Effect of Age

The effect of age on the pharmacokinetics of verteporfin was investigated using data from BPD 001, BPD PK 001A/B and BPD OCR 001. In the case of BPD 001 (study in patients with skin cancer), the effect of age was assessed by comparing the pharmacokinetic parameters in patients 65 years and older with those aged less than 65 years. For the analysis of BPD 001 data, an ANCOVA model (after determining that no interaction was present between the main effects) was used with the dose as a covariate. This analysis was applied to the main verteporfin pharmacokinetic parameters (AUC_{0-t}, AUC_{inf} and C_{max}). Results (Table 18) show that the mean observed parameter values for the two age categories do not differ significantly, except for AUC_{0-t} (32% higher for subjects 65 years and older)

TABLE 18: Analysis of the Effect of Age on Verteporfin Pharmacokinetics

Pharmacokinetic Parameters	<65 Years (n=14)		≥65 Years (n=7)		Age Category Effect[a] *P* values
	mean[b]	CV[b]	mean[b]	CV[b]	
AUC_{0-t} (μg·h/mL)	2.66	(24%)	3.50	(19%)	.022
AUC_{inf} (μg·h/mL)	2.91	(27%)	3.70	(21%)	.066
C_{max} (μg/mL)	1.03	(21%)	1.14	(20%)	.334

Data from the BPD 001 clinical study report.

a ANCOVA with age category and gender as factors, and dose as a covariate (significant in all cases).

b Least squares means and coefficient of variation.

Another comparison was performed between the patients and healthy volunteers less than 65 years old, versus 65 years and older, who participated in Studies BPD OCR 001 or BPD PK 001A/B. In these studies, participants received a dose of 6 mg/m² via a 10-minute infusion.

Because of the limited sample collection in study BPD OCR 001, the age effect assessment with BPD PK 001A/B and BPD OCR 001 studies was limited to the assessment of the differences of plasma concentrations measured 10 and 20 minutes after the start of the 10-minute infusion of 6 mg/m² verteporfin. A simple one-way ANOVA was used to compare the two age categories for these two time points. The group of subjects less than 65 years old who provided a 10-minute sample was composed of 19 healthy volunteers of BPD PK 001A/B. For the 20-minute timepoint, 20 healthy volunteers of BPD PK 001A/B and 6 patients of BPD OCR 001 provided a sample. All subjects 65 years and older were from BPD OCR 001 (n=7 and 28, for the 10- and 20-minute timepoints, respectively). All participants in this analysis had their sample taken within 5 minutes of target sampling time.

TABLE 19: Analysis of the Effect of Age on Verteporfin Pharmacokinetics

Plasma sampling time	<65 Years		≥65 Years		Age Category Effect *P* values
	mean[b]	range	mean[b]	range	
10 mimutes	1.25 (N=19)	(0.37-1.68)	1.51 (N=7)	(1.24-1.82)	.034
20 minutes	0.56 (N=26)	(0.22-1.12)	0.78 (N=28)	(0.51-1.20)	.0001

Conclusions

- The mean C_{max} values were similar (1.03 versus 1.14 μg/mL), in the patients with skin cancer less than 65 years old and those 65 years and older, respectively.
- A statistically significant difference was observed between AUC_{0-t} values (P=0.022) and, although not statistically significant, a trend toward an age-related difference was observed between AUC_{inf} values (P=0.066). Mean values were 32% and 27% higher for AUC_{0-t} and AUC_{inf}, respectively in the ≥65 years old category (patients in skin cancer).
- Significant differences were seen in the 10 minute and 20 minute plasma concentrations in a comparison between the age of healthy subjects and patients combined.

Will dosage adjustment be necessary in the elderly population?

- Age related macular degeneration is a condition in the elderly only and the prevalence of the disease increases with age, hence the differences observed may not be of clinical significance. Age related comparisons were not robust as it was done across different subject population. Age related differences have been evaluated in a clinical studies, which will give a more meaningful effect of age (subjects 60-75 years and older than 75 years).

Effect of Hepatic Impairment

The pharmacokinetics of verteporfin in patients with mild hepatic dysfunction was evaluated in study BPD 004. This single dose study was done in 17 subjects, divided in two groups, 8 with normal hepatic function and 9 with mild hepatic dysfunction. Patients with mild hepatic dysfunction included patients with a history of liver disease supported by the presence of at least two abnormal hepatic function results at the time of enrollment. All the subjects received verteporfin at a dose of 0.3 mg/kg (12 mg/m^2) body weight via intravenous infusion delivered over 45 minutes. Light doses of 20-120 J/cm^2 was administered for an exposure time of 5-33 minutes on Day 5 for the assessment of residual photosensitivity. Blood samples were collected up to 24 hours after the start of infusion. Peak photosensitivity was assessed at 1.5-6 hours post infusion only in healthy subjects at light doses of 2.5-20 J/cm^2 with an exposure time of 4-40 minutes. The higher

exposure times were for the later time post infusion. The lower limit of detection of the regioisomers was 0.005 μg/ml.

The mean plasma verteporfin concentration-time profile and pharmacokinetic parameters in both healthy subjects and patients with hepatic dysfunction is shown in the following figure.

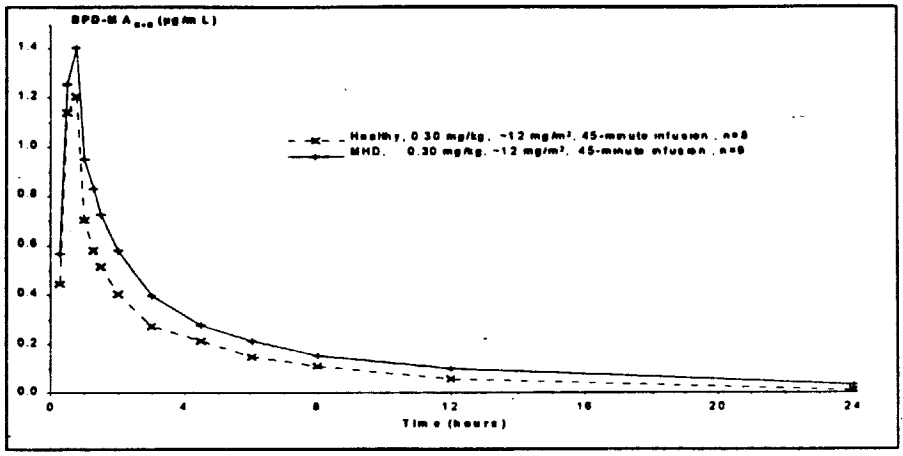

Figure: Mean plasma concentration profile of verteporfin in healthy subjects compared to patients with hepatic dysfunction

TABLE 20: Summary of Statistical Analysis of Pharmacokinetic Parameters of Verteporfin

Pharmacokinetic Parameters	Mean Values (CV%[a])				Ratio of Means (Dysfunction/ Normal)	ANOVA[b] p-value	90% Confidence Interval of Ratio of Means (Dysfunction/Normal)
	Hepatic Dysfunction (n=9)		Normal (n=8)				
AUC_{0-t} (μg•hr/mL)	4.60	(38)	3.25	(27)	1.42	0.0680	1.05 - 1.79
AUC_{inf} (μg•hr /mL)[d]	4.54	(39)	3.40	(28)	1.34	0.1264	0.97 - 1.70
AUC_{0-t}/AUC_{inf}[d]	0.95	(2)	0.96	(3)	0.99	0.5753	0.97 - 1.02
C_{max} (μg/mL)	1.4084	(30)	1.3777	(30)	1.02	0.8810	0.77 - 1.28
V_{ss} (L/kg)	0.3704	(35)	0.4177	(29)	0.89	0.4528	0.63 - 1.14
T_{max} (hr)	0.74	(13)	0.64	(19)	1.14	0.0995	1.00 - 1.29
K_{el} (1/hrs)[d]	0.1205	(17)	0.1437	(15)	0.84	0.0443	0.71 - 0.97
$t_{1/2}$[d]	5.88	(15)	4.92	(16)	1.19	0.0355	—[c]

[a] CV (Coefficient of Variation) standard deviation expressed as a percentage of the mean.
[b] One-way ANOVA with hepatic function group as the factor.
[c] Not calculated for this parameter.
[d] n=8 for these parameters

The mean AUC parameters in subjects with mild hepatic dysfunction were greater than those in subjects with normal hepatic function. AUC_{0-t} was approximately 42% greater and the AUC_{inf} was approximately 34% greater in the subjects with mild hepatic dysfunction compared to the subjects with normal hepatic function. These differences

were not statistically significant (p=0.0680 and p=0.1264, respectively). The greater mean AUC's in subjects with mild hepatic dysfunction were accompanied by a significantly smaller K_{el} and correspondingly longer elimination half-life (p=0.0355, approximately 19% greater than that in the subjects with normal hepatic function). Plasma levels of verteporfin for 4 subjects in the healthy group were close to or below the limit of detection for verteporfin by 24 hours after infusion. Subjects in the hepatic impaired group showed higher concentrations of verteporfin at 24 hours post infusion. The men plasma concentration at 24 hours post infusion in the healthy subjects was 0.0125 μg/mL vs. 0.0341 μg/mL in the hepatic impaired subjects. (see Appendix pages 38-40). The apparent volume of distribution V_{ss} indicated that the distribution was similar between the two groups. Besides the $t_{1/2}$ and K_{el} there were no other statistically significant differences between the two groups for any of the pharmacokinetic parameters.

Analysis of the ln-transformed pharmacokinetic parameters yielded similar results (See Appendix page 43). No statistically significant differences (p=0.05 level) in AUC_{0-t}, AUC_{inf}, and C_{max} were detected between the subjects with mild hepatic dysfunction and the subjects with normal hepatic function. A small difference in $t_{1/2}$ produced an increase in AUC but not C_{max} in subjects with mild hepatic dysfunction. This may not require a dose adjustment as verteporfin is intended for administration in single doses or therapy could be repeated after 3 months. The light dose will be administered around the C_{max}.

The pharmacokinetic parameters and plasma concentration profiles for the two regioisomers is given below. Both regioisomers showed similar trends. The individual pharmacokinetic parameters for the regioisomers are attached in the Appendix on pages 41-42.

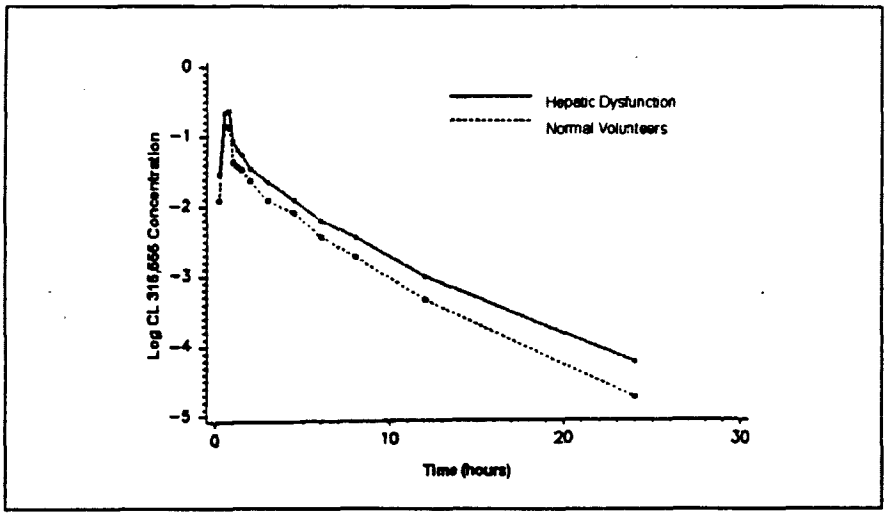

Figure: Mean plasma concentration-time profile for BPD-MA_C

TABLE 21: Summary of Statistical Analysis of Pharmacokinetic Parameters of BPD-MA_C CL 315,555)

Pharmacokinetic Parameters	Mean Values (CV%[a])				Ratio of Means (Dysfunction/ Normal)	ANOVA[b] p-value	90% Confidence Interval of Ratio of Means (Dysfunction/Normal)
	Hepatic Dysfunction (n=9)		Normal (n=8)				
AUC_{0-t} (µg•hr/mL)	2.33	(39)	1.69	(26)	1.38	0.0866	1.02 - 1.74
AUC_{inf} (µg•hr /mL)	2.55	(42)	1.79	(26)	1.42	0.0879	1.02 - 1.83
AUC_{0-t}/AUC_{inf}	0.93	(7)	0.95	(4)	0.98	0.5893	0.93 - 1.03
C_{max} (µg/mL)	0.6091	(38)	0.5415	(35)	1.12	0.5268	0.79 - 1.46
V_{ss} (L/kg)	0.4045	(37)	0.4663	(27)	0.87	0.3748	0.61 - 1.12
T_{max} (hrs)	0.65	(18)	0.64	(19)	1.01	0.8921	0.85 - 1.17
K_{el} (1/hrs)	0.1164	(23)	0.1330	(10)	0.88	0.1329	0.74 - 1.01
$t_{1/2}$ (hrs)	6.44	(38)	5.26	(10)	1.22	0.1987	[c]

[a] CV (Coefficient of Variation) standard deviation expressed as a percentage of the mean.
[b] One-way ANOVA with hepatic function group as the factor.
[c] Not calculated for this parameter.

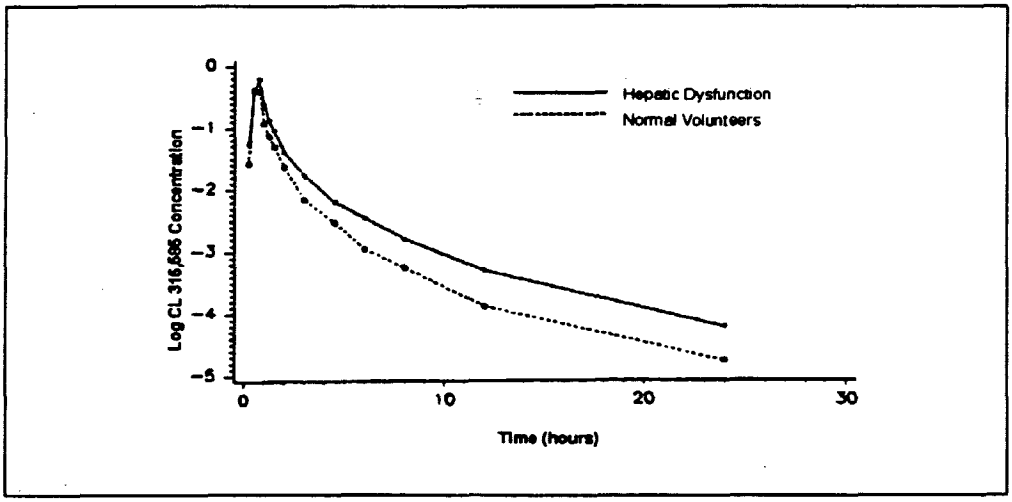

Figure: Mean plasma profile for $BPD\text{-}MA_D$

TABLE 22: Summary of Statistical Analysis of Pharmacokinetic Parameters of BPD-MA_D (CL 315,585)

Pharmacokinetic Parameters	Mean Values (CV%[a])				Ratio of Means (Dysfunction/Normal)	ANOVA[b] p-value	90% Confidence Interval of Ratio of Means (Dysfunction/Normal)
	Hepatic Dysfunction (n=9)		Normal (n=8)				
AUC_{0-t} (µg•hr/mL)	2.31	(44)	1.53	(33)	1.51	0.0675	1.06 - 1.97
AUC_{inf} (µg•hr /mL)	2.50	(47)	1.61	(31)	1.55	0.0683	1.06 - 2.05
AUC_{0-t}/AUC_{inf}	0.93	(3)	0.94	(2)	0.99	0.4004	0.97 - 1.01
C_{max} (µg/mL)	0.8665	(32)	0.8365	(27)	1.04	0.8116	0.78 - 1.30
V_{ss} (L/kg)	0.3304	(37)	0.3257	(25)	1.01	0.9269	0.74 - 1.29
T_{max} (hrs)	0.79	(11)	0.68	(17)	1.17	0.0275	1.05 - 1.30
K_{el} (1/hrs)	0.1151	(37)	0.1551	(23)	0.74	0.0538	0.53 - 0.96
$t_{1/2}$ (hrs)	6.52	(25)	4.68	(23)	1.39	0.0159	-[c]

[a] CV (Coefficient of Variation) standard deviation expressed as a percentage of the mean.
[b] One-way ANOVA with hepatic function group as the factor.
[c] Not calculated for this parameter.

Conclusions

- The mean AUC parameters of verteporfin are higher in subjects with hepatic dysfunction (34-42%). This is associated with a corresponding longer half-life (20%, p=0.0355)
- The mean AUC parameters of BPD-MA_C and BPD-MA_D are also higher by about 40% and 50% respectively. This is associated with a corresponding longer half-life of 22-39%.
- The t_{max} of verteporfin was later in subjects with mild hepatic dysfunction. This increase in t_{max} was contributed by the significantly higher t_{max} for BPD-MA_D (17%, p=0.0275).
- The apparent volume of distribution and C_{max} were comparable in the healthy and mild hepatic impaired subjects.

Is dosage adjustment necessary in patients with hepatic dysfunction?

- In summary, the significant increase in half-life (p=0.0355) produced an increase in AUC of verteporfin in patients with mild hepatic dysfunction. But since, verteporfin is intended to be administered in as a single dose or doses can be repeated at three months, dosage adjustment need not be necessary. It is around the C_{max} (i.e. at the end of infusion) that the photodynamic therapy would be administered.

- The pharmacokinetics of verteporfin in patients with moderate and severe hepatic impairment is not known. However, looking at the trend in the patients with mild hepatic dysfunction, it should not be recommended in patients with moderate and severe impairment.

Effect of Renal Impairment

The sponsor has not conducted a study on the renally impaired patients. Renal excretion of verteporfin and its metabolite is minimal and such a study is not necessary in these conditions. Combined excretion of BPD-MA_C, BPD-MA_D, and BPD-DA in urine was approximately 0.0031% of the verteporfin dose in Caucasian subjects and approximately 0.0036% in Japanese subjects (Studies BPD PK 001A/B).

DRUG INTERACTIONS

No specific drug interaction studies have been conducted with verteporfin. Verteporfin metabolism takes place mainly through liver and plasma esterases. CYP P450 and phase 2 metabolism did not appear to play a significant role. The exposure to the metabolite was 5-10% of that of the parent. Very low plasma concentrations of verteporfin were seen at 24 hours post infusion. Verteporfin half-life is about 5-6 hours and is administered intravenously as single doses separated by 3 months. Light is administered at 15 minutes after the start of the 10-minute infusion (i.e. during the distribution phase). Considering these any induction/inhibition effect of verteporfin will be only transient and any compound interacting with verteporfin elimination will have minimal effect on therapeutic outcome.

Benzoporphyrins are not largely bound to plasma proteins. It is bound mainly to plasma lipoproteins (90%), with only 5-7% bound to albumin[5].

Therefore, there seems to be a low potential for drug-drug interactions. Hence, it is acceptable that the sponsor has not conducted any drug interaction studies.

IV. OVERALL CONCLUSIONS

Absorption

- Verteporfin is immediately absorbed. C_{max} was achieved immediately after dosing at 10 minutes.
- The extent of exposure and the maximal plasma concentration are proportional to the dose between 6 and 20 mg/m^2.
- A 6 mg/m^2-10 minute infusion of verteporfin for injection in Caucasians produced a mean (%CV) AUC_{inf} of 1.63(20%) µg.h/mL.

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5 Allison B. et al. The plasma distribution of benzoporphyrin derivative and the effects on plasma lipoproteins on its distribution. Photochem Photobiol 1990, 52(3):501-507

Distribution

- Following intravenous administration verteporfin and its regioisomers BPD-MA_C and BPD-MA_D exhibited a bi-exponential decline in the plasma concentrations, a rapid distribution phase, followed by a slower elimination phase.
- The volume of distribution averaged 0.6 L/kg.
- The disposition of BPD-MA_C enantiomers was stereospecific, where as the disposition of BPD-MA_D enantiomers were not stereospecific.

Metabolism

- Verteporfin is metabolized through liver and plasma esterases to form the diacid metabolite (BPD-DA).
- The exposure of BPD-DA is approximately 5-10% of the exposure of verteporfin.
- There was no apparent evidence of conjugation with glucuronic acids.
- NADPH-dependent liver enzyme systems (including CYP P450) do not appear to play a role in the metabolism of verteporfin.

Excretion

- The excretion of verteporfin, its regioisomer and the metabolite is minimal in the urine. The combined excretion of BPD-MA_C, BPD-MA_D, and BPD-DA in urine was about 0.0031% in Caucasian subjects and about 0.0036% in Japanese subjects.
- The half-life of verteporfin is approximately 5-6 hours.
- The total body clearance averages to approximately 105 $mL \cdot h^{-1} \cdot kg^{-1}$.
- Rat experiments show that about 90% of verteporfin dose was excreted as unchanged drug through the liver.

Special Population

- Gender: No meaningful differences in pharmacokinetics were observed based on gender for the 6 and 12 mg/m^2 10 minute infusion groups.
- Race: All the pharmacokinetic parameters of verteporfin were similar in the Caucasian and Japanese men in the 6 mg/ m^2 with a 10 minute infusion group but AUC and CL were statistically different in the two races in the 14 mg/ m^2, 10 minute infusion group. Age related macular degeneration is more prevalent in Caucasians. Significant differences were not observed in clinical trial based on racial comparison. Dosage adjustment will not be necessary.
- Elderly: Robust comparisons could not be done, due to younger patients being in the healthy group and older being in the patient group. Age related differences have been evaluated in a clinical studies, which will give a more meaningful effect of age (subjects 60-75 years and older than 75 years). However, age related macular

degeneration being a condition of the elderly, and the prevalence of the disease increases with age.

- Hepatic Dysfunction: A significant increase in half-life produced an increase in AUC of verteporfin in patients with mild hepatic dysfunction. But since, verteporfin is intended to be administered in as a single dose or doses can be repeated at three months, dosage adjustment need not be necessary. It is around the C_{max} (i.e. at the end of infusion) that the photodynamic therapy would be administered. However, caution should be recommended.
  The pharmacokinetics of verteporfin in patients with moderate and severe hepatic impairment is not known. However, looking at the trend in the patients with mild hepatic dysfunction, it should not be recommended in patients with moderate and severe impairment.
- Renal Dysfunction: Renal excretion of verteporfin and its metabolite is minimal. A study is not necessary in these conditions. Combined excretion of BPD-MA_C, BPD-MA_D, and BPD-DA in urine was approximately 0.0031% of the verteporfin dose in Caucasian subjects and approximately 0.0036% in Japanese subjects (Studies BPD PK 001A/B).

VI. LABELING COMMENTS

The following labeling changes should be incorporated in the label.

Pharmacokinetics

[redacted] Following intravenous infusion, verteporfin exhibits a biexponential elimination with [redacted] a terminal elimination half-life of 5-6 hours. The extent of exposure and ~~the~~ maximal plasma concentration are proportional to the dose between 6 and 20 mg/m^2. At the intended dose, pharmacokinetic parameters are not significantly affected by gender [redacted]

Verteporfin is [redacted] metabolized to a small extent to its diacid metabolite [redacted] by liver and plasma esterases. There is no apparent evidence of conjugation with either glucuronic acid ~~and~~ or sulfate. NADPH-dependent liver enzyme systems (including the cytochrome P450 isozymes) do not appear to play a role in the metabolism of verteporfin. Elimination is by the fecal route, with less than [redacted] of the dose recovered in urine.

In a study of patients with mild hepatic insufficiency (defined as having two abnormal hepatic function tests at enrollment), AUC and Cmax were not significantly different from the control group, half-life however was significantly increased by [redacted]

/S/ 11/18/99

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. L 11/29/99 w/ noted changes

CC: NDA 21-119 (ORIG)
HFD-550/Div File
HFD-550/CSO/Gorski
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

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APPENDIX

NDA 21-119

VISUDYNE™

NDA: 21-119 Volume 2.39-2.57

Study Type: PK of verteporfin in healthy subjects *Study #BPD PK 001A &B*

Study Title: BPD PK 001A : An open study to assess the safety and tolerance of verteporfin in caucasian subjects and to compare the pharmacokinetics of verteporfin and its major metabolite in Caucasian and Japanese subjects after intravenous administration of verteporfin for injection

BPD PK 001B : An open phase I study after intravenous administration of verteporfin for injection –single dose administration

Study Site	
Clinical Site	Analytical Site
	PPD Pharmaco, Austin, TX Osaka Pharmacology Research Clinic, Japan

Single Dose	Multiple Dose	Washout Period	Cross-over	Parallel	Other Design	Fasted/ Fed	No. of fasted hrs.
X						fasted	10 hrs before and 2 hrs after dose

Subject Category					
Normal	Patients	Young	Elderly	Renal	Hepatic
(Caucasians & Japanese)		X			

Subject Type			
Males=20+24		Females=12	
Age	Weight	Age	Weight
20-35 (M=25.8 for C (M=22.2 for J)	54.4-97.2 for C 51.1-79.0 for J	20-35 (M=25.5 for C)	45.6-70.9

Subject Treatment Group			
Group No.	Total No.	Males	Females
1-A	12	8	4
2-A	12	8	4
3-A	8	4	4
1-B	8	8	
2-B	8	8	
3-B	8	8	

Treatment Group	Dose	Dosage Form	Strength	Lot #
1-A	6 mg/m^2-10 min	Inj (infusion)		TC0992
2-A	14g/m^2-10 min	Inj (infusion)		
3-A	6 mg/m^2 –1.5in	Inj (bolus)		
1-B	3mg/m^2 -10 min	Inj (infusion)		
2-B	6 mg/m^2 -10 min	Inj (infusion)		
3-B	14g/m^2 -10 min	Inj (infusion)		

Sampling Times

Plasma: predose, 7 (bolus only), 15, 20, 30, 45, 60 mins and 2, 3, 4, 6, 8, 12, 24 and 48 hrs after start of infusion

Urine: 0-6, 6-12, 12-24, 24-36, 36-48 and 48-72 hrs after start of infusion

Study #BPD PK 001 &B

TABLE 1. Summary of Baseline Demographic Variables

VARIABLE		Study A – Caucasian (USA) Total (n=32)	6 mg/m² 10-min inf. (n=12) Group 1A	14 mg/m² 10-min inf. (n=12) Group 2A	6 mg/m² bolus (n=12) Group 3A	Study B – Japanese (Japan) Total (n=24)	3 mg/m² 10-min inf. (n=8) Group 1B	6 mg/m² 10-min inf. (n=8) Group 2B	14 mg/m² 10-min inf. (n=8) Group 3B
GENDER:									
Male	No. (%)	20 (63)	8 (67)	8 (67)	4 (50)	24 (100)	8 (100)	8 (100)	8 (100)
Female	No. (%)	12 (38)	4 (33)	4 (33)	4 (50)				
AGE (years)									
Male	Range	20-33	21-33	21-26	20-32	20-25	21-24	21-23	20-25
	Mean ± SD	25.8±3.9	28.1±3.9	24.1±2.0	24.5±5.5	22.2±1.2	22.6±1.0	21.9±0.6	22.1±1.6
Female	Range	22-33	23-26	22-32	23-33				
	Mean ± SD	25.5±3.6	24.3±1.5	26.0±4.3	26.3±4.7				
HEIGHT[a] (cm)									
Male	Range	168-197	170-197	177-191	168-184	161-181	170-181	162-178	161-177
	Mean ± SD	182±8	186±8	183±5	175±7	171±5	174±4	171±5	167±5
Female	Range	157-173	166-171	157-170	167-173				
	Mean ± SD	168±5	168±2	165±7	171±3				
WEIGHT[a] (kg)									
Male	Range	54.4-97.2	73.7-97.2	71.5-84.4	54.4-66.0	51.2-79.0	52.2-69.0	51.2-79.0	52.7-78.4
	Mean ± SD	77.6±11.4	86.2±8.4	77.5±4.5	60.4±4.8	61.3±8.0	63.8±6.3	58.6±9.2	61.5±8.3
Female	Range	45.6-70.9	56.0-69.4	45.6-65.6	63.9-70.9				
	Mean ± SD	62.2±7.0	63.4±5.8	56.6±8.4	66.5±3.0				
BODY SURFACE AREA[b] (m^2)									
Male	Range	1.6-2.3	1.9-2.3	1.9-2.1	1.6-1.8	1.5-2.0	1.6-1.9	1.5-2.0	1.6-2.0
	Mean ± SD	2.0±0.2	2.1±0.1	2.0±0.1	1.7±0.1	1.7±0.1	1.8±0.1	1.7±0.1	1.7±0.1
Female	Range	1.4-1.8	1.7-1.8	1.4-1.8	1.8-1.8				
	Mean ± SD	1.7±0.1	1.7±0.1	1.6±0.2	1.8±0.0				
BODY FRAME									
Male Small	No. (%)	5 (25)	1 (13)	3 (38)	1 (25)	— —	— —	— —	— —
Medium	No. (%)	15 (75)	7 (88)	5 (63)	3 (75)	— —	— —	— —	— —
Large	No. (%)	0 (0)	0 (0)	0 (0)	0 (0)	— —	— —	— —	— —
Fem. Small	No. (%)	0 (0)	0 (0)	0 (0)	0 (0)				
Medium	No. (%)	11 (92)	4 (100)	4 (100)	3 (75)				
Large	No. (%)	1 (8)	0 (0)	0 (0)	1 (25)				
BMI[c] (kg/m^2)									
Male	Range	17.8-27.8	22.5-27.8	22.1-25.4	17.8-21.4	17.8-25.1	18.1-23.1	17.8-25.0	19.2-25.1
	Mean ± SD	23.3±2.5	25.0±1.9	23.3±1.1	19.7±1.5	21.0±2.1	21.0±1.8	20.0±2.2	21.9±2.1
Female	Range	18.5-25.4	20.1-24.7	18.5-23.0	21.5-25.4				
	Mean ± SD	22.1±2.1	22.5±2.3	20.9±2.3	22.9±1.7				

a. For Caucasian subjects, body weight and height are values recorded at screening; for Japanese subjects, on Day -1.
b. Calculated using body weights recorded on Day -1. For Caucasian subjects, these weights were not included in the case report form, database, or statistical summary and are listed for informative purposes as Appendix E.1.1.1.
c. Body mass index. Calculated as body weight (in kilograms) divided by the square of the height (in meters). Not included in the protocol.

Study #BPD PK 001 &B

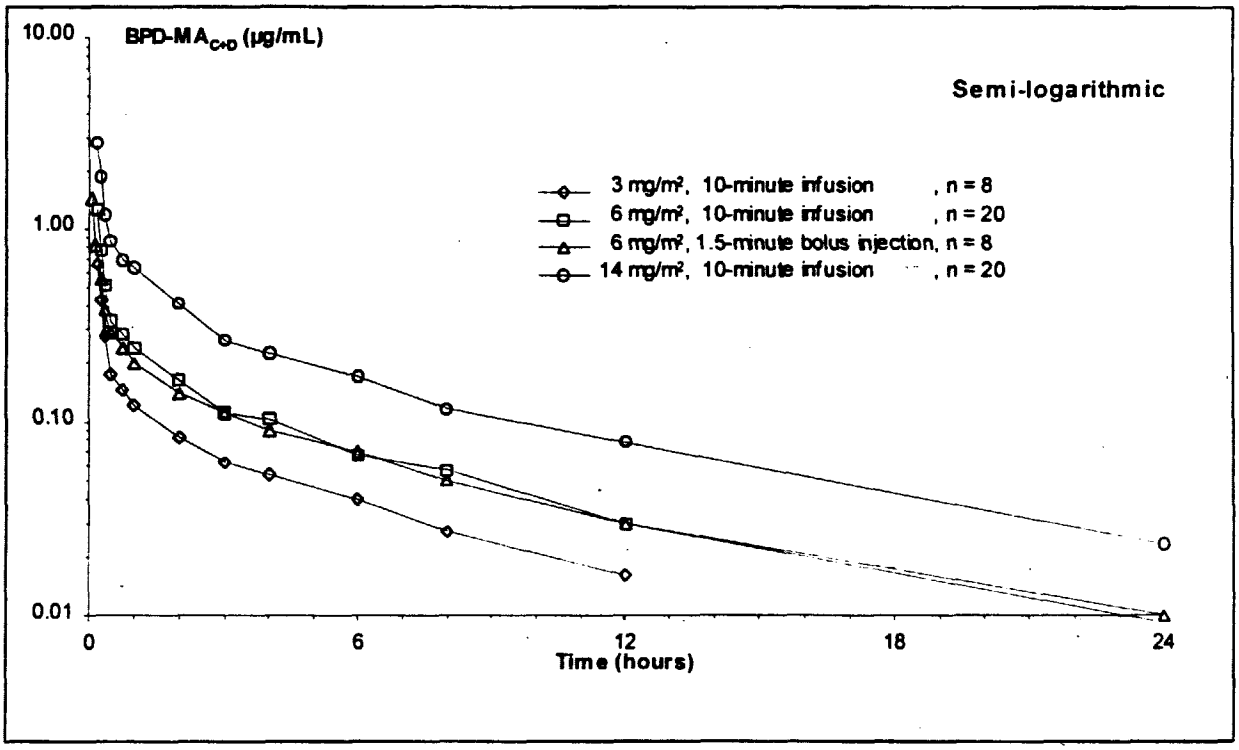
TABLE 2. Plasma Concentration Profiles

TIME	Mean (in µg/mL) and % Coefficient of Variation (in parenthesis)															
	Study A - Caucasian								Study B - Japanese							
	BPD-MAC		BPD-MAD		BPD-MAC+D		BPD-DA		BPD-MAC		BPD-MAD		BPD-MAC+D		BPD-DA	
	6 mg/m^2 – 10-minute infusion (n=12)								6 mg/m^2 – 10-minute infusion (n=8)							
10 min	0.44[b]	(29)	0.66[b]	(26)	1.10[b]	(27)	0.00	(153)	0.56	(11)	0.77	(11)	1.32	(11)	0.01	(119)
15 min	0.24	(27)	0.47	(24)	0.71	(25)	0.01	(92)	0.30	(18)	0.53	(16)	0.83	(17)	0.01	(69)
20 min	0.16	(30)	0.32	(28)	0.48	(28)	0.00	(97)	0.19	(17)	0.37	(16)	0.56	(16)	0.00	(110)
30 min	0.12[b]	(34)	0.21[b]	(37)	0.32[b]	(35)	0.01[b]	(75)	0.13	(22)	0.21	(32)	0.34	(28)	0.00	(156)
45 min	0.11	(32)	0.16	(28)	0.27	(29)	0.00[b]	(97)	0.13	(13)	0.17	(15)	0.30	(14)	0.00	(283)
60 min	0.10	(33)	0.13	(32)	0.23	(32)	0.00	(98)	0.11	(22)	0.14	(24)	0.25	(23)	0.00	(154)
2 h	0.08	(33)	0.07	(28)	0.15	(30)	0.00	(82)	0.10	(12)	0.09	(14)	0.18	(12)	0.00	(116)
3 h	0.06	(36)	0.05	(30)	0.10	(32)	0.00[b]	(72)	0.07	(19)	0.06	(22)	0.13	(20)	0.00	(96)
4 h	0.06	(30)	0.04	(26)	0.10	(27)	0.00[c]	(85)	0.06	(16)	0.04	(20)	0.11	(16)	0.00	(91)
6 h	0.04	(33)	0.02	(29)	0.06	(29)	0.01[b]	(51)	0.05	(17)	0.03	(24)	0.08	(19)	0.00	(99)
8 h	0.04	(35)	0.02	(27)	0.06	(30)	0.01[b]	(51)	0.03	(24)	0.02	(35)	0.05	(28)	0.00	(117)
12 h	0.02	(34)	0.01	(32)	0.03	(31)	0.00	(72)	0.02	(22)	0.01	(31)	0.03	(25)	0.00	(99)
24 h	0.00	(32)	0.00	(84)	0.01	(43)	0.00	(248)	0.01	(33)	0.00	(50)	0.01	(40)	0.00	(283)
30 h	0.00	(112)	0.00	(235)	0.00	(115)	0.00	(346)	0.00	(145)	0.00	(115)	0.00	(127)	0.00	(283)
36 h	0.00	(234)	0.00	(346)	0.00	(250)	0.00	(346)	0.00	(283)	0.00	(283)	0.00	(283)	0.00	–[a]
48 h	0.00	(346)	0.00	–[a]	0.00	(346)	0.00	(182)	0.00	–[a]	0.00	–[a]	0.00	–[a]	0.00	–[a]
	14 mg/m^2 – 10-minute infusion (n = 12)								14 mg/m^2 – 10-minute infusion (n = 8)							
10 min	0.96[b]	(49)	1.59[b]	(41)	2.55[b]	(43)	0.03[b]	(218)	1.27	(20)	1.87	(20)	3.13	(18)	0.01	(223)
15 min	0.60[b]	(48)	1.11[b]	(39)	1.70[b]	(42)	0.02[b]	(174)	0.73	(20)	1.35	(20)	2.07	(19)	0.01	(89)
20 min	0.38	(21)	0.74	(24)	1.12	(23)	0.02[b]	(121)	0.45	(30)	0.84	(25)	1.29	(26)	0.01	(89)
30 min	0.30	(25)	0.50	(21)	0.79	(22)	0.01[b]	(149)	0.36	(32)	0.61	(30)	0.97	(31)	0.01	(86)
45 min	0.26	(31)	0.36	(28)	0.63	(28)	0.01[b]	(171)	0.33	(31)	0.46	(30)	0.78	(31)	0.01	(94)
60 min	0.26	(29)	0.30	(24)	0.56	(26)	0.01	(192)	0.33	(39)	0.42	(40)	0.74	(40)	0.00	(62)
2 h	0.19	(29)	0.16	(27)	0.34	(27)	0.01	(72)	0.26	(30)	0.25	(35)	0.50	(32)	0.01	(87)
3 h	0.14	(27)	0.10	(27)	0.23	(26)	0.01	(82)	0.18	(25)	0.14	(32)	0.32	(28)	0.01	(55)
4 h	0.12	(21)	0.08	(24)	0.20	(21)	0.01	(97)	0.15	(23)	0.11	(30)	0.26	(25)	0.01	(54)
6 h	0.09	(23)	0.05	(23)	0.14	(21)	0.01	(60)	0.13	(32)	0.09	(43)	0.22	(36)	0.01	(64)
8 h	0.07	(20)	0.04	(18)	0.10	(17)	0.01	(59)	0.09	(28)	0.06	(38)	0.14	(32)	0.01	(49)
12 h	0.03	(25)	0.02	(24)	0.06	(22)	0.01	(58)	0.07	(42)	0.04	(50)	0.11	(45)	0.02	(49)
24 h	0.01	(30)	0.01	(31)	0.02	(25)	0.00	(65)	0.02	(47)	0.01	(43)	0.03	(44)	0.01	(30)
30 h	0.00	(30)	0.00	(66)	0.01	(32)	0.00	(152)	0.01	(64)	0.01	(69)	0.01	(64)	0.00	(53)
36 h	0.00	(93)	0.00	(185)	0.00	(95)	0.00	(153)	0.00	(100)	0.00	(87)	0.01	(91)	0.00	(113)
48 h	0.00	–[a]	0.00	–[a]	0.00	–[a]	0.00	(113)	0.00	(283)	0.00	(185)	0.00	(138)	0.00	–[a]
	6 mg/m^2 – 1.5-minute bolus injection (n = 8)								3 mg/m^2 – 10-minute infusion (n = 8)							
2 min	0.64	(20)	0.79	(13)	1.44	(15)	0.04	(128)	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]
7 min	0.28[d]	(16)	0.54[d]	(11)	0.83[d]	(12)	0.01[d]	(120)	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]
10 min	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]	0.27	(17)	0.39	(15)	0.66	(15)	0.01	(113)
15 min	0.18	(59)	0.37	(57)	0.55	(58)	0.01[d]	(105)	0.15	(17)	0.28	(18)	0.42	(17)	0.01	(72)
20 min	0.13	(29)	0.24	(26)	0.38	(27)	0.01[d]	(111)	0.09	(19)	0.18	(19)	0.27	(19)	0.00	(84)
30 min	0.11	(18)	0.18	(16)	0.29	(17)	0.00	(138)	0.07	(18)	0.11	(18)	0.18	(18)	0.00	(90)
45 min	0.10	(33)	0.14	(32)	0.24	(32)	0.00[d]	(154)	0.06	(26)	0.08	(17)	0.15	(20)	0.00	(114)
60 min	0.09	(30)	0.11	(26)	0.20	(28)	0.00[d]	(109)	0.06	(22)	0.07	(22)	0.12	(21)	0.00	(101)
2 h	0.08	(30)	0.07	(34)	0.14	(32)	0.01	(96)	0.04	(20)	0.04	(29)	0.08	(23)	0.00	(91)
3 h	0.06	(27)	0.05	(30)	0.11	(28)	0.01	(88)	0.03	(21)	0.03	(32)	0.06	(25)	0.00	(89)
4 h	0.05	(20)	0.03	(26)	0.09	(21)	0.00	(118)	0.03	(34)	0.02	(39)	0.05	(35)	0.00	(83)
6 h	0.04	(37)	0.02	(40)	0.07	(38)	0.01	(48)	0.02	(37)	0.02	(50)	0.04	(42)	0.00	(67)
8 h	0.03	(34)	0.02	(35)	0.05	(33)	0.01	(68)	0.02	(25)	0.01	(39)	0.03	(30)	0.00	(115)
12 h	0.02	(49)	0.01	(42)	0.03	(45)	0.00[d]	(64)	0.01	(30)	0.01	(36)	0.02	(32)	0.01	(39)
24 h	0.01	(74)	0.00	(108)	0.01	(79)	0.00	(187)	0.00	(72)	0.00	(109)	0.00	(80)	0.00	(119)
30 h	0.00	(121)	0.00	(139)	0.00	(119)	0.00	–[a]	0.00	(283)	0.00	(283)	0.00	(185)	0.00	(185)
36 h	0.00	(146)	0.00	–[a]	0.00	(146)	0.00	–[a]	0.00	–[a]	0.00	–[a]	0.00	–[a]	0.00	(283)
48 h	0.00	–[a]	0.00	–[a]	0.00	–[a]	0.00	(283)	0.00	–[a]	0.00	–[a]	0.00	–[a]	0.00	–[a]

Limit of quantification for BPD-MAC, BPD-MAD, and BPD-DA = 0.002 µg/mL

a. data not available.
b. n = 11.
c. n = 10.
d. n = 7.

Study #BPD PK 001 &B
Semi-logarithmic mean profile for verteporfin



NDA: 21-119 Volume 2.31-38

Study Type: PK In patients with CNV *Study #BPD OCR 001*

Study Title: An open, multicenter, non-controlled phase I/II study of the treatment of choroidal neovascularization using photodynamic therapy with liposomal BPD-MA (verteporfin)

Study Site	
Clinical Site	*Analytical Site*

Single Dose	*Multiple Dose*	*Washout Period*	*Cross-over*	*Parallel*	*Other Design*	*Fasted/ Fed*	*No. of fasted hrs.*
X						*fasted*	*10 hrs before and 2 hrs after dose*

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
	X=142				

Subject Type			
Males=75		*Females=67*	
Age (yrs)	*Weight (kg)*	*Age*	*Weight*
See demographics			

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
1-5	*See demographics*		

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
1-5				PQ002-94

Sampling Times

Plasma: Regimens 1-3 predose and at 10, 20, 30, and 40 minutes after the start of the 10-minute infusion
Regimen 5 predose and at 5, 10, 20, 30, and 40 minutes after the start of a 5-minute infusion

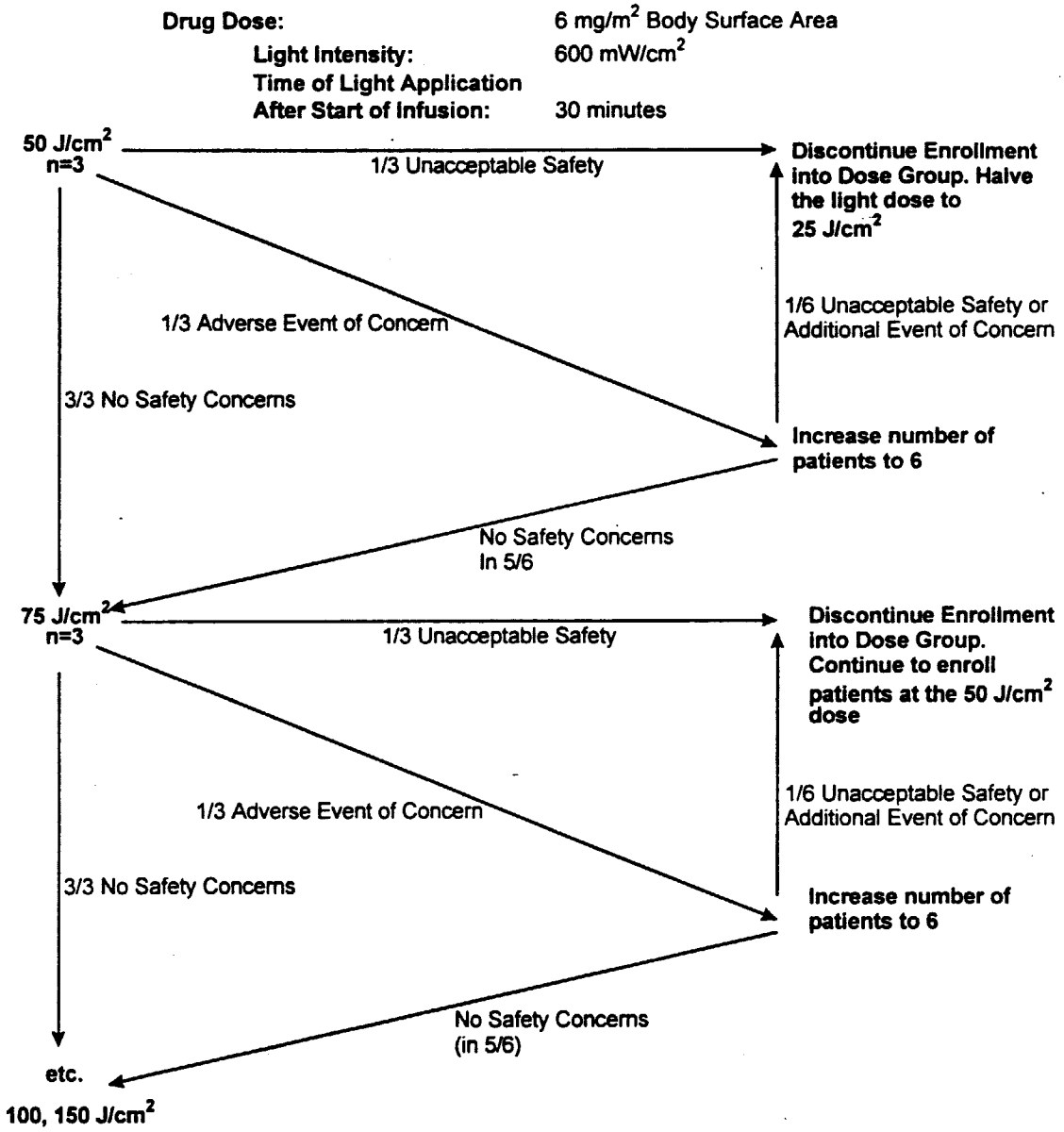


FIGURE 2. Flow Diagram for Initial Dose Escalation

TABLE 3. Patient Treatment by Course of Therapy and Regimen (All Patients)

Course of Therapy	Time of Treatment[a]	Regimen	Verteporfin Dose (mg/m^2)	Time[b] (min)	Light Dose (J/cm^2)	Number of Patients		
						AMD	Non-AMD	Total
1	Week 0	1	6	30	50	2	1	3
					75	6	1	7
					100	8	0	8
					150	6	0	6
						22	2	24
		2	6	20	50	2	1	3
					75	3	1	4
					100	29	4[c]	33
					150	3	0	3
						37	6	43
		3	12	30	50	2	1	3
					75	3	0	3
					100	9	1	10
					150	5	0	5
						19	2	21
		4	6	15	50	8	1	9
					75	6	1	7
					100	8	0	8
						22	2	24
		5[d]	6	10	12.5	4	0	4
					25	12	0	12
					50	12	2	14
						28	2	30
					TOTAL	**128**	**14**	**142**
2	Week 0[e]	2	6	20	100	5	3	8
	Week 2-6[f]	2	6	20	100	21	3[c]	24
		4[g]	6	15	50	1	0	1
					75	7	0	7
					100	2	0	2
						10	0	10
					TOTAL	**36**	**6**	**42**
3	Week 4[e]	2	6	20	100	1	2	3
	Week 4-8[f]	2	6	20	100	17	2[c]	19
		4	6	15	75	2	0	2
					TOTAL	**20**	**4**	**24**
4	Week 8[e]	2	6	20	100	1	2	3
					TOTAL	**1**	**2**	**3**

a Time of treatment relative to Day 0 of their first course.

b Time of light administration relative to beginning of IV infusion of verteporfin.

c Includes Patient 66 who had no CNV and therefore was not included in the analysis.

d Verteporfin was administered as a 10-minute infusion except Regimen 5 (5-minute infusion).

e Patients re-enrolled after their Week-12 assessment for Course 1. Time of treatment relative to Day 0 from second enrollment.

f Patients 901-905 were retreated at Weeks 3 and 8 and Patients 906-910 were retreated at Weeks 2 and 4. All other patients were retreated at approximately Week 4.

g Patients 88 and 97 were retreated at Week 5-6.

TABLE 4. Demographic and Baseline Characteristics

Characteristic	Number (%) of Patients[a] Treatment Regimen 1 n=24		2 n=43		3 n=21		4 n=24		5 n=30		Total n=142	
GENDER												
Female	8	(33)	22	(51	9	(43)	19	(79)	9	(30	67	(47)
Male	16	(67)	21	(49	12	(57)	5	(21)	21	(70	75	(53)
RACE												
Caucasian	24	(100)	43	(100	21	(100)	24	(100)	29	(97	141	(99)
Asian	0	(0)	0	(0	0	(0)	0	(0)	1	(3	1	(1)
AGE (years)												
<60	2	(8)	4	(9	2	(10)	5	(21)	2	(7	15	(11)
60-69	5	(21)	15	(35	3	(14)	4	(17)	6	(20	33	(23)
70-79	7	(29)	18	(42	13	(62)	9	(38)	14	(47	61	(43)
≥80	10	(42)	6	(14	3	(14)	6	(25)	8	(27	33	(23)
Mean	74		71		72		70		75		72	
standard deviation	10		11		9		12		8		11	
NOTABLE MEDICAL HISTORY												
No	3	(13)	5	(12	3	(14)	1	(4)	1	(3	13	(9)
Yes	21	(88)	38	(88	18	(86)	23	(96)	29	(97	129	(91)
CNV SECONDARY TO:												
AMD	22	(92)	37	(86	17	(81)	21	(88)	26	(87	123	(87)
Idiopathic cause	0	(0)	0	(0	1	(5)	0	(0)	0	(0	1	(1)
Angioid streaks	0	(0)	0	(0	0	(0)	0	(0)	1	(3	1	(1)
OHS	0	(0)	0	(0	1	(5)	0	(0)	0	(0	1	(1)
Pathologic myopia	2	(8)	5	(12	0	(0)	2	(8)	1	(3	10	(7)
No CNV - Pattern dystrophy-RPE	0	(0)	1	(2	0	(0)	0	(0)	0	(0	1	(1)
AMD+Pathologic myopia	0	(0)	0	(0	2	(10)	0	(0)	1	(3	3	(2)
AMD+OHS	0	(0)	0	(0	0	(0)	1	(4)	1	(4	2	(1)
LESION SIZE (MPS DA)												
Mean	4.7		5.5		4.0		5.0		5.2		5.0	
standard deviation	1.9		3.5		2.2		2.9		3.2		2.9	
Minimum	1		1		1		2		1		1	
Maximum	12		16		9		12		12		16	
CNV COMPONENTS OF LESION[b]												
Classic only	6	(25)	17	(40	8	(38)	7	(29)	14	(47	52	(37)
≥50% classic (+occult)	10	(42)	9	(21	7	(33)	7	(29)	7	(23	40	(28)
<50% classic (+occult)	7	(29)	13	(30	6	(29)	9	(38)	4	(13	39	(27)
No classic	1	(4)	4	(9	0	(0)	1	(4)	5	(17	11	(8)
CNV LESION LOCATION												
Subfoveal	24	(100)	41	(95	20	(95)	22	(92)	28	(93	135	(95)
Probably subfoveal	0	(0)	1	(2	1	(5)	1	(4)	0	(0	3	(2)
Not subfoveal	0	(0)	1	(2	0	(0)	1	(4)	2	(7	4	(3)

a Number (%) of patients for all parameters except for lesion size.

b The percent of classic CNV and presence or absence of occult CNV were the only components considered for this parameter.

OHS = ocular histoplasmosis syndrome

MPS DA = Macular Photocoagulation Study Disc Area

TABLE 4. Demographic and Baseline Characteristics (cont.)

Characteristic	Number (%) of Patients[a] Treatment Regimen 1 n=24	2 n=43	3 n=21	4 n=24	5 n=30	Total n=142
BEST CORRECTED VISUAL ACUITY (study eye)						
>20/40	0 (0)	0 (0)	0 (0)	0 (0)	2 (7)	2 (1)
20/40 - 20/80	9 (38)	17 (40)	9 (43)	12 (50)	10 (33)	57 (40)
20/100 - 20/200	9 (38)	15 (35)	10 (48)	9 (38)	12 (40)	55 (39)
<20/200	6 (25)	11 (26)	2 (10)	3 (13)	6 (20)	28 (20)
Mean[b]	20/125	20/125	20/100	20/100	20/125	20/125
standard deviation[c]	3	3	3	3	3	3
FIBROSIS						
No	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
0-25%	10 (42)	30 (70)	17 (81)	22 (92)	26 (87)	105 (74)
26-50%	7 (29)	9 (21)	4 (19)	1 (4)	2 (7)	23 (16)
>50%	6 (25)	3 (7)	0 (0)	1 (4)	2 (7)	12 (8)
Can't grade/determine	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (1)

[a] Number (%) of patients for all parameters except for lesion size; BCVA was presented as number (%) of patients and mean/std deviation.

[b] Snellen scores were converted to Log Mar scale for the purpose of calculating the means. The calculated means were converted back to the snellen scores as shown in the table.

[c] Provided as number of lines (1 line = 5 letters).

11 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

NDA: 21-119 Volume 2.22-2.27

Study Type: PK In patients with Basal cell acrcinoma *Study #BPD 001*

Study Title: Photodynamic therapy with benzoporphyrin derivative monoacid A ring (BPD-MA)in the treatment of malignant cutaneous lesions

Study Site	
Clinical Site	*Analytical Site*
	Lab Pharmacological research, Quebec, Canada

Single Dose	*Multiple Dose*	*Washout Period*	*Cross-over*	*Parallel*	*Other Design*	*Fasted/ Fed*	*No. of fasted hrs.*
X						*fasted*	*10 hrs before and 2 hrs after dose*

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
X=8		*X*			*X=12*

Subject Type			
Males=11		*Females=6*	
Age (yrs)	*Weight (kg)*	*Age*	*Weight*
29-60(M= 39) *N=50-99* *HD=46-101*	*46-101 (M=72)*	*29-60(M= 39)* *N=50-99* *HD=46-101*	*46-101 (M=72)*

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
Hepatic	*9*	*7*	*2*
Healthy	*8*	*4*	*4*

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
hepatic	*12 mg/m^2-45 min*	*Inj (infusion)*	*0.3 mg/kg or 2 mg/ml*	*PQ002-94*
healthy	*12 mg/m^2 -45 min*	*Inj (infusion)*	*0.3 mg/kg or 2 mg/ml*	*PQ002-94*

Sampling Times

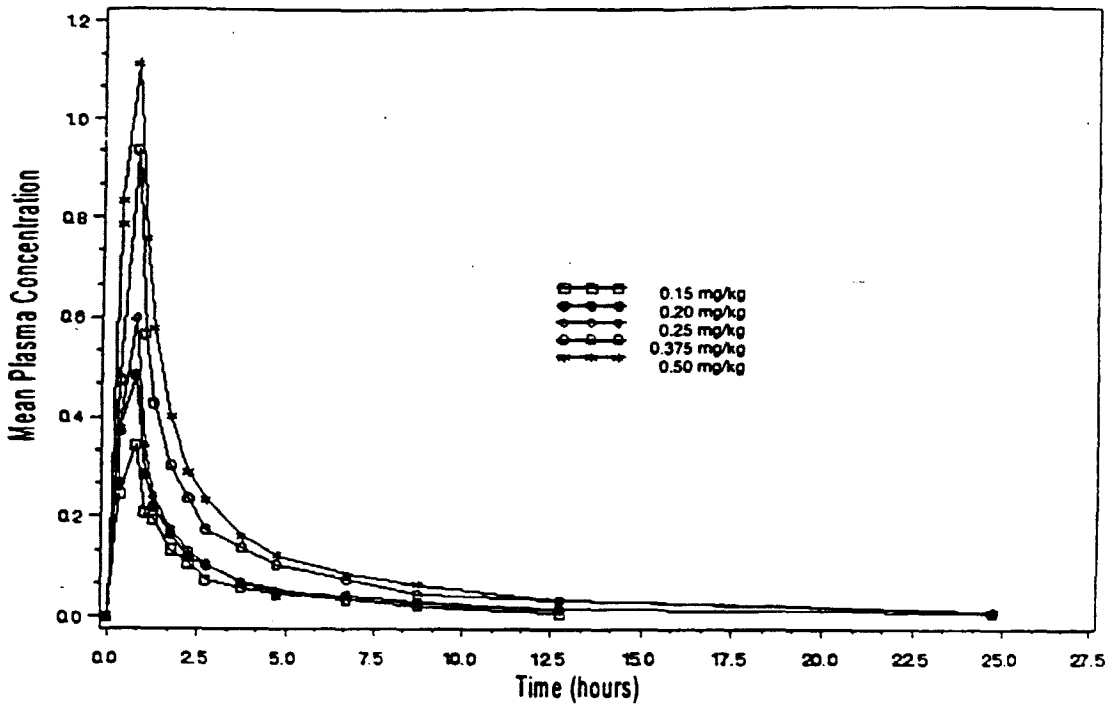
Plasma: predose, 15, 30, 45, 60, 75 and 90 mins and 2, 3, 4.5, 6, 8, 12, and 24 hrs after start of infusion

TABLE 5. Summary of Exposure to Drug and Light

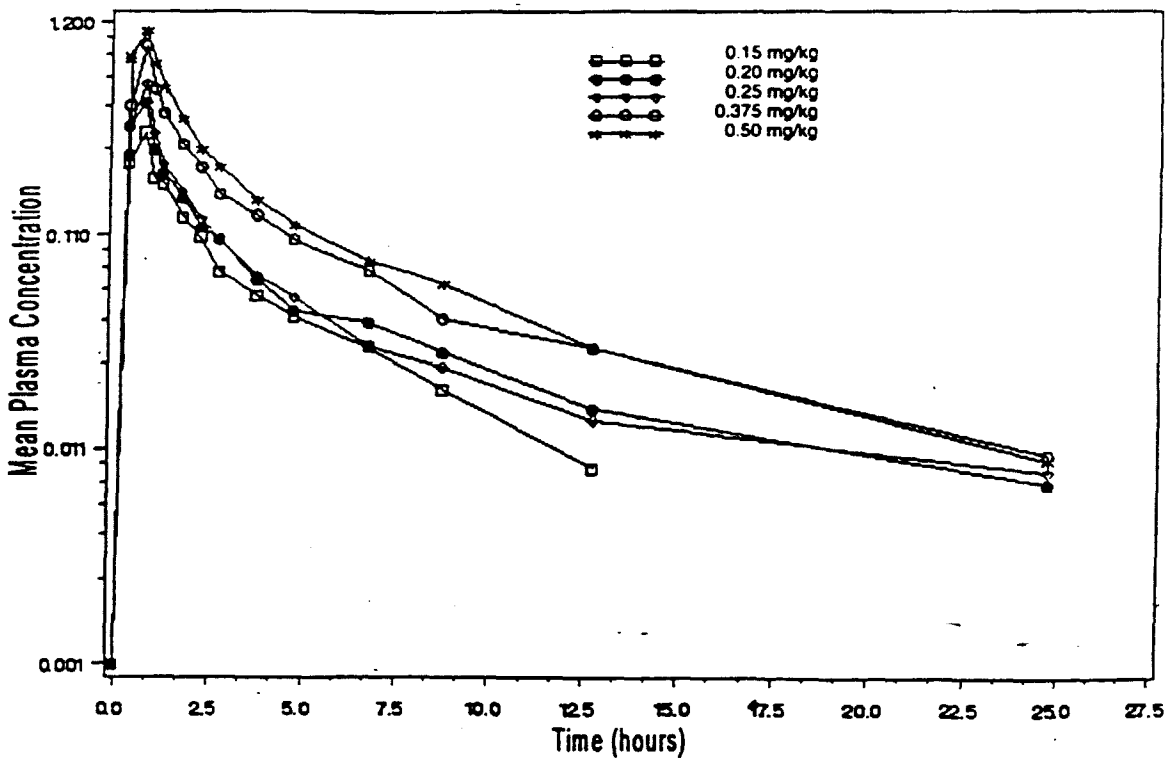
Course	Verteporfin Dose (mg/kg)	Light Dose (J/cm^2)	Number of Patients[a]	Number of Lesions	Number of Treatment Fields
1	0.15	150	2	8	5
	0.20	75	1	3	3
		125	1	2	2
		150	8	29	20
	0.25	50	3	19	9
		100	5	16	12
		150	2	5	4
	0.30	25	3	9	8
		50	9	28	22
		75	5	10	9
	0.375	50	2	7	6
	0.50	50	3	12	7
		Total	44	148	107
2	0.15	150	1	8	3
	0.30	25	1	2	2
		50	2	15	6
		75	2	2	2
		Total	6	27	13
3	0.30	50	1	6	3
		75	1	1	1
		Total	2	7	4

a Of the 35 patients enrolled in the study, 13 received 2 light doses on different treatment fields, 3 patients received two courses of PDT on separate days, and 1 patient received 3 courses of PDT. Since this column expressed exposure in terms of each drug and light combination, some of the patients were included several times opposite each light dose in each course.

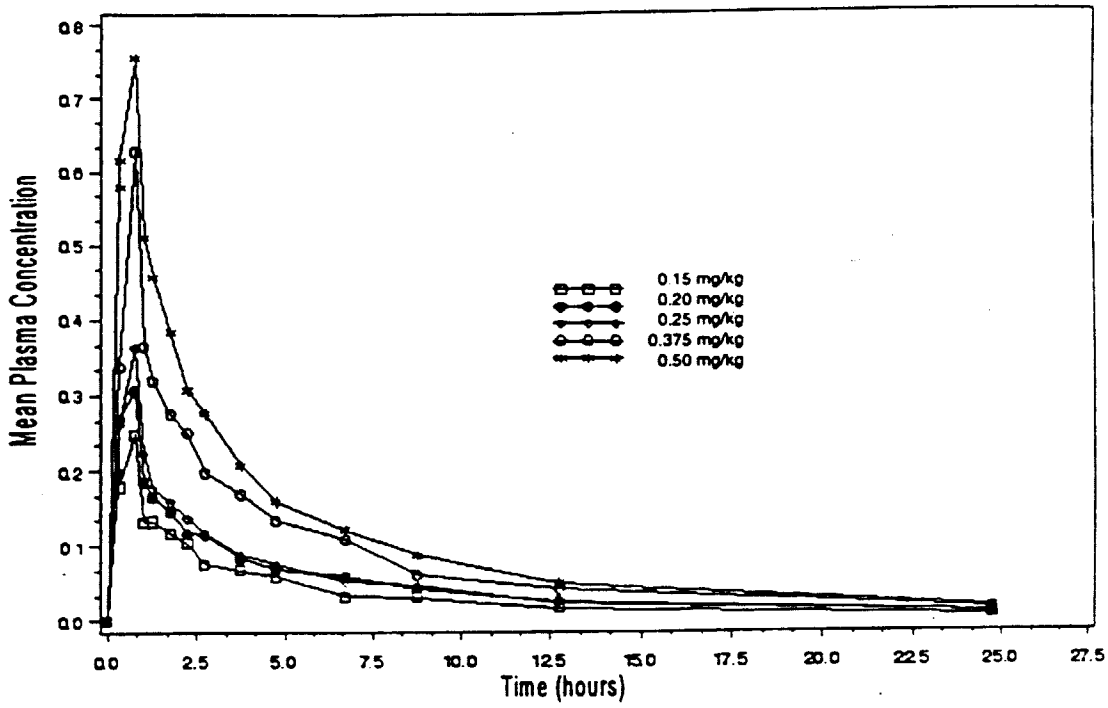
Plasma Concentration Versus Time Profiles
of Regioisomer BPD-MA_D Following a 45-Minute IV Infusion Of Verteporfin
(Linear Scale)



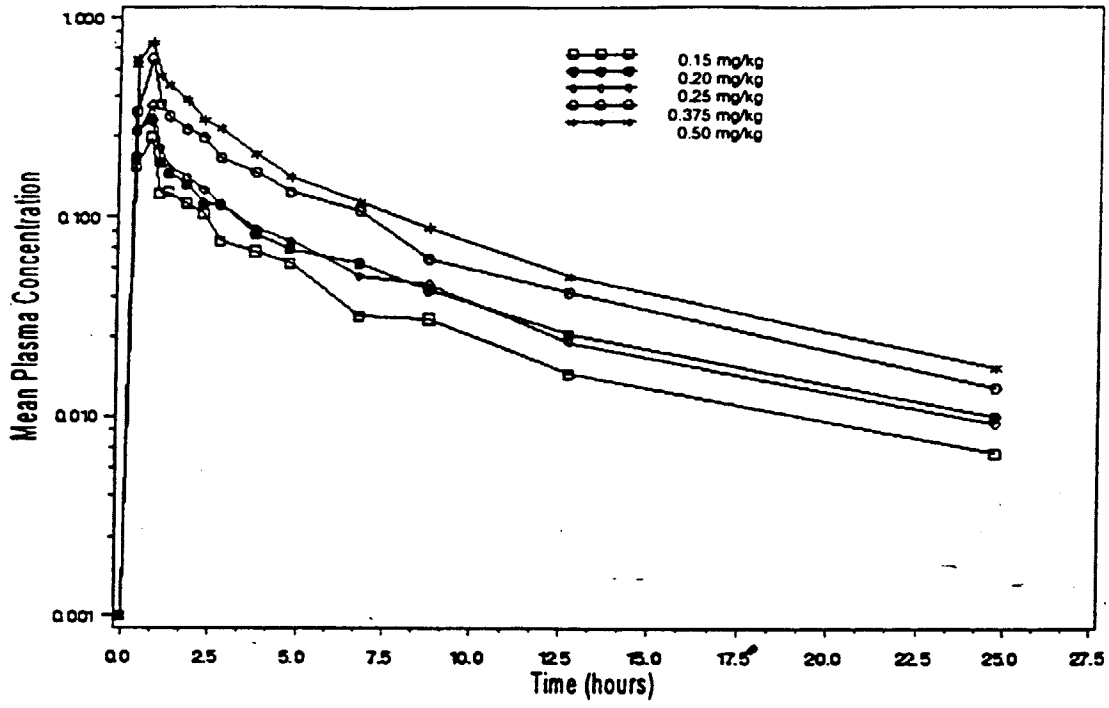
Plasma Concentration Versus Time Profiles
of Regioisomer BPD-MA_D Following a 45-Minute IV Infusion Of Verteporfin
(Semi-Log Scale)

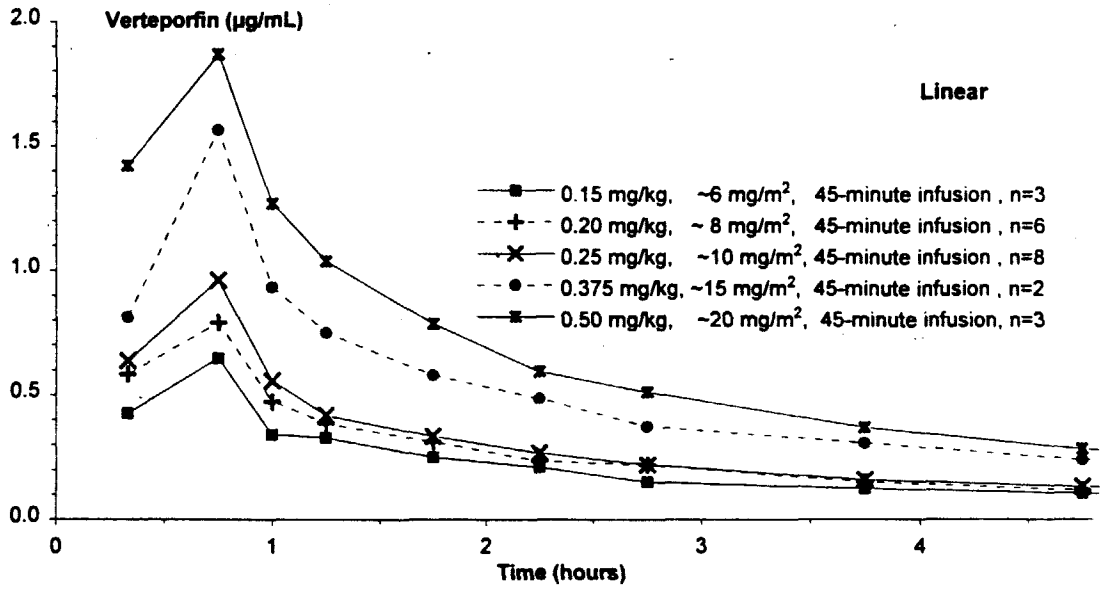


Plasma Concentration Versus Time Profiles
of Regioisomer BPD-MA_C Following a 45-Minute IV Infusion Of Verteporfin
(Linear Scale)

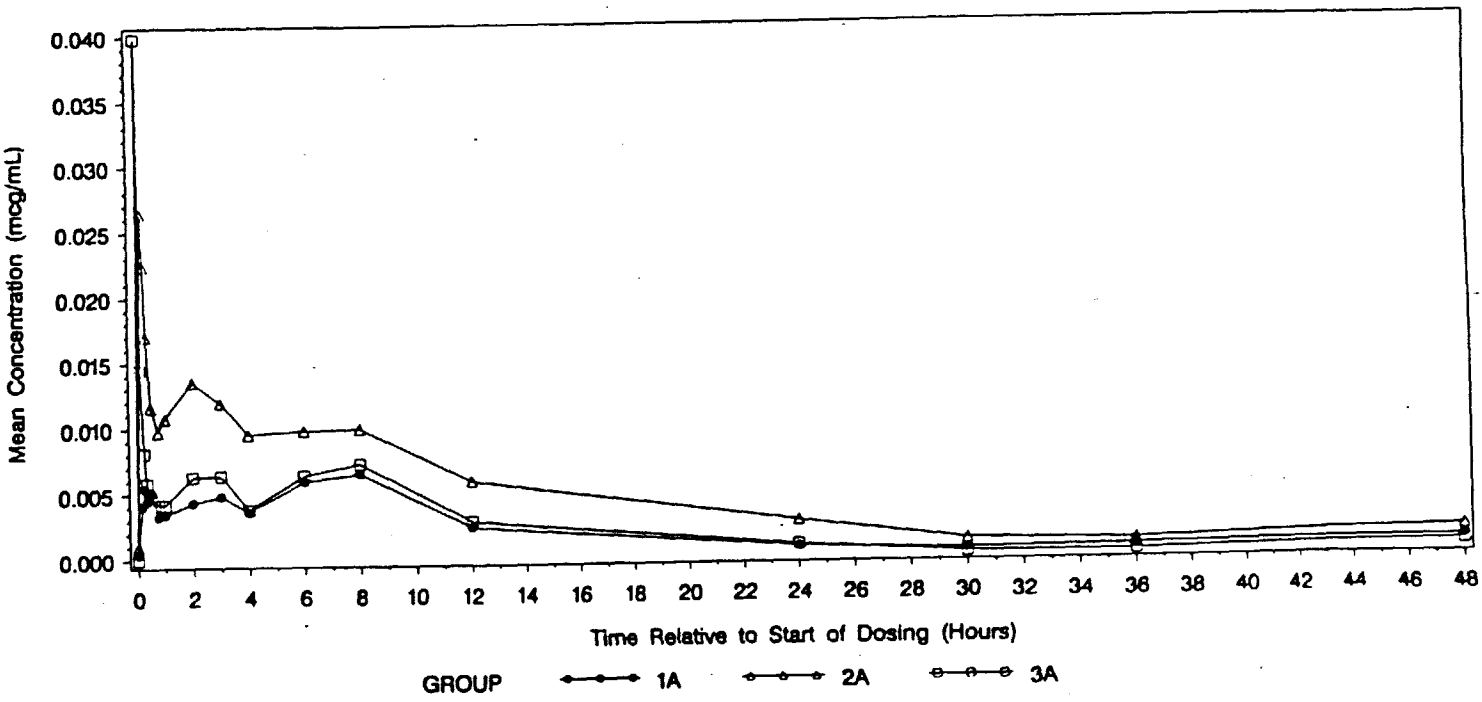


Plasma Concentration Versus Time Profiles
of Regioisomer BPD-MA_C Following a 45-Minute IV Infusion Of Verteporfin
(Semi-Log Scale)



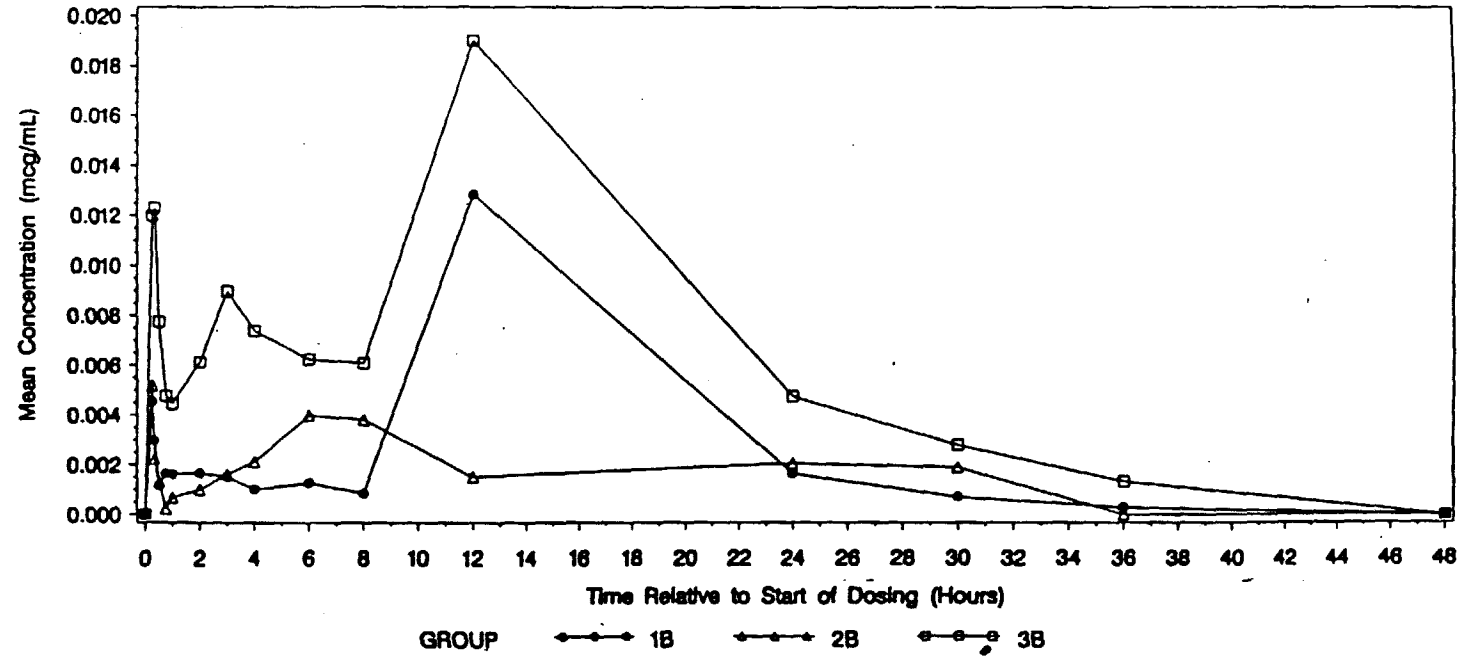

Verteporfin (µg/mL)
Linear
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
Time (hours)
0.15 mg/kg, ~6 mg/m², 45-minute infusion , n=3
0.20 mg/kg, ~ 8 mg/m², 45-minute infusion , n=6
0.25 mg/kg, ~10 mg/m², 45-minute infusion , n=8
0.375 mg/kg, ~15 mg/m², 45-minute infusion , n=2
0.50 mg/kg, ~20 mg/m², 45-minute infusion, n=3

Mean Plasma Concentrations Versus Time Curve
(Caucasian)
Assay for BPD – DA



Note: Group 1A received Vertaporfin for Injection 6 mg/m2 infused over 10 minutes.
Group 2A received Vertaporfin for Injection 14 mg/m2 infused over 10 minutes.
Group 3A received Vertaporfin for Injection 6 mg/m2 administered as an intravenous bolus over 1.5 – 2 minutes.

Mean Plasma Concentrations Versus Time Curve
(Japanese)
Assay for BPD – DA



Group 1B received Vertaporfin for Injection 3 mg/m2 infused over 10 minutes.
Group 2B received Vertaporfin for Injection 6 mg/m2 infused over 10 minutes.
Group 3B received Vertaporfin for Injection 14 mg/m2 infused over 10 minutes.

Urinary excretion (Caucasian Subjects)

Appendix A.2.15

Summary Statistics for Verteporfin for Injection Urinary Excretion (mcg) by Collection Interval
Assay for BPD-MAc

Collection Interval	Group 1A	Group 2A	Group 3A
Predose (-1 Hour)			
N	0	0	0
Mean (SD)			
Median			
Range			
CV			
0-6 Hours			
N	12	12	8
Mean (SD)	0.05 (0.160)	0.17 (0.443)	0.19 (0.432)
Median	0.00	0.00	0.00
Range			
CV	300.65	267.51	231.92
6-12 Hours			
N	12	12	8
Mean (SD)	0.00 (0.000)	0.00 (0.000)	0.07 (0.195)
Median	0.00	0.00	0.00
Range			
CV			282.84
12-24 Hours			
N	0	0	0
Mean (SD)			
Median			

Summary Statistics for Verteporfin for Injection Urinary Excretion (mcg) by Collection Interval
Assay for BPD-MAd

Collection Interval	Group 1A	Group 2A	Group 3A
Predose (-1 Hour)			
N	0	0	0
Mean (SD)			
Median			
Range			
CV			
0-6 Hours			
N	12	12	8
Mean (SD)	0.00 (0.000)	0.00 (0.000)	0.00 (0.000)
Median	0.00	0.00	0.00
Range			
CV			
6-12 Hours			
N	12	12	8
Mean (SD)	0.00 (0.000)	0.00 (0.000)	0.00 (0.000)
Median	0.00	0.00	0.00
Range			
CV			
12-24 Hours			
N	0	0	0
Mean (SD)			
Median			
Range			
CV			
24-36 Hours			
N	0	0	0
Mean (SD)			
Median			
Range			
CV			

ote: Group 1A received Verteporfin for Injection 6 mg/m^2 infused over 10 minutes.
Group 2A received Verteporfin for Injection 14 mg/m^2 infused over 10 minutes.
Group 3A received Verteporfin for Injection 6 mg/m^2 administered as an intravenous bolus over 1.5-2 minutes.
SD = Standard deviation

Appendix A.2.17
Summary Statistics for Verteporfin for Injection Urinary Excretion (mcg) by Collection Interval
Assay for BPD-DA

Collection Interval	Group 1A	Group 2A	Group 3A
Predose (-1 Hour)			
N	0	0	0
Mean (SD)			
Median			
Range			
CV			
0-6 Hours			
N	12	12	8
Mean (SD)	0.13 (0.290)	0.13 (0.316)	0.06 (0.181)
Median	0.00	0.00	0.00
Range			
CV	226.15	237.68	282.84
6-12 Hours			
N	12	12	8
Mean (SD)	0.18 (0.344)	0.28 (0.350)	0.14 (0.273)
Median	0.00	0.21	0.00
Range			
CV	188.96	125.62	193.99
12-24 Hours			
N	0	0	0
Mean (SD)			
Median			
Range			
CV			
24-36 Hours			
N	0	0	0
Mean (SD)			
Median			
Range			
CV			

Note: Group 1A received Verteporfin for Injection 6 mg/m^2 infused over 10 minutes.
Group 2A received Verteporfin for Injection 14 mg/m^2 infused over 10 minutes.
Group 3A received Verteporfin for Injection 6 mg/m^2 administered as an intravenous bolus over 1.5-2 minutes.
SD = Standard deviation

Appendix A.2.33.1

Summary Statistics and Biostatistical Assessment of Group Effect for Verteporfin for Injection
Urinary Excretion Parameters for Caucasian Subjects

	Assay for BPD-MAc				Assay for BPD-MAd			
	Group 1A	Group 2A	Group 3A	P-value [a]	Group 1A	Group 2A	Group 3A	P-value [a]
CUE (0-12) (mcg)								
N	12	12	8	0.965[a]	12	12	8	-----[a]
Mean (SD)	0.05 (0.16)	0.17 (0.44)	0.26 (0.49)	0.544[b]	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	-----[b]
Median	0.00	0.00	0.00		0.00	0.00	0.00	
Range								
CV	300.65	267.51	190.31					
Rmax (mcg/hr)								
N	12	12	8	0.965[a]	12	12	8	-----[a]
Mean (SD)	0.01 (0.03)	0.03 (0.07)	0.04 (0.08)	0.620[b]	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	-----[b]
Median	0.00	0.00	0.00		0.00	0.00	0.00	
Range								
CV	300.65	267.51	202.22					

Note: Group 1A received Verteporfin for Injection 6 mg/m^2 infused over 10 minutes.
Group 2A received Verteporfin for Injection 14 mg/m^2 infused over 10 minutes.
Group 3A received Verteporfin for Injection 6 mg/m^2 administered as an intravenous bolus over 1.5-2 minutes.
[a] P-values were calculated using a Wilcoxon Rank Sum test for a difference between Group 1A and Group 2A (dose comparison).
[b] P-values were calculated using a Wilcoxon Rank Sum test for a difference between Group 1A and Group 3A (regimen comparison).

Appendix A.2.33.2

Summary Statistics and Biostatistical Assessment of Group Effect for Verteporfin for Injection
Urinary Excretion Parameters for Caucasian Subjects

	Assay for BPD-DA			
	Group 1A	Group 2A	Group 3A	P-value
CUE (0-12) (mcg)				
N	12	12	8	0.537[a]
Mean (SD)	0.31 (0.53)	0.42 (0.58)	0.20 (0.44)	0.497[b]
Median	0.00	0.21	0.00	
Range				
CV	172.00	139.80	213.64	
Rmax (mcg)				
N	12	12	8	0.497[a]
Mean (SD)	0.04 (0.06)	0.06 (0.07)	0.02 (0.05)	0.442[b]
Median	0.00	0.03	0.00	
Range				
CV	150.10	119.79	193.99	

Note: Group 1A received Verteporfin for Injection 6 mg/m^2 infused over 10 minutes.
Group 2A received Verteporfin for Injection 14 mg/m^2 infused over 10 minutes.
Group 3A received Verteporfin for Injection 6 mg/m^2 administered as an intravenous bolus over 1.5-2 minutes.
[a] P-values were calculated using a Wilcoxon Rank Sum test for a difference between Group 1A and Group 2A (dose comparison).
[b] P-values were calculated using a Wilcoxon Rank Sum test for a difference between Group 1A and Group 3A (regimen comparison).

Appendix A.2.18
Summary Statistics for Verteporfin for Injection Urinary Excretion (mcg) by Collection Interval
Assay for BPD-MAc

Collection Interval	Group 1B	Group 2B	Group 3B
Predose (-1 Hour)			
N	0	0	0
Mean (SD)			
Median			
Range			
CV			
0-6 Hours			
N	8	8	8
Mean (SD)	0.03 (0.095)	0.03 (0.090)	0.23 (0.297)
Median	0.00	0.00	0.17
Range			
CV	282.84	282.84	127.07
6-12 Hours			
N	8	8	8
Mean (SD)	0.00 (0.000)	0.00 (0.000)	0.00 (0.000)
Median	0.00	0.00	0.00
Range			
CV			
12-24 Hours			
N	0	0	0
Mean (SD)			
Median			

Summary Statistics for Verteporfin for Injection Urinary Excretion (mcg) by Collection Interval
Assay for BPD-MAd

Collection Interval	Group 1B	Group 2B	Group 3B
Predose (-1 Hour)			
N	0	0	0
Mean (SD)			
Median			
Range			
CV			
0-6 Hours			
N	8	8	8
Mean (SD)	0.00 (0.000)	0.00 (0.000)	0.00 (0.000)
Median	0.00	0.00	0.00
Range			
CV			
6-12 Hours			
N	6	8	8
Mean (SD)	0.00 (0.000)	0.00 (0.000)	0.00 (0.000)
Median	0.00	0.00	0.00
Range			
CV			
12-24 Hours			
N	0	0	0
Mean (SD)			
Median			
Range			
CV			
24-36 Hours			
N	0	0	0
Mean (SD)			
Median			
Range			
CV			

Note: Group 1B received Verteporfin for Injection 3 mg/m^2 infused over 10 minutes.
Group 2B received Verteporfin for Injection 6 mg/m^2 infused over 10 minutes.
Group 3B received Verteporfin for Injection 14 mg/m^2 infused over 10 minutes.
SD = Standard deviation

Appendix A.2.33.4
Summary Statistics and Biostatistical Assessment of Group Effect for Verteporfin for Injection
Urinary Excretion Parameters for Japanese Subjects

	Assay for BPD-DA			
	Group 1B	Group 2B	Group 3B	P-value [a]
CUE (0-12) (mcg)				
N	8	8	8	0.098
Mean (SD)	0.13 (0.24)	0.30 (0.29)	0.85 (0.89)	
Median	0.00	0.31	0.58	
Range				
CV	185.40	96.37	104.35	
RMAX (mcg/hr)				
N	8	8	8	0.089
Mean (SD)	0.02 (0.03)	0.05 (0.05)	0.10 (0.10)	
Median	0.00	0.05	0.07	
Range				
CV	191.99	99.11	100.18	

Note: Group 1B received Verteporfin for Injection 3 mg/m^2 infused over 10 minutes.
Group 2B received Verteporfin for Injection 6 mg/m^2 infused over 10 minutes.
Group 3B received Verteporfin for Injection 14 mg/m^2 infused over 10 minutes.
[a] P-values were calculated using a Kruskal-Wallis test testing for a difference between treatments.

Appendix A.2.33.3
Summary Statistics and Biostatistical Assessment of Group Effect for Verteporfin for Injection
Urinary Excretion Parameters for Japanese Subjects

	Assay for BPD-MAc				Assay for BPD-MAd			
	Group 1B	Group 2B	Group 3B	P-value [a]	Group 1B	Group 2B	Group 3B	P-value [a]
CUE (0-12) (mcg)								
N	8	8	8	0.061	8	8	8	-----
Mean (SD)	0.03 (0.09)	0.03 (0.09)	0.23 (0.30)		0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	
Median	0.00	0.00	0.12		0.00	0.00	0.00	
Range								
CV	282.84	282.84	127.07					
RMAX (mcg/hr)								
N	8	8	8	0.061	8	8	8	-----
Mean (SD)	0.01 (0.02)	0.01 (0.01)	0.04 (0.05)		0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	
Median	0.00	0.00	0.02		0.00	0.00	0.00	
Range								
CV	282.84	282.84	127.07					

Note: Group 1B received Verteporfin for Injection 3 mg/m^2 infused over 10 minutes.
Group 2B received Verteporfin for Injection 6 mg/m^2 infused over 10 minutes.
Group 3B received Verteporfin for Injection 14 mg/m^2 infused over 10 minutes.
[a] P-values were calculated using a Kruskal-Wallis test testing for a difference between treatments.

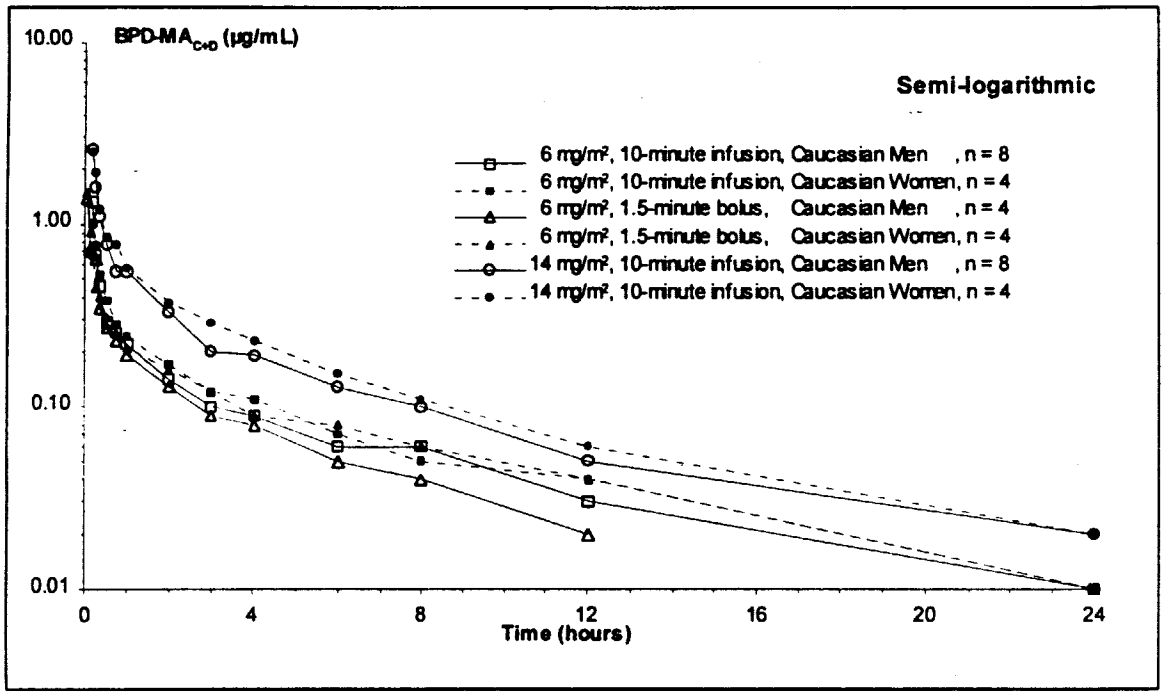
Appendix A.2.33.4
Summary Statistics and Biostatistical Assessment of Group Effect for Verteporfin for Injection
Urinary Excretion Parameters for Japanese Subjects

	Assay for BPD-DA			
	Group 1B	Group 2B	Group 3B	P-value [a]
CUE (0-12) (mcg)				
N	8	8	8	0.098
Mean (SD)	0.13 (0.24)	0.30 (0.29)	0.85 (0.89)	
Median	0.00	0.31	0.58	
Range				
CV	185.40	96.37	104.33	
RMAX (mcg/hr)				
N	8	8	8	0.089
Mean (SD)	0.02 (0.03)	0.05 (0.05)	0.10 (0.10)	
Median	0.00	0.05	0.07	
Range				
CV	191.99	99.11	100.16	

Note: Group 1B received Verteporfin for Injection 3 mg/m^2 infused over 10 minutes.
Group 2B received Verteporfin for Injection 6 mg/m^2 infused over 10 minutes.
Group 3B received Verteporfin for Injection 14 mg/m^2 infused over 10 minutes.
[a] P-values were calculated using a Kruskal-Wallis test testing for a difference between treatments.

Effect Of Gender

Semi-logrithemic plot of mean verteporfin concentrations in healthy Caucasian men and women



Appendix A.2.25A. BPD-MA$_C$ and BPD-MA$_D$ Race Pharmacokinetic Comparison

Pharmacokinetic Parameters	Mean (Coefficient of Variation) Study A – Caucasian 6 mg/m^2 10-min inf. Men (n=8)		Study A – Caucasian 14 mg/m^2 10-min inf. Men (n=8)		Study B – Japanese 6 mg/m^2 10-min inf. Men (n=8)		Study B – Japanese 14 mg/m^2 10-min inf. Men (n=8)		Race Effect[a] P value	Race by Dose Interaction[a] P value
BPD-MA$_C$										
AUC_{0-t} (µg·h/mL)	0.78	(25%)	1.67	(24%)	0.89	(15%)	2.54	(26%)	.001[c]	.097[c]
									6 mg: .170	
									14 mg: .004	
AUC_{inf} (µg·h/mL)	0.83[b]	(23%)	1.69	(24%)	0.92	(15%)	2.57	(26%)	.002[c]	.062[c]
									6 mg: .282	
									14 mg: .004	
C_{max} (µg/mL)	0.49	(29%)	0.93	(58%)	0.55	(11%)	1.27	(20%)	.022[c]	.334[c]
CL (mL·h^{-1}·kg^{-1})	92.5[b]	(18%)	110.5	(21%)	97.2	(22%)	80.4	(30%)	.110	.033
									6 mg: .646	
									14 mg: .022	
V_{ss} (L/kg)	0.62[b]	(23%)	0.73	(30%)	0.62	(13%)	0.56	(22%)	.123	.132
									6 mg: .973	
									14 mg: .074	
t_{max} (h)	0.18	(17%)	0.20	(23%)	0.17	(0%)	0.17	(0%)	.011[d]	.120[d]
K_{el} (1/h)	0.13[b]	(7%)	0.12	(9%)	0.13	(14%)	0.13	(16%)	.777	.508
$t_{½}$ (h)	5.37[b]	(7%)	5.80	(9%)	5.53	(15%)	5.66	(18%)	.968	.570
BPD-MA$_D$										
AUC_{0-t} (µg·h/mL)	0.69	(24%)	1.54	(24%)	0.81	(20%)	2.36	(31%)	.003[c]	.171[c]
									6 mg: .188	
									14 mg: .008	
AUC_{inf} (µg·h/mL)	0.76[b]	(20%)	1.57	(24%)	0.83	(19%)	2.38	(31%)	.007[c]	.081[c]
									6 mg: .386	
									14 mg: .009	
C_{max} (µg/mL)	0.74	(26%)	1.52	(49%)	0.77	(11%)	1.87	(20%)	.117[c]	.320[c]
CL (mL·h^{-1}·kg^{-1})	100.7[b]	(19%)	119.2	(21%)	108.8	(26%)	88.7	(34%)	.244	.049
									6 mg: .529	
									14 mg: .045	
V_{ss} (L/kg)	0.51[b]	(25%)	0.63	(32%)	0.52	(10%)	0.48	(20%)	.170	.089
									6 mg: .739	
									14 mg: .078	
t_{max} (h)	0.18	(17%)	0.20	(23%)	0.17	(0%)	0.17	(0%)	.011[d]	.120[d]
K_{el} (1/h)	0.13[b]	(29%)	0.11	(13%)	0.12	(26%)	0.11	(13%)	.828	.583
$t_{½}$ (h)	5.67[b]	(25%)	6.40	(12%)	5.97	(24%)	6.23	(13%)	.874	.564

Data from Appendices A.2.25, 26, 29, and 30. Gender effect P values for individual dose groups from Appendices B.1.9, 10, 13, and 14

a. Two-factor (race and dose) ANOVA with race-by-dose group interaction term; when the interaction was significant, the race difference is also presented separately for each dose level.

b. n = 7.

c. P values for C_{max} and AUC calculated from log-transformed data.

d. For t_{max}, a two-way ANOVA by ranks was performed with race, dose group and race-by-dose group as factors.

NDA: 21-119 Volume 2.27-2.31

Study Type: PK In patients with mild hepatic dysfunction *Study #BPD PK 004*

Study Title: Tolerance and safety evaluation of intravenous benzoporphyrin derivative mono-acid in healthy volunteers and in subjects with mild hepatic dysfunction.

Study Site	
Clinical Site	Analytical Site
	Lab Pharmacological research, Quebec, Canada

Single Dose	Multiple Dose	Washout Period	Cross-over	Parallel	Other Design	Fasted/ Fed	No. of fasted hrs.
X						fasted	10 hrs before and 2 hrs after dose

Subject Category					
Normal	Patients	Young	Elderly	Renal	Hepatic
X=8		X			X=12

Subject Type			
Males=11		Females=6	
Age (yrs)	Weight (kg)	Age	Weight
29-60(M= 39)	46-101 (M=72) N=50-99 HD=46-101	29-60(M= 39)	46-101 (M=72) N=50-99 HD=46-101

Subject Treatment Group			
Group No.	Total No.	Males	Females
Hepatic	9	7	2
Healthy	8	4	4

Treatment Group	Dose	Dosage Form	Strength	Lot #
hepatic	12 mg/m^2-45 min	Inj (infusion)	0.3 mg/kg or 2 mg/ml	PQ002-94
healthy	12 mg/m^2 -45 min	Inj (infusion)	0.3 mg/kg or 2 mg/ml	PQ002-94

Sampling Times

Plasma: predose, 15, 30, 45, 60, 75 and 90 mins and 2, 3, 4.5, 6, 8, 12, and 24 hrs after start of infusion

APPENDIX E.2.11
Plasma Verteporfin Concentrations (µg/mL)
Observed Data by Participant Status

Hepatic Impaired Patients

Participant	pre-dose	0.25 hour	0.50 hour	0.75 hour	1.00 hour	1.25 hours
3	0.0000	0.3862	1.5568	1.6802*	1.1188	1.1044
4	0.0000	0.4537	1.0674	1.0436	0.6704	0.4887
7	0.0000	0.3211	0.9026	0.9595	0.6386	0.5312
8	0.0000	0.7017	1.9267	2.1652	1.2033	0.9331
11	0.0000	0.3579	0.8025	1.0580	0.7657	0.5594
12	0.0000	0.6653	1.1734	1.4957	0.8520	0.7223
13	0.0000	0.3809	0.8208	0.9673	0.5356	0.3893
14	0.0000	0.3367**	1.5093***	1.7322	1.6922	1.5723
15	0.0000	1.5179**	1.5413****	1.5502**	1.0866**	0.8317
MEAN	0.0000	0.5690	1.2557	1.4058	0.9515	0.7925
STD	0.0000	0.3823	0.3950	0.4230	0.3627	0.3723
CV		67.1869	31.4581	30.0870	38.1234	46.9819

Participant	1.50 hours	2.00 hours	3.00 hours	4.50 hours	6.00 hours
3	1.0502	0.6188	0.4846	0.3674	0.3471
4	0.3758	0.3168	0.2208	0.1589	0.1354
7	0.4472	0.3270	0.2226	0.1705	0.1179
8	0.7875	0.7980	0.5209	0.3769	0.2597
11	0.6271	0.4254	0.3313	0.2129	0.1925
12	0.7211	0.5355	0.3290	0.2954	0.2284
13	0.3366	0.2820	0.2455	0.1711	0.1284
14	1.2402	0.8639	0.7486	0.4489	0.2902
15	0.7146	0.5095	0.4588	0.3130	0.1996
MEAN	0.7000	0.5197	0.3958	0.2794	0.2110
STD	0.3019	0.2091	0.1746	0.1060	0.0784
CV	43.1267	40.2382	44.1067	37.9350	37.1381

Participant	8.00 hours	12.00 hours	24.00 hours
3	0.1323+	0.2097	0.1067
4	0.0975	0.0632	0.0189
7	0.0910	0.0633	0.0180
8	0.1895	0.1547	0.0497
11	0.1348	0.0662	0.0206
12	0.1791	0.0693	0.0245
13	0.0904	0.0485	0.0159
14	0.2333	0.1476	0.0403
15	0.1630	0.0605	0.0120
MEAN	0.1457	0.0981	0.0341
STD	0.0496	0.0573	0.0299
CV	34.0470	58.3912	87.6715

* This value has been entered at the time specified + 6 minutes in the data set used for statistical analyses (late blood draw).

** This value has been entered at the time specified + 2 minutes in the data set used for statistical analyses (late blood draw).

*** This value has been entered at the time specified + 3 minutes in the data set used for statistical analyses (late blood draw).

**** This value has been entered at the time specified + 4 minutes in the data set used for statistical analyses (late blood draw).

\+ This value represents CL315555 concentration. CL315585 concentration was not reportable.

APPENDIX E.2.12
Plasma Verteporfin Concentrations (µg/mL)
Observed Data by Participant Status

Subjects = Normal Liver Function

Participant	pre-dose	0.25 hour	0.50 hour	0.75 hour	1.00 hour	1.25 hours
1	0.0000	0.0782	1.0865	0.6237*	0.5906**	0.5096
2	0.0000	0.3120	0.8192	0.4929***	0.4206	0.4063
5	0.0000	0.4918	1.5812***	1.0045	0.6689	0.5857
6	0.0000	0.5222	1.0569+	1.5054	0.8154	0.7684
9	0.0000	0.5160	0.9524	0.9351	0.5670	0.4856
10	0.0000	0.1368	0.8551	1.4192	0.4640	0.4524
19	0.0000	0.8416	1.4440	2.0798	1.4671	0.8356
20	0.0000	0.6758	1.3322	1.5779	0.6392	0.6142
MEAN	0.0000	0.4468	1.1409	1.2048	0.7041	0.5822
STD	0.0000	0.2594	0.2811	0.5343	0.3316	0.1523
CV		58.0557	24.6349	44.3487	47.0956	26.1550

Participant	1.50 hours	2.00 hours	3.00 hours	4.50 hours	6.00 hours
1	0.4453	0.3515	0.1813	0.1390	0.0941
2	0.3533	0.2777	0.1857	0.1422	0.0908
5	0.4982****	0.5171	0.2955	0.2265	0.1860
6	0.6855	0.4919	0.3319	0.2654	0.1875
9	0.4026	0.3143	0.2601	0.1803	0.1302
10	0.4217	0.3321	0.2404	0.1590	0.1112
19	0.7212	0.5345	0.3982	0.3436	0.1888
20	0.5954	0.4058	0.2877	0.2521	0.1808
MEAN	0.5154	0.4031	0.2726	0.2135	0.1462
STD	0.1366	0.0996	0.0728	0.0717	0.0440
CV	26.5119	24.7064	26.7091	33.5815	30.1142

Participant	8.00 hours	12.00 hours	24.00 hours
1	0.0802	0.0416	0.0064
2	0.0582	0.0379	0.0057
5	0.1345	0.0728	0.0252
6	0.1521	0.0679	0.0208
9	0.1172	0.0625	0.0144
10	0.0948	0.0476	0.0057
19	0.1270	0.0625	0.0219
20	0.1012	0.0690	0.0000
MEAN	0.1082	0.0577	0.0125
STD	0.0306	0.0134	0.0093
CV	28.3282	23.2285	74.3855

* This value has been entered at the time specified + 14 minutes in the data set used for statistical analyses (late blood draw).

** This value has been entered at the time specified + 2 minutes in the data set used for statistical analyses (late blood draw).

*** This value has been entered at the time specified + 9 minutes in the data set used for statistical analyses (late blood draw).

**** This value has been entered at the time specified + 4 minutes in the data set used for statistical analyses (late blood draw).

\+ This value has been entered at the time specified - 2 minutes in the data set used for statistical analyses (early blood draw).

APPENDIX K.2.13
Bioavailability Parameters of Verteporfin
Observed Results by Participant Status

---------- Hepatic Impaired Patients ----------

Participant	AUC0-t (µ·hr/mL)	AUCinf (µ·hr/mL)	AUC0-t/ AUCinf	Cmax (µg/mL)	Vss (L/kg)	Tmax (hours)	KEL (1/hours)	Halflife (hours)
3*	6.82			1.6802	0.3034	0.85		
4	2.97	3.15	0.94	1.0674	0.5033	0.50	0.1086	6.38
7	2.88	3.04	0.95	0.9595	0.5249	0.75	0.1092	6.35
8	6.40	6.92	0.93	2.1652	0.2531	0.75	0.0962	7.20
11	3.57	3.74	0.95	1.0580	0.4181	0.75	0.1222	5.67
12	4.39	4.58	0.96	1.4957	0.3228	0.75	0.1279	5.42
13	2.65	2.79	0.95	0.9673	0.5464	0.75	0.1188	5.83
14	7.00	7.35	0.95	1.7322	0.2174	0.75	0.1169	5.93
15	4.71	4.79	0.98	1.5502	0.2446	0.78	0.1641	4.22
MEAN	4.60	4.54	0.95	1.4084	0.3704	0.74	0.1205	5.88
STD	1.75	1.75	0.02	0.4205	0.1297	0.09	0.0201	0.86
CV	38.02	38.57	1.74	29.8540	35.0050	12.9	16.709	14.71

---------- Subjects = Normal Liver Function ----------

Participant	AUC0-t (µ·hr/mL)	AUCinf (µ·hr/mL)	AUC0-t/ AUCinf	Cmax (µg/mL)	Vss (L/kg)	Tmax (hours)	KEL (1/hours)	Halflife (hours)
1	2.42	2.47	0.98	1.0865	0.5114	0.50	0.1545	4.49
2	2.10	2.14	0.98	0.8192	0.6015	0.50	0.1581	4.38
5	3.79	4.02	0.94	1.5812	0.3963	0.65	0.1119	6.19
6	4.07	4.24	0.96	1.5054	0.3402	0.75	0.1281	5.41
9	3.01	3.13	0.96	0.9524	0.4881	0.50	0.1275	5.44
10	2.67	2.71	0.99	1.4192	0.4746	0.75	0.1689	4.10
19	4.69	4.86	0.97	2.0798	0.2571	0.75	0.1305	5.31
20	3.23	3.64	0.89	1.5779	0.2722	0.75	0.1703	4.07
MEAN	3.25	3.40	0.96	1.3777	0.4177	0.64	0.1437	4.92
STD	0.88	0.95	0.03	0.4088	0.1220	0.12	0.0219	0.77
CV	27.16	27.93	3.35	29.6754	29.2051	19.2	15.236	15.63

* No meaningful Kel, and therefore Halflife, AUCinf and AUC0-t/AUCinf, could be calculated for this subject.

APPEARS THIS WAY
ON ORIGINAL

APPENDIX E.2.3
Project CP300
PHARMACOKINETIC PARAMETERS OF CL 315,555
Observed Results by participant status

---------- Treatment=A:Patients ----------

participant	AUC0-t (µg.hr/mL)	AUCinf (µg.hr/mL)	AUC0-t/ AUCinf	Cmax (µg/mL)	Vss (L/kg)	Tmax (hours)	KEL (1/hours)	Halflife (hours)
3	3.17	4.19	0.76	0.6145	0.3622	0.50	0.0549	12.63
4	1.40	1.48	0.95	0.4063	0.5907	0.50	0.1148	6.04
7	1.49	1.56	0.96	0.3710	0.5462	0.75	0.1237	5.60
8	2.96	3.24	0.92	0.7581	0.2978	0.75	0.0947	7.32
11	1.86	1.95	0.95	0.4070	0.4419	0.75	0.1274	5.44
12	2.22	2.30	0.97	0.7137	0.3404	0.75	0.1396	4.97
13	1.37	1.45	0.95	0.3629	0.6025	0.75	0.1221	5.68
14	3.94	4.09	0.96	0.9611	0.1997	0.55	0.1310	5.29
15	2.58	2.67	0.97	0.8671	0.2595	0.57	0.1394	4.97
MEAN	2.33	2.55	0.93	0.6091	0.4045	0.65	0.1164	6.44
STD	0.90	1.08	0.07	0.2328	0.1481	0.12	0.0268	2.43
CV	38.55	42.38	7.22	38.2267	36.6219	18.1	23.028	37.74

---------- Treatment=B:Normal Vol ----------

participant	AUC0-t (µg.hr/mL)	AUCinf (µg.hr/mL)	AUC0-t/ AUCinf	Cmax (µg/mL)	Vss (L/kg)	Tmax (hours)	KEL (1/hours)	Halflife (hours)
1	1.30	1.35	0.96	0.4306	0.5763	0.50	0.1267	5.47
2	1.18	1.23	0.97	0.3194	0.6355	0.50	0.1350	5.13
5	1.86	1.98	0.94	0.5965	0.4574	0.65	0.1116	6.21
6	1.96	2.04	0.96	0.5633	0.3905	0.75	0.1306	5.31
9	1.56	1.63	0.96	0.3551	0.5361	0.50	0.1290	5.37
10	1.41	1.45	0.97	0.5387	0.5383	0.75	0.1444	4.80
19	2.55	2.66	0.96	0.9353	0.2802	0.75	0.1312	5.28
20	1.69	1.99	0.85	0.5930	0.3160	0.75	0.1551	4.47
MEAN	1.69	1.79	0.95	0.5415	0.4663	0.64	0.1330	5.26
STD	0.44	0.47	0.04	0.1918	0.1275	0.12	0.0128	0.51
CV	25.95	26.24	4.18	35.4293	27.3509	19.2	9.6246	9.70

APPENDIX E.2.6
Project CP300
PHARMACOKINETIC PARAMETERS OF CL 315,585
Observed Results by participant status

---------- Treatment=A:Patients ----------

participant	AUC0-t (µg.hr/mL)	AUCinf (µg.hr/mL)	AUC0-t/ AUCinf	Cmax (µg/mL)	Vss (L/kg)	Tmax (hours)	KEL (1/hours)	Halflife (hours)
3	4.17	4.84	0.86	1.1310	0.2310	0.85	0.0751	9.23
4	1.58	1.67	0.94	0.6779	0.4315	0.75	0.1019	6.80
7	1.39	1.49	0.93	0.5884	0.4988	0.75	0.0930	7.46
8	3.44	3.68	0.93	1.4071	0.2175	0.75	0.0978	7.09
11	1.70	1.78	0.95	0.6511	0.3878	0.75	0.1150	6.03
12	2.17	2.29	0.95	0.7820	0.3043	0.75	0.1159	5.98
13	1.28	1.34	0.95	0.6044	0.4801	0.75	0.1147	6.04
14	3.06	3.27	0.94	0.9918	0.2378	1.00	0.0990	7.00
15	1.98	2.09	0.95	0.9652	0.1850	0.78	0.2237	3.10
MEAN	2.31	2.50	0.93	0.8665	0.3304	0.79	0.1151	6.52
STD	1.01	1.19	0.03	0.2790	0.1211	0.08	0.0428	1.63
CV	43.96	47.48	3.10	32.1964	36.6462	10.7	37.137	25.02

---------- Treatment=B:Normal Vol ----------

participant	AUC0-t (µg.hr/mL)	AUCinf (µg.hr/mL)	AUC0-t/ AUCinf	Cmax (µg/mL)	Vss (L/kg)	Tmax (hours)	KEL (1/hours)	Halflife (hours)
1	1.04	1.12	0.93	0.6559	0.3499	0.50	0.1784	3.88
2	0.84	0.91	0.93	0.4998	0.4259	0.50	0.1892	3.66
5	1.93	2.03	0.95	0.9847	0.3395	0.65	0.1123	6.17
6	2.12	2.20	0.96	0.9421	0.2964	0.75	0.1251	5.54
9	1.45	1.50	0.97	0.5994	0.4313	0.75	0.1253	5.53
10	1.15	1.25	0.92	0.8804	0.3249	0.75	0.1860	3.73
19	2.14	2.20	0.97	1.1445	0.2195	0.75	0.1294	5.36
20	1.54	1.66	0.93	0.9850	0.2181	0.75	0.1949	3.56
MEAN	1.53	1.61	0.94	0.8365	0.3257	0.68	0.1551	4.68
STD	0.50	0.50	0.02	0.2249	0.0808	0.11	0.0349	1.07
CV	32.79	31.16	2.26	26.8900	24.8007	16.8	22.509	22.84

APPENDIX E.2.15
(ln-transformed) Bioavailability Parameters of Verteporfin
Observed Results by Participant Status

---------- Hepatic Impaired Patients ----------

Participant	AUC0-t	AUCinf	Cmax
3*	1.92		0.52
4	1.09	1.15	0.07
7	1.06	1.11	-.04
8	1.86	1.93	0.77
11	1.27	1.32	0.06
12	1.48	1.52	0.40
13	0.98	1.03	-.03
14	1.95	1.99	0.55
15	1.55	1.57	0.44
MEAN	1.46	1.45	0.30
STD	0.38	0.37	0.30
CV	26.3	25.4	97.9

---------- Subjects - Normal Liver Function ----------

Participant	AUC0-t	AUCinf	Cmax
1	0.89	0.90	0.08
2	0.74	0.76	-.20
5	1.33	1.39	0.46
6	1.40	1.44	0.41
9	1.10	1.14	-.05
10	0.98	1.00	0.35
19	1.55	1.58	0.73
20	1.17	1.29	0.46
MEAN	1.15	1.19	0.28
STD	0.27	0.29	0.31
CV	23.8	24.2	110

* No meaningful Kel, and therefore AUCinf, could be calculated for this subject.

Demographic Data For All Subjects

Subject Number	Hepatic Function	Sex	At Screening Age (years)	At Screening Height (cm)	At Screening Weight (kg)	Body-frame	Skin Type
1	Normal	F	38	167	54	Small	II
2	Normal	F	37	155	57	Small	III
3	Mild Impairment	F	47	154	62	Medium	IV
4	Mild Impairment	M	40	171	81	Medium	III
5	Normal	M	46	188	99	Medium	V
6	Normal	M	32	187	90	Medium	III
7	Mild Impairment	M	29	189	84	Medium	II
8	Mild Impairment	M	42	185	101	Large	II
9	Normal	M	33	163	65	Medium	III
10	Normal	M	33	165	67	Medium	III
11	Mild Impairment	M	39	181	72	Medium	III
12	Mild Impairment	M	36	189	85	Medium	V
13	Mild Impairment	M	36	172	73	Medium	IV
14	Mild Impairment	M	34	172	62	Medium	IV
15	Mild Impairment	F	37	146	46	Medium	II
19	Normal	F	60	167	69	Medium	I
20	Normal	F	48	157	50	Small	III

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-119 SUBMISSION DATE: 8/16/99, 10/12/99

NDA TYPE: 1P

PRODUCT: VISUDYNE™
(Verteporfin for injection, 15 mg)

SPONSOR: QLT Phototherapeutics Inc. REVIEWER: Veneeta Tandon, Ph.D.

Addendum to Review

(Additional labeling changes)

These labeling changes reflect the discussion held at the OCPB Briefing held for VISUDYNE on 1/11/2000.

1. Please replace last sentence in the first paragraph of "Pharmacokinetics" in the label with:

2. Please modify last sentence in the second paragraph of "Pharmacokinetics" in the label:

Change number from 0.004% to 0.01%

(Reason: 0.004% implies a level of high precision, which may not be justified by the sparse data)

3. Please replace second line after the comma in the third paragraph of "Pharmacokinetics" in the label with:

increased by approximately 20%.

/S/ - 1/12/2000

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. 1/12/2000

CC: NDA 21-119
HFD-550/Div File
HFD-550/CSO/Gorski
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

APPEARS THIS WAY
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APPEARS THIS WAY
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