toxic effects demonstrate significant risks of relatively short-term exposure to vitamin D in excess of the levels required to normalize calcium and PTH levels

One-Year Oral Toxicity Studies.

One-year oral toxicity studies were conducted in both rats and monkeys. Dose dependent toxic effects of 1α-OH-D_2 reflected the physiologic actions of vitamin D: diminished weight gain, renal calcification, hypercalcemia with calciuria and phosphaturia and calcification of blood vessels in numerous organs with accompanying tissue damage. All of these effects reflect the pharmacological actions of Vitamin D and are consistent with results from other toxicity testing. One effect, which was seen clearly for the first time in the rat study, was the hyperostosis in bone. This effect was dose dependent and was seen to some extent in all bones. This effect was not clearly observed in shorter-term studies because it takes a long time to develop. In moderate to severe cases the hyperostosis lead to diminished medullary space. This may be the cause of the extramedullary hematopoiesis and the changes in hematology.

Species:	NOAEL (ug/kg)	HED* (ug/kg)	Human dose multiple (HDM)*, **	Human exposure multiple (HEM)**
Rats	0.02	0.003	0.043 x	0.42 x
Monkeys	0.6	0.2	2.9x	1.6 x

* HED and HDM on a mg/m^2 basis.
** HDM and HEM on basis of 30 ug/week human dose = 0.07 ug/kg/day

As in the shorter term toxicity studies, the human dose multiple of the rat NOAEL was a ca. 10-fold underestimate of the human exposure multiple, while the monkey NOAEL dose multiple was a slight overestimate. Taken together, the results of the 1-year toxicity studies show that the NOAEL levels in both the rat and the monkey are quite low when expressed in terms of expected human exposure multiples, particularly in the rat. However, these low values do not necessarily cause concern about the proposed human dose because the toxicities seen in the animal studies appeared to result from the expected pharmacological action of the drug to cause hypercalcemia and related pathology when administered to a normal animal. Nevertheless, these toxic effects do demonstrate the significant risks of exposure to levels of vitamin D in excess of the levels required to normalize calcium and PTH levels. Patients with renal failure will be less sensitive to these effects and will be monitored to avoid hypercalcemia and secondary complications.

When calculations of human dose or exposure multiples are done for LOAEL values obtained from repeated dose studies in rats and monkeys, the result is that the ratio between exposure multiples at the LOAEL and the NOAEL is generally less than the ratio between LOAEL and NOAEL. For example the 1-year NOAEL and LOAEL levels in monkeys are 0.6 and 6 ug/kg/day while the exposure multiples at these two dose levels are 9.4 and 1.6. Again this is due to a less than proportional increase in plasma level with dose. However, we need to remember that, as in most toxicity studies, the NOAEL, LOAEL and exposure multiples derived from these AE levels, are only rough approximations since they are based on the few doses actually used in the studies.

Special Toxicity Studies

Toxic effects in these studies were consistent with toxicities noted previously in standard toxicity studies.
Metabolism of 1α-OH-D_2 was consistent with other ADME studies, and confirmed that results could be extrapolated to higher doses (100 ug/kg/d) in rats.
The urinalysis study in cynomolgus monkeys confirmed the variability in measurements of urinary parameters.

Reproductive Toxicity Studies

Segment 1:
The Segment I study revealed no significant toxicity in rats reproduction or fertility when given up to 2.5 ug/kg/day. Expected changes in serum calcium and phosphorous and weight were observed as was an increase in corneal opacities which was determined to be due to calcification. No toxic or adverse effect on reproduction or fertility was observed in this study.

Segment 2:
When 1α-OH-D_2 was administered to gravid female rats on Gestation days 6 through 17 there were no adverse effects on fetal growth or survival at up to 20 ug/kg/d. At the maximum dose tested (100 ug/kg/day) toxic maternal effects (decreased weight gain and calcification of heart, kidneys, lungs and stomach) were noted. The high dose fetuses appeared subject to a possible increased rate of resorption but there was inadequate maternal survival (1/25) to determine any consistent effect.

When BCI-101 was administered to gravid female rabbits on Gestation days 6 through 18 there were no adverse effects on fetal or maternal health at the LD of 0.03 ug/kg/d. At the MD (0.1 ug/kg/d) and HD (0.3 ug/kg/d) there was slightly increased rate of resorption (not significant). This is consistent with the rat Segment II study, where there was an increase in resorptions in the one HD dam that survived. Despite evidence of maternal toxicity (weight loss and renal foci) at the MD and HD, there was no statistically significant evidence of fetal toxicity although there were some incidence of delayed ossification in the HD litters.

Segment 3:
Although maternal toxicity was observed in the HD group (15 ug/kg/d) in the form of hypercalcemia and decreased weight, weight gain and food consumption. No maternal effects were noted at lower doses and there were no developmental or reproductive effects at any dose.

In conclusion, the lowest threshold of maternal and fetal effects was seen in the rabbit Segment II study which showed maternal effects at the 0.1 and 0.3 ug/kg MD and slightly increased resorptions with delayed fetal ossification at the 0.3 ug/kg/day HD.

Genetic Toxicology Studies

The Bacterial Reverse Mutation Assay (Ames test) in S. typhimurium and E.coli did not indicate a mutagenic potential for TSA-870 +/- S9.
The Mouse Lymphoma assay did not indicate a mutagenic potential for [redacted]870.
The *in vitro* Human Lymphocyte Chromosome Aberration Assay was positive in the presence of metabolic activation with S9. This suggests that upon metabolic activation Hectorol may induce structural chromosomal aberrations in human cells.
The *in vivo* Mouse Micronucleus Assay was negative for chromosomal aberrations.

Carcinogenicity Studies

The Sponsor did not conduct carcinogenicity studies for this NDA. However, Sponsor has been informed that these studies will be needed for an NDA with an osteoporosis indication.

ADME Studies

In rats and monkeys, 1a-OH-D2 is absorbed slowly, 25-30% bioavailable (as parent + metabolites), and extensively metabolized. 1a-OH-D2 is converted for a large part to 1a,25(OH)2D2. The plasma levels of the main circulating active metabolite, 1a,25(OH)2D2, are higher than those of the parent 1a-OH-D2. Tmax of 1a,25(OH)2D2 varied between 8h (rat) and 24 h (monkey), and T1/2 was 22-23h in rats and monkeys. In rats, there was a sex difference in levels of 1-alpha,25(OH)$_2$VitD2 (male levels ca. 2x female levels), possibly related to higher hepatic vitaminD-25-hydroxylase activity in the male rat.

Pharmacokinetics in both rat and monkey are non-linear. In both single and repeated dose studies the plasma levels of 1,25(OH)2D2 in the rat were relatively high as compared to the monkey, when doses were compared on the basis of ug/m2 body surface area.

In vitro studies indicate that the 1a,25 and 1a,24(OH)2-D2 metabolites are further hydroxylated in the side chain to metabolites with lower activity and a t1/2 of a few hours.

In rats and monkeys, urinary excretion of radiolabeled compound was <5% of dose, while fecal excretion varied between 89 and 95%. In vitro protein binding is concentration-independent, and amounts to ca. 99% in rat, monkey, human plasma or serum. Binding of radiolabeled compound to rat, monkey or human erythrocytes in blood was <5%.

BEST POSSIBLE COPY

Comparison of human and animal pharmacokinetics showed that at relatively low doses in the human therapeutic dose range, plasma levels in animals, particularly in rats, are relatively high, while at higher toxic doses animal plasma levels are disproportionally low. Thus, calculation of human dose multiples of animal doses on the basis of dose per m^2 body surface area leads to under- or overestimation of the exposure multiple, depending on the dose applied to.

Qualification of Impurities

Based on the qualification of impurities as carried out in chronic animal toxicity studies, and based on evidence from the literature about the activity of stereoisomeric vitamin D impurities, this Reviewer concludes that, at the levels specified, the safety of the impurities in the drug substance is acceptable for the clinical indication of this NDA.

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

LABELING REVIEW

PRECAUTIONS

DRAFT LABELING

[redacted]

DRAFT LABELING

[redacted]

BEST POSSIBLE COPY

PHARMACOLOGY RECOMMENDATION

Pharmacology recommends approval of NDA 20-862 for the treatment of secondary hyperparathyroidism of renal failure.

Approval is pending upon appropriate description of potential risk in the labeling (PRECAUTIONS) as suggested by the Pharmacology Reviewer.

/S/ [redacted]

Daniel T. Coleman, Ph.D.
Pharmacologist.

/S/ [redacted]

Gemma Kuijpers, Ph.D.
Pharmacologist

[redacted]

BEST POSSIBLE COPY

APPENDIX

Attachments:

1. Pharmacology review of 28 day IV rat study (3422.6) for IND [redacted]
2. Initial IND review of one year rat (295-136) and monkey (295-135) studies for IND [redacted]
3. Pharmacology review of protocol for one year rat study (295-136) for IND [redacted]
4. Initial IND review of IND [redacted] (b)(4) C/C (scanned paper copy)
5. Pharmacology review of acute (615-001) and 13-week (615-002) rat studies for IND [redacted] (scanned paper copy)
6. Pharmacology review of 13 week monkey study (615-004) for IND [redacted] (scanned paper copy)

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

IND [redacted]

Review Completed: September 29, 1997

Sponsor: Bone Care International; Madison, WI 53713

Date Submitted: August 21, 1997

Date Received: August 27, 1997

PHARMACOLOGY REVIEW OF IND AMENDMENT

Amendment to IND [redacted]

DRUG: 1-alpha-hydroxyvitamin D2; 1α-OH-D2; secoergosta-5,7,10(19),22-tetraen-1,3-diol, (1α,3B,5Z,7E,22E), BCI-101.

CATEGORY: Vitamin D analogue

INDICATION: Secondary Hyperparathyroidism Associated with End Stage Renal Disease

RELATED IND: (NDA for paracaclin under review N20-819, however, this is a different analog).

MEMOS: This IND was shifted from Dr. Jordan in August, 1996; little of the previously submitted data have been formally reviewed.

ANTICIPATED SPECIAL RISKS: Potential for hypercalcemia and/or calcium deposits.

REVIEW OF STUDY No. 3422.6:
A 28-DAY INTRAVENOUS TOXICITY STUDY IN RATS WITH BCI-101

NOTE: Performed by [redacted] Study Date August 20, 1997. (Study initiated February 17, 1997; end of in-life phase March 18, 1997). QA provided; No GLP statement [redacted] SOP's used). Lot #: K037.

PURPOSE: "To evaluate the potential toxicity of BCI-101 and the potential local irritation of the test article solution when the test article was administered daily to rats by bolus intravenous injection for a minimum of 28 consecutive days."

EXPERIMENTAL DESIGN: SD Crl:CD®BR [redacted] Rats, 10 /sex/group were dosed 0, 0.025, 0.25 and 2.5 µg/kg/day. All doses and vehicle were given at a constant volume of 400 µl/kg. The first 5 animals /group were dosed for 28 days. The second set of 5 animals /group were dosed 29 days (no explanation given for the difference).Organs examined microscopically were eyes, heart, injection site, kidneys and gross lesions from all animals. (Systemic tox is available from oral studies). Vehicle = not identified.

RESULTS

OBSERVED EFFECTS: None.

MORTALITY: One 2.5µg/kg/day male was found dead shortly following dosing on day 5. There were no clinical signs and the death was attributed to the restraint procedure during dosing and was not considered related to test article.

BODY WEIGHT: Dose related decrease in mean body weights for high dose males (-27% at 28 days). There was a slight non-significant (3-5%) decrease in mid dose males. In high

dose females, there was no significant change in body weight. However, the body weights of high dose females were decreased 7% compared to controls at day 28. Body weight gains were significantly reduced in high dose males throughout the study. In mid dose males and high dose females, there was a statistically significant decrease in body weight gain, but only from days 1-8 (i.e., transient loss).

FOOD CONSUMPTION: Food consumption was statistically significantly lower in high dose males from days 15-28 whether based on g consumed/kg/animal or g consumed/kg/day. There was no significant change in food consumption in females.

VITAL SIGNS: No data.

OPHTHALMIC EXAMINATION: Increase in number and severity of corneal crystals in both sexes, particularly in the high dose groups (100% of high dose males, 40% of high dose females). The pathologist suggested that the lesions could be an exacerbation of a preexisting condition since there was a background occurrence prior to the initiation of dosing, or that this could be a result of the test article. The pathologist also offered that changes in cholesterol, phospholipids, calcium or basement membranes or local effects on precorneal tear film or epithelial cells could also be possible causes.

HEMATOLOGY: Statistically significant increase in RBC (7%) in high dose males. In females, there was a non-significant increase of 2.6%. This is probably not biologically significant, but should be compared to other tox studies. It is noted because there was a similar change in both sexes. There was also a 3.6% increase in Hb in high dose males which was not statistically significant. There were no significant findings in any other hematology parameters.

COAGULATION: No data.

BONE MARROW: No data.

BLOOD CHEMISTRY: In low dose males, there was a statistically significant ($p<0.01$) increase in total protein (6%) and albumin (7%). There was also a non-statistically significant increase in the mid dose group for total protein and a statistically significant ($p<0.05$, 5%) increase for albumin. It is not clear what these findings mean since they were near control levels in the high dose groups. A similar trend was noted in females, but was not statistically significant. Also in males, there was a statistically significant increase in potassium ($p<0.01$, 10%) at the low dose, but a decrease ($p<0.05$, 10%) at the high dose. Cholesterol was significantly increased in high dose males ($p<0.001$, 38% from 31 to 50 mg/dL). Calcium was statistically significantly increased at the low and high dose in males, but was not increased in the mid dose group. In contrast, there were statistically significant increases in the mid and high dose groups for phosphorus and calcium for females (6.93, 7.85, 8.06*, 8.89# mg/dL for control, L, M, H dose for phosphorus; 11.10, 11.42, 11.63*, 13.39# mg/dL for control, L, M, H dose for calcium; * = $p<0.05$, # = $p<0.001$)

URINALYSIS: In males, total volume of urine increased in the treated groups, reaching statistical significance ($p<0.01$) in the high dose group (5.0, 12.7, 8.5, 27.4** for control, L, M, H dose groups, respectively). There was a slight statistically significant loss in specific gravity in the groups with increased volumes (1.05, 1.02**, 1.03, 1.02**). In

high dose males, there was a slight increase in the abundance of occurrence of amorphous crystals (shift from rare or few to moderate). Similar results were found in females.

ORGAN WEIGHTS: Changes were found only in high dose males: Decreased absolute brain weight and decreased absolute and relative (to brain weight) heart (19%), kidney (12%) and liver weights (25%). In both high dose males and females, there was a decrease in thyroid/parathyroid weights relative to brain weights, but these were not statistically significant. Relative to final body weight, there were significantly higher brain, kidney and testes weights.

GROSS PATHOLOGY: High dose male that died on dose day 5 had reddened salivary gland and dark red axillary, scapular and mediastinal lymphnodes. Death was proposed to be caused by restraint procedures.

Dilated renal pelvis and distended ureter in one high dose female and body fat depletion and a kidney with dilated pelvis in another high dose females. No treatment-related gross findings were listed for any other test animals.

HISTOPATHOLOGY: High dose males: mineralization of large vessels at the base of the heart and in the tunica media of the ciliary artery of 4/10 males and in the lumen of the collecting ducts in the renal medulla in 9/10 males. Severity was minimal to mild. There were also more calculi observed in the renal pelvis of high dose males compared to controls. Interestingly, only one high dose male was noted with slight to moderate corneal crystal formation in contrast to the ophthalmic findings. There were no treatment-related findings at the injection site beyond those observed in the control animals.

SUMMARY

Toxicity of BCI-101 appeared to be primarily limited to the high dose group and was largely related to the physiological activities of the test agent. The primary toxicity findings included the following:

- Loss of body weight, primarily in high dose males (-27%). Weight loss in the mid dose males and high dose females ranged from 3-7%.
- Decreased food consumption in high dose males.
- Slight increase in RBC and Hb in high dose males. (This should be re-examined in other tox studies with this agent to determine the consistency of this finding).
- Increases in serum calcium and phosphorus in mid and high dose females; in males, increases in calcium were found in the low and high dose, but not at the mid dose.
- Increase in total urine volume in treated males, reaching statistical significance in high dose males. There was a slight decrease in specific gravity with the increase in volume.
- Increase in abundance of amorphous crystals in the urine of high dose males and females.
- Two high dose females had dilated kidney pelvis. One of these also had a distended ureter.
- High dose males: mineralization of large vessels at the base of the heart and in the tunica media of the ciliary artery of 4/10 males and in the lumen of the collecting ducts in the renal medulla in 9/10 males. Severity was minimal to mild. There were also more calculi observed in the renal pelvis of high dose males compared to controls.
- Increase in number and severity of corneal crystals in both sexes, particularly in the high dose groups (100% of high dose males, 40% of high dose females). It is not clear

BEST POSSIBLE COPY

what the mechanism of this effect is, but should be watched in other toxicology studies with this agent.

Based on these results, this reviewer believes that the NOAEL is 0.25 µg/kg/day when male and female rats are administered a bolus intravenous injection of BCI-101 for a minimum of 28 consecutive days.

TO BE COMMUNICATED TO SPONSOR

NAI from pharmacology at this time.

/S/ [redacted]

Ronald W. Steigerwalt, Ph.D.

cc: IND Arch
HFD510
HFD510/Steigerwalt/Hedin

APPEARS THIS WAY ON ORIGINAL