

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-119

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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.

NDA Review

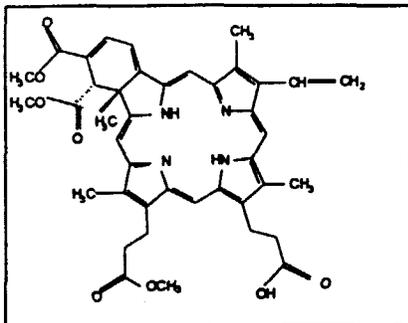
I. BACKGROUND

Dosage Form: Injection for intravenous infusion supplied as lyophilized powder (15 mg of lyophilized cake/vial)

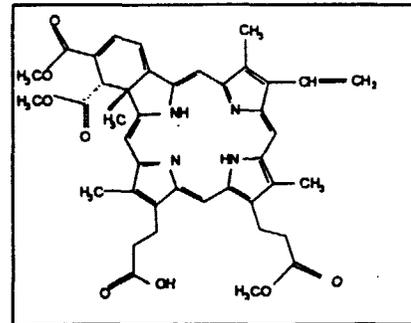
Reconstituted with sterile water for injection to obtain a solution containing 2 mg/mL of verteporfin.

Indication: For the treatment of age related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.

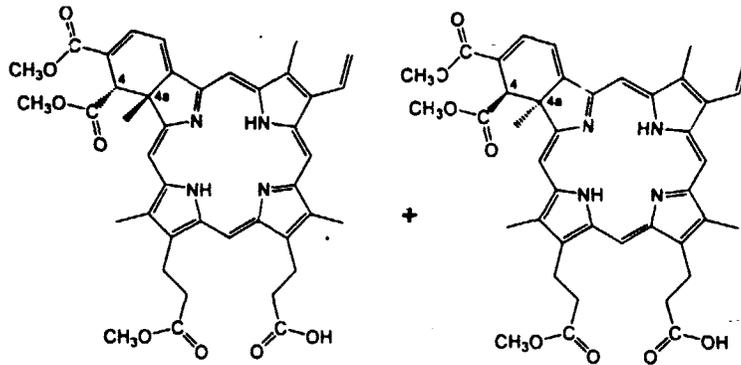
Drug Class: Common name: Benzoporphyrin derivative monoacid A. (BPD-MA), a second generation light activated molecule. It is a structural 1:1 mixture of two isomers (regioisomers), BPD-MA_C (CL 315,555) and BPD-MA_D (CL 315, 585). Each of these structural isomer is also a mixture of two enantiomers, due to the optically active carbon.



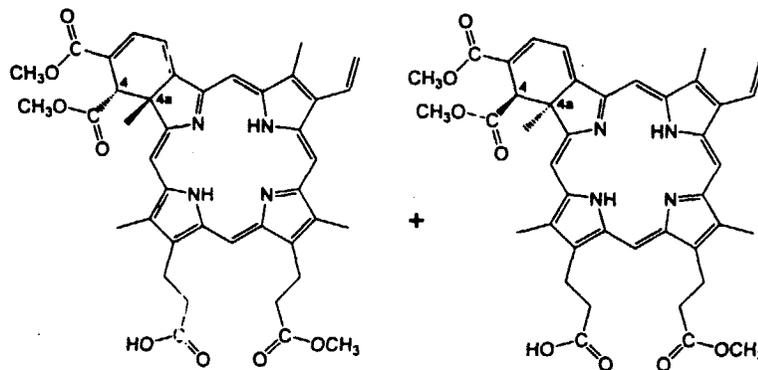
9-Methyl trans-(±)-18-ethenyl-4, 4a-dihydro-3, 4-bis(methoxycarbonyl)-4a, 8, 14, 19-tetramethyl-23H, 25H-benzo[b]porphine-9,13-dipropanoate
BPD-MAC



13-Methyl trans-(±)-18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23H, 25H-benzo[b]porphine-9,13-dipropanoate
BPD-MAD



Enantiomers of BPD-MAC



Enantiomers of BPD-MAD

Dose and administration: VISUDYNE™ therapy is a two step process:

1. Intravenous infusion of VISUDYNE™ 6 mg/m² for 10 minutes
2. Activation of VISUDYNE™ with light from a nonthermal diode laser for 2 minutes, 15 minutes after start of infusion. The recommended light dose is 50 J/cm² administered at an intensity of 600mW/cm². This dose is administered over 83 seconds.

The laser system must deliver a stable power output at a wavelength of 689±3 nm to the retina as a single circular spot via a fiber optic and slit lamp.

Target tissue: endothelial cells lining the choroidal neovasculature

Therapy could be repeated after 3 months if needed.

Mechanism of Action: Verteporfin is transported in the plasma primarily by low-density lipoprotein and is preferentially retained in the walls of the new blood vessels, including choroidal neovasculature. Once verteporfin is activated by light in the presence of oxygen, highly reactive short lived singlet oxygen is generated. Light activation of verteporfin results in selective and local damage to neovascular

endothelium, resulting in vessel occlusion. Damaged endothelium is known to release procoagulant and vasoactive factors through the lipo-oxygenase and cyclo-oxygenase pathways, resulting in platelet aggregation, fibrin clot formation and vasoconstriction.

Foreign Marketing History: Not yet marketed anywhere

Formulation:

Ingredient	Quantity (mg/Vial)	Function
Verteporfin	15	Active
Butylated hydroxytoluene		
Ascorbyl palmitate		
Egg phosphatidylglycerol		
Dimiristoyl phosphatidylcholine		
Lactose (NF)		

II. RECOMMENDATION

The reviewer recommends approval of the application from the clinical pharmacokinetics standpoint. The labeling changes recommended on page 51 of the review should be conveyed to the sponsor. The sponsor has adequately evaluated the pharmacokinetics of verteporfin for injection.

The clinical pharmacokinetic studies and the clinical trials have been conducted using the to-be marketed formulation, but there is a difference in the manufacturing process. This formulation differs from the commercial lot in a manner in which the liposomes are dried (small scale versus a large commercial scale). This issue is being resolved by the review chemist.

¹ Fogelman et al, Lipoprotein receptor an dendothelial cells, Sem Throm Hemos, 1988, 14(2):206-209

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III. ANALYTICAL VALIDATION

Are the assays for the determination of verteporfin, its regioisomers and enantiomers adequately validated?

Yes, the sponsor has satisfactorily conducted the assay validation for the regioisomers of verteporfin, its enantiomers and the metabolite of verteporfin in human plasma and urine. The sponsor has submitted complete validation reports at the end of each study with the chromatograms, raw data for the samples and quality control samples.

There were two different limits of detection for the regioisomers of verteporfin depending on the time when the study was conducted. The most recent study (BPD PK 001 A & B) uses the more sensitive assay methodology, with a lower limit of detection (2 ng/ml vs. 5 ng/ml in the studies conducted during early drug development). Both these assay validation reports have been summarized under separate report numbers.

Analytical validation for evaluation of the regioisomers BPD-MA_c (CL 315,555) and BPD-MA_D (CL 315, 585), the enantiomeric ratios and the metabolite (BPD-DA) in human plasma and urine is discussed below. Necessary comments regarding the reports have been provided at the end of this section under 'Reviewer's Comment'.

Report EP090/BOD

CL315,555 (BPD-MA_c)

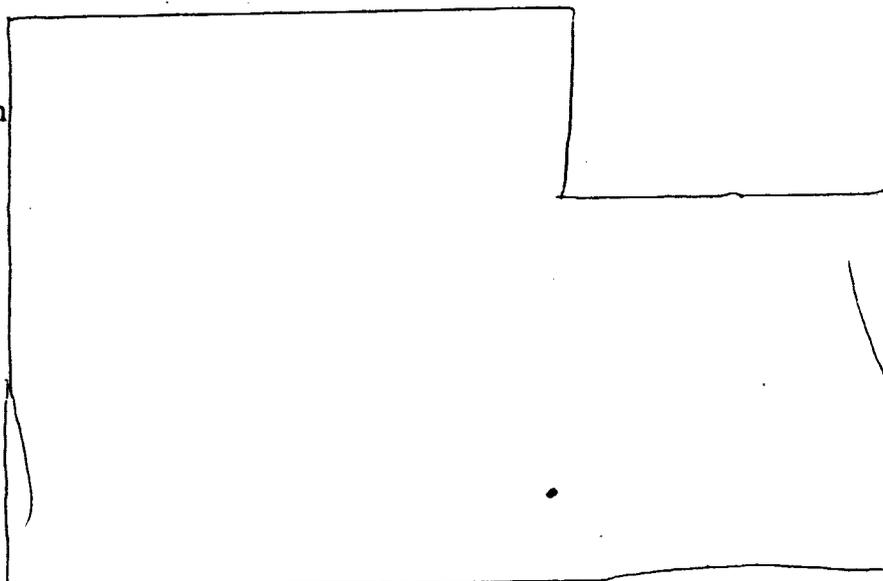
Methodology:
Internal standard:
Limit of quantitation:
Goodness of fit:

Specificity:

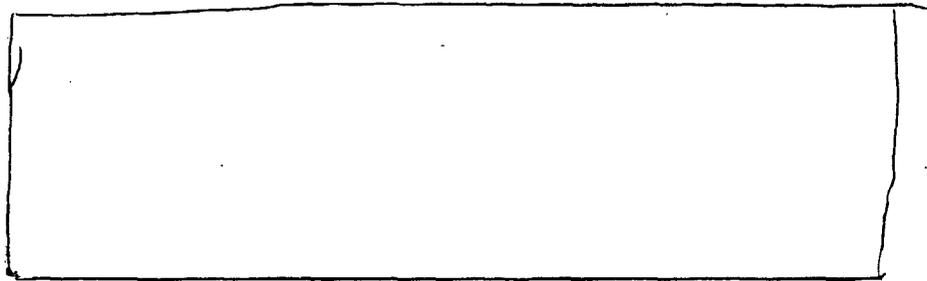
Accuracy:

Precision:

Stability:



Recovery:



CL315,585 (BPD-MA_D)

Methodology:
Internal standard:
Limit of quantitation
Goodness of fit:

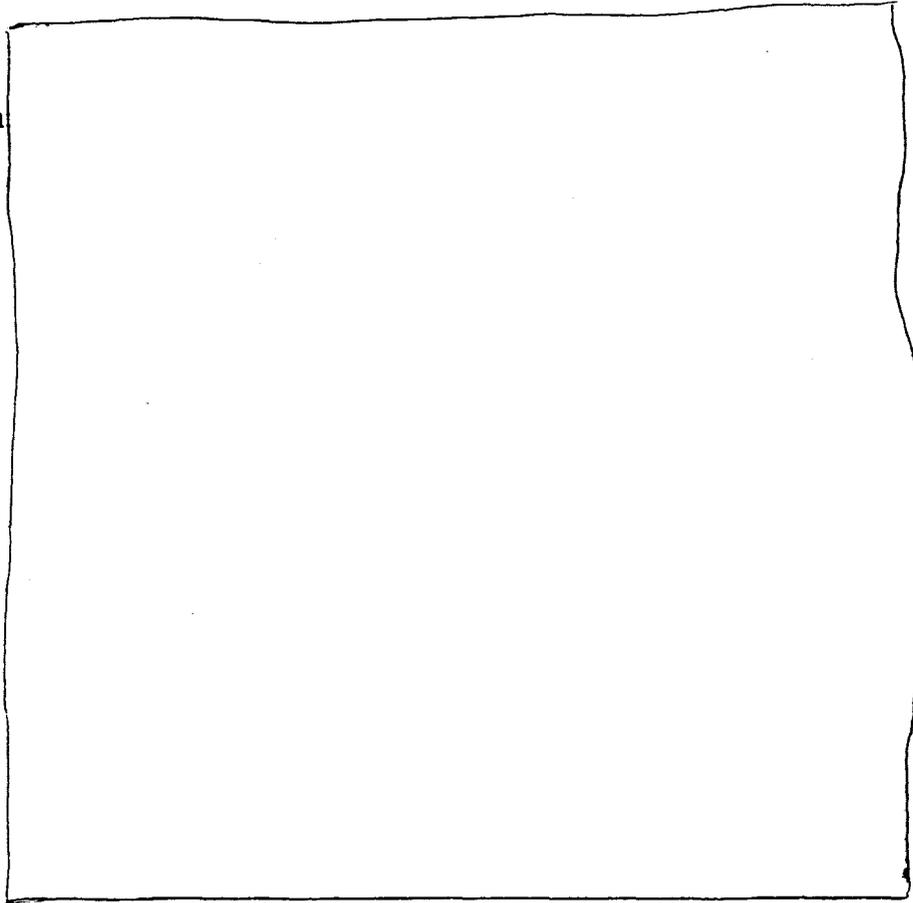
Specificity:

Accuracy:

Precision:

Stability:

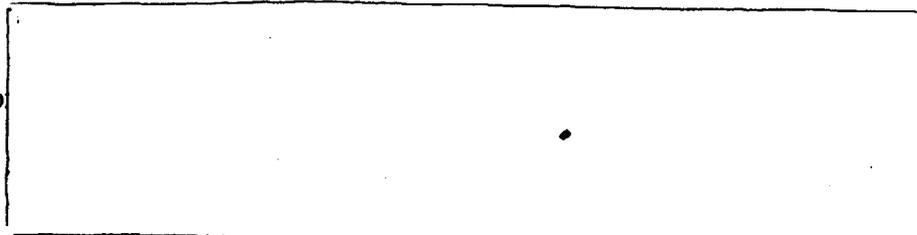
Recovery:



CL315,555 (BPD-MA_c)

Methodology:
Internal standard:
Limit of quantitation
Goodness of fit:

Specificity:

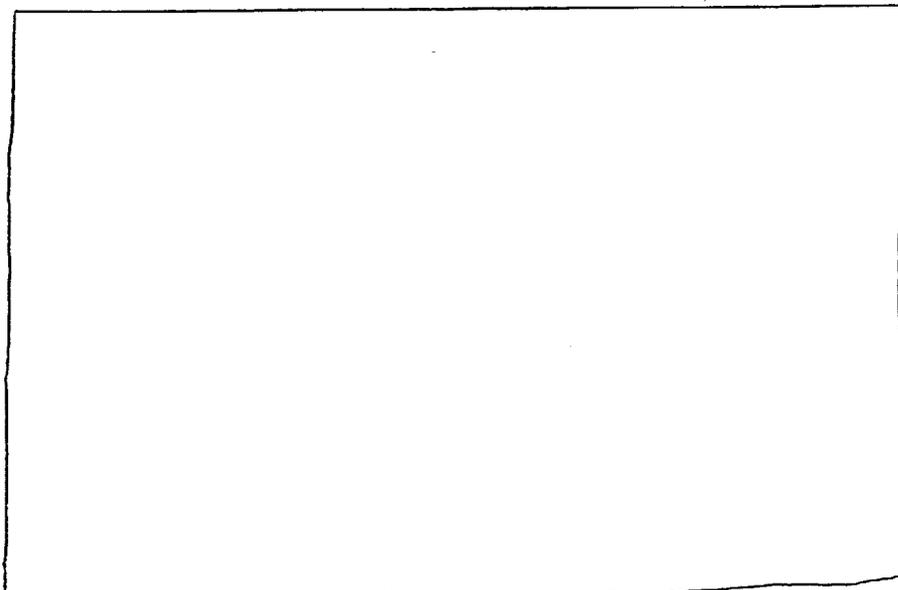


Accuracy:

Precision:

Stability:

Recovery:



CL315,585 (BPD-MA_D)

Methodology:

Internal standard:

Limit of quantitation:

Good ness of fit:

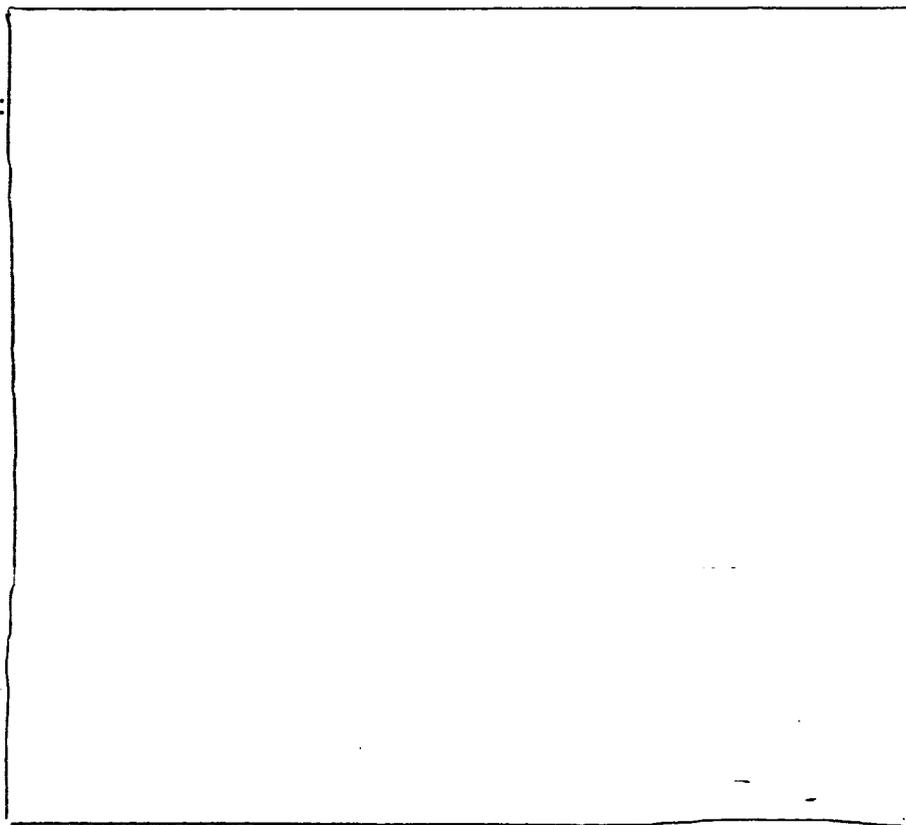
Specificity:

Accuracy:

Precision:

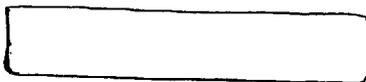
Stability:

Recovery:



BPD-DA (metabolite of verteporfin)

Methodology:



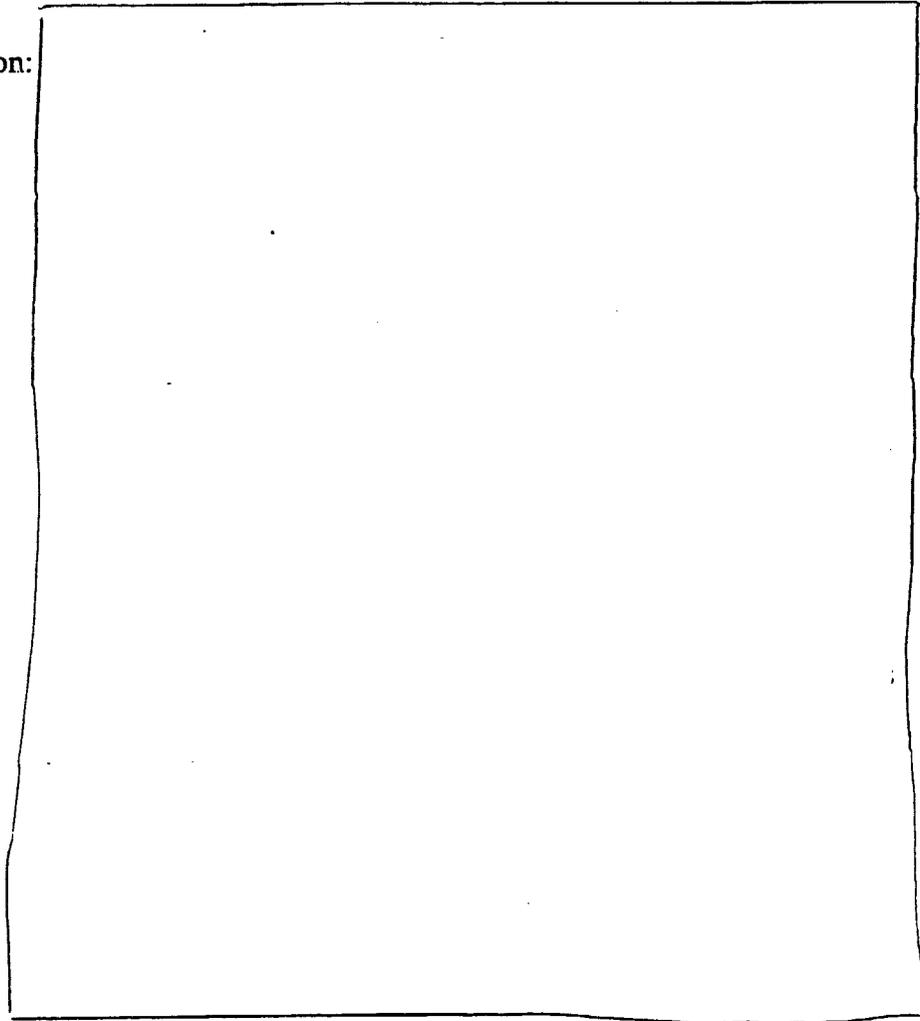
Internal standard:
Limit of quantitation:
Good ness of fit:

Specificity:
Accuracy:

Precision:

Stability:

Recovery:



Evaluation of enantiomeric ratios of BPD-MA_c And BPD-MA_D and BPD-DA in human plasma:

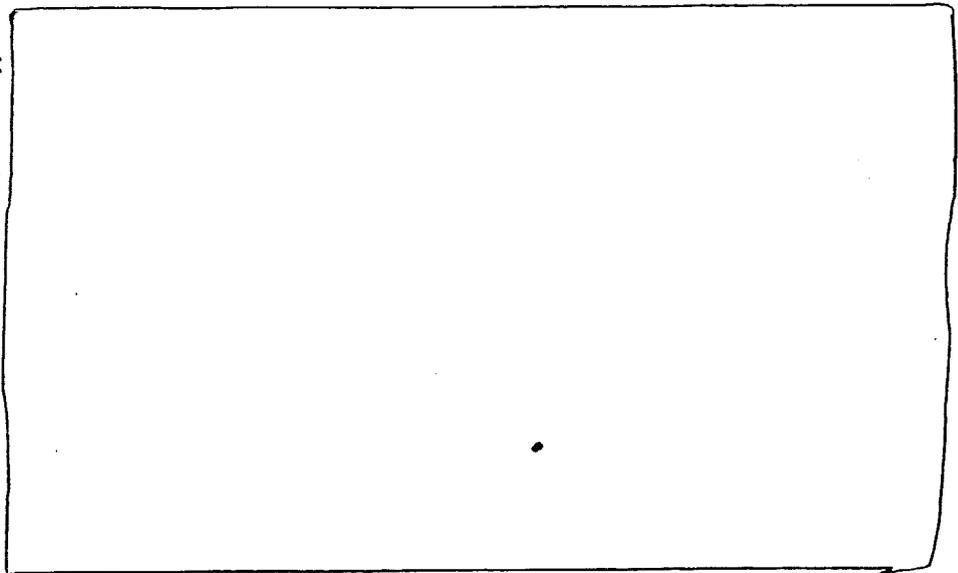
Method:
Limit of quantitation:

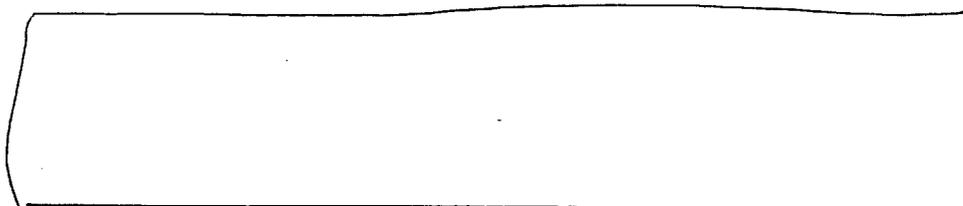
Intra-assay precision:

Inter-assay precision:

Recovery:

Stability:





Evaluation of enantiomeric ratios of BPD-MA_c And BPD-MA_D and BPD-DA in human urine:

Method:

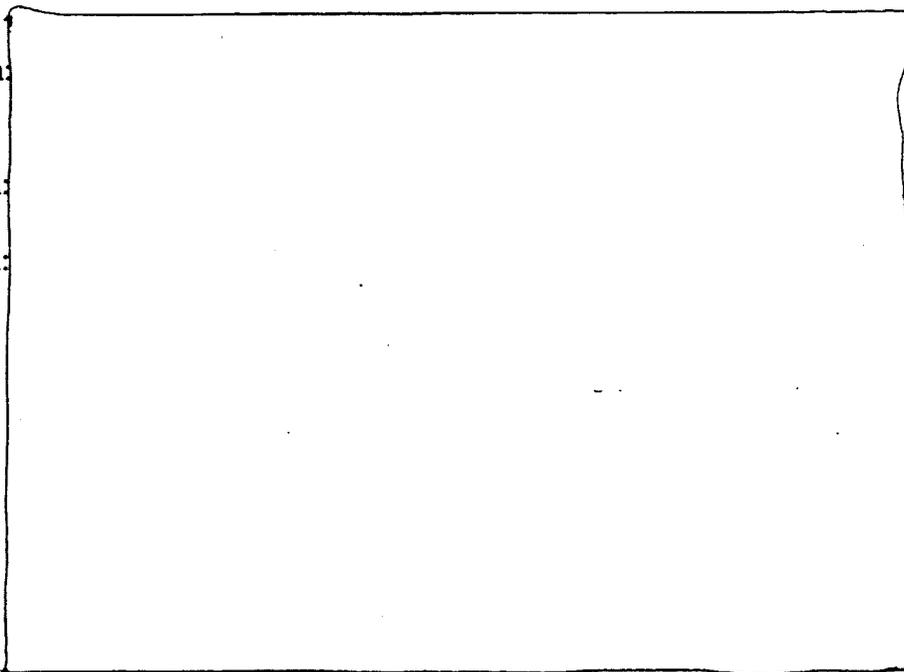
Limit of quantitation:

Intra-assay precision:

Inter-assay precision:

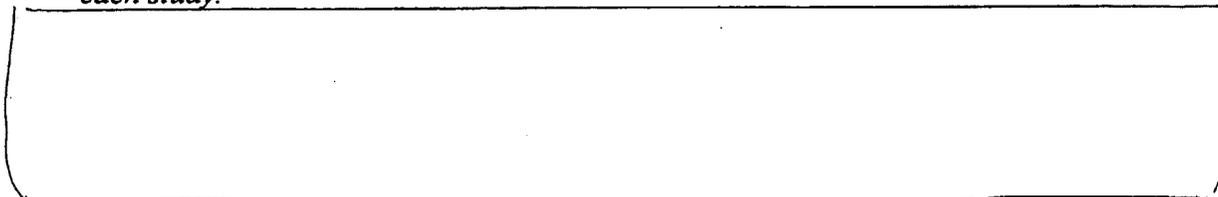
Recovery:

Stability:



Reviewer's Comment

- *The analytical validation report and quality control assays have been provided after each study.*



IV. PHARMACOKINETIC STUDIES

Absorption and Disposition

What is the pharmacokinetics (mainly absorption, and disposition characteristics) of Verteporfin, its two regioisomers and its enantiomers of the in healthy subjects and in patients?

The pharmacokinetics of verteporfin in healthy subjects and in patients and have evaluated in different studies. The key conclusions drawn regarding the absorption and

disposition characteristics of verteporfin will be outlined at the end of the results from the studies, which will aim at answering the question raised in this section.

SINGLE DOSE STUDIES

In healthy subjects

The sponsor has evaluated the pharmacokinetics of verteporfin and its two regioisomers in healthy subjects in two studies (BPD PK 001A and B). These studies were the most recent studies conducted as part of the development of verteporfin and have evaluated the two regioisomers, its enantiomers and metabolite in a greater detail than any other study submitted. Hence, these studies will be most informative in describing the basic pharmacokinetics of verteporfin.

Study BPD PK 001 A was done in healthy Caucasians involving both men (N=20) and women (N=12) and Study BPD PK 001 B was done in Japanese male subjects (N=24) only. The sponsor has used the dosage and administration similar to the to-be marketed regimen, but has also added higher dose (14 mg/m² in Study A) and both, a lower and higher dose (3 and 14 mg/m² in Study B) to assess dose proportionality, which will be discussed in later sections of the review. The doses studied were 3, 6 and 14 mg/m² with a 10 minute IV infusion. The sponsor has also added an arm of 1.5 minute bolus dose at 6 mg/m² or comparative purposes. Details of the study groups and study design are provided in the Appendix on page 1 along with demographics in Table 1 on page 2. The dosage was assigned in ascending order after evaluation of the safety from the previous dose. No efficacy evaluation was performed and there was no control group in either study.

The administration procedures consisted of reconstituting verteporfin with sterile water for injection to 2 mg/mL, diluting the necessary dose to 30 mL with 5% dextrose solution, and administering the 30 mL over 10 minutes or over 1.5 minutes for the bolus injection dose group.

Blood samples were obtained and pharmacokinetic parameters were calculated for all subjects enrolled in the two studies: 32 subjects for Study A and 24 subjects for Study B. Plasma and urine samples were collected and assayed using HPLC to determine the concentrations of: 1) the two regioisomers of verteporfin (BPD-MA_C and BPD-MA_D), and 2) their main metabolite, BPD-DA. Plasma concentrations of BPD-MA_C and BPD-MA_D were added to obtain verteporfin. Samples were also assayed using capillary electrophoresis (CE) to determine the ratio of enantiomers of BPD-MA_C, BPD-MA_D, and their main metabolite, BPD-DA. Results of these assays were used to determine whether the dispositions of BPD-MA_C, BPD-MA_D, and BPD-DA are stereospecific. The assay validation has been discussed in the previous section of this review.

Verteporfin and its regioisomers BPD-MA_C and BPD-MA_D

The mean plasma concentrations at each time point for BPD-MA_C, BPD-MA_D, their sum (BPD-MA_{C+D} = verteporfin), and BPD-DA for all dose groups in Studies A and B is attached in Table 2 of the Appendix on page 3. The figures below depict the mean plasma concentration profiles for BPD-MA_C, BPD-MA_D, and verteporfin, respectively, for Studies A and B. The first four hours were plotted in the linear scale to get a greater detail of the relationship between plasma levels and the dose. (Note that for the 6 mg/m² and 14 mg/m², 10-minute infusion dose groups where data for Caucasian and Japanese subjects are combined, the means are weighed to take into account the sample size of each dose group.)

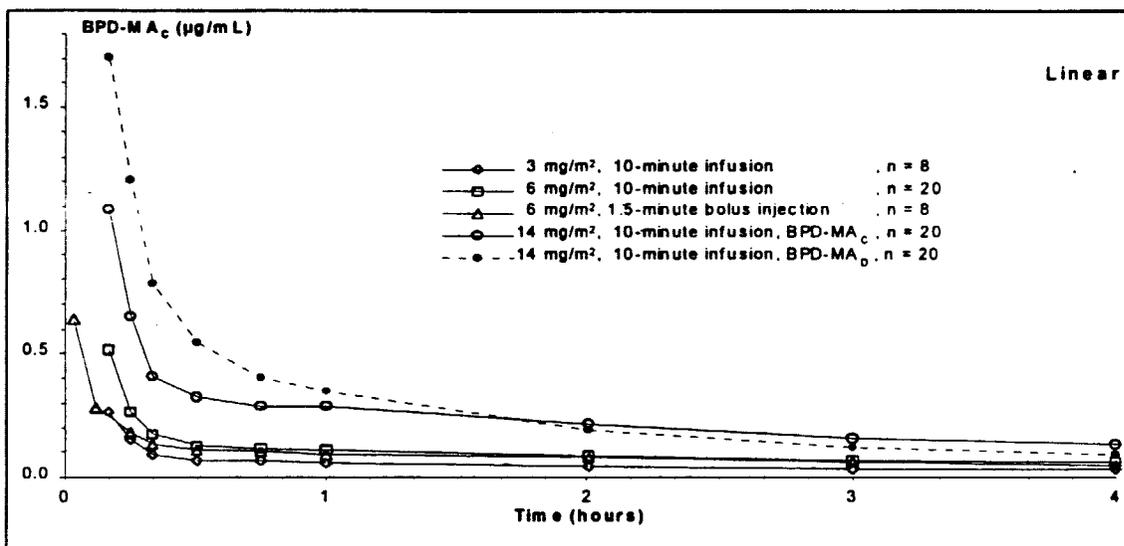


Figure: Plasma concentration profile of BPD-MA_C

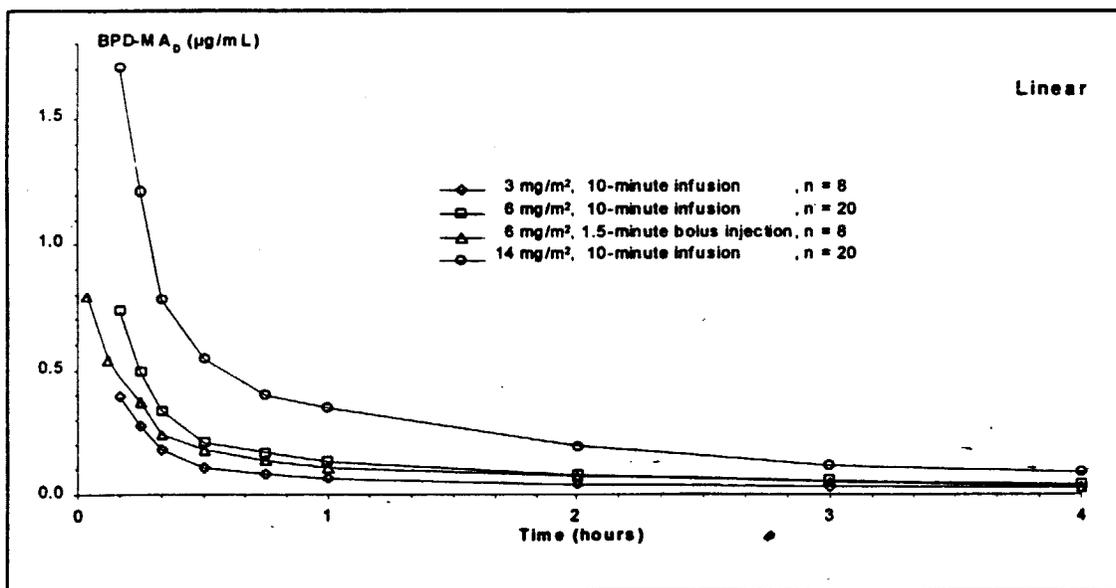


Figure: Plasma concentration profile of BPD-MA_D

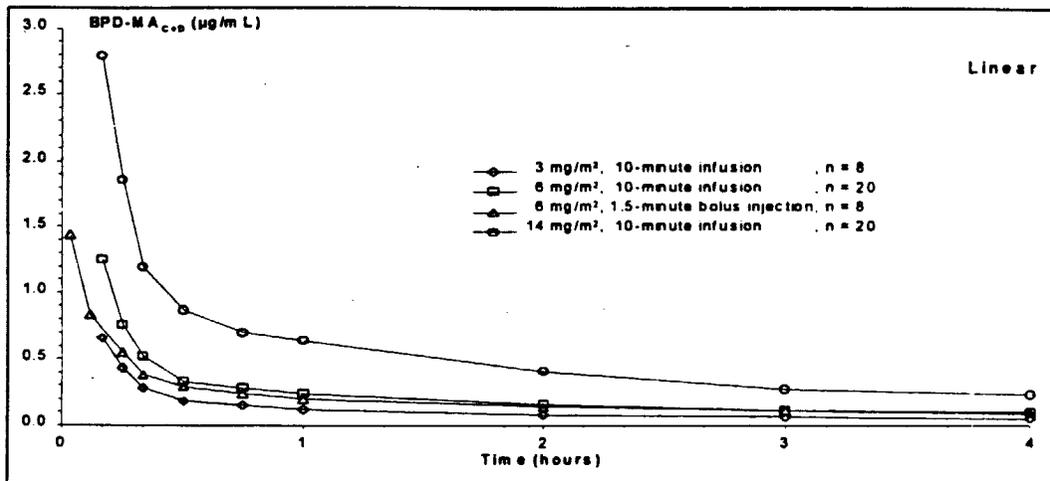
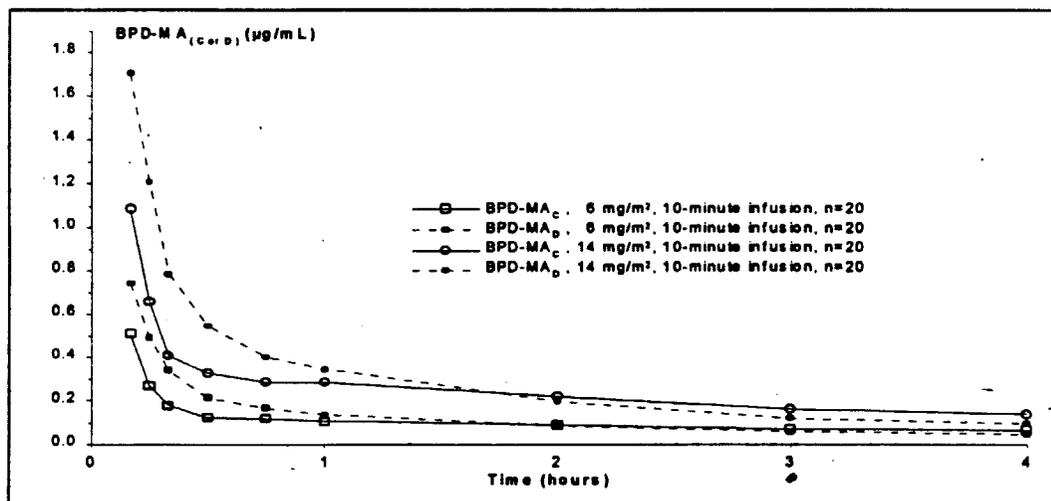


Figure: Plasma concentration profiles of verteporfin

The semi-logarithmic mean profile for verteporfin (0-24 hours) is attached in the Appendix on page 4 to show the elimination part of the profile. The mean plasma profiles of BPD-MA_C, BPD-MA_D, and their sum, verteporfin, exhibited similar disposition characteristics among the doses and rates of administration studied. A clear bi-exponential decline in the plasma concentrations was observed, with a rapid distribution phase followed by a slower elimination phase. Over the dose range (3-14 mg/m²) and infusion regimens (1.5 minute bolus and 10-minute infusion) administered in Studies A and B, verteporfin is almost entirely cleared from the vascular compartment by 24 hours following drug administration. This can also be seen in the mean plasma concentration values at each time point in Table 2 attached in the Appendix on page 3. The C_{max} was in most cases the time of first blood collection after dosing. Mean plasma concentration profile in Caucasians and Japanese for the regioisomers is shown in the same graph in the following figure, which shows that the initial concentrations of BPD-MA_D were higher.



Figures: Plasma concentration profiles of BPD-MA_C, BPD-MA_D (Caucasians and Japanese subjects combined)

The summary of BPD-MA_C, BPD-MA_D, their sum (verteporfin), and BPD-DA plasma pharmacokinetic parameters is presented in the following Table 1.

TABLE 1: Overall Plasma Pharmacokinetic Analysis for BPD-MA_C, BPD-MA_D, Verteporfin, and BPD-DA

Pharmacokinetic Parameter	Mean (Coefficient of Variation) for Study A – Caucasian ^a						Mean (Coefficient of Variation) for Study B – Japanese ^a									
	BPD-MA _C		BPD-MA _D		Verteporfin (BPD-MA _C +D)		BPD-MA _C		BPD-MA _D		Verteporfin (BPD-MA _C +D)		BPD-DA			
	6 mg/m ² – 10-min infusion (n=12)															
AUC _{0-t} (µg·h/mL)	0.83	(23%)	0.71	(22%)	1.56	(21%)	0.07	(78%)	0.89	(15%)	0.81	(20%)	1.71	(16%)	0.06	(128%)
AUC _{inf} (µg·h/mL)	0.88 ^b	(21%)	0.77 ^b	(19%)	1.63	(20%)	— ^g	— ^g	0.92	(15%)	0.83	(19%)	1.75	(16%)	0.04 ^e	(7%)
C _{max} (µg/mL)	0.47	(28%)	0.72	(24%)	1.18	(25%)	0.01	(53%)	0.55	(11%)	0.77	(11%)	1.32	(11%)	0.01	(56%)
CL (mL·h ⁻¹ ·kg ⁻¹)	91.1 ^b	(17%)	103.3 ^b	(19%)	97.3 ^b	(18%)	— ^g	— ^g	97.2	(22%)	108.8	(26%)	102.7	(23%)	— ^g	— ^g
V _{ss} (L/kg)	0.65 ^b	(23%)	0.51 ^b	(25%)	0.63	(36%)	— ^g	— ^g	0.62	(13%)	0.52	(10%)	0.57	(11%)	— ^g	— ^g
t _{max} (h)	0.18	(18%)	0.18	(18%)	0.18	(18%)	4.01	(91%)	0.17	(0%)	0.17	(0%)	0.17	(0%)	3.93	(213%)
K _{el} (1/h)	0.13 ^b	(15%)	0.14 ^b	(30%)	0.13	(25%)	— ^g	— ^g	0.13	(14%)	0.12	(26%)	0.13	(20%)	0.18 ^e	(7%)
t _{1/2} (h)	5.66 ^b	(19%)	5.55 ^b	(30%)	5.84	(36%)	— ^g	— ^g	5.53	(15%)	5.97	(24%)	5.72	(20%)	3.89 ^e	(7%)
14 mg/m ² – 10-min infusion (n=12)																
AUC _{0-t} (µg·h/mL)	1.77	(20%)	1.60	(20%)	3.38	(20%)	0.19	(81%)	2.54	(26%)	2.36	(31%)	4.91	(28%)	0.28	(41%)
AUC _{inf} (µg·h/mL)	1.80	(20%)	1.63	(20%)	3.41	(20%)	0.17 ^c	(19%)	2.57	(26%)	2.38	(31%)	4.95	(28%)	0.32 ^f	(45%)
C _{max} (µg/mL)	0.95	(53%)	1.54	(43%)	2.48	(46%)	0.04	(146%)	1.27	(20%)	1.87	(20%)	3.13	(19%)	0.03	(60%)
CL (mL·h ⁻¹ ·kg ⁻¹)	107.8	(18%)	118.6	(17%)	113.3	(17%)	— ^g	— ^g	80.4	(30%)	88.7	(34%)	84.5	(32%)	— ^g	— ^g
V _{ss} (L/kg)	0.70	(27%)	0.58	(32%)	0.63	(28%)	— ^g	— ^g	0.56	(22%)	0.48	(20%)	0.51	(21%)	— ^g	— ^g
t _{max} (h)	0.20	(27%)	0.18	(23%)	0.19	(20%)	1.26	(141%)	0.17	(0%)	0.17	(0%)	0.17	(0%)	6.47	(92%)
K _{el} (1/h)	0.12	(10%)	0.12	(15%)	0.13	(13%)	0.08 ^c	(35%)	0.13	(16%)	0.11	(13%)	0.13	(17%)	0.06 ^f	(20%)
t _{1/2} (h)	5.83	(9%)	5.95	(15%)	5.36	(12%)	10.2 ^c	(42%)	5.66	(18%)	6.23	(13%)	5.62	(17%)	11.8 ^f	(20%)
6 mg/m ² – 1.5-min bolus (n=8)																
AUC _{0-t} (µg·h/mL)	0.80	(32%)	0.67	(28%)	1.49	(29%)	0.10	(91%)	0.41	(27%)	0.40	(31%)	0.83	(28%)	0.09	(77%)
AUC _{inf} (µg·h/mL) ^e	0.83	(32%)	0.70	(25%)	1.52	(28%)	0.22 ^d	— ^g	0.45	(25%)	0.44	(28%)	0.88	(25%)	0.28 ^d	— ^g
C _{max} (µg/mL)	0.64	(21%)	0.81	(12%)	1.44	(15%)	0.04	(162%)	0.27	(17%)	0.39	(15%)	0.66	(15%)	0.01	(35%)
CL (mL·h ⁻¹ ·kg ⁻¹)	110.8	(35%)	126.5	(28%)	118.8	(32%)	— ^g	— ^g	100.1	(31%)	104.7	(35%)	102.1	(31%)	— ^g	— ^g
V _{ss} (L/kg) ^e	0.73	(21%)	0.57	(26%)	0.63	(19%)	— ^g	— ^g	0.66	(17%)	0.52	(28%)	0.58	(25%)	— ^g	— ^g
t _{max} (h)	0.04	(21%)	0.06	(122%)	0.06	(122%)	1.82	(179%)	0.17	(0%)	0.17	(0%)	0.17	(0%)	9.04	(61%)
K _{el} (1/h) ^e	0.12	(34%)	0.14	(25%)	0.14	(27%)	0.09 ^d	— ^g	0.12	(26%)	0.12	(30%)	0.13	(23%)	0.04 ^d	— ^g
t _{1/2} (h) ^e	6.09	(29%)	5.26	(23%)	5.16	(25%)	7.94 ^d	— ^g	6.00	(25%)	6.07	(26%)	5.77	(22%)	18.8 ^d	— ^g
3 mg/m ² – 10-min infusion (n=8)																

a. Four female subjects in each of the Caucasian dose groups. Japanese subjects are all men.

b. n = 11.

c. n = 7.

d. n = 1.

e. n = 2.

f. n = 4.

g. Data not available.

As can be seen from the Table 1, similar disposition pharmacokinetic parameters were observed across different dosage regimen and in the Caucasian and Japanese group. Verteporfin exhibits a rapid distribution phase followed by an elimination phase characterized by a half-life of approximately 5-6 hours, independent of the dose regimen. The volume of distribution averaged 0.6 L/kg and the total body clearance averaging 105 mL·h⁻¹·kg⁻¹.

The two structural isomers of verteporfin showed similar behavior and their pharmacokinetic parameters were comparable, exhibiting the same distribution, clearance and elimination kinetics. However, the initial plasma concentrations of BPD-MA_D are slightly higher (see Figure) than those of BPD-MA_C, but the overall exposure (AUC) is slightly lower. However, this difference was not significant.

Enantiomeric ratios

Each structural isomer of verteporfin is present as a pair of enantiomers. For BPD-MA_C, the two enantiomers are named Ib-1 and Ib-2, for BPD-MA_D, they are named Ia-1 and Ia-2, and for BPD-DA (metabolite) they are named II-1 and II-2. This nomenclature is based on their order of migration on an electropherogram (Capillary Electrophoresis). For each pair of enantiomers, the enantiomer named "1" appears first and the enantiomer named "2" appears second.

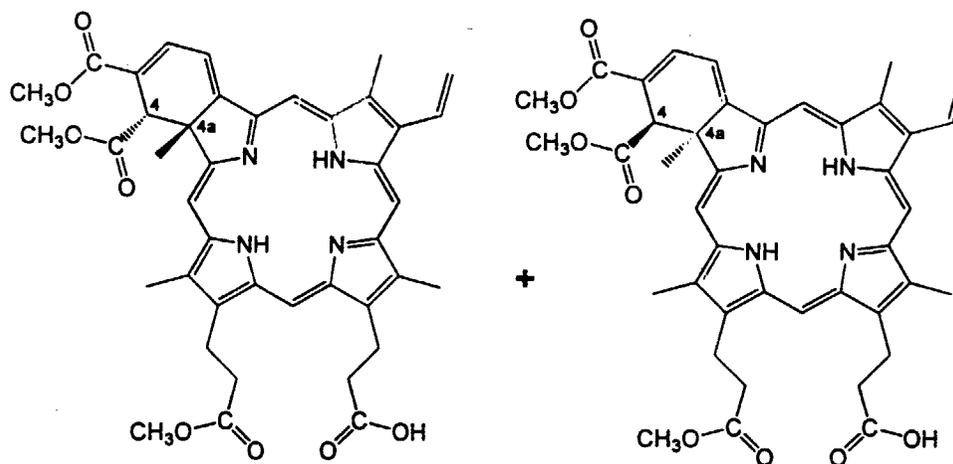


Figure: Enantiomers of BPD-MA_C

The sponsor has made an attempt to determine the optical rotation characteristics of each enantiomer or their exact configuration. Enantiomeric ratios for BPD-MA_C and BPD-MA_D in Caucasian and Japanese subjects are depicted in the following figures.

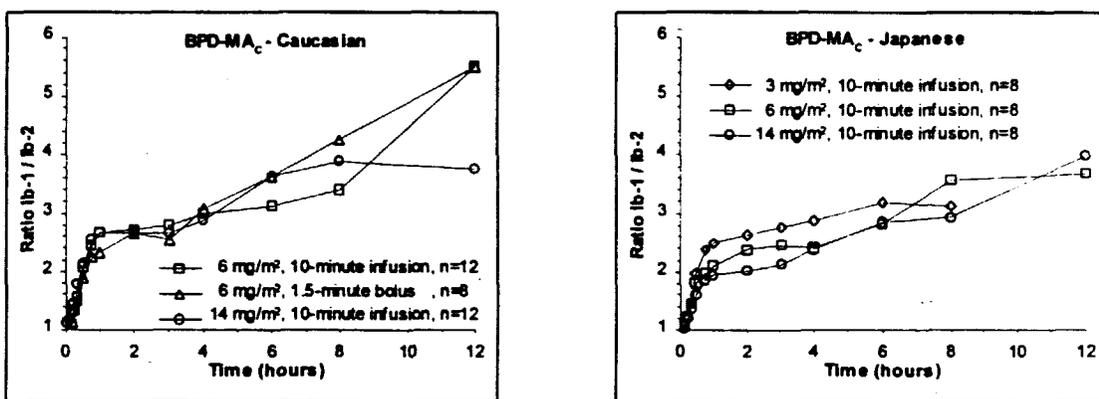


Figure: Mean Enantiomeric ratios of BPD-MA_c in Caucasian and Japanese subjects

A stereospecific disposition was observed for BPD-MA_c. In both Caucasian and Japanese subjects, the ratio of enantiomer Ib-1 over Ib-2 in plasma was close to unity at the end of drug administration but increased rapidly to approximately 2-3 one hour after the infusion. From 1 to 12 hours after the infusion the ratio (Ib-1/Ib-2) increased slowly to approximately 3.5-5.5 in Caucasian subjects and to approximately 3.5-4.0 in Japanese subjects. No dose dependent differences in the ratio were noted ($p=0.8172$). A repeat measure statistical analysis for done by the sponsor to see the effect of time and time*race interaction. Significant effects of time ($p=0.001$) and time*race interaction ($p=0.0017$) was observed.

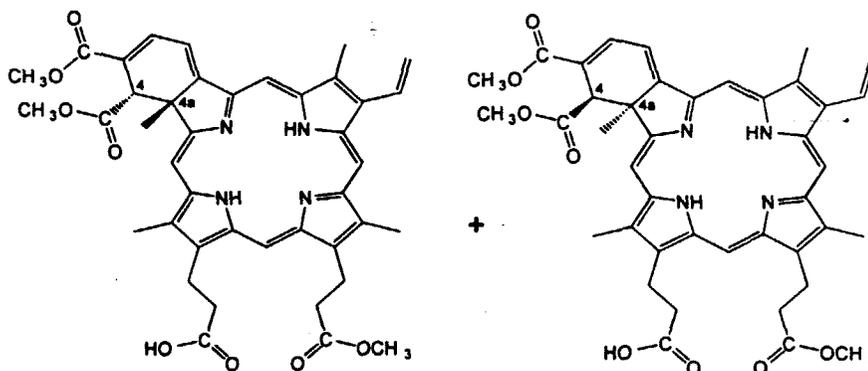


Figure: Enantiomers of BPD-MAD

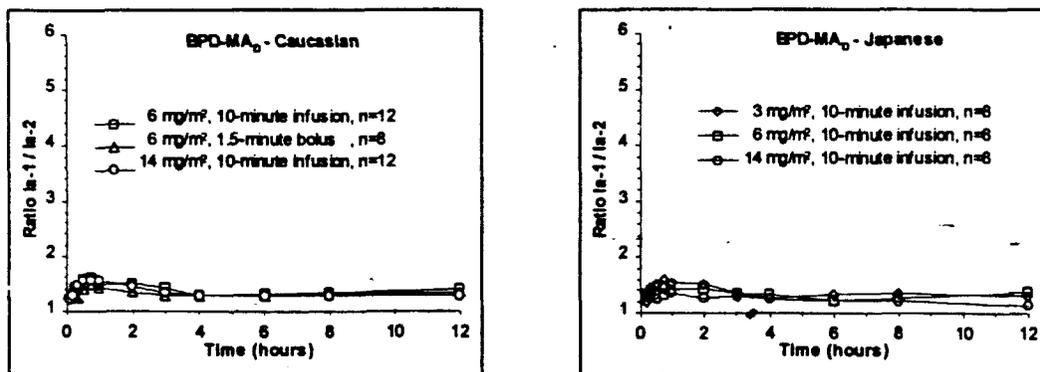


Figure: Mean Enantiomeric ratios of BPD-MA_o in Caucasian and Japanese subjects

Conversely for BPD-MA_D, no stereospecific disposition was observed. In both Caucasian and Japanese subjects the ratio of enantiomer Ia-1 over Ia-2 was approximately 1.2-1.3 at the end of the infusion, increasing to approximately 1.3-1.6 by the end of the first hour after the infusion. From 1 to 4 hours after the infusion, the ratio of Ia-1:Ia-2 gradually declined to the original values (i.e., approximately 1.3), remaining stable afterwards. No dose-related differences were apparent. A repeat measure statistical analysis was done by the sponsor to see the effect of time and time*race interaction. Significant effects of time (p=0.0242) was observed, but was consistent across both races. An interaction between dose*time was also observed (p=0.003).

Because of low BPD-DA plasma concentrations, enantiomeric ratios were obtained in few cases with mean values for the ratio of enantiomers II-1:II-2 of 2.2:1 (Caucasian and Japanese 14 mg/m², 10-minute infusion dose groups, both n=7, at 10 minutes after the start of dosing) and 2.9:1 (Japanese 14 mg/m², 10-minute infusion dose group, n=8, at 15 minutes after the start of dosing). These values suggest that metabolism of BPD-MA to BPD-DA may be stereospecific, at least immediately after the infusion.

Reviewer's Comment

The sponsor has discussed the enantiomers based on its ratios, but the absolute amount present at a particular time is unknown.

Bolus Injection comparison

A pharmacokinetic comparison of the 6 mg/m², 10-minute infusion dose group versus the 6 mg/m² 1.5-minute bolus injection dose group is presented in Table 2.

Because of the difference in the rate of verteporfin administration, BPD-MA_C, BPD-MA_D, and verteporfin mean maximal concentration (C_{max}) were 36%, 13%, and 22% higher, respectively, after a 1.5-minute bolus compared with a 10-minute infusion of the same dose, although these differences were not statistically significant (P=0.241, P=0.606, and P=0.436, respectively). However, the calculation of a C_{max} in this case may be questionable, with the dosing being a 1.5-minute bolus injection and the first sample being taken at 7 minutes. Plasma concentrations decreased very rapidly after administration of the dose. Approximately 10-15 minutes after C_{max} was reached, mean plasma concentrations of BPD-MA_C, BPD-MA_D, and verteporfin were similar in the bolus and 10-minute infusion dose groups.

TABLE 2: Pharmacokinetic Comparison of Bolus Injection vs. 10-minute Infusion

Pharmacokinetic Parameter		Mean (% Coefficient of Variation) – Study A (Caucasian) 6 mg/m ² Dose Only					
		10-minute Infusion (n=12) vs. 1.5-minute Bolus Injection (n=8)					
		BPD-MA _C	P value ^a	BPD-MA _D	P value ^a	BPD-MA _{C+D}	P value ^a
AUC _{0-t} (µg·h/mL)	10-min infusion	0.83 (23%)	.829	0.71 (22%)	.683	1.56 (21%)	.751
	1.5-min bolus	0.80 (32%)		0.67 (28%)		1.49 (29%)	
AUC _{inf} (µg·h/mL)	10-min infusion	0.88 ^b (21%)	.727	0.77 ^b (19%)	.533	1.63 ^b (20%)	.648
	1.5-min bolus	0.83 (32%)		0.70 (25%)		1.52 (28%)	
C _{max} (µg/mL)	10-min infusion	0.47 (28%)	.241	0.72 (24%)	.606	1.18 (25%)	.436
	1.5-min bolus	0.64 (21%)		0.81 (12%)		1.44 (15%)	
CL (mL·h ⁻¹ ·kg ⁻¹)	10-min infusion	91.1 ^b (17%)	.097	103.3 ^b (19%)	.057	97.3 ^b (18%)	.073
	1.5-min bolus	110.8 (35%)		126.5 (28%)		118.8 (32%)	
V _{ss} (L/kg)	10-min infusion	0.65 ^b (23%)	.309	0.51 ^b (25%)	.469	0.63 ^b (36%)	.983
	1.5-min bolus	0.73 (21%)		0.57 (26%)		0.63 (19%)	
t _{max} (h)	10-min infusion	0.18 (18%)	<.001	0.18 (18%)	.002	0.18 (18%)	.002
	1.5-min bolus	0.04 (21%)		0.06 (122%)		0.06 (122%)	
K _{el} (1/h)	10-min infusion	0.13 ^b (15%)	.889	0.14 ^b (30%)	.842	0.13 ^b (25%)	.322
	1.5-min bolus	0.12 (34%)		0.14 (25%)		0.14 (27%)	
t _{1/2} (h)	10-min infusion	5.66 ^b (19%)	.428	5.55 ^b (30%)	.642	5.84 ^b (36%)	.340
	1.5-min bolus	6.09 (29%)		5.26 (23%)		5.16 (25%)	

a. P value for the infusion length effect (bolus vs. 10-minute infusion), from the group effect analysis.

b. n = 11.

Conclusions (In healthy subjects)

- 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.
- They exhibited similar disposition characteristics across all doses and rates of administration.
- C_{max} was achieved after 10 minutes, immediately after dosing.
- Volume of distribution averaged 0.6 L/kg for verteporfin. The volume of distribution was about 20-27% lower for BPD-MA_D regioisomer as compared to BPD-MA_C regioisomer.
- The total body clearance for verteporfin averaged 105 mL·h⁻¹·kg⁻¹ and the half life was between 5-6 hours for verteporfin as well as the regioisomers
- The disposition of BPD-MA_C enantiomers were stereospecific, where as the disposition of BPD-MA_D enantiomers was not stereospecific.

In patients with choroidal neovascularization (CNV)

The pharmacokinetics of verteporfin in patients with CNV was assessed in study number BPD OCR 001. However, blood sampling was not done to a sufficient time to determine the pharmacokinetic parameters. The primary objective of this study was to assess ocular safety of photodynamic therapy (PDT) using different drug-dose/light-dose regimens of

verteporfin and red light to treat CNV with subfoveal involvement and to get preliminary efficacy data. The secondary objective was to assess basic pharmacokinetic parameters of verteporfin following intravenous administration. The study will be described briefly and conclusions will be stated at the end of this section.

The drug dose used in the study was 6 mg/m² or 12 mg/m² administered over 5 or 10 minutes. These doses approximated to 0.15 or 0.30 mg/kg body weight respectively. Verteporfin was reconstituted with sterile water to give a concentration of 2 mg/ml. This required volume was further diluted to 30 ml with 5% dextrose in water.

Light activation was performed at 10 minutes after the start of a 5-minute infusion and at 15, 20 or 30 minutes after the start of 10-minute infusion of verteporfin. The initial light dose (50 J/cm² at an intensity of 600 mW/cm²) was used in this study and was administered 30 minutes after the start of the infusion. This timing was based on preclinical studies in primates that showed the optimal selectivity and effectiveness was between 20-50 minutes after the IV dose. Further, different light doses were evaluated to define the maximum tolerated light dose in a specific treatment regimen.

Verteporfin treatment regimens are shown in Table 3. Initial treatment was started with regimen 1, the other regimens were added in several amendments to the protocol after evaluating the results of regimen 1. It was felt that higher plasma concentration could be achieved by either shortening the time between verteporfin infusion and the time of light application (regimens 2, 4 and 5) or by doubling the verteporfin dose and applying light at the same time (regimen 3).

TABLE 3: Treatment regimens

Treatment Regimen	Verteporfin Dose ^a (mg/m ²)	Light Dose (J/cm ²)	Time of light application after start of infusion (mins)
1	6	50, 75, 100, 150	30
2	6	50, 75, 100, 150	20
3	12	50, 75, 100, 150	30
4	6	50, 75, 100	15
5	6 ^b	12.5, 25, 50	10

a Verteporfin was administered in 30 mL D5W and infused at a rate 3 ml/min (10-minute infusion)

b Verteporfin was administered in 30 mL D5W and infused at a rate 6 ml/min (5-minute infusion)

Patients were allowed more than one verteporfin treatment at intervals of 2 to 8 weeks. Increasing the drug and light dose was done sequentially and depended on the acceptable safety in the patients. The criteria for light dose escalation is presented in a flow diagram in the Appendix on page 6. Different treatment regimens were added to the protocol in various amendments to evaluate optimal therapy. The initial protocol had a plan for only treatment regimen 1.

A total of 142 patients (67F & 75M) participated in this study. Some patients received only one course of treatment, while the others received two or more. Patients who

received multiple courses of therapy were referred to as "retreated" (if they received a second course before the 12-week follow-up for the first course) or "re-enrolled" (if they completed the 12-week follow-up for the first course then re-enrolled into the study to receive additional courses). 100 patients received a single course and 42 received multiple treatments. 8 patients finished the follow up and re-enrolled. For retreatment, patients did not have to wait until completing the 12-week follow-up of their first course. Planned assessments for retreatment were at intervals of 4 weeks, but they varied sometimes from week 3 to week 8. The number of patients by course of therapy and regimen is attached in the Appendix on pages 7-9 along with the subject demographics.

Blood samples (5ml) were collected from selected patients in Regimens 1-3 predose and at 10, 20, 30, and 40 minutes after the start of the 10-minute infusion of verteporfin at either 6 or 12 mg/m². Blood samples were also collected from selected patients in Regimen 5 predose and at 5, 10, 20, 30, and 40 minutes after the start of a 5-minute infusion of verteporfin at 6 mg/m². The plasma concentrations of the two regioisomers of verteporfin were estimated at each sample time.

The mean plasma concentrations at the different sampling times are shown in Table 4. The individual subject plasma concentrations are attached in the Appendix on pages 10-20.

TABLE 4: Summary of Mean Plasma Concentration of Verteporfin After 5- or 10-Minute Infusions

Time After Start of Infusion (min)	Mean Plasma Concentration (µg Verteporfin/mL ± STD)					
	After 6 mg/m ²				After 12 mg/m ²	
	5-minute Infusion		10-minute Infusion		10-minute Infusion	
	n	Mean±STD	n	Mean±STD	n	Mean±STD
5	10	2.85±0.92	0	—	0	—
10	13	1.35±0.51	12	1.58±0.39	15	3.24±0.76
20	13	0.84±0.27	37	0.76±0.18	16	1.81±0.30
30	14	0.64±0.25	20	0.45±0.14	15	1.22±0.29
40	13	0.61±0.28	21	0.42±0.09	16	1.06±0.25

The mean plasma concentrations at the time of light administration in Regimens 1, 2, 3 and 5 (see Table 3 for light administration times) were approximately 0.45, 0.76, 1.22 and 1.35 µg/mL, respectively.

The following plasma concentration versus time curve displays the 5- and 10-minute infusions of verteporfin 6 mg/m² and the 10-minute infusion of verteporfin 12 mg/m².

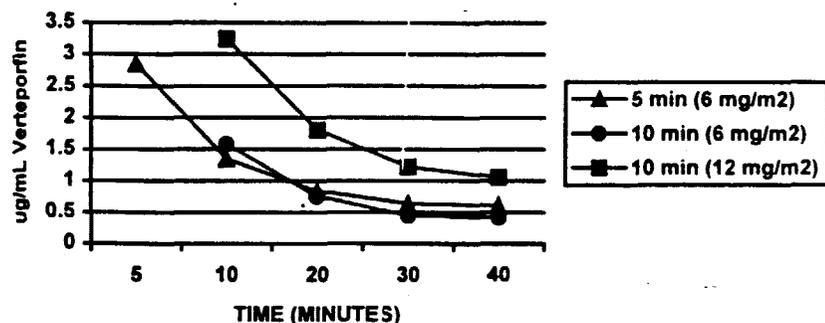


Figure: Mean plasma concentration profile of verteporfin in patients

Kinetic interpolation of the available plasma concentrations suggests that the verteporfin plasma concentration is approximately 1.2 $\mu\text{g}/\text{mL}$ when light is applied 15 minutes after the start of a 6 mg/m^2 verteporfin infusion (Regimen 4). This result is similar (1.22 $\mu\text{g}/\text{ml}$) to the plasma concentration measured when light is applied 30 minutes after the start of a 12 mg/m^2 verteporfin infusion (Regimen 3).

The plasma concentrations based on treatment regimens and the various light doses used in these regimens is tabulated in table 5.

TABLE 5: Summary of Mean Plasma Concentration of Verteporfin after 5 or 10 Minute Infusions, by Regimen and Light Dose

Time (mins)	Regimen 5			Regimen 1			
	5 minute infusion 6 mg/m^2 Light Dose (J/cm^2)			10 minute infusion 6 mg/m^2 Light Dose (J/cm^2)			
	12.5	25	50	50	75	100	150
5	1.15 n=1	3.05±0.87 n=5	3.03±0.67 n=4	n/a n/a	n/a n/a	n/a n/a	n/a n/a
10	0.99±0.41 n=3	1.64±0.62 n=4	1.34±0.42 n=6	n/a n=0	1.41±0.77 n=2	1.59±0.21 n=4	1.59±0.45 n=5
20	0.86±0.13 n=2	0.92±0.36 n=6	0.74±0.16 n=5	0.67±0.08 n=3	0.73±0.16 n=7	0.77±0.13 n=6	1.59±0.09 n=6
30	0.60±0.07 n=3	0.74±0.40 n=5	0.57±0.11 n=6	0.46±0.07 n=3	0.43±0.08 n=4	0.39±0.20 n=6	1.52±0.11 n=4
40	0.41±0.02 n=2	0.69±0.26 n=5	0.62±0.33 n=6	0.44±0.09 n=3	0.37±0.08 n=5	0.40±0.05 n=6	1.47±0.11 n=4

Time	Regimen 2				Regimen 3			
	10 minute infusion 6 mg/m ² Light Dose (J/cm ²)				10 minute infusion 12mg/m ² Light Dose (J/cm ²)			
	50	75	100	150	50	75	100	150
5	n/a n/a	n/a n/a	n/a n/a	n/a n/a	n/a n/a	n/a n/a	n/a n/a	n/a n/a
10	n/a n=0	n/a n=0	1.82 n=1	n/a n=0	2.60±0.46 n=2	3.04±0.34 n=2	3.30±0.92 n=8	3.62±0.43 n=3
20	0.56±0.28 n=3	0.81±0.43 n=2	0.77±0.13 n=7	0.91±0.27 n=3	1.78±0.37 n=3	1.46 n=1	1.80±0.28 n=9	1.99±0.36 n=3
30	n/a n=0	n/a n=0	0.57 n=1	n/a n=0	1.32±0.38 n=3	1.20±0.46 n=2	1.08±0.24 n=7	1.44±0.11 n=3
40	n/a n=0	n/a n=0	0.54 n=1	n/a n=0	1.04±0.39 n=3	0.91 n=1	1.01±0.23 n=9	1.26±0.09 n=3

The time of light application was 10, 30, 20 and 30 minutes, respectively for regimens 5, 1, 2 and 3. The sponsor has not evaluated all possible doses with different light timings. The regimens that looked promising in terms of efficacy were regimen 2 and 4, as we can see very few samples were taken for regimen 2 and none for regimen 4.

Conclusions (In patients)

- Plasma samples were taken only up to 40 minutes post infusion, hence the pharmacokinetic parameters of verteporfin in patients is unknown. Pharmacokinetic sampling was not done in the to-be-marketed dosage regimen for verteporfin and the light treatment. For comparison of data with previous study in healthy subjects see page 23 of this review.
- Kinetic extrapolation of the 40 minute profile showed that the mean plasma concentration when the light will be applied at 15 minutes post infusion for a 6 mg/m² dose of verteporfin will be 1.2 µg.ml

Reviewer's Comment

No information is available regarding the metabolite in patients. The enantiomeric ratios of the two regioisomers in patients was also not determined.

How was human dose for the treatment of age related macular degeneration selected?

A dose of 6 mg/m² was the lowest dose studied in the first human study in patients with basal cell carcinoma at an infusion of 45 minutes (this study will be described in the following section). Initially a light dose of 50 J/cm² was chosen based on studies in animals. The initial timing of light dose as 30 minutes after infusion was chosen based

preclinical studies in primates that showed optimal selectivity and effectiveness between 20-50 minutes. Other information regarding the optimal dose was based on study BPD OCR 001 (in patients with CNV).

The primate studies indicated that the dose of verteporfin and the timing of light application were very important for selective effects on CNV. The preclinical studies also showed that the higher the verteporfin dose, the later the light dose could be applied to obtain closure of the CNV lesion. The initial dose regimen (Regimen 1, see Table 3) in this study was a safe low verteporfin dose, light dose and time of light dose based on the primate data. Regimen 1 (light applied 30 minutes after the start of a 10-minute infusion of 6 mg/m² verteporfin) was safe up to light doses of 150 J/cm². However, the duration of effect on cessation of CNV fluorescein leakage was not achieved. It was not practical to increase the light dose (150 J/cm² required maintaining continuous light application to the retina for over 4 minutes at the intensity of 600 mW/cm² used in the study). The maximum well tolerated dose of light was 100 J/cm². Therefore, the sponsor looked at strategies to increase the plasma concentration of verteporfin and/or selectivity in the target tissue at the time of light administration and thereby increase the duration of the CNV effect seen initially in Regimen 1. In Regimens 2 and 4, light was applied earlier so the plasma concentration and concentration in the presumed target tissue (endothelial cells) was higher. This appeared to be successful. In Regimen 3, the verteporfin dose was doubled and the light was applied at the same time as in Regimen 1. This did not appear to be as effective and there were high progression rates for CNV leakage of fluorescein associated with poorer vision outcomes than Regimens 2 and 4. This may have been due to extravascular distribution of verteporfin at this later time leading to greater non-target tissue damage and resulting inflammatory reactions and cytokine production that promoted CNV reperfusion or new CNV proliferation. In Regimen 5, the rate of infusion of 6 mg/m² was doubled (5-minute infusion) and the light dose was applied earlier (at 10 minutes after the start of the infusion). Regimen 5 appeared to be less effective than Regimens 2 and 4 even at 50 J/cm². This may have been due to inadequate time for the distribution of the verteporfin from the blood into the endothelial cells.

The most promising treatment regimens were Regimens 2 and 4 in which light was applied 20 and 15 minutes, respectively, after the start of a 10-minute infusion of verteporfin. Overall, Regimen 4 tended to have slightly better results for CNV closure and visual acuity outcome than Regimen 2, but no statistical differences were found between these two regimens. Regimens 2 and 4 were associated with less leakage and/or less growth of the lesion beyond that seen at baseline than when light was applied 30 minutes after the start of the verteporfin infusion (Regimen 3). The reason for this observation is unclear, but the sponsor explains it as follows: at the later time it is expected that a greater proportion of the verteporfin will be in extravascular compartments. It is possible that greater photodynamic damage to extravascular compartments at these later times after dosing may initiate local inflammation and cytokine release which could lead to proliferative reactions and eventual recanalization of

the original lesion or growth of new CNV in the same location. Retreatments did not help to increase the persistence on CNV closure.

On the basis of these results it was considered acceptable to assess the long-term efficacy and safety using the lowest effective light dose established for Regimen 4 (verteporfin dose of 6 mg/m² and light dose of 50 J/cm² applied 15 minutes after the start of the 10-minute IV infusion).

Reviewer's Comment

Although the kinetic extrapolation showed that the plasma concentration of Regimen 4 (6 mg/m², 15 min light) was similar to the Regimen 3 (12 mg/m², 30 min light), yet they varied in effectiveness. This shows that the concentration at the effect site (i.e retina) is determinant of the response rather than the plasma concentration in this case.

Is the pharmacokinetics of verteporfin similar in healthy subjects and the patients with CNV?

The study in patients was not conducted with extensive plasma sampling (40 minutes in patients vs. 48 hours in the healthy subjects). Hence direct comparison with the pharmacokinetic parameters cannot be done. However, the initial time points from the study in healthy subjects and patients can be compared in the following Table 6.

TABLE 6: Verteporfin plasma concentrations in patients with choroidal Neovascularization and in healthy volunteers (Caucasians and Japanese)

Time After Start of Infusion (min)	Mean Plasma Concentration (µg Verteporfin/mL ± STD)					
	After 6 mg/m ² 10 minute infusion				After 6 mg/m ² 10 minute infusion	
	Healthy subjects Caucasians		Healthy Subjects Japanese		Patients	
	n	Mean±STD	n	Mean±STD	n	Mean±STD
10	12	1.10±0.29	8	1.32±0.14	12	1.58±0.39
20	12	0.48±0.13	8	0.56±0.09	37	0.76±0.18
30	12	0.32±0.11	8	0.34±0.10	20	0.45±0.14
40 or 45	12	0.27±0.07 ^a	8	0.30±0.05 ^a	21	0.42±0.09

^a 45 minutes in healthy subjects

When comparing the healthy Caucasians to the patients on the same dose, the patients had up to 30-40% higher concentrations in samples up to 45 minutes post infusion. Mean verteporfin concentrations across the three regimens studied in Study BPD OCR 001 and the Japanese and Caucasian subjects combined from study BPD PK 001A/B is shown in the Table 7.

TABLE 7: Verteporfin Plasma Concentrations in Patients with Choroidal Neovascularization and in Healthy Volunteers (All subjects)

Time After Start of Infusion (min)	Verteporfin (BPD-MAC+D) Plasma Concentration (µg/mL)										
	Study BPD OCR 001						Studies BPD PK 001A/B				
	12 mg/m ² dose			6 mg/m ² dose			6 mg/m ² dose			6 mg/m ² dose	
	10-minute Infusion			5-minute Infusion			10-minute Infusion			10-minute Infusion	
	n	Mean (CV)	n	Mean (CV)	n	Mean (CV)	n	Mean (CV)	n	Mean (CV)	
5	—	—	10	2.85 (32%)	—	—	—	—	—	—	
10	15	3.24 (23%)	13	1.35 (38%)	12	1.58 (25%)	19	1.25 (21%)	19	1.25 (21%)	
15	—	—	—	—	—	—	20	0.76 (23%)	20	0.76 (23%)	
20	16	1.81 (17%)	13	0.84 (32%)	37	0.76 (23%)	20	0.51 (24%)	20	0.51 (24%)	
30	15	1.22 (24%)	14	0.64 (38%)	20	0.45 (30%)	19	0.33 (32%)	19	0.33 (32%)	
40	16	1.06 (23%)	13	0.61 (45%)	21	0.42 (21%)	—	—	—	—	
45	—	—	—	—	—	—	19	0.28 (24%)	19	0.28 (24%)	

The plasma concentration profile comparing the healthy subjects and patients with CNV is shown in the following figure.

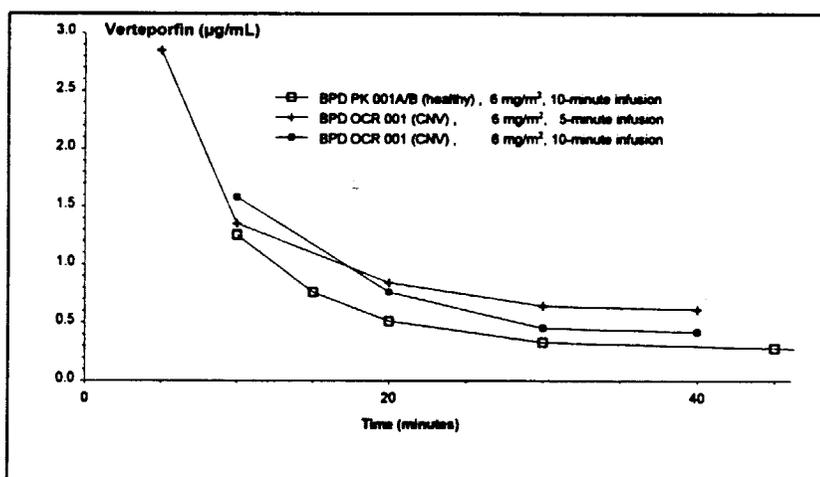


Figure: Plasma concentration profile of verteporfin in patients and healthy volunteers

During the first 45 minutes following verteporfin infusion, elderly patients with choroidal neovascularization (BPD OCR 001 study) have higher plasma verteporfin concentrations (20-30%) compared to young healthy Japanese and Caucasian subjects combined (BPD PK 001A/B studies). For example, when the 6 mg/m² dose was infused over a 10-minute period, mean concentration at the end of the infusion was 1.58 µg/mL (range 0.86 to 2.38 µg/mL) for patients with choroidal neovascularization, compared with 1.25 µg/mL (range 0.37-1.68 µg/mL) for combined data for healthy Caucasian and Japanese subjects. Patients with choroidal neovascularization (CNV) were much older than the healthy volunteers (mean age 76 and 25 years respectively). The age difference may have contributed to the slightly higher exposure in CNV patients. The target

population is the elderly subjects only. Therefore, the difference seen may not be clinically significant.

Conclusions

- No meaningful differences were observed in the pharmacokinetics of verteporfin in patients with CNV compared to the healthy subjects, since these differences could be either due to age or the disease. Hence, is not a robust comparison of the data.

In patients with Skin Cancer

This study was the first human study of verteporfin. The objectives of this Phase I/II study were to evaluate the systemic toxicity of verteporfin, to evaluate PDT-induced skin reaction in the peritumoral area, to estimate the duration of normal skin photosensitivity to broad spectrum light after verteporfin infusion, to determine the pharmacokinetic profile of verteporfin, and to assess the potential efficacy of PDT (with various combinations of verteporfin and 690 nm light) in treating cutaneous lesions.

This study, though not for the indication for this current application was reviewed to determine the pharmacokinetic profile (up to 96 hours). The duration of infusion was longer in this study and the doses used were also higher than that proposed for the treatment of age related macular degeneration.

This was an open-label, ascending-dose study with various combinations of verteporfin and light doses. In the protocol, ascending drug doses of 0.25, 0.50, and 0.70 mg/kg and light doses of 50, 100, and 150 J/cm² at 690 nm wavelength were planned. However, upon reaching 0.5 mg/kg verteporfin + 50 J/cm² of light, a Grade-4 skin reaction in the peritumoral area was observed in 2 out of 3 patients and drug escalation was terminated. Subsequent patients were given lower drug doses. At the end of the study, twelve drug-light combinations involving 6 drug doses (0.15, 0.20, 0.25, 0.30, 0.375, and 0.50 mg/kg, equal to approximately 6, 8, 10, 15 and 20 mg/m² respectively and 6 light doses (25, 50, 75, 100, 125, and 150 J/cm²) were used. Time for light applications was between 1.5 and 6 hours post the start of drug infusion. A minimum of 7 days was required before escalation to a new level of drug. Patients had to have at least 1 cutaneous lesion caused by metastatic disease, basal cell carcinoma or squamous cell carcinoma. Each patient was to receive a single drug-light dose on all lesions. Patients were followed for 3 months. Blood was drawn for pharmacokinetic analysis at various times between 0 and 96 hours post drug infusion. The summary of number of subjects exposed to a drug and light dose is attached in the Appendix in Table 5 on page 22.

Verteporfin for injection was supplied in 25 mg vials. To reconstitute, 12 mL of sterile water was added for a total volume of 12.5 mL (i.e., 2 mg/mL) of reconstituted drug. The desired drug concentrations were prepared by further diluting the reconstituted drug in 5%

dextrose-water (D5W). Each patient was to receive drug in a total volume of 100 mL. Verteporfin was injected intravenously with an infusion pump at a rate of 1 mL/min for the first 10 minutes and then the infusion rate was increased to 3 mL/min if vital signs were stable until the bag containing verteporfin was emptied (about 35 minutes). The infusion lines were then flushed with D5W at a rate of 3 mL/min to give a total infusion time of 45 minutes.

Pharmacokinetic data are available for 21 patients who received single intravenous drug doses of 0.15, 0.20, 0.25, 0.375 or 0.50 mg/kg (or 6, 8, 10, 15 and 20 mg/m² respectively). Of the 21 patients who provided plasma samples for pharmacokinetic analysis, one patient provided two sets of samples after receiving two different doses (0.50 and 0.15 mg/kg) more than a year apart. Therefore, 22 sets of plasma samples were included in the analyses. Since PK data was available from 8 patients receiving 0.25 mg/kg of verteporfin, the amendment specified that no further PK sampling would be done at this drug dose. Because of the occurrence of Grade-4 local peritumoral PDT-induced skin reactions in Patients 10, 11, 12, and 13, who had received 0.50 mg/kg or 0.375 mg/kg of verteporfin, the amendment suggested that the drug dose not be further increased, but be kept at 0.25 mg/kg and increase the light dose to 150 J/cm².

Plasma was collected and assayed for the two regioisomers of verteporfin, BPD-MA_C (CL 315,555) and BPD-MA_D (CL 315,585). The results were used to determine the pharmacokinetic parameters of the two analytes and their sum. Data past 24.75 hour sampling time was below the quantifiable level in all patients except for one single value, therefore this data was not included in the pharmacokinetic calculations. The protocol required that 2 urine samples be collected from each patient at 0-12 hours and 12-24 hours for pharmacokinetic analysis. But, no analysis of samples was performed due to the insensitivity of the assay for urine samples. Analysis of verteporfin in plasma was not performed on samples collected after 24 hours. Initially, each patient was to receive only one drug and light dose combination. As the study progressed, some patients were given one drug dose but were exposed to two light doses at different treatment fields. Based on this analysis of the results based on treatment regimen would be difficult.

First, the analyses based on the sum of the two regioisomers will be summarized based on the applicant's analyses, which will be followed by individual discussion of each regioisomer.

Noncompartmental analyses of verteporfin (sum of BPD-MA_C and BPD-MA_D)

The figure below shows the mean plasma concentration of verteporfin at each sampling time in a semi-log scale.

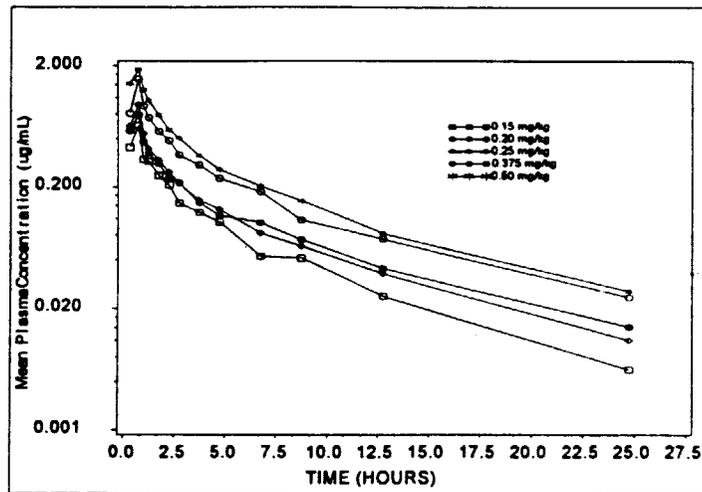


Figure: Mean plasma verteporfin concentrations

The mean derived pharmacokinetic parameters are tabulated below in Table 8.

TABLE 8: Mean Pharmacokinetic Data for Verteporfin

No. of Patients	Drug Dose (mg/kg)	C_{max}		AUC_{0-24}		AUC_{0-12h}		$T_{1/2}$		V_{ss}		CL	
		($\mu\text{g/mL}$)	SD	($\mu\text{g}\cdot\text{hr/mL}$)	SD	($\mu\text{g}\cdot\text{hr/mL}$)	SD	(hr)	SD	(L/kg)	SD	(mL/hr/kg)	SD
2 ^a	0.15	0.68	0.24	1.81	0.71	2.27	0.13	5.46	0.51	0.35	0.00	66.26	3.90
6	0.20	0.79	0.14	2.40	0.59	2.51	0.66	5.79	1.00	0.51	0.14	85.40	27.0
8	0.25	0.97	0.09	2.38	0.55	2.49	0.60	5.12	1.31	0.52	0.03	105.8	26.3
2	0.38	1.56	0.04	4.26	0.40	4.48	0.49	6.25	0.77	0.53	0.03	84.16	9.25
3	0.50	1.87	0.47	5.53	1.28	5.77	1.39	5.94	0.23	0.50	0.11	90.14	21.6

^a For C_{max} and AUC_{0-24} , No. of Patients = 3.

From the table we can see that the mean apparent elimination half life ranged from 5.12 to 6.25 hours, without a definite trend as a function of dose. The clearance appears to be in similar across the dose range studied, suggesting absence of dose dependent kinetics, although at 0.15 mg/kg dose it is lower. The proportionality was more evident from C_{max} and from AUC parameters, which is discussed in the dose proportionality section of the review.

Non-Compartmental Analysis of Regioisomer BPD-MA_C

TABLE 9: Mean Pharmacokinetic Data for BPD-MA_C

No. of Patients	Drug Dose (mg/kg)	C _{max}		AUC ₀₋₂₄		AUC _{0-∞}		T _{1/2}		V _{ss}		CL	
		(µg/mL)	SD	(µg•hr/mL)	SD	(µg•hr/mL)	SD	(hr)	SD	(L/kg)	SD	(mL/hr/kg)	SD
3	0.15	0.26	0.08	0.92	0.35	1.00	0.33	6.71	1.08	0.56	0.14	82.94	34.26
7	0.20	0.31	0.05	1.24	0.27	0.35	0.32	7.34	1.14	0.64	0.18	78.15	22.01
8	0.25	0.38	0.04	1.23	0.28	0.32	0.31	5.59	1.75	0.64	0.06	99.69	25.80
2	0.38	0.63	0.02	2.16	0.20	2.29	0.27	6.24	1.05	0.57	0.04	82.36	9.81
3	0.50	0.76	0.20	2.83	0.88	3.00	1.01	6.28	0.97	0.57	0.14	90.28	32.17

BPD-MA_C exhibits similar very similar distribution and disposition kinetics within the range of doses studied. The AUC parameter shows a small deviation from linearity in the 0.20 to 0.25 mg/kg dose range.

Non-Compartmental Analysis of Regioisomer BPD-MA_D

Similar to BPD-MA_C, the regioisomer BPD-MA_D shows similarity among doses studied for the distribution and disposition parameters. The mean pharmacokinetic parameters are shown in the following table.

TABLE 10: Mean Pharmacokinetic Data for BPD-MA_D

No. of Patients	Drug Dose (mg/kg)	C _{max}		AUC ₀₋₂₄		AUC _{0-∞}		T _{1/2}		V _{ss}		CL	
		(µg/mL)	SD	(µg•hr/mL)	SD	(µg•hr/mL)	SD	(hr)	SD	(L/kg)	SD	(mL/hr/kg)	SD
3	0.15	0.41	0.15	1.07	0.63	1.15	0.69	3.64	0.14	0.28	0.18	84.64	51.56
7	0.20	0.48	0.09	1.10	0.35	1.18	0.35	5.06	1.52	0.42	0.13	92.30	32.51
8	0.25	0.60	0.05	1013	0.30	1.20	0.31	4.73	1.45	0.43	0.05	109.91	27.87
2	0.38	0.94	0.06	2.10	0.19	2.19	0.22	6.26	0.40	0.48	0.01	85.96	8.51
3	0.50	1.11	0.29	2.70	0.42	2.78	0.43	5.68	0.33	0.43	0.10	91.39	13.09

An average elimination half life of 5 hours was observed except for the lowest dose (0.15mg/kg). This could be due to plasma samples being detected for only up to 12.5 hours as compared to 25 hours in the other cases. The mean pharmacokinetic profiles are attached in the Appendix on pages 23-24. The C_{max} exhibits a linear ($r^2=0.799$, $p<0.001$) and proportional increase with the dose. For AUCs, the linear dose-parameter value relationship is similar ($r^2=0.797$, $p<0.001$), with almost no change between the 0.20 and 0.25 mg/kg doses.

Comparison of the Non-Compartmental Analysis of BPD-MA_C and BPD-MA_D

Comparison of the two regioisomers reveal that their initial maximal plasma concentrations differ: the BPD-MA_C regioisomer being consistently lower than the BPD-MA_D counterpart. Animal pharmacokinetics showed a similar trend. For regioisomer BPD-MA_D, the initial concentrations are higher but the distribution and elimination are apparently faster, resulting

in a lower $AUMC_{0-inf}$ than for regioisomer BPD-MA_C. Similar trends were also seen in Study BPD PK 001A/B in Caucasian and Japanese healthy subjects. The volume of distribution was slightly different (being more for BPD-MA_C regioisomer). The total body clearance was the same among the two regioisomers.

Compartmental Analysis of BPD-MA_C and BPD-MA_D

The sponsor has also conducted compartmental analysis using NLIN of SAS. The plasma concentration versus time profiles of BPD-MA_C and BPD-MA_D were best described by a two-compartment model with intravenous administration and elimination from the central compartment. The sponsor has provided the output of the analysis of each patient. At all doses investigated, the maximal plasma concentration were generally observed at the end of the infusion and followed by a rapid decrease of the plasma concentration (alpha half-life ranging from 0.25 to 0.57 hours for BPD-MA_C and 0.40 to 0.58 hours for BPD-MA_D). After approximately 2-3 hours, the disposition of BPD-MA_C and BPD-MA_D had an apparent beta half-life of 5.33 to 6.32 hours and 4.57 to 5.72 hours respectively and were independent of the dose. The mean elimination half-lives obtained by non-compartmental analysis and the beta half-life obtained by the compartmental method of estimation were similar.

MULTIPLE DOSE STUDIES

Are the multiple dose pharmacokinetics predicted from single dose pharmacokinetics?

Verteporfin for injection is to be used as a single dose. Treatment can be repeated after 3 months if needed. Hence, the assessment of verteporfin pharmacokinetics after multiple doses is not necessary in this situation. The plasma concentrations of verteporfin are below the limit of quantitation after 24 hours post the start of infusion.

Are the pharmacokinetics of verteporfin linear?

Dose proportionality was evaluated in Study BPD PK 0011B (Japanese study), which studied 3 dose levels (3, 6 and 14 mg/m² in a 10 minute infusion). Dose proportionality was evaluated by regression analysis, graphical method and analysis of variance following dose normalization of pharmacokinetic parameters depicting exposure (AUC and C_{max}) at all doses studied (3, 6 and 14 mg/m²). Dose-adjusted pharmacokinetic parameters are presented in Table 11 and a linear regression analysis of dose proportionality is presented in Table 12.

As seen in the previous sections of the review (Disposition of verteporfin), the distribution and elimination kinetics remained unchanged across the doses, with a half-

life of about 5-6 hours and a volume of distribution of 0.5-0.6 L/kg. The total body clearance was between 84.5-113.3 mL.h⁻¹.kg⁻¹ across different dose groups. These differences were not statistically significant. SAS-GLM statistical outputs for the assessment of group effect have been provided.

The dose normalized pharmacokinetic parameters along with the ANOVA results for testing differences among groups is shown in the following Table 11. From the ANOVA results we can see a linear and dose proportional relationship across the dose levels. The p-values show no statistical differences, but there is a trend towards increased exposure at the 14 mg/m² dose level.

TABLE 11: Dose-Adjusted Pharmacokinetic Parameters – Study 001B

Normalized Pharmacokinetic Parameters ^a	Mean (Coefficient of Variation) – Study B (Japanese) Only			P value ^b
	3 mg/m ² 10-min Infusion (n=8)	6 mg/m ² 10-min Infusion (n=8)	14 mg/m ² 10-min Infusion (n=8)	
BPD-MAC				
AUC _{0-t} (µg·h/mL) / (mg/m ²)	0.138 (27%)	0.148 (15%)	0.181 (26%)	.074
AUC _{inf} (µg·h/mL) / (mg/m ²)	0.149 (25%)	0.153 (15%)	0.184 (26%)	.153
C _{max} (µg/mL) / (mg/m ²)	0.089 (17%)	0.092 (11%)	0.090 (20%)	.869
BPD-MAD				
AUC _{0-t} (µg·h/mL) / (mg/m ²)	0.134 (31%)	0.135 (20%)	0.168 (31%)	.195
AUC _{inf} (µg·h/mL) / (mg/m ²)	0.145 (28%)	0.139 (19%)	0.170 (31%)	.289
C _{max} (µg/mL) / (mg/m ²)	0.131 (15%)	0.128 (11%)	0.133 (20%)	.867
Verteporfin (BPD-MAC+D)				
AUC _{0-t} (µg·h/mL) / (mg/m ²)	0.276 (28%)	0.284 (16%)	0.351 (28%)	.132
AUC _{inf} (µg·h/mL) / (mg/m ²)	0.292 (25%)	0.292 (16%)	0.353 (28%)	.204
C _{max} (µg/mL) / (mg/m ²)	0.220 (15%)	0.220 (11%)	0.224 (18%)	.969

- a. Normalized by dividing the parameter by the dose in mg/m².
b. One way ANOVA for a difference among groups

Dose proportionality based on linear regression analysis is shown in Table 11.

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TABLE 11: Dose-Proportionality Linear Regression Analysis – Study 001B

Pharmacokinetic Parameters ^a	R ²	Slope		P value ^b
		Parameter Estimate	Standard Error	
BPD-MAC				
AUC _{0-t} (µg·h/mL) / (mg/m ²)	.855	0.196	0.017	<.001
AUC _{inf} (µg·h/mL) / (mg/m ²)	.853	0.196	0.017	<.001
C _{max} (µg/mL) / (mg/m ²)	.894	0.090	0.007	<.001
BPD-MAD				
AUC _{0-t} (µg·h/mL) / (mg/m ²)	.805	0.181	0.019	<.001
AUC _{inf} (µg·h/mL) / (mg/m ²)	.805	0.181	0.019	<.001
C _{max} (µg/mL) / (mg/m ²)	.896	0.135	0.010	<.001
Verteporfin (BPD-MAC+D)				
AUC _{0-t} (µg·h/mL) / (mg/m ²)	.833	0.377	0.036	<.001
AUC _{inf} (µg·h/mL) / (mg/m ²)	.832	0.376	0.036	<.001
C _{max} (µg/mL) / (mg/m ²)	.911	0.225	0.015	<.001

a. Units are for the slope parameter estimates and standard error.

b. P value for the null hypothesis: slope parameter estimate = 0

Dose proportionality was also evaluated from Study BPD 001 (skin cancer patients). The doses studied were 0.15, 0.20, 0.25, 0.375 and 0.50 mg/kg (equivalent to 6, 8, 10, 15 and 20 mg/m² respectively). The mean AUC parameter deviates from linearity between the 0.20 (8 mg/m²) and 0.25 mg/kg (10 mg/m²) doses. Dose proportionality based on dose normalized AUC₀₋₂₄ has been shown in the following figure.

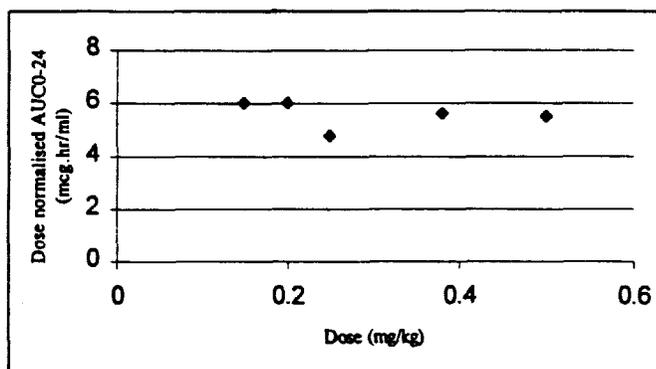


Figure: Dose proportionality based on AUC₀₋₂₄ in patients with skin cancer

Correlation analysis of the C_{max} and AUC parameters also shows the linearity of dose-parameter relation (r² of 0.815, p<0.001, and 0.757, p<0.001, respectively).

Conclusions

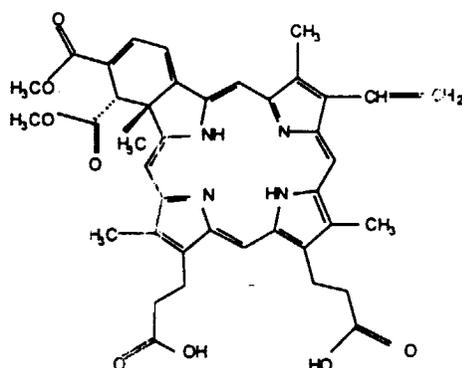
- Verteporfin pharmacokinetics were linear in the range of 3-14 mg/m² based on statistical analysis, but there is a trend towards increased exposure at 14 mg/m² dose (study BPD PK 001B).

- The volume of distribution, clearance and half-life parameters were similar across dose groups.
- Verteporfin kinetics were also shown to be linear in the range of 6-20 mg/m² in a study on skin cancer patients.
- Because of the low BPD-DA concentrations at all doses, the dose proportionality analysis for the metabolite was not done.

Metabolism

- | |
|---|
| <ul style="list-style-type: none"> • Is verteporfin metabolized? • If yes, then what is the enzymatic pathway of metabolism? • Is the metabolite(s) active? |
|---|

Yes, the benzoporphyrin monoacid (verteporfin) is metabolized to the diacid (BPD-DA) through esterases.



BPD-DA (Diacid metabolite)

In-vitro studies:

Using liver slices, S9 fraction and liver microsomes:

An in vitro metabolism study was undertaken to determine the extent of NADPH-dependent and NADPH-independent metabolism of BPD-MA (verteporfin) by human liver S9 supernatant and microsomes². Commercially available human liver 9000g supernatant (S9) and human liver microsomes (HLM) were used for this experiment. Verteporfin for Injection was used for the incubations, which were carried out in the presence and the absence of NADPH. In addition, the formation of conjugates was also tested by the further addition of UDPGA and PAPS to the incubation medium. Samples

² Patten CJ. Metabolism of BPD-MA (verteporfin) by human liver S9 and microsomes. QLT report PK-98002, 1998.

were collected prior to reaction initiation and at various time points after initiation of the reaction (incubation of 2 hours). The samples were analyzed by HPLC for the quantitative determination of the two structural isomers of verteporfin (BPD-MA_C and BPD-MA_D) and their main metabolite, BPD-DA. Positive controls for NADPH-mediated metabolism, glucuronic acid conjugation, sulfoconjugation and esterase metabolism were also tested in the experimental conditions used for verteporfin.

These results suggest that NADPH-dependent enzymes (such as cytochrome P450 isozymes) do not appear to play a significant role in the disposition of verteporfin when active esterase metabolism is present. Likewise, conjugation of BPD-MA_C, BPD-MA_D or BPD-DA does not seem to occur. Metabolism is apparently carried out uniquely by esterases.

The metabolite is active although 4-5 fold less potent than the parent. These in vitro studies have been reviewed by Dr. Susan Wilson (Pharmacologist).

Reviewer's Comment

The sponsor has not formally determined the enzyme induction/inhibition properties of verteporfin. However, the large interval between doses (3 months) and the short half-life (~5 hours) would only result in transient and short lived effects on drug disposition, if any.

In-Vivo Studies:

The metabolite was evaluated in only one study in the NDA (Study BPD 001A and B). The details of the study design has been discussed in the previous section of this review. The limit of quantitation of the detection of the metabolite BPD-DA was 2 ng/ml.

Mean plasma BPD-DA concentrations for every dose and rate of administration studied (3, 6 and 14 mg/m²), were low at all times, even immediately post-dose (C_{max} range was 0.00-0.21 µg/mL in Caucasian subjects and 0.00-0.06 µg/mL in Japanese subjects). Small concentrations of BPD-DA were detected up to 48 hours postdose in Caucasian subjects and up to 36 hours postdose in Japanese subjects. Because of the extremely low plasma BPD-DA concentrations, no consistent concentration profile was apparent and no definite relation between the BPD-DA concentrations and the verteporfin dose levels was observed. The mean plasma concentration profile for BPD-DA in Japanese and

Caucasian subjects is attached in the Appendix on page 26. Looking at individual plasma concentration profiles for each subject, it interesting to note the trends in the profile of Caucasian and Japanese subjects. All Caucasian subjects showed a peak ranging between 1-8 hours, with 1 hour being the peak in majority of the subjects. The Japanese showed a peak ranging from 3-12 hours, with 12 hours being the peak in majority of the subjects. The shows the variability in the rates of hydrolysis of verteporfin to form the metabolite and also possibly due to the racial difference in the presence of the esterases.

The sponsor has calculated the pharmacokinetic parameters of the metabolite as well, as seen in Table 13. However, these numbers should be interpreted with caution due to the small number of observation and also the high variability of the concentrations. Based on the calculations the exposure of BPD-DA is approximately 5-10% of the exposure of verteporfin.

TABLE 13: Plasma Pharmacokinetic Analysis for the Main Verteporfin Metabolite

Pharmacokinetic Parameters	BPD-DA – Mean (Coefficient of Variation)					
	Study BPD PK 001A – Caucasian ^a			Study BPD PK 001B – Japanese ^a		
	6 mg/m ² 10-min inf. (n=12)	14 mg/m ² 10-min inf. (n=12)	6 mg/m ² 1.5-min bol. (n=8)	3 mg/m ² 10-min inf. (n=8)	6 mg/m ² 10-min inf. (n=8)	14 mg/m ² 10-min inf. (n=8)
AUC _{0-t} (µg·h/mL)	0.07 (78%)	0.19 (81%)	0.10 (91%)	0.09 (77%)	0.06 (128%)	0.28 (41%)
AUC _{inf} (µg·h/mL)	—	0.17 ^b (19%)	0.22 ^c —	0.28 ^c —	0.04 ^d (7%)	0.32 (45%)
C _{max} (µg/mL)	0.01 (53%)	0.04 (146%)	0.04 (162%)	0.01 (35%)	0.01 (56%)	0.03 (60%)
t _{max}	4.01 (91%)	1.26 (141%)	1.82 (179%)	9.04 (61%)	3.93 (213%)	6.47 (92%)
K _{el} (1/h)	—	0.08 ^b (35%)	0.09 ^c —	0.04 ^c —	0.18 ^d (7%)	0.06 (20%)
t _{1/2} (h)	—	10.2 ^b (42%)	7.94 ^c —	18.8 ^c —	3.89 ^d (7%)	11.8 ^e (20%)

Data from the BPD PK 001A/B clinical study report.

^a Four female subjects in each of the Caucasian groups. Japanese subjects are all men.

^b n=7

^c n=1

^d n=2

^e n=4

Reviewer's Comment

The evaluation of metabolite BPD-DA in patients was not conducted. In the healthy volunteers the amount of metabolite was 5-10% of the exposure to the parent compound. The patient population for age related macular degeneration would be elderly. The level of esterases is lower in the elderly subjects. Hence, the amount of metabolite in the patient population should be lower. However, the amount of parent of in the patients (being mostly elderly) would be higher in this case. And this is what was actually observed.

Conclusions

- Verteporfin is hydrolyzed through esterases to form the Diacid metabolite (BPD-DA).

- The metabolite is 4-5 fold less active than the parent drug.
- CYP-P450 induction and inhibition properties, though not evaluated, is unlikely to be of significance in the dosing regimen for verteporfin.
- The exposure of BPD-DA is approximately 5-10% of the exposure of verteporfin.

Excretion

How is Verteporfin excreted?

Verteporfin is mainly eliminated in the bile as unchanged drug. This has been studied in radiolabeled mass balance experiments conducted in rats^{3,4}, which indicated that approximately 90% is eliminated by the liver (biliary excretion). Drug related radioactivity was eliminated rapidly during the first 48 hours in the feces. 7 days after dosing the percent recovered in the feces was 90.3%. Urinary excretion was less than 1%. The total recovered radioactivity was 94.5% of the injected dose.

The renal excretion of verteporfin, its isomers and the metabolite is minimal. The sponsor has evaluated the urinary excretion of the isomers of verteporfin and its metabolite in Study BPD PK 001 A and B (a study in Caucasians and Japanese). The urine was collected for 72 hours following dosing in these studies. The limit of detection of the isomers and its metabolite in urine was 0.0005 µg/ml. Either very low concentrations or absence of both verteporfin regioisomers (BPD-MA_C and BPD-MA_D) and of BPD-DA were observed during the 0-6-hour and 6-12-hour periods, despite the high sensitivity of the assay.

For BPD-MA_C, minimal concentrations in urine above the quantifiable limit were reached in only 6 Caucasian and 7 Japanese subjects during the 0-6-hour period (range of concentrations above quantifiable limit: 0.001-0.002 µg/mL), and in 1 Caucasian subject during the 6-12-hour period.

For BPD-MA_D, all samples assayed were below the quantifiable limit.

For BPD-DA, minimal concentrations in urine above the quantifiable limit were reached in only 6 Caucasian and 7 Japanese subjects during the 0-6-hour period, and in 12 Caucasian and 12 Japanese subjects during the 6-12-hour period (range of concentrations above quantifiable limit: 0.001-0.004 µg/mL).

Therefore, cumulative urine excretion was calculated only from 0 to 12 hours (CUE₀₋₁₂) instead of the 72-hour period originally planned. Mean values for CUE₀₋₁₂ were minimal and for several subjects, no urine excretion was detected. The combined excretion of

³ Excretion and mass balance of radioactivity following single i.v. administration of 4 mg/kg 14C BPD-MA in rat, QLT report PH-011090, 1990

⁴ Excretion and mass balance of radioactivity following single i.v. dose in rat, QLTV reference TX-94038

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. Because of these low concentration values, no enantiomeric ratios in urine were calculated. The urinary excretion data for the Caucasians and the Japanese is provided in the Appendix on pages 27-34.

As seen in the table showing the pharmacokinetic parameters on page 13, the half-life of verteporfin is approximately 5-6 hours.

Conclusions

- 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·h⁻¹·kg⁻¹.
- Rat experiments show that about 90% of verteporfin dose was excreted as unchanged drug through the liver.

Reviewer's Comment

The sponsor has not conducted any mass balance study in humans for evaluating the excretion of verteporfin. Fecal excretion of verteporfin was also not evaluated in any study. Animal experiments show that it is primarily excreted by the bile. However, it seems logical that it would be quite likely eliminated in the bile based on its high molecular weight of 718.814 and its polar nature due to hydrolysis of the ester group to form the diacid.

SPECIAL POPULATION

Effect of Gender

In healthy subjects

The effect of gender was evaluated in study BPD PK 001A, which was conducted in Caucasian men and women. The different dose groups studied were: 6 mg/m² with 10 minute infusion (8M & 4M), 14 mg/m² with 10 minute infusion (8M & 4W) and 6mg/m² with 1.5 minute bolus injection (4M & 4W). The plasma concentration profiles in these groups based on the gender in each dosage regimen is shown in the following figure.

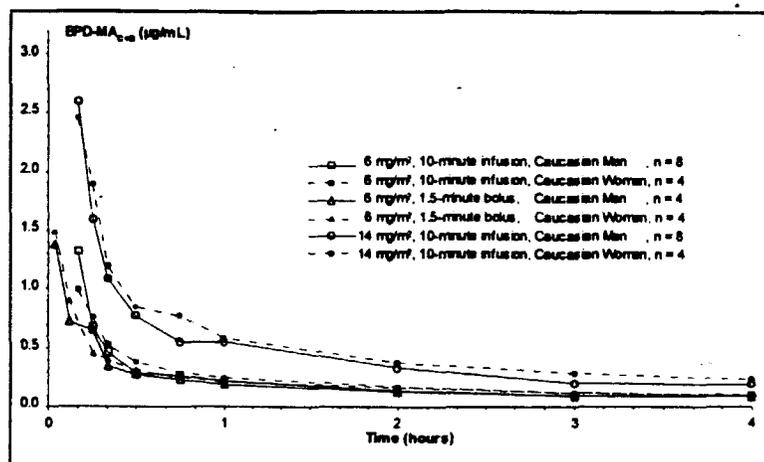


Figure: Linear plot of mean verteporfin concentrations in healthy Caucasians men and women

The semilogarithmic plot showing the profile from 0-24 hours is attached in the Appendix on page 35.

The gender comparison in the pharmacokinetic parameters is shown in the Table 14.

TABLE 14: Gender Pharmacokinetic Comparison – Study A only

Pharmacokinetic Parameters	Gender	6 mg/m ² 10-min infusion			14 mg/m ² 10-min infusion			6 mg/m ² 1.5-min Bolus			Gender Effect P values ^b	Gender by Dose Group Interaction P values ^b
		Men: n=8 / Women: n=4			Men: n=8 / Women: n=4			Men: n=4 / Women: n=4				
		Mean ^a	(CV) ^a	P value ^a	Mean ^a	(CV) ^a	P value ^a	Mean ^a	(CV) ^a	P value ^a		
Verteporfin (BPD-MAC+D)												
AUC _{0-t} (µg·h/mL)	Men	1.49	(23%)		3.21	(24%)		1.24	(29%)		.013 ^c	.550 ^c
	Women	1.69	(16%)	(.214 ^e)	3.70	(6%)	(.324 ^e)	1.73	(21%)	(.004 ^e)	(.899 ^d)	(.033 ^d)
AUC _{inf} (µg·h/mL)	Men	1.56 ^f	(22%)		3.25	(24%)		1.28	(28%)		.019 ^c	.543 ^c
	Women	1.74	(17%)	(.256 ^e)	3.72	(6%)	(.408 ^e)	1.76	(21%)	(.007 ^e)	(.856 ^d)	(.054 ^d)
C _{max} (µg/mL)	Men	1.23	(27%)		2.45	(51%)		1.40	(7%)		.938 ^c	.860 ^c
	Women	1.09	(21%)		2.54	(39%)		1.49	(20%)			
CL (mL·h ⁻¹ ·kg ⁻¹)	Men	97.4 ^f	(19%)	.986	115.0	(20%)	.715	142.4	(24%)	.007	.049	.078
	Women	97.2	(19%)	(.352 ^e)	109.9	(9%)	(.505 ^e)	95.2	(26%)	(.004 ^e)	(.596 ^d)	
V _{ss} (L/kg)	Men	0.64 ^f	(43%)		0.67	(31%)		0.66	(27%)		.383	.905
	Women	0.61	(21%)		0.56	(17%)		0.60	(5%)			
t _{max} (h)	Men	0.18	(17%)	.694 ^c	0.20	(23%)	.448 ^c	0.09	(124%)	1.00 ^c		
	Women	0.19	(22%)		0.18	(10%)		0.04	(22%)			
K _{el} (1/h)	Men	0.13 ^f	(27%)	.930	0.13	(11%)	.410	0.16	(25%)	.042	.404	.101
	Women	0.13	(25%)		0.14	(13%)		0.12	(21%)			(.553 ^d)
t _{1/2} (h)	Men	5.97 ^f	(43%)		5.55	(11%)		4.43	(24%)		.756	.329
	Women	5.62	(28%)		4.98	(11%)		5.89	(19%)			

- Arithmetic means, coefficient of variation, and gender effect P values for each individual dose group (when the gender by dose group interaction was significant: P<.200).
- ANOVA with gender, dose group, and gender by dose group as factors, except for t_{max} (Wilcoxon test).
- P values for C_{max} and AUC calculated from log-transformed data. P value for t_{max} (gender only) calculated using the Wilcoxon test.
- P values for which statistical significance changed after addition of body weight as a covariate to the ANOVA analysis.
- Gender effect P values for individual dose groups derived from the ANCOVA model with body weight as a covariate.
- n = 11.

Gender effect on all parameters except t_{max} was assessed by the sponsor using an analysis of variance (ANOVA) with gender, dose group and gender-by-dose group interaction or

an analysis of covariance (ANCOVA) with an added covariate, body weight or body mass index (BMI). The t_{max} was analyzed by a Wilcoxon rank-sum test. While BMI had little contribution to the variation of any of the parameters studied, body weight contributed significantly ($P < .050$) to the variations of AUC, CL and Kel.

The gender difference analysis based on the individual isomers is shown in the following Table 15.

TABLE 15: Gender pharmacokinetic comparison for the regioisomers

Pharmacokinetic Parameters	Gender	6 mg/m ² 10-min Infusion			14 mg/m ² 10-min Infusion			6 mg/m ² 1.5-min Bolus			Gender Effect P values ^b	Gender by Dose Group Interaction P values ^b
		Men: n=8 / Women: n=4		P value ^a	Men: n=8 / Women: n=4		P value ^a	Men: n=4 / Women: n=4		P value ^a		
		Mean ^a	(CV) ^a		Mean ^a	(CV) ^a		Mean ^a	(CV) ^a			
Verteporfin (BPD-MAC)												
AUC _{0-t} (µg·h/mL)	Men	0.78	(25%)	.213 ^g	1.57	(24%)	.312 ^e	0.64	(31%)	.001 ^e	.005 ^c	.481 ^c
	Women	0.92	(18%)		1.98	(6%)		0.96	(23%)			
AUC _{inf} (µg·h/mL)	Men	0.83 ^f	(23%)	.286 ^e	1.69	(24%)	.429 ^e	0.67	(29%)	.002 ^e	.006 ^c	.425 ^c
	Women	0.95	(17%)		2.00	(6%)		0.99	(23%)			
C _{max} (µg/mL)	Men	0.49	(29%)	.766	0.93	(58%)	.539	0.30	(8%)	.002	.878 ^c	.835 ^c
	Women	0.43	(26%)		0.98	(47%)		0.68	(27%)			
CL (mL·h ⁻¹ ·kg ⁻¹)	Men	95.5 ^f	(18%)	.405 ^e	110.5	(21%)	.540 ^e	133.5	(25%)	.001 ^e	.015	.057
	Women	88.5	(18%)		102.3	(10%)		95.0	(28%)			
V _{ss} (L/kg)	Men	0.62 ^f	(23%)	.694 ^c	0.73	(30%)	.586 ^c	0.77	(29%)	1.00 ^c	.652	.556
	Women	0.69	(24%)		0.65	(16%)		0.69	(6%)			
t _{max} (h)	Men	0.18	(17%)	.398	0.20	(23%)	.922	0.04	(22%)	.004	.018	.075
	Women	0.19	(22%)		0.22	(37%)		0.04	(22%)			
Kel (1/h)	Men	0.13 ^f	(7%)	.194	0.12	(9%)	.886	0.15	(30%)	.003	.018	.075
	Women	0.12	(25%)		0.12	(13%)		0.10	(22%)			
t _{1/2} (h)	Men	5.37 ^f	(7%)	.886	5.80	(9%)	.886	4.96	(26%)	.003	.018	.075
	Women	6.18	(27%)		5.89	(12%)		7.22	(20%)			
Verteporfin (BPD-MAD)												
AUC _{0-t} (µg·h/mL)	Men	0.69	(24%)	.255 ^e	1.54	(24%)	.417 ^e	0.57	(30%)	.025 ^e	.062 ^c	.601 ^c
	Women	0.74	(21%)		1.72	(6%)		0.75	(22%)			
AUC _{inf} (µg·h/mL)	Men	0.76 ^f	(21%)	.270 ^e	1.57	(24%)	.529 ^e	0.62	(26%)	.038 ^e	.090 ^c	.566 ^c
	Women	0.79	(21%)		1.74	(6%)		0.79	(21%)			
C _{max} (µg/mL)	Men	0.74	(26%)	.635	1.52	(49%)	.906	0.82	(8%)	.025	.933 ^c	.863 ^c
	Women	0.66	(18%)		1.57	(35%)		0.81	(17%)			
CL (mL·h ⁻¹ ·kg ⁻¹)	Men	100.7 ^f	(19%)	.359 ^e	119.2	(21%)	.604 ^e	146.7	(23%)	.019 ^e	.206	.109
	Women	107.9	(22%)		117.5	(8%)		106.3	(27%)			
V _{ss} (L/kg)	Men	0.51 ^f	(25%)	.694 ^c	0.63	(32%)	.072 ^c	0.61	(33%)	1.00 ^c	.225	.451
	Women	0.53	(28%)		0.48	(20%)		0.52	(12%)			
t _{max} (h)	Men	0.18	(17%)	.398	0.20	(23%)	.922	0.09	(124%)	1.00 ^c	.018	.075
	Women	0.19	(22%)		0.16	(11%)		0.04	(22%)			
Kel (1/h)	Men	0.13 ^f	(29%)	.194	0.11	(13%)	.886	0.15	(23%)	.003	.018	.075
	Women	0.15	(34%)		0.14	(6%)		0.13	(28%)			
t _{1/2} (h)	Men	5.67 ^f	(25%)	.886	6.40	(12%)	.886	4.92	(25%)	.003	.018	.075
	Women	5.33	(42%)		5.06	(6%)		5.61	(22%)			

- Arithmetic means, coefficient of variation, and gender effect P values for each individual dose group (when the gender by dose group interaction was significant: $P < .200$).
- ANOVA with gender, dose group, and gender by dose group as factors, except for t_{max} (Wilcoxon test).
- P values for C_{max} and AUC calculated from log-transformed data. P value for t_{max} (gender only) calculated using the Wilcoxon test.
- P values for which statistical significance changed after addition of body weight as a covariate to the ANOVA analysis.
- Gender effect P values for individual dose groups derived from the ANCOVA model with body weight as a covariate.
- $n = 11$.

The conclusions obtained from the statistical analysis for gender differences is summarized below.

Conclusions

- The C_{max} , V_{ss} , and $t_{1/2}$ of verteporfin and the individual regioisomers were not influenced by gender in the three dose groups. Adjustment to body weight also did not change the results. However, since dosing was in per m^2 , one would not expect weight to be a factor
- For AUC_{0-t} and AUC_{0-inf} , the gender effect for verteporfin was not consistent across different dose groups. Mean AUC_{0-t} and AUC_{0-inf} were comparable between males and females for the 6 mg/m^2 and 14 mg/m^2 , 10-minute infusion groups. The differences were less than 15% and were not statistically significant (see p-values in the bracket). In the bolus group, however, male subjects had a nearly 28% lower AUC than female subjects and this difference was statistically significant ($P < .050$). These differences were also seen in the individual regioisomers of verteporfin. However, the overall gender effect for AUC_{0-t} and AUC_{0-inf} was not statistically significant after body weight adjustment. Looking at the pharmacokinetic parameters for BPD- MA_C and BPD- MA_D , it appears that the trends observed for the gender is largely contributed by BPD- MA_C regioisomer.
- Similarly, there were no apparent differences between males and females for CL for the 6 mg/m^2 and 14 mg/m^2 , 10-minute infusion groups but the differences between males and females were statistically significant ($P < .050$) for the bolus injection group. Similar trends were also seen for the two regioisomers of verteporfin. However, the overall gender effect for CL was not statistically significant after body weight adjustment.
- There was sparse data available for the metabolite BPD-DA. No conclusions regarding gender differences in the levels of metabolite can be derived based the variable levels obtained.
- In summary, Caucasian men and women exhibited similar verteporfin pharmacokinetics, based on a study population of 12 subjects in the infusion group and 8 subjects in the bolus group. The trends in gender difference was more apparent in the bolus injection group and not in the 10- minute infusion group, which will be the to-be marketed regimen.

In patients

The gender analysis of the plasma concentrations in patients is shown in the following Table 16.

**TABLE 16: Summary of Mean Plasma Concentration of Verteporfin
By Gender After a 5- or 10-Minute Infusion (Study BPD OCR 001)**

Time after start of infusion	Mean Plasma Concentration (μg Verteporfin/mL \pm STD)											
	MALE					FEMALE						
	After 6 mg/m ²		After 12 mg/m ²			After 6 mg/m ²		After 12				
	5-minute Infusion	10-minute Infusion	10-minute Infusion	10-minute Infusion	10-minute Infusion	5-minute Infusion	10-minute Infusion	10-minute Infusion	10-minute Infusion	10-minute Infusion		
mins	n	Mean \pm STD	n	Mean \pm STD	n	Mean \pm STD	n	Mean \pm STD	n	Mean \pm STD	n	Mean \pm STD
5	7	2.43 \pm 0.72	0	—	0	—	3	3.85 \pm 0.33	0	—	0	—
10	8	1.19 \pm 0.45	8	1.66 \pm 0.38	10	3.07 \pm 0.76	5	1.61 \pm 0.53	4	1.41 \pm 0.41	5	3.57 \pm 0.69
20	8	0.70 \pm 0.12	24	0.75 \pm 0.19	12	1.80 \pm 0.31	5	1.07 \pm 0.29	13	0.79 \pm 0.16	4	1.85 \pm 0.33
30	9	0.52 \pm 0.12	15	0.47 \pm 0.09	9	1.11 \pm 0.22	5	0.85 \pm 0.28	5	0.41 \pm 0.24	5	1.48 \pm 0.26
40	9	0.48 \pm 0.10	15	0.42 \pm 0.09	12	0.99 \pm 0.20	4	0.90 \pm 0.35	6	0.43 \pm 0.10	4	1.28 \pm 0.27

Conclusions

No gender effect was evident from these plasma concentrations of patients.

Will dosage adjustment be necessary based on differences across gender?

Dosage adjustment would not be necessary based on the pharmacokinetic study in healthy volunteers. The differences were not statistically significant in the 6 and 14 mg/m² - 10 minute infusion group. The differences were seen only in the bolus infusion group, which is not the to-be marketed regimen for verteporfin for injection for the treatment of age related macular degeneration. These differences were not significant after body weight adjustment. No gender effect was evident from these plasma concentrations of patients. However, the overall efficacy and safety across the genders should be taken into consideration before making a recommendation.

Effect of Race

The sponsor has evaluated racial differences in the plasma concentration of verteporfin in the Caucasian and Japanese men. The effect of race was evaluated in study BPD PK 001A and 001B, which was conducted in Caucasian men and Japanese men respectively. The different dose groups compared were: 6 mg/m² with 10 minute infusion (8M) and 14 mg/m² with 10 minute infusion (8M) and 6mg/m². The plasma concentration profiles in these groups based on the race in each dosage regimen is shown in the following figure.

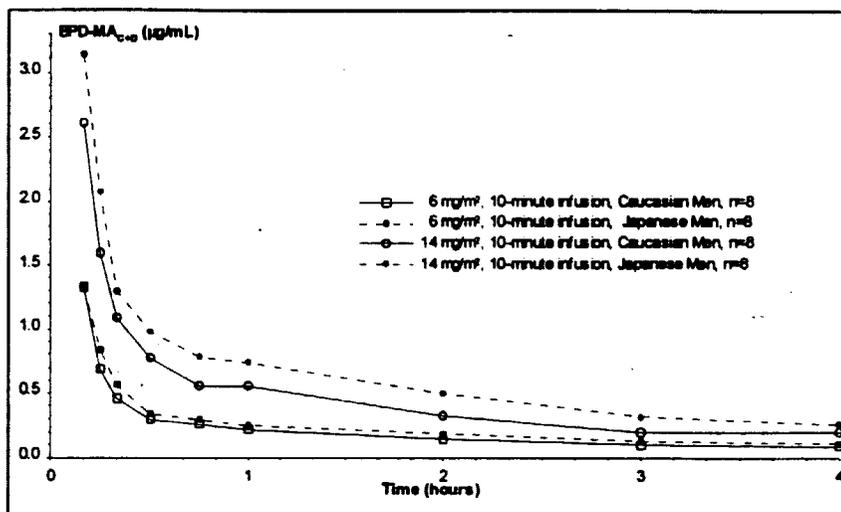


Figure: Linear plot of mean verteporfin concentrations in healthy Caucasians men and Japanese men

A summary table for race comparison for verteporfin is shown in the Table 17. A race comparison for the regioisomers is attached in the Appendix on page 36.

TABLE 17: Race Pharmacokinetic Comparison for Verteporfin

Pharmacokinetic Parameters	Mean (Coefficient of Variation)				Race Effect ^a P value	Race by Dose Interaction ^a P value
	Study A – Caucasian		Study B – Japanese			
	6 mg/m ² 10-min inf. Men (n=8)	14 mg/m ² 10-min inf. Men (n=8)	6 mg/m ² 10-min inf. Men (n=8)	14 mg/m ² 10-min inf. Men (n=8)		
Verteporfin (BPD-MAC+D)						
AUC _{0-t} (µg·h/mL)	1.49 (23%)	3.21 (24%)	1.71 (16%)	4.91 (28%)	.002 ^c 6 mg: .178 14 mg: .005	.105 ^c
AUC _{inf} (µg·h/mL)	1.56 ^b (22%)	3.25 (24%)	1.75 (16%)	4.95 (28%)	.003 ^c 6 mg: .262 14 mg: .005	.091 ^c
C _{max} (µg/mL)	1.23 (27%)	2.45 (51%)	1.32 (11%)	3.13 (18%)	.056 ^c	.321 ^c
CL (mL·h ⁻¹ ·kg ⁻¹)	97.4 ^b (19%)	115.0 (20%)	102.7 (23%)	84.5 (32%)	.148 6 mg: .648 14 mg: .029	.044
V _{ss} (L/kg)	0.64 ^b (43%)	0.67 (31%)	0.57 (11%)	0.51 (21%)	.101	.510
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 (27%)	0.13 (11%)	0.13 (20%)	0.13 (17%)	.884	.871
t _{1/2} (h)	5.97 ^b (43%)	5.55 (12%)	5.72 (20%)	5.62 (17%)	.865	.757

- 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.
- n = 7.
- P values for C_{max} and AUC calculated from log-transformed data.
- For t_{max}, a two-way ANOVA by ranks was performed with race, dose group and race-by-dose group as factors. Since this comparison is dependent on the sampling and samples from Japanese were all collected at the scheduled time, variance is equal to zero for the Japanese. The comparison is meaningless and no comparison by dose level was done, even if the race-by-dose group interaction term is significant.

The race effect analysis on all parameters was assessed by ANOVA with race, dose group and race-by-dose group interaction or ANCOVA with an added covariate, weight or BMI in the model. Neither body weight nor BMI had a significant contribution to the variation

of the main pharmacokinetic parameters tested. For the parameters where the race effect was significant, individual dose comparisons were performed (p-values given in the table). The conclusions based on the ANOVA analysis is summarized here.

Conclusions

- There was no statistically significant difference in volume of distribution and half-life amongst the Caucasian and Japanese men and was also similar in the two dose groups.
- The C_{max} between Caucasians and Japanese were close to being statistically significantly different ($p=0.056$). This difference may be of limited value due to the infusion methodology.
- For AUC_{0-4} and AUC_{0-inf} , the effect of race was not consistent between the two dose groups. Mean AUC_{0-4} and AUC_{0-inf} were comparable between Japanese men and Caucasian men for 6 mg/m², 10-minute infusion groups. The differences were less than 15% and were not statistically significant ($P \geq 0.178$). In the 14 mg/m², 10-minute infusion groups, however, Japanese men had approximately 50% higher AUC than Caucasian men and this difference was statistically significant ($P=0.005$).
- For CL also the effect of race was not consistent between the two dose groups. There were no apparent differences between Japanese men and Caucasian men for CL ($P=0.648$) for the 6 mg/m², 10-minute infusion groups but the differences between Japanese men and Caucasian men were statistically significant ($P = 0.029$) for the 14 mg/m², 10-minute infusion groups.
- Similar pharmacokinetics were observed with the two structural isomers as well. A table showing the BPD-MA_C and BPD-MA_D race pharmacokinetic comparison is attached in the Appendix on page 36.
- The metabolite concentrations were low in both Japanese and Caucasians. No formal race analysis was done. However, visually looking at the metabolite profiles, all Caucasian subjects showed a peak ranging between 1-8 hours, with 1 hour being the peak in majority of the subjects. The Japanese showed a peak ranging from 3-12 hours, with 12 hours being the peak in majority of the subjects. This shows the variability in the rates of hydrolysis of verteporfin to form the metabolite and also probably due to the racial difference in the presence of the esterases.

Will dosage adjustment be necessary based on racial differences?

- In summary, all the pharmacokinetic parameters of verteporfin were similar in the Caucasian and Japanese men in the 6 mg/m² with a 10 minute infusion group but AUC and CL were statistically different in the two races in the 14 mg/m², 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.