

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-119**

**MEDICAL REVIEW**

Medical Officer's Review of NDA 21-119  
Original

NOV 30 1999

1 of 83

NDA #21-119  
M.O. Review #1

Submission: 8/14/99  
Review completed: 11/30/99

Proposed Trade name: Visudyne  
Generic name: Verteporfin for injection

Common names for the verteporfin regioisomers are:

Benzoporphyrin derivative monoacid ring C (BPD-MA<sub>C</sub>) and  
Benzoporphyrin derivative monoacid ring D (BPD-MA<sub>D</sub>)

Chemical names for the verteporfin regioisomers are:

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 and

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.

Sponsor: QLT PhotoTherapeutics Inc.

Pharmacologic Category: Photoenhancer

Proposed Indication(s): The treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.

Dosage Form(s) and Route(s) of Administration: Lyophilized cake for intravenous injection

NDA Drug Classification: 1 P

Related Applications:

[Redacted] Verteporfin for Injection (QLT PhotoTherapeutics)  
[Redacted]

Related Drug Products:

[Redacted]

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**3 Material Reviewed**

Volumes 2.1, 2.63-135  
 Clinical Photographs of first 5% of patients treated

**4 Chemistry/Manufacturing Controls**

Verteporfin is a 1:1 mixture of two regioisomers, BPD-MA<sub>C</sub> and BPD-MA<sub>D</sub>. Each regioisomer is composed of a racemic mixture of enantiomers with substituents at 4 and 4a in the two possible *trans* positions to each other. Verteporfin is insoluble in water.

**Drug Product Composition**

Component	Function	Drug product Target (mg/vial)
Verteporfin	Active	15
Butylated hydroxytoluene		
Ascorbyl palmitate		
Egg phosphatidylglycerol		
Dimyristoyl phosphatidylcholine		
Lactose		

**Reviewer's Comments:** *Pending completion of the Chemistry Review, no specific additional clinical issues have been noted at this time.*

## 5 Nonclinical/Animal Pharmacology/Toxicology

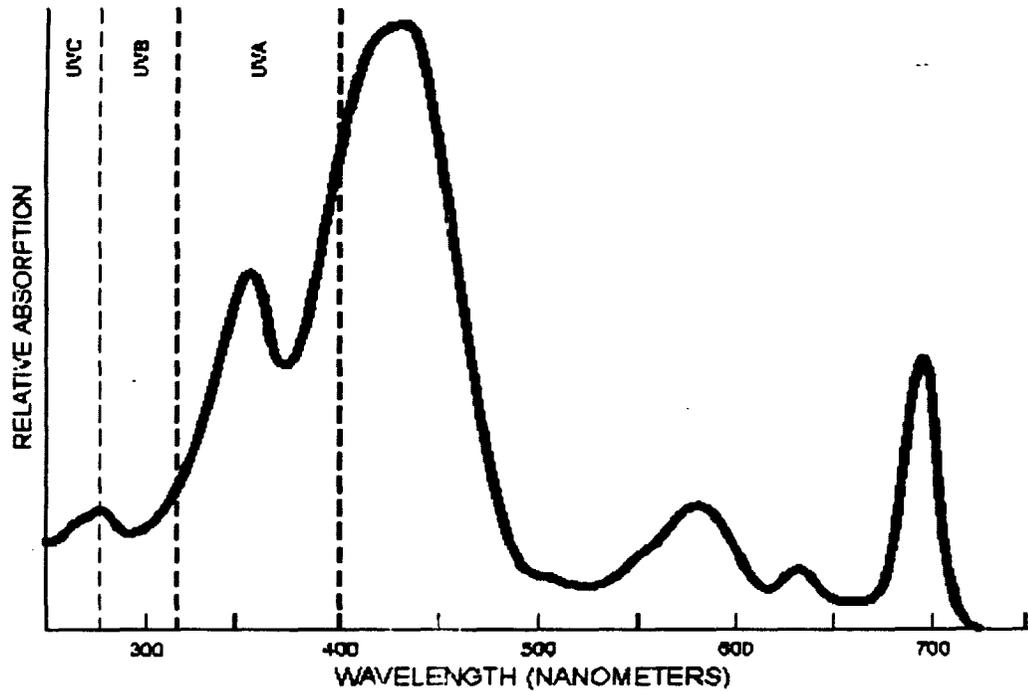
The photosensitizer benzoporphyrin derivative monoacids A ring, verteporfin, is a chlorin-like compound composed of a 1:1 mixture of two regioisomers, BPD-MA<sub>C</sub> and BPD-MA<sub>D</sub>. Each regioisomer is present as a 1:1 pair of enantiomers. All four isomers of verteporfin possess similar photosensitizing activity. Verteporfin, as a lipid-based formulated drug product, Verteporfin for Injection, is being investigated for its ability upon light activation to close neovasculature in age-related macular degeneration (AMD) and in other ocular diseases associated with neovascularization. The target of this photodynamic action is the neovascular endothelium. Photodynamically damaged endothelium is known to generate and release procoagulant and vasoactive factors through the lipo-oxygenase (leukotrienes) and cyclo-oxygenase (ecosanoids such as thromboxane) pathways. These factors may result in platelet aggregation, fibrin clot formation and vasoconstriction, leading to potential vascular occlusion.

Treatment with verteporfin depends on activation of this otherwise inactive compound with visible light in the presence of oxygen, a procedure known as Photodynamic Therapy (PDT). Both photosensitizer and light must be simultaneously present in a target location. The intensity of PDT depends on the combination of photosensitizer concentration and light dose employed, each of which can be separately varied to compensate for the other. During the period of light exposure, light energy is transferred via the photosensitizer to oxygen and highly reactive short-lived singlet oxygen is generated. Singlet oxygen causes damage to biological structures within the diffusion range, leading to potential localized vascular occlusion, localized cell damage and, under certain conditions, localized cell death.

Following IV infusion, verteporfin is activated in the target tissue by exposure to intense, non-thermal light. Verteporfin absorbs light strongly at 689 nm, a wavelength that is minimally absorbed by hemoglobin and that penetrates solid tissue well. Verteporfin is minimally activated by light wavelengths above 700 nm.

Verteporfin temporarily sensitizes skin to light. Verteporfin cleared over a period of hours from rabbit and pig skin, indicated by the reduction in skin photosensitivity, as measured by the degree of photoreactivity following light activation. During a steady-state prolonged infusion in pigs, the degree of skin photosensitivity was proportional to the combination of the plasma drug level and the light dose. After a single IV injection, skin reactivity at sites exposed soon after drug injection (60-150 minutes) was considered to be due to vascular damage and attributable to high levels of drug in the blood vessels, whereas the lower skin reactivity at sites exposed at 3 hours and later times after drug administration appeared to be due to effects on both the vasculature and skin cells. Skin photosensitivity was also used as a model to test the pharmacokinetics of photosensitization in vivo and to address various light activation parameters.

Several types of light sources, with different activating efficiencies depending on their spectral output, can be used for drug excitation. In vitro the verteporfin action spectrum is found to follow the drug's absorption spectrum.



When tissue penetration is considered as a factor, red light may be more effective than UVA or blue.

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## 6 Clinical Background

### Foreign Marketing Experience

Not marketed in any jurisdiction.

### Human Pharmacology, pharmacokinetics, pharmacodynamics

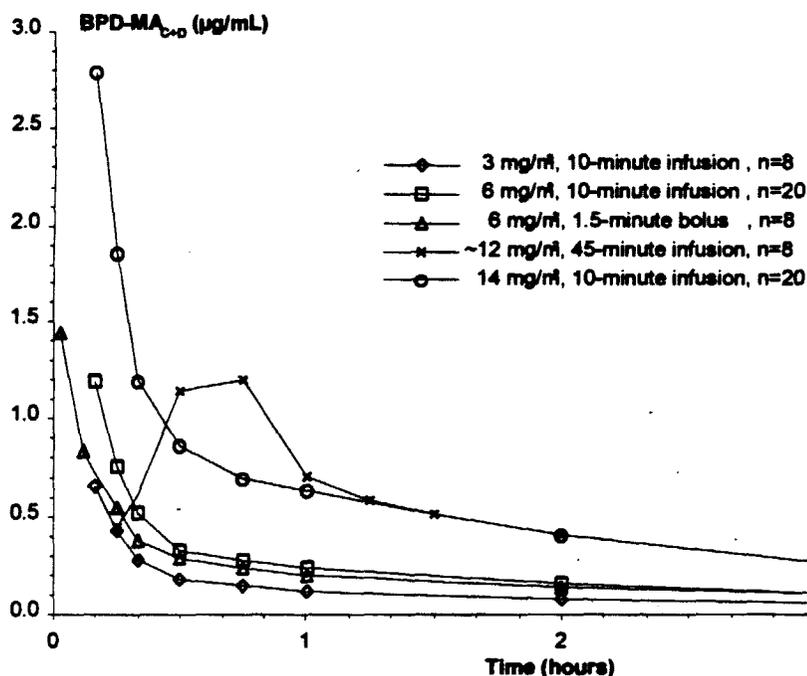
#### Applicant Reported Verteporfin Pharmacokinetic Parameters in Healthy Volunteers

Pharmacokinetic Parameters	Mean (Coefficient of Variation)				
	Study BPD PK 001A	Study BPD PK 001B	Studies BPD PK 001A/B Combined		Study BPD 004
	6 mg/m <sup>2</sup> 1.5-min bolus (n=8)	3 mg/m <sup>2</sup> 10-min infusion (n=8)	6 mg/m <sup>2</sup> 10-min infusion (n=20)	14 mg/m <sup>2</sup> 10-min infusion (n=20)	~12 mg/m <sup>2</sup> 45-min infusion (n=8)
AUC <sub>0-t</sub> (µg·h/mL)	1.49 (29%)	0.83 (28%)	1.62 (19%)	3.99 (31%)	3.25 (27%)
AUC <sub>inf</sub> (µg·h/mL)	1.52 (28%)	0.88 (25%)	1.68* (18%)	4.02 (31%)	3.40 (28%)
C <sub>max</sub> (µg/mL)	1.44 (15%)	0.66 (15%)	1.24 (21%)	2.74 (36%)	1.38 (30%)
CL (mL·h <sup>-1</sup> ·kg <sup>-1</sup> )	118.8 (32%)	102.1 (31%)	99.6* (20%)	101.8 (26%)	—
V <sub>ss</sub> (L/kg)	0.63 (19%)	0.58 (25%)	0.61* (29%)	0.59 (28%)	0.42 (29%)
T <sub>max</sub> (h)	0.06(122%)	0.17 (0%)	0.18 (15%)	0.18 (18%)	0.64 (19%)
K <sub>el</sub> (1/h)	0.14 (27%)	0.13 (23%)	0.13* (22%)	0.13 (14%)	0.14 (15%)
t <sub>1/2</sub> (h)	5.16 (25%)	5.77 (22%)	5.79* (31%)	5.46 (14%)	4.92 (16%)

\*n=19

No dose-dependent trends in verteporfin distribution or elimination parameters were apparent. In general, half-life, volume of distribution, clearance, and elimination rate did not vary across the various doses and infusion rates evaluated in healthy volunteers. Mean half-life was approximately 5-6 hours, clearance was 100-119 mL·h<sup>-1</sup>·kg<sup>-1</sup> and mean volumes of distribution were 0.4-0.6 L/kg.

**Reviewer's Comments:** *Subject to review by the Biopharmaceutics Team.*



The mean plasma concentrations over the first 4 hours are shown above. In these healthy subjects, plasma verteporfin concentrations exhibited similar disposition across all doses and rates of administration studied. A clear bi-exponential decline of verteporfin concentrations in plasma was observed with a rapid distribution phase followed by a slower elimination phase. After the rapid distribution phase, the plasma concentrations were very similar for any given verteporfin dose, the slopes of elimination for all dose regimens were similar. By 24 to 36 hours or less, the plasma concentrations of verteporfin fall below detectable levels in humans (limit of quantitation of 2.0 ng/mL which corresponds to less than 1% of the maximal plasma concentrations).

**Reviewer's Comments:**     *Subject to review by the Biopharmaceutics Team.*

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## 7 Description of Clinical Data Sources

### Clinical Studies with Verteporfin

Protocol	Study Design	Treatment Regimen	Population Treated
BPD PK 001A 1 center: US Status: Completed  Enrollment period: 18 MAY 98-19 JUN 98	Open-label, randomized, parallel group, Phase I, 7 days of follow-up	Verteporfin: 6 or 14 mg/m <sup>2</sup> as 10-minute IV infusion, or 6 mg/m <sup>2</sup> bolus IV  Single dose	32 Healthy Volunteers 20 ♂ 12 ♀ 32 Caucasian  Age: 20-33 years (Mean: 26 years)
BPD PK 001 B  1 center: Japan  Status: Completed  Enrollment period: 20 AUG 98-24 SEP 98	Open-label, nonrandomized, sequential ascending dose, Phase I, 21 days of follow-up	Verteporfin: 3, 6 or 14 mg/m <sup>2</sup> as 10-minute IV infusion  Single dose	24 Healthy Volunteers 24 ♂ 0 ♀ 24 Japanese  Age: 20-25 years (Mean: 22 years)
BPD 004 1 center: Canada  Status: Completed  Enrollment period: 11 NOV 94-28 MAR 95	Open-label, Phase 1, 21 days of follow-up	Verteporfin: 0.3 mg/kg (~12 mg/m <sup>2</sup> ) as 45-minute IV infusion  Single dose	17 Subjects (8 healthy; 9 with mild liver dysfunction) 11 ♂ 6 ♀  17 Caucasian Age: 29-60 years (Mean: 39 years)
Review Study #1			
Review Study #2			

Protocol	Study Design	Treatment Regimen	Population Treated
<b>Review Study #4 BPD OCR 001</b> 4 centers: US (1), Germany (1), Switzerland (2)  Status: Completed  Enrollment period: 10 APR 95-08 AUG 98	Open-label, dose and light escalation, Phase I/II, single and multiple doses q. 2-8 weeks, 12 weeks of follow-up	Verteporfin: 6 or 12 mg/m <sup>2</sup> as 5- or 10- minute IV infusion, 689 nm laser light (and 12.5, 25, 50, 75, 100, or 150 J/cm <sup>2</sup> ) applied 10, 15, 20, or 30 min after start of infusion  Retreatment option q2-8 weeks	142 Patients with CNV  75 ♂ 67 ♀  141 Caucasian  Age: 34-89 years (Mean: 72 years)
<b>BPD 001</b> 3 centers: US (2), Canada (1)  Status: Completed  Enrollment period: 15 NOV 91-27 MAR 95	Open-label, Phase I/II ascending dose, 90 days of follow-up	Verteporfin: 0.15-0.5 mg/kg as 45-minute IV infusion, 690 nm laser light (25-150 J/cm <sup>2</sup> ) applied 1.5-6.0 hours after start of infusion.  Single dose (3 patients received multiple courses)	35 Patients with cutaneous lesions caused by metastatic malignancy, basal cell carcinoma, or squamous cell carcinoma  17 ♂ 18 ♀  Race not collected  Age: 23-80 years (Mean: 59 years)
<b>BPD PSI 001</b> 3 centers: US (2), Canada (1)  Status: Completed  Enrollment period: 17 MAY 95-16 NOV 95	Open-label, Phase II, 70 days, 56 days of follow-up	Verteporfin: 8 mg/m <sup>2</sup> as 5-10 minute IV infusion, LED light (688±10 nm) applied 1 or 3 hours after start of infusion  Multiple dose: 5 courses, q. 7-10 days	6 Patients with moderate to severe, stable chronic plaque psoriasis  4 ♂ 2 ♀  6 Caucasian  Age: 25-65 years (Mean: 42 years)

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## Ongoing and Future Studies

### Ongoing

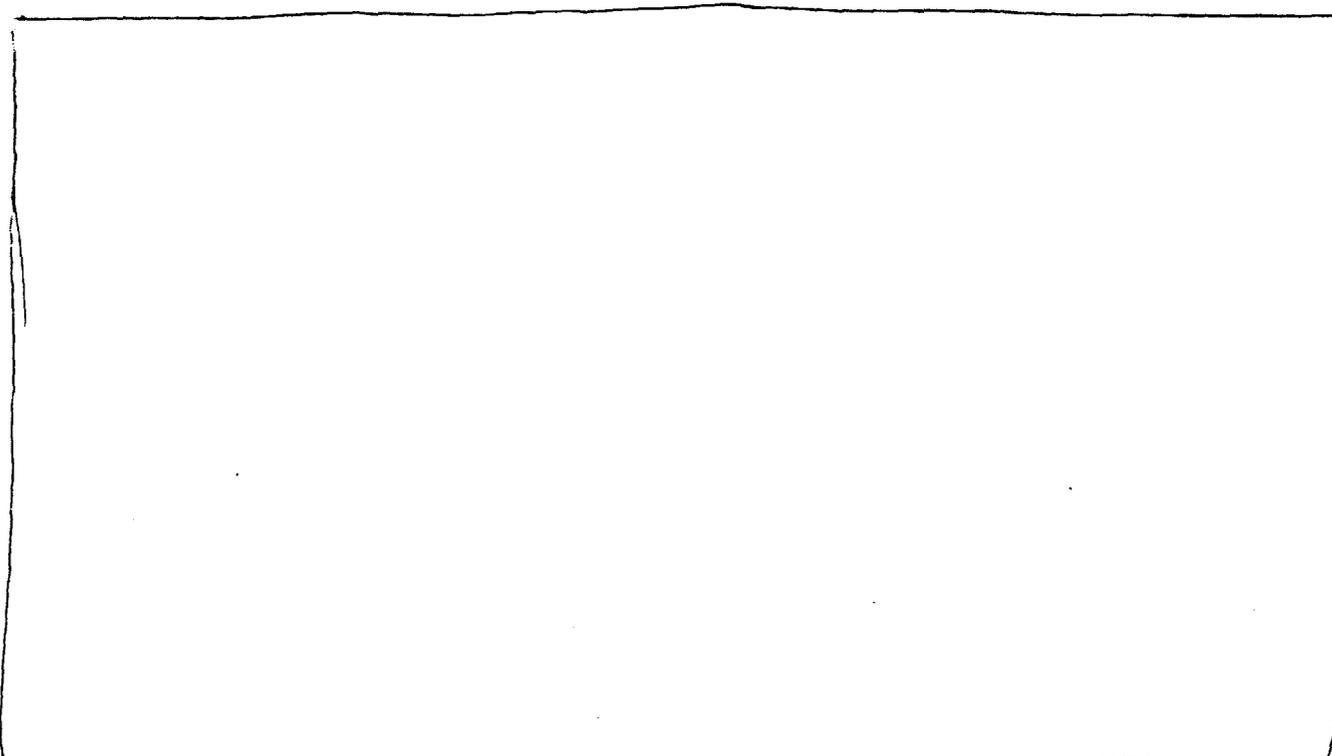
Study BPD OCR 002 is ongoing to establish safety and efficacy for 2 years (end of September 1999). An open-label extension to this study has been implemented for an additional 2 years. Patients who have reached the 24-month visit of the placebo-controlled trial may receive active treatment with verteporfin for one or both eyes if eligible. Physicians and patients will remain masked to treatment assignment until all patients have completed the 24-month visit. This study extension also allows both eyes to be treated after a single verteporfin infusion and will provide data to assess the safety and practicality of this bilateral treatment procedure.

Study BPD OCR 003 was initiated in March 1998 for the treatment of early neovascular AMD (mainly occult CNV) and for the treatment of CNV secondary to pathologic myopia (PM). A total of 339 AMD and 120 PM patients have been enrolled and randomized at a 2:1 ratio for verteporfin vs placebo. The primary analysis will be conducted after all patients have completed the 1-year follow-up visit (after September 1999). The full statistical plan will be submitted to the IND prior to this analysis.

Study BPD OCR 004 was initiated in July 1998 for the treatment of CNV secondary to ocular histoplasmosis syndrome. A total of 15 patients have been enrolled as of the data cutoff for this NDA.

Two of the non-ocular, company-sponsored studies are ongoing: the rheumatoid arthritis and non-melanoma skin cancer trials.

### Planned Studies



42 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.

Reviewer's Study #4

Applicant's Protocol BPD OCR 001

**An Open, Multicenter, Non-controlled Phase I/II Study of the Treatment of Choroidal Neovascularization using Photodynamic Therapy with Liposomal BPD-MA (verteporfin)**

**Primary Objectives:**

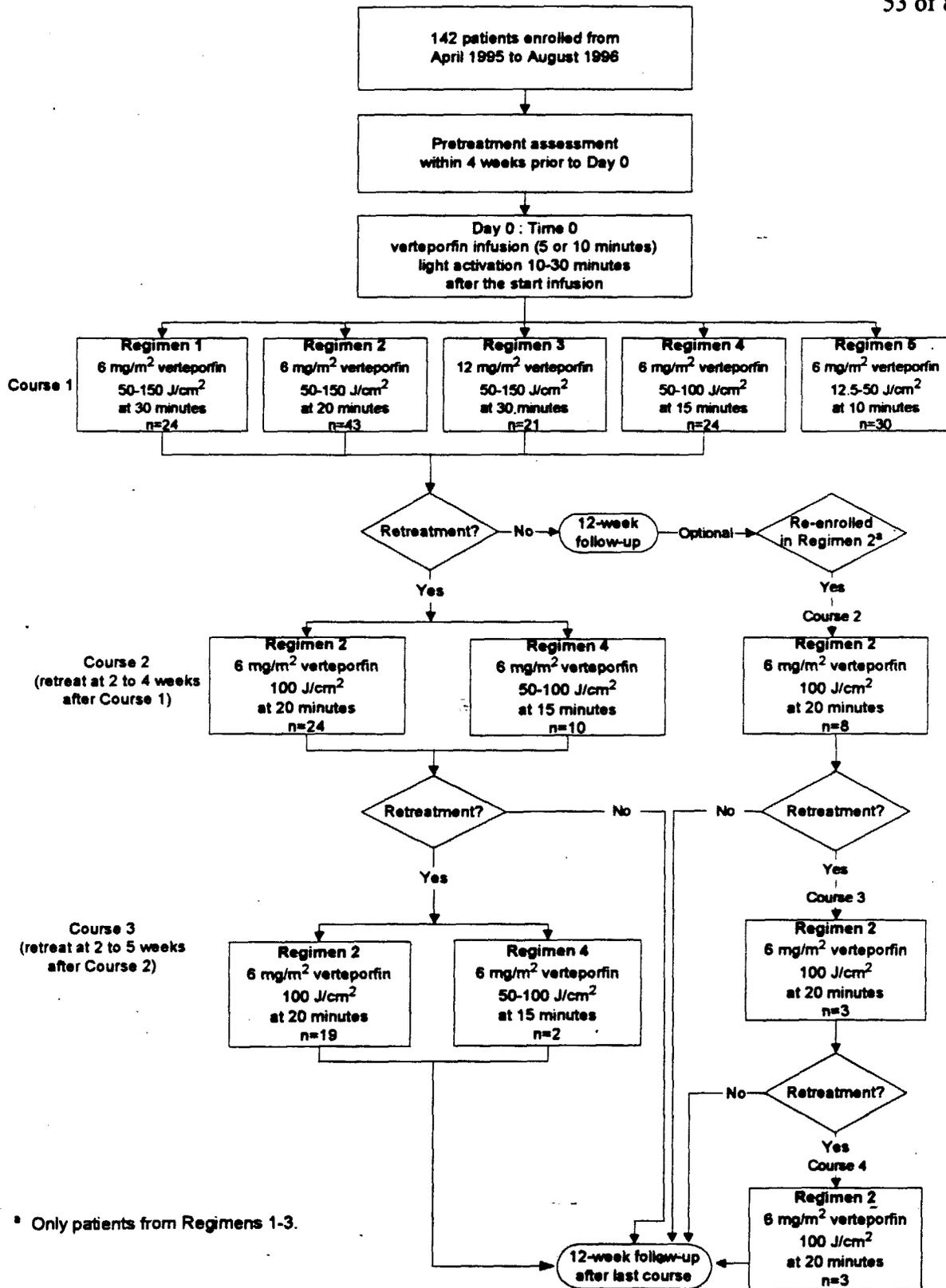
1. To determine the ocular safety of photodynamic therapy (PDT) using different drug-dose/light-dose regimens of verteporfin and red light to treat choroidal neovascularization (CNV) with subfoveal involvement.
2. To demonstrate the proof of concept and preliminary efficacy of PDT using verteporfin to close CNV, determined by fluorescein angiograms.

**Study Design:**

BPD OCR 001 was a multicenter, open-label, non-controlled, dose-escalation study to evaluate safety and dose-response characteristics of a number of different treatment regimens using photodynamic therapy with verteporfin in patients with subfoveal choroidal neovascularization.

The initial proposed drug dose used in this study was  $6 \text{ mg/m}^2$  administered over 10 minutes. This dose approximated  $0.15 \text{ mg/kg}$  body weight. The initial light dose ( $50 \text{ J/cm}^2$  at a fluence rate or intensity of  $600 \text{ mW/cm}^2$ ) used in this study was administered 30 minutes after the start of the infusion. This time of light administration was based upon the preclinical studies showing that optimal selectivity and effectiveness were found in primates at times between 20-50 minutes after the IV dose. Plasma concentrations expected in humans 30 minutes after the start of a 10-minute infusion of  $6 \text{ mg/m}^2$  verteporfin were modeled using data from previous clinical pharmacokinetic studies that used a 45-minute infusion (BPD 001 and BPD 004). Using conservative estimates of the distribution rate, the plasma concentration at 30 minutes in humans was considered to be lower than those associated with ocular adverse events in primates.

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### Protocol Amendments and the PDT Treatment Regimens

Protocol Amendment	Treatment Regimen <sup>a</sup>	Treatment Regimen
Initial Protocol	1	6 mg/m <sup>2</sup> , 50-150 J/cm <sup>2</sup> at 30 minutes
Amendment 4 July 18, 1995	2	6 mg/m <sup>2</sup> , 50-150 J/cm <sup>2</sup> at 20 minutes
Amendment 4 July 18, 1995	3	12 mg/m <sup>2</sup> , 50-150 J/cm <sup>2</sup> at 30 minutes
Amendment 6 <sup>b</sup> November 6, 1995	2	6 mg/m <sup>2</sup> , 100 J/cm <sup>2</sup> at 20 minutes (Retreatment)
Amendment 7 January 18, 1996	4	6 mg/m <sup>2</sup> , 50-100 J/cm <sup>2</sup> at 15 minutes
Amendment 8 May 10, 1996	5 <sup>c</sup>	6 mg/m <sup>2</sup> , 12.5-50 J/cm <sup>2</sup> at 10 minutes

- <sup>a</sup> Verteporfin was administered in 30 mL D5W and infused at a rate of 3 mL/min (10-minute infusion).  
<sup>b</sup> Amendment allowing retreatment up to a maximum of 3 courses of therapy.  
<sup>c</sup> Verteporfin was administered in 30 mL D5W and infused at a rate of 6 mL/min (5-minute infusion).

### Schedule of Evaluations for a Single Treatment with PDT

Visit	Screening/ Baseline	Day 0	Day 1	Week 1	Week 2 <sup>a</sup>	Week 4	Week 12
Demography	X						
Medical History	X						
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Concomitant Medications	X	X	X	X	X	X	X
Physical Examination	X						X
Vital Signs	X	X	X				X
EKG	X						X
Laboratory Tests	X			X			X
Pregnancy Test	X						
Visual Acuity	X	X	X	X	X	X	X
Color Fundus Photography	X			X	X	X	X
Fluorescein Angiography	X			X	X	X	X
Dilated Ophthalmoscopy	X	X		X	X	X	X
Verteporfin Infusion		X					
Blood Sampling for PK		X					
Light Application		X					
Adverse Events/Ocular Safety		X	X	X	X	X	X

- <sup>a</sup> Week-2 assessments were only required if any dose-limiting ocular adverse events were observed at Week 1.

**CNV Closure<sup>a</sup> Grades**

	Complete Closure or 100% Closed and No Progression	Partial Closure or 50% - < 100% Closed and No Progression	Minimal Closure or <50% Closed and No Progression	Progression <sup>b</sup> (New Area of Fluorescein Leakage)	Can't Grade
1. Classic CNV	A	B	C	D	E
2. Occult CNV if none at baseline	F	—	—	G	H
3. Occult CNV if present at baseline	I	J	K	L	M

- <sup>a</sup> The terms CNV closure (100%, partial or minimal) and CNV progression have been adopted throughout the report and reflect the area of fluorescein leakage relative to baseline assessed from the fluorescein angiograms.
- <sup>b</sup> Classic or occult CNV progression was defined as fluorescein leakage associated with either classic or occult CNV that extended beyond the area of leakage seen before PDT.

**Investigators**

Country	Investigator	Study Center	Number of Patients Enrolled
United States	Joan W. Miller, MD		54
Germany	Ursula Schmidt-Erfurth, MD		61
Switzerland	Leonidas Zografos, MD		22
	Constantin Pourmaras, MD		5
		<b>Total</b>	<b>142</b>

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Closure of Classic CNV by Visit and Treatment Regimen (AMD Patients<sup>a</sup> After a First PDT Course)

Drug Dose (mg/m <sup>2</sup> )	Time <sup>b</sup> (min)	Light (J/cm <sup>2</sup> )	Number (%) of Patients																
			Week 1					Week 4					Week 12 <sup>c</sup>						
			100%	50-<100%	< 50%	Progress	n	100%	50-<100%	< 50%	Progress	n	100%	50-<100%	< 50%	Progress	n		
<b>Regimen 1</b>																			
6	30	50	1 (50)	1 (50)	0 (0)	0 (0)	2	0 (0)	1 (50)	1 (50)	0 (0)	0 (0)	2	0 (0)	0 (0)	0 (0)	2	█	2
		75	5 █	1 (17)	0 (0)	0 (0)	6	0 (0)	4 (67)	1 (17)	1 (17)	6	0 (0)	0 (0)	4 █	2 (33)	6		
		100	2 (29)	4 (57)	1 (14)	0 (0)	7	2 (29)	2 (29)	1 (14)	2 (29)	7	0 (0)	2 (40)	0 (0)	3	█	5	
		150	3 (50)	3 (50)	0 (0)	0 (0)	6	0 (0)	1 (17)	4 (67)	1 (17)	6	0 (0)	1 (17)	1 (17)	4	█	6	
<b>Total 50-150</b>			11 (52)	9 (43)	1 (5)	0 (0)	21	2 (10)	8 (38)	7 (33)	4 (19)	21	0 (0)	3 (16)	5 (26)	11 (58)	19		
<b>Regimen 2</b>																			
6	20	50	2 █	0 (0)	0 (0)	0 (0)	2	0 (0)	1 (50)	1 (50)	0 (0)	0 (0)	2	0 (0)	0 (0)	1 (50)	1 (50)	2	
		75	2 █	1 (33)	0 (0)	0 (0)	3	1 (33)	1 (33)	0 (0)	1 (33)	3	0 (0)	1 (50)	0 (0)	1 (50)	2		
		100	21	2 (8)	2 (8)	0 (0)	25	5 (29)	5 (29)	6 (35)	1 (6)	17	1 (13)	2 (25)	2 (25)	3 (38)	8		
		150	2	0 (0)	1 (33)	0 (0)	3	0 (0)	2 (67)	1 (33)	0 (0)	3	0 (0)	1 (33)	2 █	0 (0)	3		
<b>Total 50-150</b>			27 (82)	3 (9)	3 (9)	0 (0)	33	6 (24)	9 (36)	8 (32)	2 (8)	25	1 (7)	4 (27)	5 (33)	5 (33)	15		
<b>Regimen 3</b>																			
12	30	50	1 (50)	1 (50)	0 (0)	0 (0)	2	0 (0)	0 (0)	0 (0)	2 █	2	0 (0)	0 (0)	0 (0)	2 █	2		
		75	2 █	1 (33)	0 (0)	0 (0)	3	0 (0)	0 (0)	1 (50)	1 (50)	2	0 (0)	0 (0)	1 (50)	1 (50)	2		
		100	8 █	0 (0)	1 (11)	0 (0)	9	1 (11)	4 (44)	3 (33)	1 (11)	9	0 (0)	0 (0)	4 (44)	5 █	9		
		150	5	0 (0)	0 (0)	0 (0)	5	1 (20)	4 (80)	0 (0)	0 (0)	5	0 (0)	0 (0)	2 (40)	3 █	5		
<b>Total 50-150</b>			16 (84)	2 (11)	1 (5)	0 (0)	19	2 (11)	8 (44)	4 (22)	4 (22)	18	0 (0)	0 (0)	7 (39)	11 (61)	18		
<b>Regimen 4</b>																			
6	15	50	7 █	0 (0)	0 (0)	0 (0)	7	4 █	1 (14)	1 (14)	1 (14)	7	0 (0)	3 (60)	0 (0)	2 (40)	5		
		75	6	0 (0)	0 (0)	0 (0)	6	0 (0)	2 (33)	3 (50)	1 (17)	6	0 (0)	0 (0)	0 (0)	0 (0)	6		
		100	8	0 (0)	0 (0)	0 (0)	8	2 (25)	2 (25)	3 (38)	1 (12)	8	3 █	2 (40)	0 (0)	0 (0)	5		
<b>Total 50-100</b>			21 (100)	0 (0)	0 (0)	0 (0)	21	6 (29)	5 (24)	7 (33)	3 (14)	21	3 (30)	5 (50)	0 (0)	2 (20)	16		
<b>Regimen 5</b>																			
6	10 <sup>d</sup>	12.5	1 (33)	0 (0)	2 (67)	0 (0)	3	0 (0)	1 (33)	2 (67)	0 (0)	3	0 (0)	0 (0)	3 (100)	0 (0)	3		
		25	5 █	2 (25)	1 (13)	0 (0)	8	0 (0)	2 (25)	4 (50)	2 (25)	8	0 (0)	3 (38)	0 (0)	5 █	8		
		50	8	3 (27)	0 (0)	0 (0)	11	0 (0)	3 (27)	5 (45)	3 (27)	11	0 (0)	1 (10)	1 (10)	8 █	10		
<b>Total 12.5-50</b>			14 (64)	5 (23)	3 (14)	0 (0)	22	0 (0)	6 (27)	11 (50)	5 (23)	22	0 (0)	4 (19)	4 (19)	13 (62)	21		
<b>Regimen 1-5 Total<sup>e</sup></b>			89 (77)	19 (16)	8 (7)	0 (0)	116	16 (15)	3 (34)	37 (35)	18 (17)	107	4 (5)	16 (19)	21 (25)	42 (51)	83		

<sup>a</sup> Excluding Patients 73, 77, 78, 80, 104, 108, 114, 122, 126, 133 due to no classic CNV at baseline.

<sup>b</sup> Time of light application after start of 10-minute verteporfin infusion.

<sup>c</sup> Week 12 includes only patients who received a single course of PDT and were followed for 12 weeks, including the initial 12-week visit for re-enrolled patients.

<sup>d</sup> Time of light application after start of 5-minute verteporfin infusion.

<sup>e</sup> Sample size varies due to 2 missing at Week 1, 11 missing at Week 4, and 35 missing at Week 12.

n = number of evaluable patients.

Highlighted color represents greater than 50% of group (█, xx, █).

Closure of Occult CNV by Visit and Treatment Regimen (AMD Patients<sup>a</sup> After a First PDT Course)

Drug Dose (mg/m <sup>2</sup> )	Time <sup>b</sup> (min)	Light (J/cm <sup>2</sup> )	Number (%) of Patients														
			Week 1					Week 4					Week 12 <sup>c</sup>				
			100%	50-<100%	< 50%	Progress	n	100%	50-<100%	< 50%	Progress	n	100%	50-<100%	< 50%	Progress	n
<b>Regimen 1</b>																	
6	30	50	1 (50)	0 (0)	1 (50)	0 (0)	2	0 (0)	0 (0)	2 (100)	0 (0)	2	0 (0)	0 (0)	0 (0)	2	2
		75	4	1 (17)	1 (17)	0 (0)	6	2 (33)	1 (17)	3 (50)	0 (0)	6	1 (17)	1 (17)	1 (17)	3 (50)	6
		100	3 (43)	3 (43)	1 (14)	0 (0)	7	0 (0)	0 (0)	5 (71)	2 (29)	7	0 (0)	0 (0)	4 (90)	1 (20)	5
		150	1 (33)	1 (33)	1 (33)	0 (0)	3	1 (33)	0 (0)	1 (33)	1 (33)	3	0 (0)	0 (0)	2 (67)	1 (33)	3
<b>Total</b>	<b>50-150</b>		9 (50)	5 (28)	4 (22)	0 (0)	18	3 (17)	1 (6)	11 (61)	3 (17)	18	1 (6)	1 (6)	7 (44)	7 (44)	16
<b>Regimen 2</b>																	
6	20	50	0 (0)	0 (0)	0 (0)	2	1 (50)	0 (0)	0 (0)	1 (50)	2	0 (0)	0 (0)	1 (50)	1 (50)	2	2
		75	1 (33)	1 (33)	1 (33)	0 (0)	3	0 (0)	0 (0)	2 (87)	1 (33)	3	1 (50)	0 (0)	1 (50)	0 (0)	2
		100	5 (31)	8 (50)	3 (19)	0 (0)	16	1 (7)	7 (47)	6 (40)	1 (7)	15	0 (0)	2 (29)	4 (57)	1 (14)	7
		150	2	0 (0)	1 (33)	0 (0)	3	2 (67)	0 (0)	1 (33)	0 (0)	3	0 (0)	0 (0)	3 (100)	0 (0)	3
<b>Total</b>	<b>50-150</b>		8 (33)	9 (38)	5 (21)	2 (8)	24	4 (17)	7 (30)	9 (39)	3 (13)	23	1 (7)	2 (14)	9 (64)	2 (14)	14
<b>Regimen 3</b>																	
12	30	50	1 (50)	1 (50)	0 (0)	0 (0)	2	0 (0)	0 (0)	1 (50)	1 (50)	2	0 (0)	0 (0)	1 (50)	1 (50)	2
		75	2	0 (0)	0 (0)	0 (0)	2	0 (0)	0 (0)	1 (100)	0 (0)	1	0 (0)	0 (0)	1 (100)	0 (0)	1
		100	1 (20)	3 (60)	0 (0)	1 (20)	5	1 (20)	0 (0)	1 (20)	3	5	1 (20)	0 (0)	1 (20)	3 (60)	5
		150	3	0 (0)	1 (25)	0 (0)	4	2 (50)	0 (0)	2 (50)	0 (0)	4	0 (0)	0 (0)	1 (25)	3	4
<b>Total</b>	<b>50-150</b>		7 (54)	4 (31)	1 (8)	1 (8)	13	3 (25)	0 (0)	5 (42)	4 (33)	12	1 (8)	0 (0)	4 (33)	7 (58)	12
<b>Regimen 4</b>																	
6	15	50	2 (29)	5 (71)	0 (0)	0 (0)	7	0 (0)	2 (29)	4 (57)	1 (14)	7	0 (0)	0 (0)	2 (40)	3	5
		75	0 (0)	0 (0)	3 (100)	0 (0)	3	0 (0)	0 (0)	2 (67)	1 (33)	3	0 (0)	0 (0)	0 (0)	0 (0)	0
		100	2 (40)	0 (0)	2 (40)	1 (20)	5	0 (0)	2 (40)	3 (60)	0 (0)	5	1 (33)	0 (0)	1 (33)	1 (33)	3
<b>Total</b>	<b>50-100</b>		4 (27)	5 (33)	5 (33)	1 (7)	15	0 (0)	4 (27)	9 (60)	2 (13)	15	1 (13)	0 (0)	3 (38)	4 (50)	8
<b>Regimen 5</b>																	
6	10 <sup>d</sup>	12.5	0 (0)	0 (0)	2 (67)	1 (33)	3	0 (0)	0 (0)	2 (67)	1 (33)	3	0 (0)	0 (0)	2 (67)	1 (33)	3
		25	1 (13)	2 (25)	5 (62)	0 (0)	8	0 (0)	0 (0)	8 (100)	0 (0)	8	0 (0)	0 (0)	5 (71)	2 (29)	7
		50	1 (25)	1 (25)	1 (25)	1 (25)	4	1 (25)	1 (25)	2 (50)	0 (0)	4	1 (25)	0 (0)	3 (75)	0 (0)	4
<b>Total</b>	<b>12.5-50</b>		2 (13)	3 (20)	8 (53)	2 (13)	15	1 (7)	1 (7)	12 (80)	1 (7)	15	1 (7)	0 (0)	10 (71)	3 (21)	14
<b>Regimen 1-5 Total<sup>e</sup></b>																	
			30 (35)	26 (31)	23 (27)	6 (7)	85	11 (13)	13 (16)	46 (55)	13 (16)	83	5 (8)	3 (5)	33 (52)	23 (36)	64

<sup>a</sup> Occult CNV was not present in all patients. Frequencies are therefore based on the number of patients reported with occult at baseline.

<sup>b</sup> Time of light application after start of 10-minute verteporfin infusion

<sup>c</sup> Week 12 includes only patients who received a single course of PDT and were followed for 12 weeks, including the initial visit for re-enrolled patients.

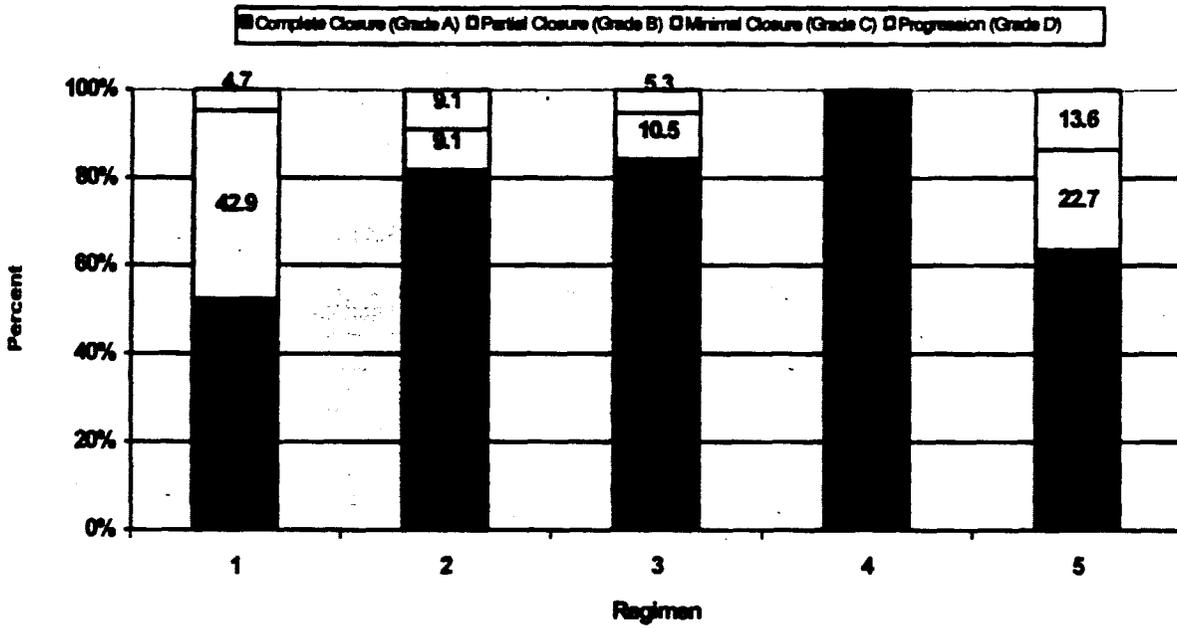
<sup>d</sup> Time of light application after start of 5-minute infusion

<sup>e</sup> Sample size varies due to 2 missing values at Week 4 and 21 missing values at Week 12.

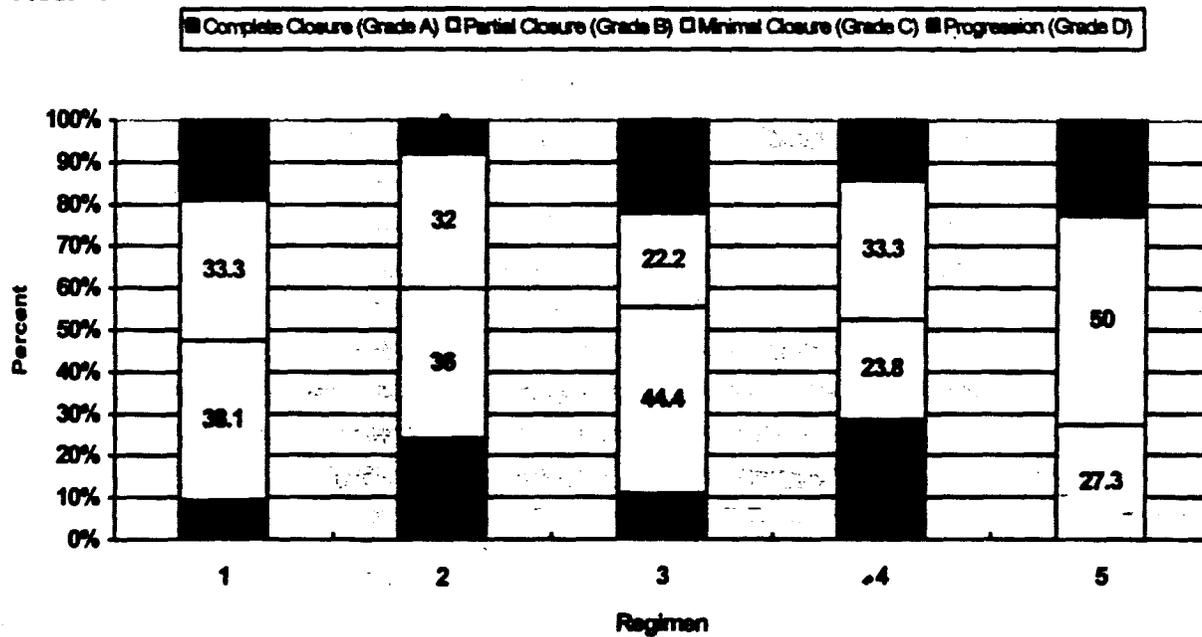
n = number of evaluable patients

Highlighted color represents greater than 50% of group (■, xx, ■)

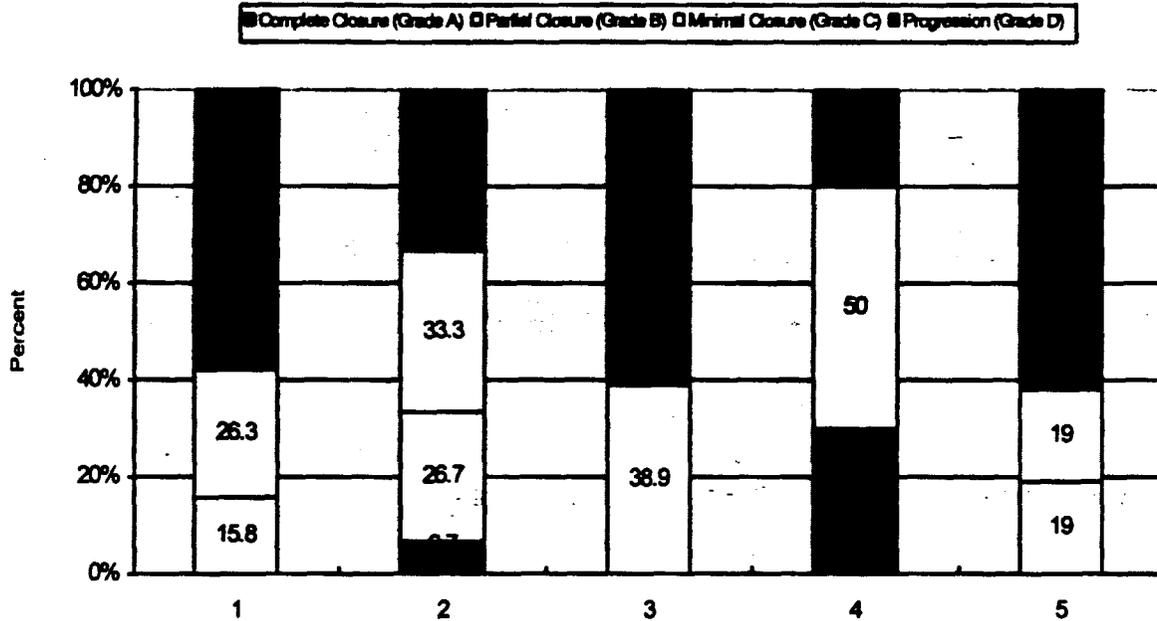
**Week 1**



**Week 4**



Week 12



**Applicant's Conclusions:**

Results suggest that Regimen 4 was associated with the best efficacy (effect on extent of classic CNV leakage and visual acuity). As a result, the lowest effective light dose tested in Regimen 4 (50 J/cm<sup>2</sup>) was chosen for evaluation in the long term Phase III efficacy and safety investigations.

**Reviewer's Comments:**

*Concur that Regimen 4 was best of those tested, however, there is still a significant percentage of patients with leakage at 3 months.*

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## 9 Overview of Efficacy

Efficacy Variable	Study A		Study B		Study A+B		Predominantly Classic CNV, Studies A+B	
	Verteporfin N=204	Placebo N=107	Verteporfin N=198	Placebo N=100	Verteporfin N=402	Placebo N=207	Verteporfin n=159	Placebo N=84
<15 letters lost								
% of responders	59.8%*	45.8%	62.6%**	47.0%	61.2%***	46.4%	67.3%***	39.3%
Difference (%)	(14.0)		(15.6)		(14.8)		(28.0)	
<30 letters lost								
% of responders	84.8%	79.4%	85.9%**	73.0%	85.3%**	76.3%	88.1%***	66.7%
Difference (%)	(5.4)		(12.9)		(9.0)		(21.4)	
Patients with VA <34 letters	37%	46%	33%**	50%	35%**	48%	37%***	63%
Visual acuity, mean change in letters	-12.3**	-17.8	-10.0***	-17.0	-11.2***	-17.4	-9.9***	-20.8
Contrast sensitivity, mean change in letters	-1.7***	-5.0	-0.8***	-4.1	-1.3***	-4.5	-0.4***	-5.5
Progression of classic CNV	44%***	66%	41%***	72%	43%***	69%	57%***	82%
Progression of occult CNV	71%	71%	63%*	78%	67%	74%	59%	64%
Lesion size ≤6 MPS DA	53%***	20%	52%***	29%	52%***	24%	53%***	24%

\* $P < .050$ , \*\* $P \leq .010$ , \*\*\* $P \leq .001$  for statistical significance of difference between verteporfin and placebo

**Reviewer's Comments:**

*Efficacy has been demonstrated with respect to decreasing the rate of visual loss in patients with predominately classic CNV without occult CNV.*

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10 Overview of Safety

Deaths

Deaths (Primary Ocular Studies)

Study OCR 001 VERTEPORFIN					
50	72/F	C2 D123	C2 D123	Acute ventricle failure due to myocardial infarction	Not related
95	71/M	C1 D81	C1 D81	Myocardial infarction	Not related

Deaths (Dermatology Studies)

Verteporfin BPD 001					
3	65/F			Increasing peripheral lymphadenopathy	Not related
11	59/M			Progressive liver disease/ gastrointestinal hemorrhage	Possible
18	76/F			Respiratory arrest and progression of underlying metastatic disease	Not related
29	69/F			Breast carcinoma with progressive metastases	Remote

## Exposure/ Overdose Experience

## Exposure to Verteporfin in All Studies

Verteporfin Dose (mg/m <sup>2</sup> )	Light Dose (J/cm <sup>2</sup> )	Number of Verteporfin Treatment Courses			Total Verteporfin Courses
		Clinical Pharmacology Studies	Dermatology Studies	Ocular Studies OCR 001	
3	0	8	0	0	8
6	0	28	0	0	31
	12.5	0	0	4	4
	25	0	0	12	12
	50	0	0	30	1817
	75	0	6	27	33
	100	0	0	107	107
	150	0	3	9	12
	374	0	0	1	1
8	40.5	0	29	0	29
	60	0	3	0	3
	75	0	12	0	12
	125	0	1	0	1
	150	0	8	0	8
10	50	0	3	0	3
	100	0	5	0	5
	150	0	2	0	2
12	0	17	0	0	17
	25	0	2	0	2
	50	0	4	3	7
	75	0	8	3	11
	100	0	0	10	10
	150	0	0	5	5
14	0	20	0	0	20
15	50	0	2	0	2
20	50	0	3	0	3
Total		73	91	211	2165

Maximum verteporfin exposure per treatment course was 20 mg/m<sup>2</sup> and maximum light exposure was 150 J/cm<sup>2</sup>, each of which is approximately three times the recommended drug (6 mg/m<sup>2</sup>) and light dose (50 J/cm<sup>2</sup>).

**Reviewer's Comments:** *No specific overdose events have been observed.*

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*This page of the document  
contains confidential  
information that will not  
be included in the  
redacted portion of the  
document for the public to  
obtain.*

Incidence of Ocular Adverse Events<sup>a</sup>

BODY SYSTEM Adverse Event	Number (%) of Patients	
	OCR 001	
Treat Site Ocular - Study Eye	44	(31.0)
Blepharitis	0	(0.0)
Cataract	0	(0.0)
Conjunctivitis	0	(0.0)
Corneal lesion <sup>b</sup>	0	(0.0)
Dry eyes	0	(0.0)
Eye disorder <sup>c</sup>	0	(0.0)
Eye hemorrhage <sup>d</sup>	0	(0.0)
Eye itching	0	(0.0)
Eye pain	4	(2.8)
Fibrosis	5	(3.5)
Fibrosis increased	11	(7.7)
Glaucoma	0	(0.0)
Hemorrhage increased	3	(2.1)
Lacrimation disorder	3	(2.1)
Photophobia	0	(0.0)
Retinal vessel Nonperfusion <sup>e</sup>	5	(3.5)
Branch retinal artery/vein Nonperfusion <sup>f</sup>	3	(2.1)
Retinal capillary nonperfusion	3	(2.1)
Retinal ischemia	4	(2.8)
Retinal vascular leakage	0	(0.0)
RPE atrophy increased	5	(3.5)
Staining of choroidal Vessels	2	(1.4)
Subretinal fluid Increased	9	(6.3)
Subretinal hemorrhage	5	(3.5)
Subretinal hemorrhage increased	13	(9.2)
Visual disturbance <sup>e</sup>	7	(4.9)
Vision abnormal	0	(0.0)
Vision decreased	7	(4.9)
Visual field defect	0	(0.0)
Vitreous disorder	0	(0.0)
Vitreous hemorrhage	2	(1.4)
SPECIAL SENSES (Including Nonstudy Eye Events) <sup>g</sup>	5	(3.5)
AMD progression	0	(0.0)
Cataract	0	(0.0)
Conjunctivitis	3	(2.1)
Corneal lesion <sup>b</sup>	0	(0.0)
Dry eyes	0	(0.0)
Eye itching	0	(0.0)
Visual Disturbance <sup>e</sup>	0	(0.0)
Vision abnormal	0	(0.0)
Vision decreased	0	(0.0)
Visual field defect	0	(0.0)

<sup>a</sup> Adverse events that were reported at an incidence of at least 1.0% (study eye) or 2.0% (nonstudy eye) in Study OCR 001 or in either treatment group.

<sup>b</sup> Corneal lesion reported terms included the following: arcus, corneal abrasion, corneal erosion, corneal punctate, epitheliopathy, guttata, inferior punctate epithelial staining, posterior crocodile shagreen of cornea, and punctate epithelial erosion.

<sup>c</sup> Eye disorder reported terms included the following: tingling sensation by tear duct and tired eyes.

<sup>d</sup> Eye hemorrhage reported terms included the following: conjunctival hemorrhage, peripapillary hemorrhage, and red and irritated eye (subconjunctival hemorrhage).

<sup>e</sup> Retinal vessel nonperfusion and visual disturbance are summary terms; individual terms are indented below them. Visual disturbance events were from subjective spontaneous reporting by patients. All individual terms included in each summary term are presented here, whether or not they occurred in  $\geq 1.0\%$  (study eye) or  $\geq 2.0\%$  (nonstudy eye) of patients.

<sup>f</sup> This term includes events reported as three different terms in Study OCR 001: branch retinal artery occlusion, branch retinal vein occlusion, and branch retinal artery/vein nonperfusion.

<sup>g</sup> The total number of patients with at least one event under "Special Senses" also included nonocular events such as deafness, otitis, and ear pain, each occurring at an incidence of  $< 1.0\%$ .

Incidence of Non-ocular Adverse Events  $\geq 2\%$ 

	Number (%) of Patients	
	OCR 001	
BODY SYSTEM	Verteporfin	
Adverse Event	N=142	
<b>BODY AS A WHOLE</b>	27 (19.0)	
Abdominal pain	1 (0.7)	
Accidental injury	0 (0.0)	
Allergic reaction	0 (0.0)	
Asthenia	7 (4.9)	
Back pain	4 (2.8)	
Chest pain	1 (0.7)	
Fever	0 (0.0)	
Flu syndrome	2 (1.4)	
Headache	10 (7.0)	
Infection	2 (1.4)	
<b>Injection site adverse events</b>	6 (4.2)	
Inj. site edema	1 (0.7)	
Inj. site extravasation	0 (0.0)	
Inj. site fibrosis	0 (0.0)	
Inj. site hemorrhage	1 (0.7)	
Inj. site hypersensitivity	0 (0.0)	
Inj. site inflammation	0 (0.0)	
Inj. site pain	3 (2.1)	
Inj. site rash	3 (2.1)	
Inj. site skin discolor.	1 (0.7)	
Pain	2 (1.4)	
Photosensitivity reaction	0 (0.0)	
<b>CARDIOVASCULAR</b>	7 (4.9)	
Arrhythmia	0 (0.0)	
Atrial fibrillation	0 (0.0)	
Cardiovascular disorder	0 (0.0)	
Hypertension	1 (0.7)	
Myocardial infarction	3 (2.1)	
<b>DIGESTIVE</b>	8 (5.6)	
Diarrhea	2 (1.4)	
Nausea	3 (2.1)	
Vomiting	1 (0.7)	
<b>HEMIC AND LYMPHATIC</b>	4 (2.8)	
Anemia	3 (2.1)	
<b>METABOLIC/NUTRITIONAL</b>	9 (6.3)	
Creatinine increased	0 (0.0)	
Glycosuria	0 (0.0)	
Hypercholesteremia	0 (0.0)	
Ketosis	0 (0.0)	
Peripheral edema	2 (1.4)	
<b>MUSCULOSKELETAL</b>	1 (0.7)	
Arthritis	0 (0.0)	
Myalgia	0 (0.0)	
Pathological fracture	1 (0.7)	
<b>NERVOUS</b>	10 (7.0)	
Depression	2 (1.4)	
Dizziness	6 (4.2)	
<b>RESPIRATORY</b>	13 (9.2)	
Bronchitis	3 (2.1)	
Cough increased	1 (0.7)	
Dyspnea	1 (0.7)	
Pharyngitis	4 (2.8)	
Pneumonia	0 (0.0)	
Rhinitis	3 (2.1)	
<b>SKIN AND APPENDAGES</b>	7 (4.9)	
Pruritus	1 (0.7)	
Rash	2 (1.4)	
<b>UROGENITAL</b>	4 (2.8)	
Cystitis	0 (0.0)	

## Incidence of Systemic (Non-Treatment Site) Adverse Events in All Studies

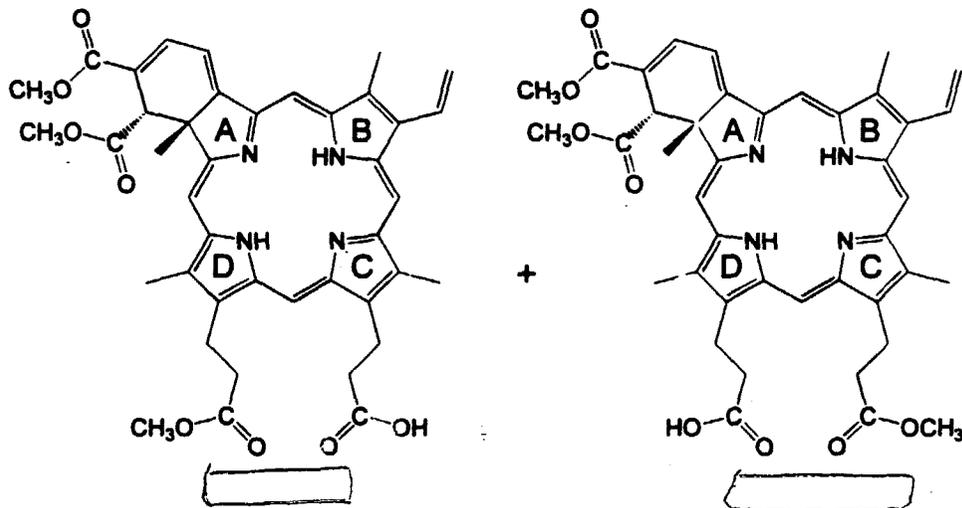
BODY SYSTEM Adverse Event	Number (%) of Subjects/Patients				Total Verteporfin N=679
	Study Group				
	Clin. Pharm. Verteporfin N=73	Dermatology Verteporfin N=62	OCR 001 Verteporfin N=142	Other	
Patients with at least one event	17 (23.3)	50 (80.6)	50 (35.2)		431 (63.5)
Headache	4 (5.5)	16 (25.8)	10 (7.0)		69 (10.2)
Injection site events	0 (0.0)	3 (4.8)	6 (4.2)		63 (9.3)
Injection site pain	0 (0.0)	2 (3.2)	3 (2.1)		40 (5.9)
Nausea	3 (4.1)	11 (17.7)	3 (2.1)		39 (5.7)
Asthenia	2 (2.7)	9 (14.5)	7 (4.9)		38 (5.6)
Infection	0 (0.0)	4 (6.5)	2 (1.4)		34 (5.0)
Hypertension	0 (0.0)	2 (3.2)	1 (0.7)		32 (4.7)
Dizziness	0 (0.0)	9 (14.5)	6 (4.2)		32 (4.7)
Visual disturbance	1 (1.4)	6 (9.7)	0 (0.0)		29 (4.3)
Back pain	1 (1.4)	3 (4.8)	4 (2.8)		25 (3.7)
Pain	0 (0.0)	9 (14.5)	2 (1.4)		25 (3.7)
Rash	5 (6.8)	7 (11.3)	2 (1.4)		25 (3.7)
Hypercholesteremia	0 (0.0)	2 (3.2)	0 (0.0)		24 (3.5)
Accidental injury	0 (0.0)	2 (3.2)	0 (0.0)		23 (3.4)
Conjunctivitis	2 (2.7)	1 (1.6)	3 (2.1)		23 (3.4)
Injection site edema	0 (0.0)	1 (1.6)	1 (0.7)		19 (2.8)
Diarrhea	1 (1.4)	4 (6.5)	2 (1.4)		19 (2.8)
Pharyngitis	1 (1.4)	4 (6.5)	4 (2.8)		19 (2.8)
Vision abnormal	1 (1.4)	6 (9.7)	0 (0.0)		18 (2.7)
Anemia	0 (0.0)	1 (1.6)	3 (2.1)		17 (2.5)
Peripheral edema	0 (0.0)	7 (11.3)	2 (1.4)		16 (2.4)
Rhinitis	0 (0.0)	5 (8.1)	3 (2.1)		16 (2.4)
Cystitis	0 (0.0)	0 (0.0)	0 (0.0)		16 (2.4)
Fever	0 (0.0)	7 (11.3)	0 (0.0)		15 (2.2)
Flu syndrome	0 (0.0)	1 (1.6)	2 (1.4)		15 (2.2)
Vomiting	0 (0.0)	7 (11.3)	1 (0.7)		15 (2.2)
Photosensitivity reaction	0 (0.0)	2 (3.2)	0 (0.0)		14 (2.1)
Creatinine increased	0 (0.0)	0 (0.0)	0 (0.0)		14 (2.1)
Inject site extravasation	0 (0.0)	1 (1.6)	0 (0.0)		13 (1.9)
Depression	0 (0.0)	1 (1.6)	2 (1.4)		13 (1.9)
Bronchitis	0 (0.0)	0 (0.0)	3 (2.1)		13 (1.9)
Pruritus	0 (0.0)	5 (8.1)	1 (0.7)		13 (1.9)
Vision decreased	0 (0.0)	0 (0.0)	0 (0.0)		13 (1.9)
Abdominal pain	3 (4.1)	3 (4.8)	1 (0.7)		12 (1.8)
Glycosuria	0 (0.0)	0 (0.0)	0 (0.0)		12 (1.8)
Dyspnea	0 (0.0)	4 (6.5)	1 (0.7)		12 (1.8)
Chest pain	0 (0.0)	2 (3.2)	1 (0.7)		11 (1.6)
Cough increased	0 (0.0)	1 (1.6)	1 (0.7)		11 (1.6)
Cataract	0 (0.0)	0 (0.0)	0 (0.0)		11 (1.6)
Inject site hemorrhage	0 (0.0)	0 (0.0)	1 (0.7)		10 (1.5)
Inject site persensitivity	0 (0.0)	0 (0.0)	0 (0.0)		9 (1.3)
Inject site inflammation	0 (0.0)	0 (0.0)	0 (0.0)		9 (1.3)
Arthritis	0 (0.0)	0 (0.0)	0 (0.0)		9 (1.3)
Corneal lesion	0 (0.0)	0 (0.0)	0 (0.0)		9 (1.3)
Ketosis	0 (0.0)	0 (0.0)	0 (0.0)		7 (1.0)
Myalgia	0 (0.0)	3 (4.8)	0 (0.0)		7 (1.0)
Allergic reaction	0 (0.0)	0 (0.0)	0 (0.0)		5 (0.7)
Pathological fracture	0 (0.0)	0 (0.0)	1 (0.7)		5 (0.7)
AMD progression	0 (0.0)	0 (0.0)	0 (0.0)		5 (0.7)
Arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)		4 (0.6)
Injection site rash	0 (0.0)	0 (0.0)	3 (2.1)		3 (0.4)
Visual field defect	0 (0.0)	0 (0.0)	0 (0.0)		2 (0.3)
Injection site fibrosis	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.1)
Inject site reaction	0 (0.0)	1 (1.6)	0 (0.0)		1 (0.1)
Inject site skin discolor	0 (0.0)	0 (0.0)	1 (0.7)		1 (0.1)

2 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.

## 11 Labeling Review

**VISUDYNE™**  
(verteporfin for injection)**DESCRIPTION**

VISUDYNE™ (verteporfin for injection) is a light activated drug used in photodynamic therapy [redacted]. The finished drug product is a lyophilized dark green cake. Verteporfin is a 1:1 mixture of two regioisomers [redacted] represented by the following structures:



[redacted]

The chemical names for the verteporfin regioisomers are:

[redacted]

Each mL of reconstituted VISUDYNE contains:

ACTIVE: Verteporfin, 2 mg

INACTIVES: Lactose, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine, ascorbyl palmitate and butylated hydroxytoluene

### CLINICAL PHARMACOLOGY

#### Mechanism of Action

VISUDYNE therapy is a two-stage process requiring administration of both verteporfin for injection and nonthermal red light.

Verteporfin is transported in the plasma primarily by [redacted] [redacted] 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 [redacted] local damage to neovascular endothelium, resulting in vessel occlusion. Damaged endothelium is known to release procoagulant and vasoactive factors through the lipo-oxygenase (leukotriene) and cyclo-oxygenase (eicosanoids such as thromboxane) pathways, resulting in platelet aggregation, fibrin clot formation and vasoconstriction. [redacted]

[redacted] The temporary occlusion of choroidal neovascularization (CNV) following VISUDYNE therapy has been confirmed in humans by fluorescein angiography.

#### Pharmacokinetics

[redacted]

Verteporfin is [redacted] to its diacid metabolite [redacted] by liver and plasma esterases. [redacted] 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

0.004% of the dose recovered in urine.

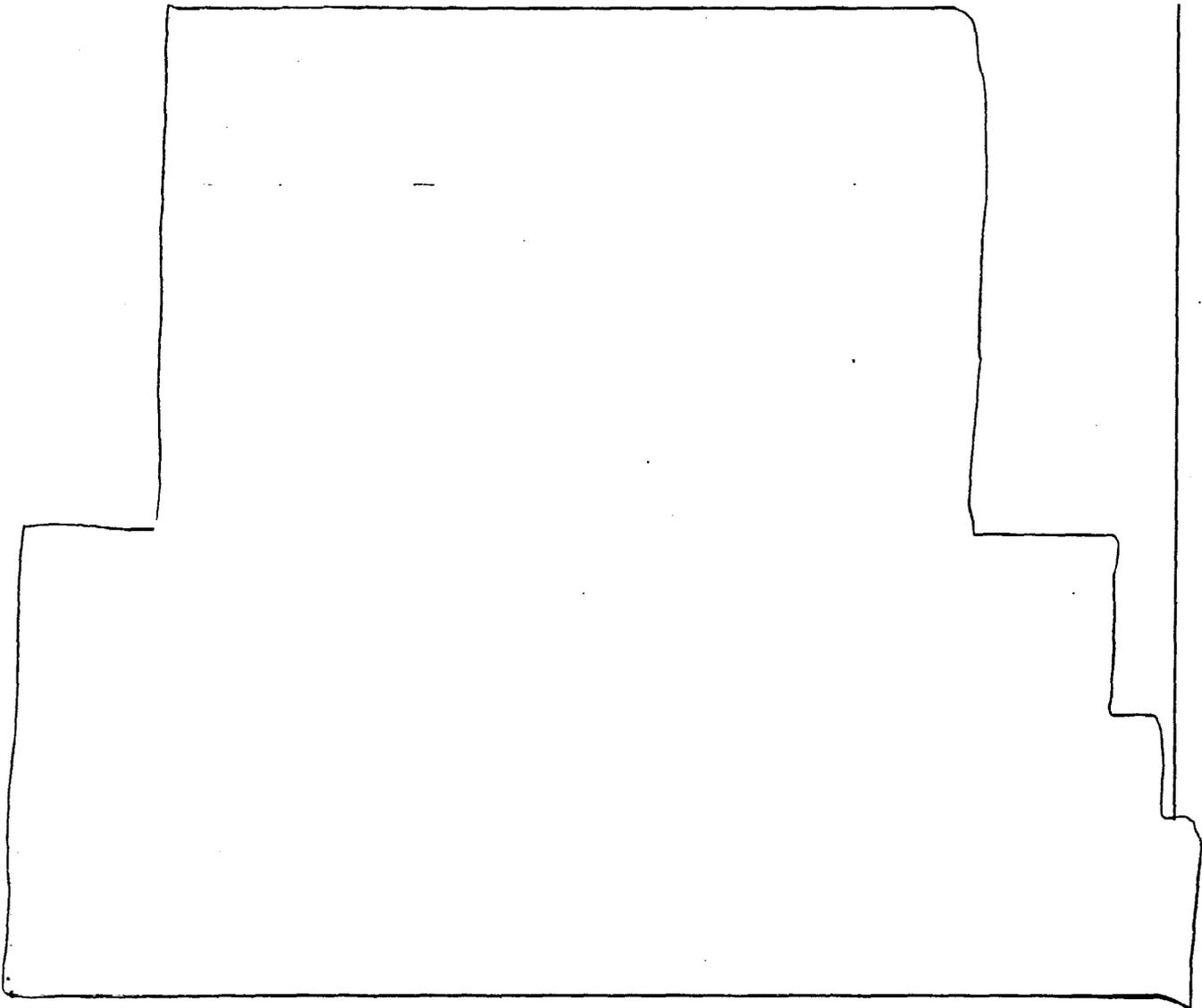
### Clinical Studies

Two adequate and well-controlled, double-masked, placebo-controlled, randomized studies were conducted in patients with classic-containing subfoveal CNV secondary to age-related macular degeneration. A total of 609 patients (VISUDYNE 402, placebo 207) were enrolled in these two studies. A planned analysis of safety and efficacy was conducted at 1 year, with 94% of patients completing that portion of the study. During these studies, retreatment was allowed every 3 months if angiograms showed any recurrence or persistence of leakage. The placebo control (sham treatment) consisted of intravenous administration of Dextrose 5% in Water, followed by light application identical to that used for VISUDYNE therapy.

The difference between treatment groups statistically favored VISUDYNE at the 1-year analysis for visual acuity endpoints.

The subgroup of patients with predominantly classic CNV lesions were more likely to exhibit a treatment benefit (N=243; VISUDYNE 159, placebo 84). Predominantly classic CNV lesions were defined as those in which the classic component comprised 50% or more of the area of the entire lesion.

For the primary efficacy endpoint (percentage of patients who lost less than 3 lines of visual acuity), these patients showed a difference of 28% between treatment groups (67% for VISUDYNE patients compared to 39% for placebo patients,  $P < .001$ ). Severe vision loss ( $\geq 6$  lines of visual acuity from baseline) was experienced by only 12% of VISUDYNE-treated patients compared to 33% of placebo-treated patients.



Patients with predominantly classic CNV lesions that did not contain occult CNV exhibited the greatest benefit (N=134; VISUDYNE 90, placebo 44). These patients demonstrated a 49% difference between treatment groups when assessed by the <3 lines-lost definition (77% vs. 27%). Severe vision loss was experienced by only 10% of VISUDYNE-treated patients compared to 41% of placebo-treated patients.

Older patients (>75 years), patients with dark iridies, patients with occult lesions, patients with less than 50% classic CNV were less likely to benefit from Visudyne therapy.

The safety and efficacy of VISUDYNE beyond 1 year have not been demonstrated.

**INDICATIONS AND USAGE**

VISUDYNE therapy is indicated for the treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.

**CONTRAINDICATIONS**

VISUDYNE is contraindicated for patients with porphyria or a known hypersensitivity to any component of this preparation.

**WARNINGS**

Following injection with VISUDYNE, care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for [REDACTED] In the event of extravasation during infusion, the extravasation area must be thoroughly protected from direct light until the swelling and discoloration have faded in order to prevent the occurrence of a local burn which could be severe. If emergency surgery is necessary within 24 hours after treatment, as much of the internal tissue as possible should be protected from intense light.

Patients who experience severe decrease of vision of 4 lines or more within 1 week after treatment should not be retreated, at least until their vision completely recovers to pretreatment levels and the potential benefits and risks of subsequent treatment are carefully considered by the treating physician.

Use of incompatible lasers that do not provide the required characteristics of light for the photoactivation of VISUDYNE could result in incomplete treatment due to partial photoactivation of VISUDYNE, overtreatment due to overactivation of VISUDYNE, or damage to surrounding normal tissue.

## PRECAUTIONS

### General

Standard precautions should be taken during infusion of VISUDYNE to avoid extravasation. Examples of standard precautions include, but are not limited to:

- A free-flowing IV line should be established before starting VISUDYNE infusion and the line should be carefully monitored.
- Due to the possible fragility of vein walls of some elderly patients, it is strongly recommended that the largest arm vein possible, preferably antecubital, be used for injection.
- Small veins in the back of the hand should be avoided.

If extravasation does occur, the infusion should be stopped immediately and cold compresses applied (see Warnings).

VISUDYNE therapy should be considered carefully in patients with moderate to severe hepatic impairment since there is no clinical experience with verteporfin in such patients.

There is no clinical data related to the use of VISUDYNE in anesthetized patients. At a >10-fold higher dose given by bolus injection to anesthetized pigs [REDACTED]

[REDACTED] verteporfin caused severe hemodynamic effects, including death, probably as a result of complement activation. These effects were diminished or abolished by pretreatment with antihistamine and they were not seen in conscious pigs or in any other species, whether conscious or under general anesthesia.

### Information for Patients

Patients who receive VISUDYNE will become temporarily photosensitive [REDACTED] after the infusion. During that period, patients should avoid exposure of unprotected skin, eyes or other body organs to direct sunlight or bright indoor light. [REDACTED] but is not limited to, tanning salons, bright halogen lighting and high power lighting used in surgical operating rooms or dental offices.

If treated patients must go outdoors in daylight during the first [REDACTED] after treatment, they [REDACTED] should protect all parts of their skin and their eyes by wearing protective clothing and dark sunglasses. [REDACTED]

[REDACTED] UV sunscreens are not effective in protecting against photosensitivity reactions because photoactivation of the residual drug in the skin can be caused by visible light.

Patients should not stay in the dark and should be encouraged to expose their skin to ambient indoor light, as it will help inactivate the drug in the skin through a process called photobleaching.

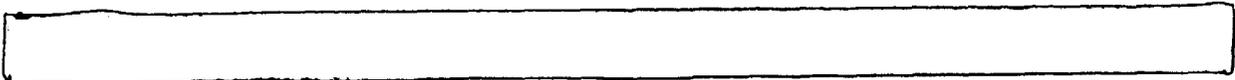
Drug Interactions

Drug interaction studies in humans have not been conducted with VISUDYNE.

Verteporfin is rapidly eliminated by the liver, mainly as unchanged drug. Metabolism is limited and occurs by liver and plasma esterases. Microsomal cytochrome P450 does not appear to play a role in verteporfin metabolism.

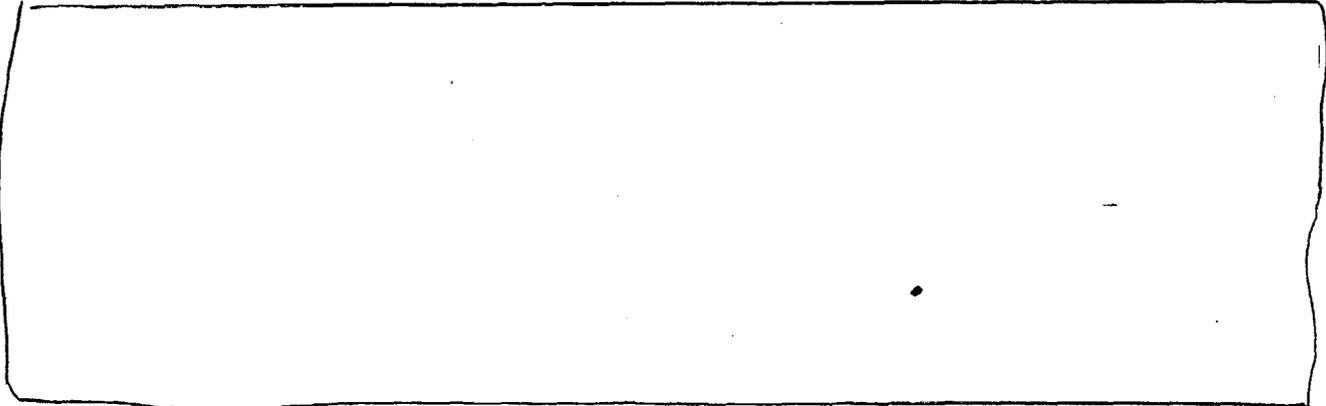
Based on the mechanism of action of verteporfin, many drugs used concomitantly could influence the effect of VISUDYNE therapy. Possible examples include the following.

Calcium channel blockers, polymyxin B or radiation therapy could enhance the rate of VISUDYNE uptake by the vascular endothelium. Other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide, diuretics and griseofulvin) could increase the potential for skin photosensitivity reactions. Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide,  $\beta$ -carotene, ethanol, formate and mannitol, would be expected to decrease VISUDYNE activity. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A<sub>2</sub> inhibitors, could also decrease the efficacy of VISUDYNE therapy.



Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to evaluate the carcinogenic potential of



Pregnancy

**Teratogenic Effects**

[redacted] n  
pregnant rabbits, a decrease in body weight gain and food consumption was observed in animals that received 10 mg/kg/day [redacted]. The no observed effect level (NOEL) for maternal toxicity was 3 mg/kg/day [redacted].

Nursing Mothers

It is not known whether [redacted] is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VISUDYNE is administered to a women who is nursing. [redacted]

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Approximately 90% of the patients treated with VISUDYNE in the [redacted] efficacy trials were over the age of 65 [redacted]. A reduced treatment effect was seen with increasing age [redacted].

**ADVERSE REACTIONS**

The most frequently reported adverse events to VISUDYNE are headaches, injection site

reactions (including extravasation and rashes) and visual disturbances (including blurred vision, decreased visual acuity and visual field defects). These events occurred in approximately 10-20% of patients. The following events were reported more frequently with VISUDYNE therapy than with placebo therapy and occurred in 1-10% of patients. [redacted]

Ocular Treatment Site: Conjunctivitis, conjunctival injection, dry eyes, ocular itching, subconjunctival, subretinal or vitreous hemorrhage.

Body as a Whole: Asthenia, back pain (primarily during infusion), fever, flu syndrome, photosensitivity.

Cardiovascular: [redacted]

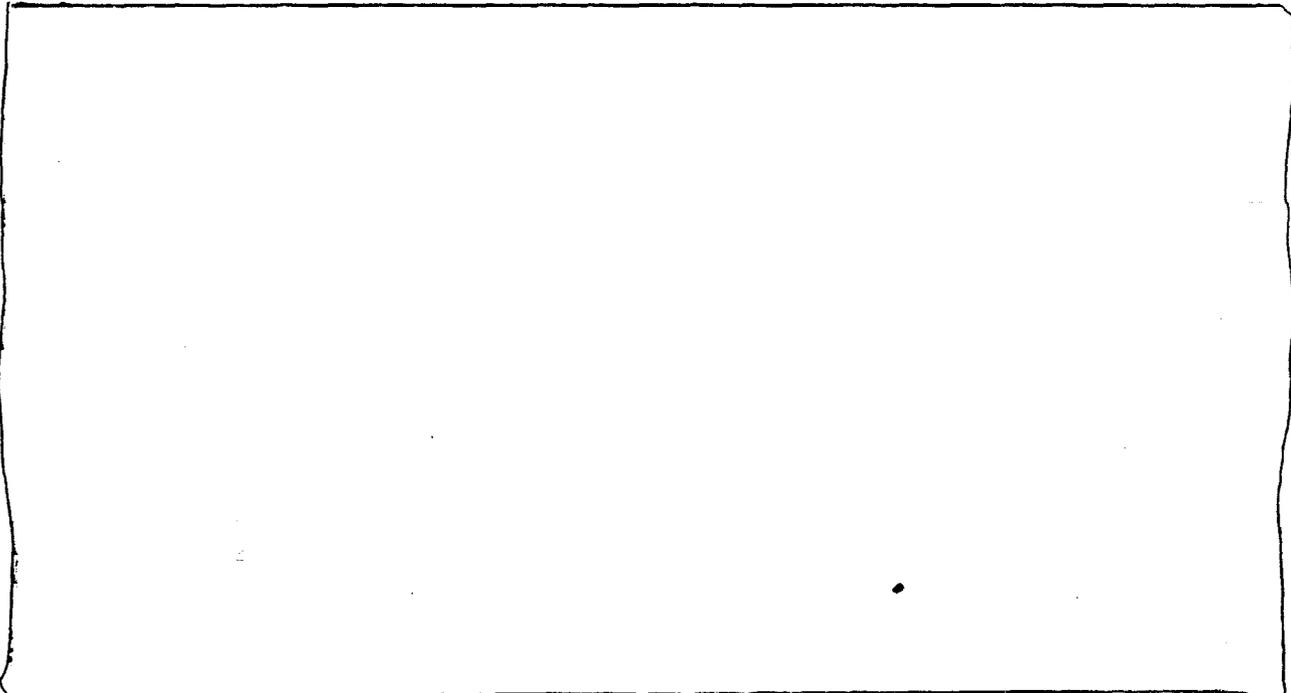
Dermatologic: [redacted]

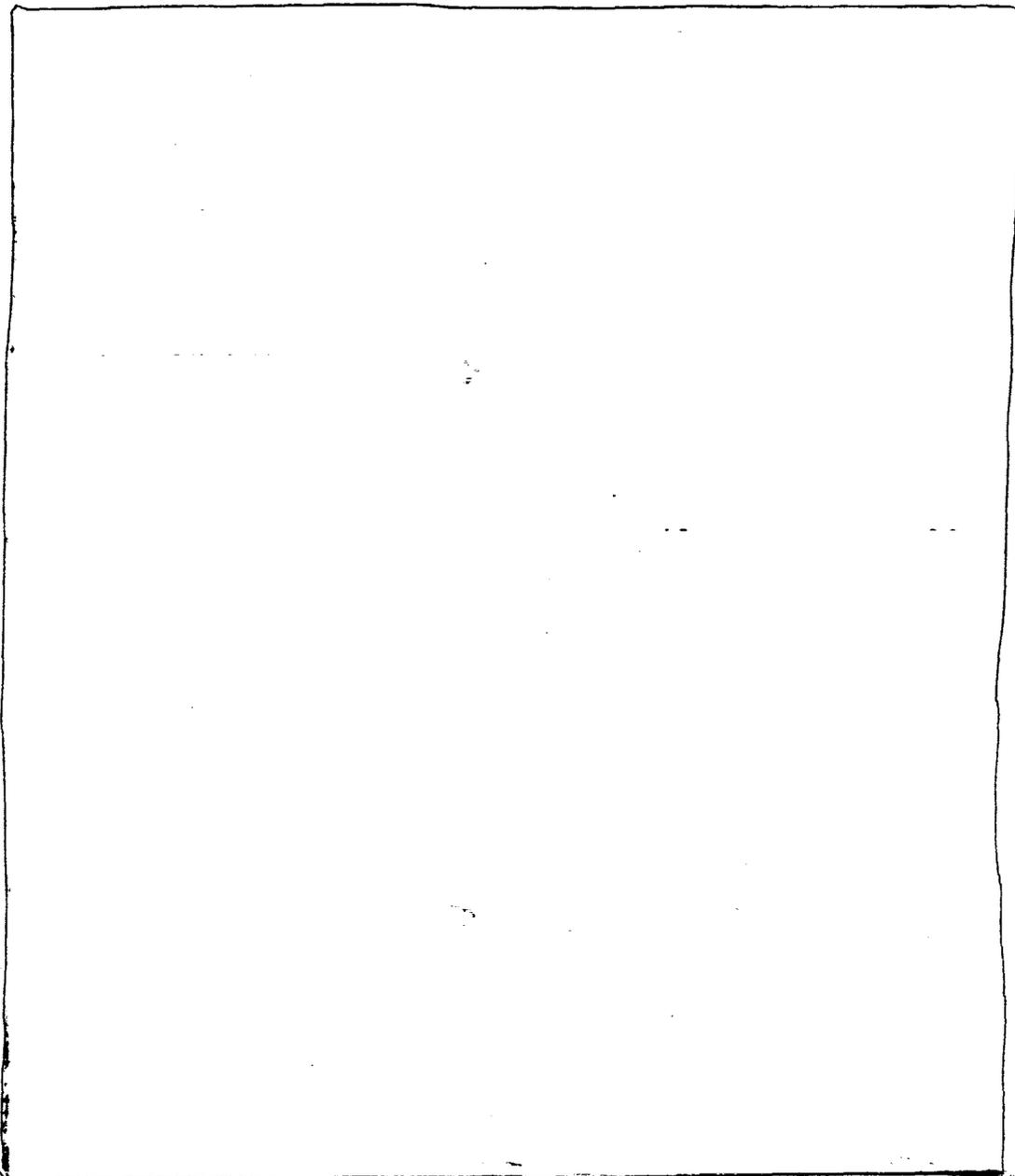
Digestive: Nausea

Hemic and Lymphatic: Anemia [redacted]

Metabolic/Nutritional: [redacted]

Respiratory: Pharyngitis, Pneumonia





~~Most adverse events were mild to moderate and transient in nature. Severe vision decrease, equivalent of 4 lines or more, within 7 days [redacted] has been reported in 1-4% of patients.~~

~~Partial recovery of vision was observed in [redacted] many patients. Photosensitivity reactions [redacted] occurred in the form of skin sunburn following exposure to sunlight [redacted] avoided by compliance with photosensitivity protection instructions (see Warnings). The higher incidence of back pain in the VISUDYNE group [redacted].~~

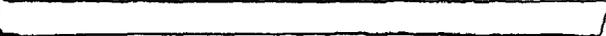
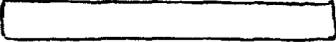


## OVERDOSAGE

Overdose of drug and/or light in the treated eye may result in nonperfusion of normal retinal vessels with the possibility of severe decrease in vision that could be permanent. An overdose of drug will also result in the prolongation of the period during which the patient remains photosensitive to bright light. In such cases, it is recommended to extend the photosensitivity precautions for a time proportional to the overdose.

## DOSAGE AND ADMINISTRATION

A course of VISUDYNE therapy is a two-step process requiring administration of both drug and light.

The first step is the intravenous infusion of VISUDYNE. The second step is the activation of VISUDYNE with light from a nonthermal diode laser.   


The physician should re-evaluate the patient every 3 months and if choroidal neovascular leakage is detected, therapy should be repeated.   
  


### Lesion Size Determination

The greatest linear dimension (GLD) of the lesion is estimated by fluorescein angiography and color fundus photography. All classic and occult CNV, blood and/or blocked fluorescence, and any serous detachments of the retinal pigment epithelium should be included for this measurement. Fundus cameras with magnification within the range of 2.4-2.6X are recommended. The GLD of the lesion on the fluorescein angiogram must be corrected for the magnification of the fundus camera to obtain the GLD of the lesion on the retina.

### Spot Size Determination

The treatment spot size should be 1000 microns larger than the GLD of the lesion on the retina to allow a 500 micron border, ensuring full coverage of the lesion. The maximum spot size used in the clinical trials was 6400 microns.

The nasal edge of the treatment spot must be positioned at least 200 microns from the temporal edge of the optic disc, even if this will result in lack of photoactivation of CNV within 200 microns of the optic nerve.

### VISUDYNE Administration

Reconstitute each vial of VISUDYNE with 7 mL of sterile Water for Injection to provide 7.5 mL containing 2 mg/mL. Reconstituted VISUDYNE must be protected from light and used within 4 hours. It is recommended that reconstituted VISUDYNE be inspected visually for particulate matter and discoloration prior to administration. Reconstituted VISUDYNE is an opaque dark green solution.

The volume of reconstituted VISUDYNE required to achieve the desired dose of 6 mg/m<sup>2</sup> body surface area is withdrawn from the vial and diluted with 5% Dextrose for Injection to a total infusion volume of 30 mL. The full infusion volume is administered intravenously over 10 minutes at a rate of 3 mL/minute, using an appropriate syringe pump.

Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, protect the site from light (See Precautions).

### Light Administration

Initiate 689 nm wavelength laser light delivery to the patient 15 minutes after the start of the 10-minute infusion with VISUDYNE.

Photoactivation of VISUDYNE is controlled by the total light dose delivered. In the treatment of choroidal neovascularization, the recommended light dose is 50 J/cm<sup>2</sup> of neovascular lesion administered at an intensity of 600 mW/cm<sup>2</sup>. This dose is administered over 83 seconds.

Light dose, light intensity, ophthalmic lens magnification factor and zoom lens setting are important parameters for the appropriate delivery of light to the predetermined treatment spot. Follow the laser system manuals for procedure set up and operation.

The laser system must  deliver a stable power output at a wavelength

of  $689\pm 3$  nm. Light is delivered to the retina as a single circular spot via a fiber optic and a slit lamp, using a suitable ophthalmic magnification lens.

~~The following laser systems have been tested for compatibility with VISUDYNE and [redacted] are approved for delivery of a stable power output at a wavelength of  $680\pm 3$  nm:~~

~~Coherent Opal Photoactivator Laser Console and LaserLink Adapter,  
Manufactured by Coherent, Inc., Santa Clara, CA~~

~~Zeiss VISULAS 600c laser and [redacted] VISULINK PDT [redacted]  
Manufactured by Carl Zeiss Inc., Thornwood, NY~~

### Concurrent Bilateral Treatment

The controlled trials only allowed treatment of one eye per patient. In patients who present with eligible lesions in both eyes, physicians should evaluate the potential benefits and risks of treating both eyes concurrently. If the patient has already received previous VISUDYNE therapy in one eye with an acceptable safety profile, both eyes can be treated concurrently after a single administration of VISUDYNE. The more aggressive lesion should be treated first, at 15 minutes after the start of infusion. Immediately at the end of light application to the first eye, the laser settings should be adjusted to introduce the treatment parameters for the second eye, with the same light dose and intensity as for the first eye, starting no later than 20 minutes from the start of infusion.

In patients who present for the first time with eligible lesions in both eyes without prior VISUDYNE therapy, it is prudent to treat only one eye (the most aggressive lesion) at the first course. One week after the first course, if no significant safety issues were identified, the second eye can be treated using the same treatment regimen after a second VISUDYNE infusion. Approximately 3 months later, both eyes can be evaluated and concurrent treatment following a new VISUDYNE infusion can be started if both lesions still show evidence of leakage.

APPEARS THIS WAY  
ON ORIGINAL

## **HOW SUPPLIED**

VISUDYNE is supplied in single use glass vials  The product is intended for intravenous injection only.

### **Spills and Disposal**

Spills of VISUDYNE should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light. Use of rubber gloves and eye protection is recommended. All materials should be disposed of properly.

### **Accidental Exposure**

Because of the potential to induce photosensitivity reactions, it is important to avoid contact with the eyes and skin during preparation and administration of VISUDYNE. Any exposed person must be protected from bright light (See Warnings).

NDC 58768-150-15

Store VISUDYNE between 20 and 25°C (68-77°F).

Rx Only

Manufactured by:

Parkedale Pharmaceuticals, Inc.  
Rochester, MI 48307

For:

QLT PhotoTherapeutics, Inc.  
Seattle, WA 98101

Co-developed and Distributed by:

CIBA Vision  
A Novartis Company  
Duluth, GA 30097

**Issues raised in this review**

1. All patients continue to lose best corrected visual acuity
2. Photosensitivity- 48 hour precautions were not sufficient
3. Lesions demonstrate leakage within 3 months after treatment
4. Repeat treatments have not been studied beyond 24 months (only 12 month data submitted to agency)
5. Repeat treatments have not been studied at intervals less than 3 months
6. Bilateral treatments have not been adequately studied
7. Discrepancies existed between the reading center and the treatment centers (reading center more sensitive)

**Advisory Committee Discussion**

*The Ophthalmologic sub-committee of the Dermatology and Ophthalmology Advisory Committee met on November 17, 1999, and discussed the issues raised in this review. There was concurrence that the use of the product appeared to produce a mild to moderate benefit for the patients with predominately classic type lesions and that in the absence of <sup>any</sup> other alternatives, the benefits outweighed the risks. The issues raised in this review continued to be of concern to this reviewer and the committee. Additionally, the committee was very interested in reviewing the 2 year follow-up data when available.*

**Recommendations:**

1. The applicant should provide revised draft labeling based on the discussions from the advisory committee meeting and the comments listed in this review.
2. The applicant should provide the 2 year follow-up data as soon as possible and should commit to a timetable for the submission of this information before the application is approved.
3. A decision on this application should be made after the other disciplines have completed their reviews.

/S/

Wiley A. Chambers, M.D.  
Supervisory Medical Officer, Ophthalmology

Cc: Orig NDA 21-119  
HFD-550  
HFD-550/PM/Gorski  
HFD-550/Chem/Fenselau  
HFD-550/Pharm/Wilson  
HFD-725/Stat/Li  
HFD-880/Biopharm/Tandon  
HFD-805/Micro/Vincent  
HFZ-440/Felten  
HFD-550/SMO/Chambers

Medical Officer's Review of NDA 21-119  
Revised labeling and Safety Update

NDA #21-119  
M.O. Review #2

Submission: 11/26/99 & 12/1/99  
Review completed: 1/7/00

Proposed Trade name: Visudyne  
Generic name: Verteporfin for injection

Common names for the verteporfin regioisomers are:

Benzoporphyrin derivative monoacid ring C (BPD-MA<sub>C</sub>) and  
Benzoporphyrin derivative monoacid ring D (BPD-MA<sub>D</sub>)

Chemical names for the verteporfin regioisomers are:

9-methyl trans-(±)-18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14, 19-tetramethyl-23*H*, 25*H*-benzo(b)porphine-9,13-dipropanoate and

13-methyl trans (±)-18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14, 19-tetramethyl-23*H*, 25*H*-benzo(b)porphine-9,13-dipropanoate.

Sponsor: QLT PhotoTherapeutics Inc.

Pharmacologic Category: Photoenhancer

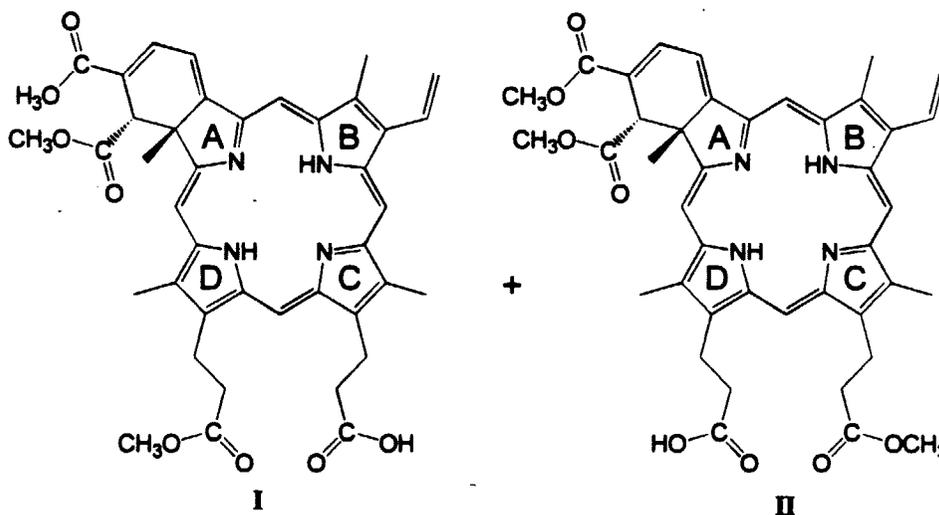
Proposed Indication(s): The treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.

APPEARS THIS WAY  
ON ORIGINAL

## 11 Labeling Review

**VISUDYNE™**  
(verteporfin for injection)**DESCRIPTION**

VISUDYNE™ (verteporfin for injection) is a light activated drug used in photodynamic therapy. The finished drug product is a lyophilized dark green cake. Verteporfin is a 1:1 mixture of two regioisomers (I) and (II), represented by the following structures:



The chemical names for the verteporfin regioisomers are:

9-methyl (I) and 13-methyl (II) trans-(±)-18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23H,25H-benzo(b)porphine-9,13-dipropionate

The molecular formula is  $C_{41}H_{42}N_4O_8$  with a molecular weight of approximately 718.8.

Each mL of reconstituted VISUDYNE contains:

ACTIVE: Verteporfin, 2 mg

INACTIVES: Lactose, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine, ascorbyl palmitate and butylated hydroxytoluene

## CLINICAL PHARMACOLOGY

### Mechanism of Action

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Verteporfin is transported in the plasma primarily by lipoproteins.

Once verteporfin is activated by light in the presence of oxygen, highly reactive, short-lived singlet oxygen and reactive oxygen radicals are generated. Light activation of verteporfin results in local damage to neovascular endothelium, resulting in vessel occlusion. Damaged endothelium is known to release procoagulant and vasoactive factors through the lipo-oxygenase (leukotriene) and cyclo-oxygenase (eicosanoids such as thromboxane) pathways, resulting in platelet aggregation, fibrin clot formation and vasoconstriction,

Verteporfin appears to somewhat preferentially accumulate in neovasculature, including choroidal neovasculature. However, animal models indicate that the drug is also present in the retina. Therefore, there may be collateral damage to retinal structures following photactivation including the retinal pigmented epithelium and outer nuclear layer of the retina. The temporary occlusion of choroidal neovascularization (CNV) following VISUDYNE therapy has been confirmed in humans by fluorescein angiography.

### Pharmacokinetics

Following intravenous infusion, verteporfin exhibits a biexponential elimination with [redacted] a terminal elimination half-life of approximately 5-6 hours. The extent of exposure and the maximal plasma concentration are proportional to the dose between 6 and 20 mg/m<sup>2</sup>. 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. 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 C<sub>max</sub> were not significantly different from the control group, half-life however was significantly increased by approximately 20%.

### Clinical Studies

Two adequate and well-controlled, double-masked, placebo-controlled, randomized studies were conducted in patients with classic-containing subfoveal CNV secondary to age-related macular degeneration. A total of 609 patients (VISUDYNE 402, placebo 207) were enrolled in these two studies. A planned analysis of safety and efficacy was conducted at 1 year, with 94% of patients completing that portion of the study. During these studies, retreatment was allowed every 3 months if angiograms showed any recurrence or persistence of leakage. The placebo control (sham treatment) consisted of intravenous administration of Dextrose 5% in Water, followed by light application identical to that used for VISUDYNE therapy.

The difference between treatment groups statistically favored VISUDYNE at the 1-year analysis for visual acuity [redacted] endpoints.

The subgroup of patients with predominantly classic CNV lesions were more likely to exhibit a treatment benefit (N=243; VISUDYNE 159, placebo 84). Predominantly classic CNV lesions

were defined as those in which the classic component comprised 50% or more of the area of the entire lesion. For the primary efficacy endpoint (percentage of patients who lost less than 3 lines of visual acuity), these patients showed a difference of 28% between treatment groups (67% for VISUDYNE patients compared to 39% for placebo patients,  $P < .001$ ). Severe vision loss ( $\geq 6$  lines of visual acuity from baseline) was experienced by only 12% of VISUDYNE-treated patients compared to 33% of placebo-treated patients.

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## WARNINGS

Following injection with VISUDYNE, care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for 5 days. In the event of extravasation during infusion, the extravasation area must be thoroughly protected from direct light until the swelling and discoloration have faded in order to prevent the occurrence of a local burn which could be severe. If emergency surgery is necessary within  48 hours after treatment, as much of the internal tissue as possible should be protected from intense light.

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- Small veins in the back of the hand should be avoided.

If extravasation does occur, the infusion should be stopped immediately and cold compresses applied (see Warnings).

VISUDYNE therapy should be considered carefully in patients with moderate to severe hepatic impairment since there is no clinical experience with verteporfin in such patients.

There is no clinical data related to the use of VISUDYNE in anesthetized patients. At a >10-fold higher dose given by bolus injection to anesthetized pigs [redacted]

[redacted] verteporfin caused severe hemodynamic effects, including death, probably as a result of complement activation. These effects were diminished or abolished by pretreatment with antihistamine and they were not seen in conscious pigs or in any other species, whether conscious or under general anesthesia.

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Patients who receive VISUDYNE will become temporarily photosensitive [redacted] after the infusion. Patients should wear a wrist band to remind them to avoid direct sunlight. During that period, patients should avoid exposure of unprotected skin, eyes or other body organs to direct sunlight or bright indoor light. [redacted] but not limited to, tanning salons, bright halogen lighting and high power lighting used in surgical operating rooms or dental offices.

If treated patients must go outdoors in daylight during the first 5 days after treatment, they should protect all parts of their skin and their eyes by wearing protective clothing and dark sunglasses. UV sunscreens are not effective in protecting against photosensitivity reactions because photoactivation of the residual drug in the skin can be caused by visible light.

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#### Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to evaluate the carcinogenic potential of VISUDYNE.

Photodynamic therapy has been reported to result in DNA damage including DNA strand breaks, alkali-labile sites, DNA degradation, and DNA-protein cross links which may result in chromosomal aberrations, sister chromatid exchanges (SCE), and mutations. In addition, other photodynamic therapeutic agents have been shown to increase the [redacted] [redacted] with visible light and in Chinese hamster lung fibroblasts irradiated with near UV light, increase mutations and DNA-protein crosslinking in mouse L5178 cells, and increase DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. Verteporfin was not evaluated in these systems. It is not known how the potential for DNA damage with PDT agents translates into human risk. [redacted]

[redacted]

No effect on male or female [redacted] observed [redacted] in rats [redacted] following intravenous administration of [redacted] up to [redacted] 10 mg/kg/day [redacted] (approximately 60 and [redacted] fold human exposure at 6 mg/m<sup>2</sup> based on AUC<sub>0-24</sub> in male and female rats, respectively).

[redacted]

[redacted]

Pregnancy  
Teratogenic Effects: Pregnancy Category C.

[redacted]

Rat fetuses of dams [redacted] administered [redacted] at  $\geq 10$  mg/kg/day during organogenesis (approximately 40 fold human [redacted] exposure at 6 mg/m<sup>2</sup> based on AUC<sub>0-24</sub> in female rats) [redacted] exhibited an increase [redacted] in the incidences of anophthalmia/micropthalmia. Rat fetuses of dams administered 25 mg/kg/day (approximately 125 fold the human exposure at 6 mg/m<sup>2</sup> based on AUC<sub>0-24</sub> in female rats) had an increased incidence of wavy ribs and [redacted]

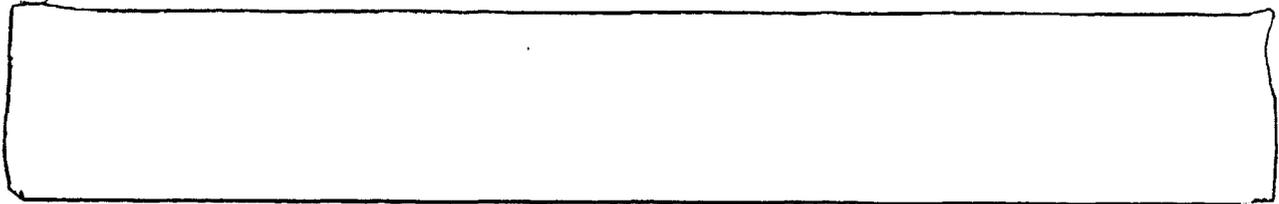
-In pregnant rabbits, a decrease in body weight gain and food consumption was observed in animals that received [redacted] 10 mg/kg/day during organogenesis [redacted]. The no observed adverse effect level (NOAEL) for maternal toxicity was 3 mg/kg/day (approximately 7 fold human exposure at 6 mg/m<sup>2</sup> based on body surface area).

[redacted]

There were no teratogenic effects observed in rabbits at doses up to 10

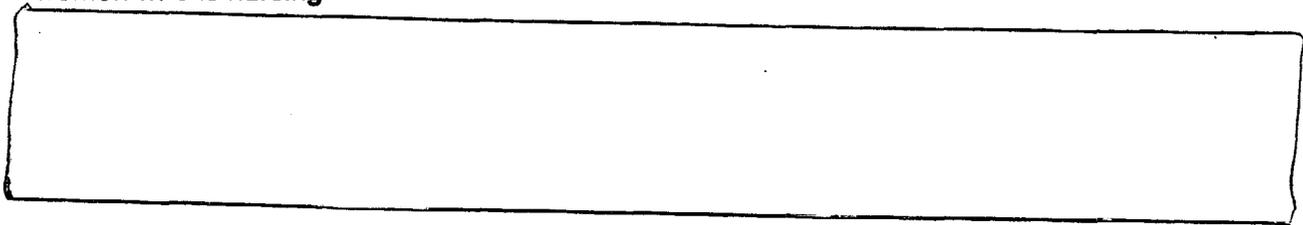
mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. VISUDYNE should be used during pregnancy only if the benefit justifies the potential risk to the fetus.



**Nursing Mothers**

It is not known whether [redacted] is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VISUDYNE is administered to a women who is nursing.



**Pediatric Use**

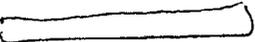
Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

Approximately 90% of the patients treated with VISUDYNE in the [redacted] efficacy trials were over the age of 65. A reduced treatment effect was seen with increasing age.

**ADVERSE REACTIONS**

The most frequently reported adverse events to VISUDYNE are headaches, injection site reactions (including extravasation and rashes) and visual disturbances (including blurred vision, decreased visual acuity and visual field defects). These events occurred in approximately 10-20% of patients. The following events were reported more frequently with VISUDYNE therapy than with placebo therapy and occurred in 1-10% of patients [redacted]



Ocular Treatment Site: Cataracts, conjunctivitis, conjunctival injection, dry eyes, ocular itching, severe vision loss, subconjunctival, subretinal or vitreous hemorrhage.

**Body as a Whole:** Asthenia, back pain (primarily during infusion), fever, flu syndrome, photosensitivity.

**Cardiovascular:** Atrial fibrillation, [redacted]

**Dermatologic:** [redacted]

**Digestive:** Constipation, Nausea

**Hemic and Lymphatic:** Anemia, [redacted] white blood cell count, [redacted]

**Hepatic:** Elevated liver function tests

**Metabolic/Nutritional:** Albuminuria, creatinine increased [redacted]

**Musculoskeletal** Arthralgia

**Nervous system:** Vertigo

**Respiratory:** Pharyngitis, Pneumonia

Severe vision decrease, equivalent of 4 lines or more, within 7 days has been reported in 1-4% of patients. Partial recovery of vision was observed in many patients. Photosensitivity reactions occurred in the form of skin sunburn following exposure to sunlight. The higher incidence of back pain in the VISUDYNE group occurred primarily during infusion.

## OVERDOSAGE

Overdose of drug and/or light in the treated eye may result in nonperfusion of normal retinal vessels with the possibility of severe decrease in vision that could be permanent. An overdose of drug will also result in the prolongation of the period during which the patient remains photosensitive to bright light. In such cases, it is recommended to extend the photosensitivity precautions for a time proportional to the overdose.

## DOSAGE AND ADMINISTRATION

A course of VISUDYNE therapy is a two-step process requiring administration of both drug and light.

The first step is the intravenous infusion of VISUDYNE. The second step is the activation of VISUDYNE with light from a nonthermal diode laser.

The physician should re-evaluate the patient every 3 months and if choroidal neovascular leakage is detected, therapy should be repeated.

#### Lesion Size Determination

The greatest linear dimension (GLD) of the lesion is estimated by fluorescein angiography and color fundus photography. All classic and occult CNV, blood and/or blocked fluorescence, and any serous detachments of the retinal pigment epithelium should be included for this measurement. Fundus cameras with magnification within the range of 2.4-2.6X are recommended. The GLD of the lesion on the fluorescein angiogram must be corrected for the magnification of the fundus camera to obtain the GLD of the lesion on the retina.

#### Spot Size Determination

The treatment spot size should be 1000 microns larger than the GLD of the lesion on the retina to allow a 500 micron border, ensuring full coverage of the lesion. The maximum spot size used in the clinical trials was 6400 microns.

The nasal edge of the treatment spot must be positioned at least 200 microns from the temporal edge of the optic disc, even if this will result in lack of photoactivation of CNV within 200 microns of the optic nerve.

#### VISUDYNE Administration

Reconstitute each vial of VISUDYNE with 7.5 mL of sterile Water for Injection to provide 7.5 mL containing 2 mg/mL. Reconstituted VISUDYNE must be protected from light and used within 4 hours. It is recommended that reconstituted VISUDYNE be inspected visually for particulate matter and discoloration prior to administration. Reconstituted VISUDYNE is an opaque dark green solution.

The volume of reconstituted VISUDYNE required to achieve the desired dose of 6 mg/m<sup>2</sup> body surface area is withdrawn from the vial and diluted with 5% Dextrose for Injection to a total infusion volume of 30 mL. The full infusion volume is administered intravenously over 10 minutes at a rate of 3 mL/minute, using an appropriate syringe pump.

Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, protect the site from light (See Precautions).

**Light Administration**

Initiate 689 nm wavelength laser light delivery to the patient 15 minutes after the start of the 10-minute infusion with VISUDYNE.

Photoactivation of VISUDYNE is controlled by the total light dose delivered. In the treatment of choroidal neovascularization, the recommended light dose is 50 J/cm<sup>2</sup> of neovascular lesion administered at an intensity of 600 mW/cm<sup>2</sup>. This dose is administered over 83 seconds.

Light dose, light intensity, ophthalmic lens magnification factor and zoom lens setting are important parameters for the appropriate delivery of light to the predetermined treatment spot. Follow the laser system manuals for procedure set up and operation.

The laser system must deliver a stable power output at a wavelength of 689±3 nm. Light is delivered to the retina as a single circular spot via a fiber optic and a slit lamp, using a suitable ophthalmic magnification lens.

The following laser systems have been tested for compatibility with VISUDYNE [redacted] and are approved for delivery of a stable power output at a wavelength of 689±3 nm:

Coherent Opal Photoactivator Laser Console and LaserLink Adapter,  
Manufactured by Coherent, Inc., Santa Clara, CA

Zeiss VISULAS 690s laser and VISULINK PDT adapter, Manufactured by  
Carl Zeiss Inc., Thornwood, NY

**Concurrent Bilateral Treatment**

The controlled trials only allowed treatment of one eye per patient. In patients who present with eligible lesions in both eyes, physicians should evaluate the potential benefits and risks of treating both eyes concurrently. If the patient has already received previous VISUDYNE therapy in one eye with an acceptable safety profile, both eyes can be treated concurrently after a single administration of VISUDYNE. The more aggressive lesion should be treated first, at 15 minutes after the start of infusion. Immediately at the end of light application to the first eye, the laser settings should be adjusted to introduce the treatment parameters for the second eye, with the same light dose and intensity as for the first eye, starting no later than 20 minutes from the start of infusion.

In patients who present for the first time with eligible lesions in both eyes without prior VISUDYNE therapy, it is prudent to treat only one eye (the most aggressive lesion) at the first course. One week after the first course, if no significant safety issues were identified, the

second eye can be treated using the same treatment regimen after a second VISUDYNE infusion. Approximately 3 months later, both eyes can be evaluated and concurrent treatment following a new VISUDYNE infusion can be started if both lesions still show evidence of leakage.

#### **HOW SUPPLIED**

VISUDYNE is supplied in single use glass vial  The product is intended for intravenous injection only.

#### **Spills and Disposal**

Spills of VISUDYNE should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light. Use of rubber gloves and eye protection is recommended. All materials should be disposed of properly.

#### **Accidental Exposure**

Because of the potential to induce photosensitivity reactions, it is important to avoid contact with the eyes and skin during preparation and administration of VISUDYNE. Any exposed person must be protected from bright light (See Warnings).

NDC 58768-150-15

Store VISUDYNE between 20 and 25°C (68-77°F).

Rx Only

Manufactured by:

Parkedale Pharmaceuticals, Inc.  
Rochester, MI 48307

For:

QLT PhotoTherapeutics, Inc.  
Seattle, WA 98101

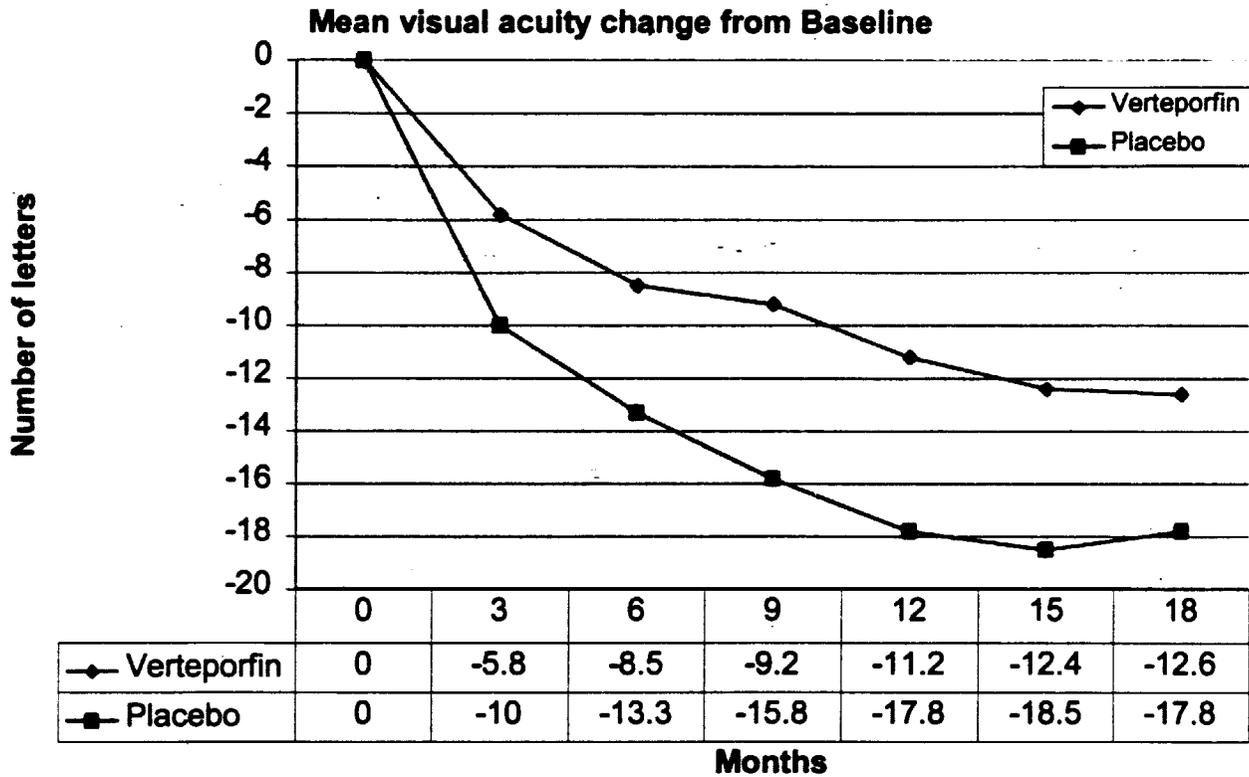
Co-developed and Distributed by:

CIBA Vision  
A Novartis Company  
Duluth, GA 30097

Safety Update

The cutoff date for this safety update was March 25, 1999. Additional adverse experiences have been reported in updated tables.

**Reviewer's Comments:** *The cutoff date should be more recent. The additional adverse experiences have been incorporated in this reviewer's proposed labeling.*



**Reviewer's Comments:** *The difference between groups appears to be decreasing with time after 12 months.*

APPEARS THIS WAY

**Recommendations:**

1. The applicant should provide revised draft labeling based on the discussions from the advisory committee meeting and the comments listed in this review.
2. The applicant should provide the 2 year follow-up data as soon as possible and should commit to a timetable for the submission of this information before the application is approved.

**/S/**

**Wiley A. Chambers, M.D.**  
Supervisory Medical Officer, Ophthalmology

**Cc:** Orig NDA 21-119  
HFD-550  
HFD-550/PM/Gorski  
HFD-550/Chem/Fenselau  
HFD-550/Pharm/Wilson  
HFD-725/Stat/Li  
HFD-880/Biopharm/Tandon  
HFD-805/Micro/Vincent  
HFZ-440/Felten  
HFD-550/SMO/Chambers

**APPEARS THIS WAY  
ON ORIGINAL**



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.

Reviewer's Comments: *Concur.*

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

[redacted] half-life was [redacted] increased by approximately 20%.

Reason:

[redacted]

Reviewer's Comments: *Disagree. The accuracy of findings which are not statistically significant is highly questionable and could be misleading.*

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL



	INFUSION RELATED BACK PAIN	5	2.5	0	0
	INJECTION SITE EDEMA	9	4.4	0	0
	INJECTION SITE EXTRAVASATION	9	4.4	5	4.7
	INJECTION SITE FIBROSIS	1	0.5	0	0
	INJECTION SITE HEMORRHAGE	7	3.4	4	3.7
	INJECTION SITE HYPERSENSITIVITY	3	1.5	0	0
	INJECTION SITE INFLAMMATION	4	2.0	1	0.9
	INJECTION SITE PAIN	18	8.8	1	0.9
	LAB TEST ABNORMAL	2	1.0	3	2.8
	MALaise	2	1.0	0	0
	NECK PAIN	0	0	2	1.9
	NEOPLASM	2	1.0	3	2.8
	PAIN	19	9.3	7	6.5
	PHOTOSENSITIVITY REACTION	6	2.9	0	0
	SEPSIS	2	1.0	1	0.9
	SHOCK	0	0	2	1.9
	VIRAL INFECTION	3	1.5	1	0.9
CARDIOVASCULAR SYSTEM	ANGINA PECTORIS	3	1.5	1	0.9
	AORTIC STENOSIS	1	0.5	1	0.9
	ARRHYTHMIA	8	3.9	4	3.7
	ARTERIAL ANOMALY	2	1.0	0	0
	ARTERIOSCLEROSIS	3	1.5	1	0.9
	ARTERITIS	1	0.5	0	0
	ATRIAL FIBRILLATION	4	2.0	3	2.8
	ATRIAL FLUTTER	1	0.5	1	0.9
	AV BLOCK FIRST DEGREE	2	1.0	0	0
	BRADYCARDIA	3	1.5	0	0
	CARDIOMEGALY	4	2.0	3	2.8
	CARDIOVASCULAR DISORDER	12	5.9	6	5.6
	CEREBROVASCULAR DISORDER	2	1.0	0	0
	CONGESTIVE HEART FAILURE	5	2.5	4	3.7
	CDR PULMONALE	1	0.5	1	0.9
	CORONARY ARTERY DISORDER	8	3.9	4	3.7
	DEEP THROMBOPHLEBITIS	0	0	1	0.9
	ELECTROCARDIOGRAM ABNORMAL	6	2.9	2	1.9
	EXTRASYSTOLES	1	0.5	0	0
	HEART FAILURE	4	2.0	2	1.9
	HYPERTENSION	18	8.8	7	6.5
	HYPOTENSION	2	1.0	2	1.9
	LEFT HEART FAILURE	1	0.5	0	0
	MIGRAINE	4	2.0	0	0
	MYOCARDIAL INFARCT	3	1.5	4	3.7
	MYOCARDIAL ISCHEMIA	1	0.5	0	0
	PALPITATION	2	1.0	0	0
	PERIPHERAL VASCULAR DISORDER	3	1.5	2	1.9
	PHLEBITIS	0	0	2	1.9
	PULMONARY EMBOLUS	2	1.0	0	0
	PULMONARY HYPERTENSION	1	0.5	0	0
	PULMONARY INFARCT	0	0	1	0.9
	PULMONARY THROMBOSIS	0	0	1	0.9
	SINUS BRADYCARDIA	1	0.5	0	0
	SUPRAVENTR EXTRASYSTOLES	2	1.0	0	0
	SUPRAVENTR TACHYCARDIA	0	0	2	1.9
	SYNCOPE	5	2.5	4	3.7
	TACHYCARDIA	2	1.0	3	2.8
	THROMOPHLEBITIS	2	1.0	0	0
	THROMBOSIS	2	1.0	1	0.9
	VARICOSE VEIN	6	2.9	1	0.9
	VASCULAR ANOMALY	2	1.0	0	0
	VASCULAR DISORDER	4	2.0	0	0
	VASODILATATION	1	0.5	1	0.9
	VENTRICULAR EXTRASYSTOLES	3	1.5	1	0.9
DIGESTIVE SYSTEM	ABNORMAL STOOLS	0	0	1	0.9
	ANOREXIA	1	0.5	1	0.9
	APHTHOUS STOMATITIS	1	0.5	0	0
	BLOODY DIARRHEA	1	0.5	0	0
	CARCINOMA	0	0	1	0.9
	CHOLECYSTITIS	3	1.5	2	1.9

	CHOLELITHIASIS	4	2.0	1	0.9
	COLITIS	1	0.5	1	0.9
	CONSTIPATION	5	2.5	0	0
	DIARRHEA	13	6.4	6	5.6
	DRY EYES	1	0.5	1	0.9
	DRY MOUTH	0	0	1	0.9
	DUODENAL ULCER	0	0	2	1.9
	DYSPEPSIA	0	0	2	1.9
	DYSPHAGIA	1	0.5	2	1.9
	ENTERITIS	1	0.5	0	0
	ESOPHAGEAL HEMORRHAGE	1	0.5	0	0
	ESOPHAGITIS	2	1.0	1	0.9
	FECAL INCONTINENCE	0	0	1	0.9
	FLATULENCE	1	0.5	1	0.9
	GASTROENTERITIS	2	1.0	1	0.9
	GASTROINTESTINAL CARCINOMA	5	2.5	0	0
	GASTROINTESTINAL DISORDER	8	3.9	5	4.7
	GASTROINTESTINAL HEMORRHAGE	1	0.5	1	0.9
	GINGIVITIS	1	0.5	0	0
	HEMATEMESIS	1	0.5	0	0
	HEMORRHAGIC GASTRITIS	1	0.5	0	0
	HEPATIC NEOPLASIA	1	0.5	0	0
	HEPATITIS	1	0.5	0	0
	HEPATOMEGALY	1	0.5	1	0.9
	INTESTINAL OBSTRUCTION	2	1.0	1	0.9
	LIVER DAMAGE	0	0	1	0.9
	LIVER FUNCTION TESTS ABNORMAL	0	0	1	0.9
	MOUTH ULCERATION	2	1.0	0	0
	NAUSEA	19	9.3	7	6.5
	NECROTIZING PANCREATITIS	1	0.5	0	0
	ORAL MONILIASIS	1	0.5	1	0.9
	PANCREAS DISORDER	1	0.5	0	0
	PERIODONTAL ABSCESS	2	1.0	2	1.9
	RECTAL DISORDER	1	0.5	0	0
	SIALADENITIS	2	1.0	0	0
	STOMACH ULCER HEMORRHAGE	2	1.0	0	0
	TONGUE EDEMA	1	0.5	0	0
	TOOTH CARIES	0	0	1	0.9
	TOOTH DISORDER	0	0	1	0.9
	VOMITING	3	1.5	3	2.8
ENDOCRINE SYSTEM	GOITER	1	0.5	0	0
	HYPERTHYROIDISM	2	1.0	1	0.9
	HYPOTHYROIDISM	4	2.0	2	1.9
	THYROIDITIS	1	0.5	0	0
HEMIC AND LYMPHATIC SYSTEM	ANEMIA	17	8.3	6	5.6
	BASOPHILIA	2	1.0	0	0
	BLOOD DYSCRASIA	1	0.5	0	0
	ECCHYMOSIS	4	2.0	3	2.8
	EOSINOPHILIA	4	2.0	0	0
	IRON DEFICIENCY ANEMIA	2	1.0	0	0
	LEUKOCYTOSIS	7	3.4	5	4.7
	LEUKOPENIA	10	4.9	1	0.9
	LYMPHADENOPATHY	1	0.5	0	0
	LYMPHOCYTOSIS	2	1.0	1	0.9
	LYMPHOMA LIKE REACTION	2	1.0	0	0
	MEGALOBLASTIC ANEMIA	0	0	1	0.9
	MONOCYTOSIS	3	1.5	1	0.9
	PETECHIA	1	0.5	0	0
	POLYCYTHEMIA	1	0.5	0	0
	PROTHROMBIN DECREASED	1	0.5	0	0
	THROMBOCYTOPENIA	3	1.5	1	0.9
MEDABOLIC AND NUTRITIONAL	ALBUMINURIA	9	4.4	3	2.8
	ALKALINE PHOSPH INCREASED	5	2.5	4	3.7
	BILIRUBINEMIA	1	0.5	0	0
	BUN INCREASED	0	0	1	0.9
	CREATINE PHOSPHOKINASE INCR	0	0	1	0.9
	CREATININE INCREASED	10	4.9	3	2.8
	DEHYDRATION	1	0.5	0	0

	DIABETES MELLITUS	3	1.5	3	2.8
	ELECTROLYTE ABNORMALITY	0	0	1	0.9
	GAMMA GLOBULINS INCREASED	1	0.5	0	0
	GLYCOSURIA	20	9.8	9	8.4
	GOUT	1	0.5	0	0
	HEALING ABNORMAL	1	0.5	0	0
	HYPERCHOLESTEREMIA	25	12.3	13	12.1
	HYPERGLYCEMIA	3	1.5	2	1.9
	HYPERKALEMIA	5	2.5	1	0.9
	HYPERLIPEMIA	0	0	1	0.9
	HYPERURICEMIA	3	1.5	0	0
	HYPOCHLOREMIA	1	0.5	0	0
	HYPOGLYCEMIA	3	1.5	2	1.9
	HYPOKALEMIA	2	1.0	4	3.7
	KETOSIS	11	5.4	6	5.6
	OBESITY	1	0.5	0	0
	PERIPHERAL EDEMA	13	6.4	6	5.6
	SGOT INCREASED	6	2.9	2	1.9
	SGPT INCREASED	5	2.5	2	1.9
MUSCULOSKELETAL SYSTEM	WEIGHT LOSS	3	1.5	2	1.9
	ARTHRALGIA	13	6.4	6	5.6
	ARTHRITIS	12	5.9	8	7.5
	ARTHROSIS	3	1.5	1	0.9
	BONE DISORDER	5	2.5	3	2.8
	BONE PAIN	0	0	1	0.9
	BURSITIS	0	0	2	1.9
	JOINT DISORDER	0	0	1	0.9
	LEG CRAMPS	1	0.5	1	0.9
	MYALGIA	2	1.0	3	2.8
	MYASTHENIA	5	2.5	0	0
	MYOPATHY	2	1.0	1	0.9
	OSTEOPOROSIS	5	2.5	4	3.7
	OSTEOPOROSIS FRACTURE	0	0	1	0.9
	PROSTATE CARCINOMA	1	0.5	0	0
	SPINAL MALFORMATION	1	0.5	2	1.9
	TENDON DISORDER	1	0.5	1	0.9
NERVOUS SYSTEM	TENOSYNOVITIS	2	1.0	0	0
	ABNORMAL GAIT	3	1.5	1	0.9
	AMNESIA	1	0.5	0	0
	ANXIETY	2	1.0	0	0
	APHASIA	1	0.5	0	0
	ATAXIA	0	0	1	0.9
	BRAIN EDEMA	2	1.0	0	0
	CEREBRAL INFARCT	2	1.0	0	0
	CEREBRAL ISCHEMIA	5	2.5	0	0
	CEREBROVASCULAR ACCIDENT	3	1.5	1	0.9
	CEREBROVASCULAR DISORDER	1	0.5	0	0
	CNS NEOPLASIA	1	0.5	0	0
	COMA	0	0	1	0.9
	CONFUSION	2	1.0	2	1.9
	CONVULSION	0	0	1	0.9
	DEMENTIA	0	0	1	0.9
	DEPRESSION	9	4.4	7	6.5
	DIZZINESS	15	7.4	8	7.5
	DYSTONIA	1	0.5	1	0.9
	EMOTIONAL LABILITY	1	0.5	0	0
	ENCEPHALOPATHY	0	0	1	0.9
	HALLUCINATIONS	1	0.5	0	0
	HEMIPLEGIA	2	1.0	1	0.9
	HYPERTONIA	1	0.5	0	0
	HYPERTONIA	2	1.0	1	0.9
	HYPESTHESIA	3	1.5	1	0.9
	INSOMNIA	4	2.0	3	2.8
	NERVOUSNESS	1	0.5	1	0.9
	NEURALGIA	3	1.5	2	1.9
	NEUROPATHY	2	1.0	0	0
	PARESTHESIA	1	0.5	5	4.7
	REFLEXES DECREASED	0	0	2	1.9

	REFLEXES INCREASED	1	0.5	0	0
	SLEEP DISORDER	5	2.5	0	0
	SOMNOLENCE	3	1.5	1	0.9
	SPEECH DISORDER	0	0	1	0.9
	STUPOR	0	0	1	0.9
	SUBDURAL HEMATOMA	0	0	1	0.9
	THINKING ABNORMAL	1	0.5	0	0
	TREMOR	2	1.0	0	0
	TWITCHING	2	1.0	0	0
	VERTIGO	6	2.9	3	2.8
RESPIRATORY SYSTEM	APNEA	1	0.5	3	2.8
	ASPIRATION PNEUMONIA	0	0	1	0.9
	ASTHMA	2	1.0	5	4.7
	BRONCHIECTASIS	0	0	1	0.9
	BRONCHITIS	8	3.9	6	5.6
	CARCINOMA OF LUNG	3	1.5	2	1.9
	COUGH INCREASED	13	6.4	8	7.5
	DYSPINEA	14	6.9	7	6.5
	EMPHYSEMA	4	2.0	2	1.9
	EPISTAXIS	0	0	1	0.9
	HYPOXIA	0	0	2	1.9
	LARYNGEAL NEOPLASIA	0	0	1	0.9
	LARYNGITIS	2	1.0	2	1.9
	LUNG DISORDER	7	3.4	5	4.7
	LUNG EDEMA	3	1.5	1	0.9
	LUNG FUNCTION DECREASED	0	0	1	0.9
	PHARYNGITIS	6	2.9	4	3.7
	PLEURAL EFFUSION	1	0.5	0	0
	PNEUMONIA	8	3.9	6	5.6
	PNEUMOTHORAX	1	0.5	1	0.9
	RESPIRATORY DISORDER	0	0	1	0.9
	RHINITIS	7	3.4	7	6.5
	SINUSITIS	5	2.5	4	3.7
	VOCAL CORD PARALYSIS	1	0.5	0	0
SKIN AND APPENDAGES	VOICE ALTERATION	0	0	1	0.9
	ACNE	0	0	2	1.9
	ALOPECIA	1	0.5	1	0.9
	APPLICATION SITE REACTION	0	0	1	0.9
	CONTACT DERMATITIS	1	0.5	0	0
	DRY SKIN	2	1.0	3	2.8
	ECZEMA	3	1.5	1	0.9
	FUNGAL DERMATITIS	0	0	1	0.9
	HERPES SIMPLEX	0	0	1	0.9
	HERPES ZOSTER	4	2.0	1	0.9
	LICHENOID DERMATITIS	1	0.5	0	0
	NAIL DISORDER	1	0.5	2	1.9
	PRURITUS	2	1.0	3	2.8
	PSORIASIS		0.90	0	1
	RASH	12	5.9	4	3.7
	SEBORRHEA	1	0.5	0	0
	SKIN BENIGN NEOPLASM	4	2.0	3	2.8
	SKIN CARCINOMA	4	2.0	1	0.9
	SKIN DISCOLORATION	3	1.5	0	0
	SKIN DISORDER	2	1.0	1	0.9
	SKIN HYPERTROPHY	2	1.0	1	0.9
	SKIN MELANOMA	1	0.5	0	0
	SKIN ULCER	4	2.0	2	1.9
	SUBCUTANEOUS NODULE	1	0.5	0	0
	SWEATING	3	1.5	0	0
	URTICARIA	1	0.5	0	0
SPECIAL SENSES	VESICULOBULLOUS RASH	1	0.5	0	0
	AMD PROGRESSION	6	2.9	4	3.7
	BLEPHARITIS	1	0.5	1	0.9
	CATARACT	9	4.4	7	6.5
	CONJUNCTIVITIS	9	4.4	4	3.7
	CORNEAL OPACITY	1	0.5	0	0
	DEAFNESS	5	2.5	1	0.9
	DIPLOPIA	2	1.0	0	0

	DRY EYES	0	0	2	1.9
	EAR DISORDER	1	0.5	2	1.9
	EAR PAIN	1	0.5	1	0.9
	EYE DISORDER	3	1.5	5	4.7
	EYE HEMORRHAGE	4	2.0	0	0
	EYE ITCHING	3	1.5	1	0.9
	EYE PAIN	5	2.5	1	0.9
	GLAUCOMA	2	1.0	1	0.9
	LACRIMATION DISORDER	5	2.5	1	0.9
	MELANOSIS	0	0	1	0.9
	OTTITIS EXTERNA	1	0.5	0	0
	OTTITIS MEDIA	3	1.5	1	0.9
	PHOTOPHOBIA	1	0.5	1	0.9
	RETINAL DETACHMENT	1	0.5	1	0.9
	RETINAL HEMORRHAGE	1	0.5	0	0
	RETINAL VEIN THROMBOSIS	1	0.5	0	0
	TINNITUS	1	0.5	1	0.9
	VESTIBULAR DISORDER	1	0.5	0	0
	VISION ABNORMAL	6	2.9	9	8.4
	VISION DECREASED	9	4.4	1	0.9
	VISUAL FIELD DEFECT	1	0.5	2	1.9
	VITREOUS DISORDER	2	1.0	1	0.9
	VITREOUS HEMORRHAGE	1	0.5	0	0
TREATMENT SITE - OCULAR	AMD PROGRESSION	0	0	2	1.9
	CATARACT	15	7.4	10	9.3
	CONJUNCTIVITIS	11	5.4	5	4.7
	CORNEAL LESION	2	1.0	1	0.9
	DRY EYES	2	1.0	3	2.8
	EYE DISORDER	2	1.0	2	1.9
	EYE ITCHING	6	2.9	1	0.9
	EYE PAIN	11	5.4	9	8.4
	FACE EDEMA	1	0.5	0	0
	GLAUCOMA	4	2.0	2	1.9
	GRANULOMA	0	0	1	0.9
	LACRIMATION DISORDER	4	2.0	2	1.9
	MELANOSIS	0	0	1	0.9
	OPTIC NEURITIS	0	0	1	0.9
	PHOTOPHOBIA	1	0.5	2	1.9
	RETINAL CAPIL NON-PERFUSION	0	0	1	0.9
	RETINAL DETACHMENT	3	1.5	0	0
	RETINAL DISORDER	2	1.0	5	4.7
	RETINAL HEMORRHAGE	1	0.5	1	0.9
	RUBEOSIS IRIDIS	0	0	1	0.9
	SKIN BENIGN NEOPLASM	1	0.5	1	0.9
	SUBRETINAL HEMORRHAGE	5	2.5	1	0.9
	VISION ABNORMAL	25	12.3	11	10.3
	VISION DECREASED	19	9.3	1	0.9
	VISUAL FIELD DEFECT	9	4.4	2	1.9
	VITREOUS DISORDER	1	0.5	3	2.8
	VITREOUS HEMORRHAGE	5	2.5	1	0.9
UROGENITAL SYSTEM	ACUTE KIDNEY FAILURE	1	0.5	0	0
	BLADDER CARCINOMA	2	1.0	0	0
	BLADDER NEOPLASM	1	0.5	0	0
	BREAST CARCINOMA	2	1.0	0	0
	BREAST ENLARGEMENT	1	0.5	0	0
	BREAST NEOPLASM	2	1.0	1	0.9
	BREAST PAIN	2	1.0	0	0
	CYSTITIS	10	4.9	6	5.6
	DYSURIA	2	1.0	0	0
	ENDOMETRIAL DISORDER	1	0.5	0	0
	ENDOMETRIAL HYPERPLASIA	1	0.5	0	0
	GYNecomastia	1	0.5	0	0
	HEMATURIA	2	1.0	0	0
	IMPOTENCE	0	0	1	0.9
	KIDNEY CALCULUS	0	0	1	0.9
	KIDNEY FUNCTION ABNORMAL	0	0	1	0.9
	METrorrhagia	1	0.5	0	0
	NEPHRITIS	1	0.5	1	0.9

POLYCYSTIC KIDNEY	1	0.5	0	0
PROSTATIC CARCINOMA	2	1.0	0	0
PROSTATIC DISORDER	9	4.4	1	0.9
PROSTATIC SPECIFIC ANTIGEN INCREASE	3	1.5	0	0
PYELONEPHRITIS	0	0	2	1.9
PYURIA	2	1.0	0	0
TESTIS DISORDER	0	0	1	0.9
URINARY FREQUENCY	1	0.5	1	0.9
URINARY INCONTINENCE	3	1.5	1	0.9
URINARY RETENTION	2	1.0	2	1.9
URINARY TRACT DISORDER	2	1.0	0	0
URINARY TRACT INFECTION	10	4.9	9	8.4
URINARY URGENCY	1	0.5	0	0
URINE ABNORMALITY	4	2.0	2	1.9
UROLITHIASIS	0	0	1	0.9
UTERINE DISORDER	0	0	1	0.9
VAGINAL HEMORRHAGE	1	0.5	0	0
VULVOVAGINAL DISORDER	0	0	1	0.9
COLD/CHILL	1	0.5	0	0

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## STUDY OCR 002 B

-ALL- TOTAL PATIENTS EXPOSED TO TREATMENT	198	100.0	100	100.0
-TOTAL WITH AT LEAST ONE EVENT	184	92.9	88	88.0
BODY AS A WHOLE				
ABDOMINAL PAIN	8	4.0	3	3.0
ACCIDENTAL INJURY	23	11.6	11	11.0
ADENOMA	2	1.0	0	0
ALLERGIC REACTION	4	2.0	1	1.0
ASTHENIA	13	6.6	5	5.0
BACK PAIN	10	5.1	6	6.0
CARCINOMA	2	1.0	0	0
CHEST PAIN	5	2.5	6	6.0
CHILLS	1	0.5	0	0
CHILLS AND FEVER	1	0.5	0	0
CYST	2	1.0	0	0
FLU SYNDROME	17	8.6	2	2.0
GRANULOMA	0	0	2	2.0
HEADACHE	21	10.6	13	13.0
HERNIA	3	1.5	1	1.0
HYPERTENSION	1	0.5	0	0
INFECTION	27	13.6	10	10.0
INFECTION BACTERIAL	0	0	2	2.0
INFECTION FUNGAL	0	0	1	1.0
INFUSION RELATED BACK PAIN	5	2.5	0	0
INJECTION SITE DISCOLORATION	2	1.0	0	0
INJECTION SITE EDEMA	17	8.6	1	1.0
INJECTION SITE EXTRAVASATION	16	8.1	1	1.0
INJECTION SITE HEMORRHAGE	2	1.0	0	0
INJECTION SITE HYPERSENSITIVITY	3	1.5	0	0
INJECTION SITE HYPERSENSITIVITY	1	0.5	0	0
INJECTION SITE INFLAMMATION	8	4.0	0	0
INJECTION SITE PAIN	28	13.1	0	0
LAB TEST ABNORMAL	0	0	1	1.0
MALAISE	2	1.0	0	0
NEOPLASM	5	2.5	2	2.0
PAIN	19	9.6	7	7.0
PHOTOSENSITIVITY REACTION	8	4.0	0	0
VIRAL INFECTION	1	0.5	0	0
CARDIOVASCULAR SYSTEM				
ANGINA PECTORIS	6	3.0	6	6.0
AORTIC STENOSIS	0	0	1	1.0
ARRHYTHMIA	0	0	1	1.0
ARTERIOSCLEROSIS	2	1.0	3	3.0
ARTERITIS	0	0	1	1.0
ATRIAL FIBRILLATION	7	3.5	1	1.0
BRADYCARDIA	1	0.5	0	0
BUNDLE BRANCH BLOCK	4	2.0	3	3.0
CARDIOMEGALY	2	1.0	0	0
CARDIOVASCULAR DISORDER	3	1.5	2	2.0
CONGESTIVE HEART FAILURE	1	0.5	0	0
CORONARY ARTERY DISORDER	2	1.0	1	1.0
ELECTROCARDIOGRAM ABNORMAL	2	1.0	1	1.0
HEART ARREST	2	1.0	0	0
HEART FAILURE	2	1.0	2	2.0
HEMORRHAGE	2	1.0	0	0
HYPERTENSION	23	11.6	10	10.0
HYPOTENSION	1	0.5	0	0
MIGRAINE	0	0	1	1.0
MYOCARDIAL INFARCT	5	2.5	3	3.0
PALPITATION	0	0	1	1.0
PERICARDIAL EFFUSION	0	0	1	1.0
PERIPHERAL VASCULAR DISORDER	5	2.5	0	0
PULMONARY EMBOLUS	1	0.5	0	0
SINUS BRADYCARDIA	1	0.5	0	0
SYNCOPE	2	1.0	0	0
TACHYCARDIA	2	4.0	1	1.0
THROMBOSIS	1	0.5	1	1.0
VARICOSE VEIN	1	0.5	0	0
VASCULAR ANOMALY	1	0.5	0	0

	VASODILATATION	0	0	2	2.0
	VENTRICULAR EXTRASYSTOLES	1	0.5	0	0
DIGESTIVE SYSTEM	ANOREXIA	0	0	1	1.0
	CHOLECYSTITIS	2	1.0	0	0
	CHOLELITHIASIS	1	0.5	0	0
	COLITIS	1	0.5	1	1.0
	CONSTIPATION	5	2.5	1	1.0
	DIARRHEA	6	3.0	6	6.0
	DYSPEPSIA	5	2.5	5	5.0
	ERUCTATION	0	0	1	1.0
	GASTROINTESTINAL CANCER	1	0.5	0	0
	GASTRITIS	2	1.0	0	0
	GASTROENTERITIS	4	2.0	3	3.0
	GASTROINTESTINAL CARCINOMA	2	1.0	0	0
	GASTROINTESTINAL DISORDER	4	2.0	5	5.0
	LIVER FUNCTION TESTS ABNORMAL	1	0.5	1	1.0
	NAUSEA	10	5.1	6	6.0
	PEPTIC ULCER	0	0	1	1.0
	PERIODONTAL ABSCESS	1	0.5	1	1.0
	RECTAL DISORDER	3	1.5	1	1.0
	RECTAL HEMORRHAGE	0	0	1	1.0
	SALIVARY GLAND ENLARGEMENT	2	1.0	0	0
	STOMACH ULCER	1	0.5	1	1.0
	STOMACH ULCER HEMORRHAGE	2	1.0	0	0
	TONGUE DISORDER	1	0.5	0	0
	TOOTH DISORDER	3	1.5	1	1.0
	VOMITING	8	4.0	3	3.0
ENDOCRINE SYSTEM	ADH INAPPROPRIATE	0	0	1	1.0
	HYPERTHYROIDISM	1	0.5	0	0
	HYPOTHYROIDISM	2	1.0	2	2.0
	THYROID DISORDER	1	0.5	0	0
HEMIC AND LYMPHATIC SYSTEM	ANEMIA	6	3.0	6	6.0
	DEFICIENCY ANEMIA	1	0.5	0	0
	ECCHYMOSIS	5	2.5	3	3.0
	EOSINOPHILIA	1	0.5	0	0
	IRON DEFICIENCY ANEMIA	1	0.5	0	0
	LEUKEMIA	1	0.5	0	0
	LEUKOCYTOSIS	2	1.0	0	0
	LYMPHADENOPATHY	0	0	1	1.0
	MEGALOBlastic ANEMIA	1	0.5	0	0
	MICROCYTIC ANEMIA	0	0	1	1.0
	MYELOMA	0	0	1	1.0
METABOLIC AND NUTRITIONAL	SEDIMENTATION RATE INCREASED	1	0.5	0	0
	ALBUMINURIA	0	0	1	1.0
	ALKALINE PHOSPHATASE INCR	1	0.5	1	1.0
	AMYLASE INCREASED	0	0	1	1.0
	BILIRUBINEMIA	0	0	2	2.0
	CREATININE INCREASED	5	2.5	2	2.0
	DEHYDRATION	0	0	1	1.0
	DIABETES MELLITUS	0	0	2	2.0
	GENERALIZED EDEMA	1	0.5	0	0
	GLYCOSURIA	1	0.5	3	3.0
	GOUT	2	1.0	1	1.0
	HYPERCHOLESTEREMIA	9	4.5	10	10.0
	HYPERGLYCEMIA	1	0.5	1	1.0
	HYPERKALEMIA	0	0	1	1.0
	HYPERLIPEMIA	0	0	1	1.0
	HYPERNATREMIA	1	0.5	0	0
	HYPOCHLOREMIA	0	0	1	1.0
	HYPOKALEMIA	5	2.5	2	2.0
	HYPONATREMIA	0	0	2	2.0
	KETOSIS	1	0.5	2	2.0
	LACTIC DEHYDROGENASE INCR	0	0	1	1.0
	PERIPHERAL EDEMA	12	6.1	5	5.0
	WEIGHT GAIN	1	0.5	0	0
	WEIGHT LOSS	1	0.5	2	2.0
MUSCULOSKELETAL SYSTEM	ARTHRALGIA	8	4.0	3	3.0
	ARTHRITIS	7	3.5	6	6.0

	ARTHROSIS	5	2.5	0	0	
	BONE DISORDER	1	0.5	3	3.0	
	BONE PAIN	1	0.5	1	1.0	
	BURSITIS	1	0.5	0	0	
	LEG CRAMPS	1	0.5	1	1.0	
	MUSCULOSKEL CONG ANOMALY	1	0.5	0	0	
	MYALGIA	3	1.5	2	2.0	
	MYASTHENIA	1	0.5	1	1.0	
	DSTEOPOROSIS	4	2.0	1	1.0	
	SYNOVITIS	1	0.5	0	0	
	TENDON DISORDER	1	0.5	1	1.0	
	TENOSYNOVITIS	1	0.5	0	0	
NERVOUS SYSTEM	ABNORMAL GAIT	3	1.5	2	2.0	
	AMNESIA	3	1.5	1	1.0	
	ANXIETY	4	2.0	4	4.0	
	ATAXIA	4	2.0	1	1.0	
	CEREBRAL HEMORRHAGE	1	0.5	0	0	
	CEREBRAL ISCHEMIA	2	1.0	3	3.0	
	CEREBROVASCULAR ACCIDENT	3	1.5	2	2.0	
	CEREBROVASCULAR DISORDER	1	0.5	0	0	
	COMA	1	0.5	0	0	
	CONFUSION	2	1.0	1	1.0	
	CONVULSION	0	0	1	1.0	
	DEPRESSION	7	3.5	6	6.0	
	DIZZINESS	8	4.0	4	4.0	
	EXTRAPYRAMIDAL SYNDROME	2	1.0	0	0	
	HEMIPLEGIA	1	0.5	0	0	
	HYPERTONIA	1	0.5	0	0	
	HYPESTHESIA	4	2.0	0	0	
	HYPOTONIA	2	1.0	0	0	
	ILEUS	1	0.5	0	0	
	INCOORDINATION	0	0	1	1.0	
	INSOMNIA	6	3.0	1	1.0	
	NERVOUSNESS	1	0.5	0	0	
	NEURALGIA	4	2.0	1	1.0	
	NEURITIS	1	0.5	0	0	
	NEUROPATHY	0	0	1	1.0	
	PARESTHESIA	1	0.5	0	0	
	REFLEXES DECREASED	1	0.5	0	0	
	SLEEP DISORDER	3	1.5	0	0	
	SOMNOLENCE	0	0	2	2.0	
	THINKING ABNORMAL	1	0.5	0	0	
	TREMOR	1	0.5	0	0	
	VERTIGO	7	3.5	1	1.0	
	RESPIRATORY SYSTEM	ASTHMA	3	1.5	0	0
		BRONCHITIS	10	5.1	5	5.0
		CARCINOMA OF LARYNX	1	0.5	0	0
		CARCINOMA OF LUNG	1	0.5	1	1.0
		COUGH INCREASED	6	3.0	2	2.0
		DYSPNEA	3	1.5	1	1.0
		EMPHYSEMA	1	0.5	0	0
		EPISTAXIS	2	1.0	0	0
LARYNGITIS		1	0.5	0	0	
LUNG DISORDER		2	1.0	0	0	
LUNG FUNCTION DECREASED		0	0	2	2.0	
PHARYNGITIS		9	4.5	2	2.0	
PNEUMONIA		8	4.0	2	2.0	
PULMONARY MYCOSIS		1	0.5	0	0	
RESPIRATORY DISORDER		1	0.5	0	0	
RHINITIS		6	3.0	4	4.0	
SINUSITIS		2	1.0	0	0	
SPUTUM INCREASED		1	0.5	1	1.0	
VOICE ALTERATION		1	0.5	0	0	
SKIN AND APPENDAGES		ACNE	4	2.0	0	0
		ALOPECIA	1	0.5	1	1.0
		CONTACT DERMATITIS	1	0.5	1	1.0
		DRY SKIN	1	0.5	1	1.0
	ECZEMA	3	1.5	0	0	

	HERPES ZOSTER	2	1.0	1	1.0
	MACULOPAPULAR RASH	1	0.5	1	1.0
	PRURITUS	4	2.0	3	3.0
	RASH	7	3.5	7	7.0
	SEBORRHEA	1	0.5	1	1.0
	SKIN BENIGN NEOPLASM	3	1.5	0	0
	SKIN CARCINOMA	3	1.5	2	2.0
	SKIN DISCOLORATION	1	0.5	0	0
	SKIN DISORDER	3	1.5	0	0
	SKIN HYPERTROPHY	1	0.5	1	1.0
	SKIN MELANOMA	1	0.5	1	1.0
	SKIN NODULE	1	0.5	0	0
	SKIN ULCER	2	1.0	1	1.0
	URTICARIA	1	0.5	1	1.0
SPECIAL SENSES	AMD PROGRESSION	5	2.5	9	9.0
	BLEPHARITIS	6	3.0	3	3.0
	CATARACT	20	10.1	8	8.0
	CONJUNCTIVITIS	11	5.6	7	7.0
	CORNEAL LESION	10	5.1	7	7.0
	DEAFNESS	2	1.0	0	0
	DIPLOPIA	3	1.5	0	0
	DRY EYES	9	4.5	3	3.0
	EAR DISORDER	1	0.5	0	0
	EAR PAIN	2	1.0	1	1.0
	EYE DISORDER	4	2.0	4	4.0
	EYE HEMORRHAGE	0	0	2	2.0
	EYE ITCHING	7	3.5	3	3.0
	EYE PAIN	8	4.0	5	5.0
	GLAUCOMA	5	2.5	3	3.0
	IRIS ATROPHY	1	0.5	1	1.0
	KERATITIS	0	0	1	1.0
	LACRIMATION DISORDER	3	1.5	1	1.0
	OPTIC ATROPHY	1	0.5	0	0
	OTTITIS MEDIA	1	0.5	1	1.0
	PAPILLOEDEMA	1	0.5	0	0
	PHOTOPHOBIA	2	1.0	3	3.0
	RETINAL DETACHMENT	0	0	1	1.0
	RETINAL DISORDER	2	1.0	0	0
	RETINAL EDEMA	0	0	1	1.0
	RETINAL VEIN THROMBOSIS	1	0.5	0	0
	SUBRETINAL HEMORRHAGE	2	1.0	1	1.0
	TASTE PERVERSION	0	0	1	1.0
	UVEITIS	1	0.5	0	0
	VESTIBULAR DISORDER	1	0.5	1	1.0
	VISION ABNORMAL	10	5.1	4	4.0
	VISION DECREASED	8	4.0	5	5.0
	VISUAL FIELD DEFECT	1	0.5	3	3.0
	VITREOUS DISORDER	1	0.5	0	0
	VITREOUS HEMORRHAGE	0	0	1	1.0
TREATMENT SITE - OCULAR	AMD PROGRESSION	6	3.0	2	2.0
	BLEPHARITIS	7	3.5	3	3.0
	CATARACT	45	22.7	21	21.0
	CHOROIDAL NON-PERFUSION	1	0.5	0	0
	CONJUNCTIVITIS	17	8.6	7	7.0
	CORNEAL LESION	9	4.5	7	7.0
	CORNEAL OPACITY	0	0	1	1.0
	CORNEAL ULCER	0	0	1	1.0
	DIPLOPIA	2	1.0	0	0
	DRY EYES	9	4.5	3	3.0
	EYE DISORDER	4	2.0	5	5.0
	EYE HEMORRHAGE	4	2.0	1	1.0
	EYE ITCHING	8	4.0	3	3.0
	EYE PAIN	12	6.1	9	9.0
	GLAUCOMA	4	2.0	3	3.0
	GRANULOMA	1	0.5	2	2.0
	IRIS ATROPHY	1	0.5	1	1.0
	IRITIS	1	0.5	0	0
	KERATITIS	0	0	1	1.0

LACRIMATION DISORDER	5	2.5	3	3.0
OPHTHALMITIS	1	0.5	0	0
OPTIC ATROPHY	1	0.5	0	0
OPTIC NEURITIS	0	0	1	1.0
PHOTOPHOBIA	4	2.0	3	3.0
RETINAL CAP NON-PERFUSION	1	0.5	1	1.0
RETINAL DETACHMENT	1	0.5	0	0
RETINAL DISORDER	1	0.5	5	5.0
RETINAL EDEMA	1	0.5	0	0
SUBRETINAL HEMORRHAGE	4	2.0	2	2.0
UVEITIS	1	0.5	0	0
VISION ABNORMAL	33	16.7	13	13.0
VISION DECREASED	22	11.1	12	12.0
VISUAL FIELD DEFECT	15	7.6	5	5.0
VITREOUS DISORDER	5	2.5	0	0
VITREOUS HEMORRHAGE	2	1.0	1	1.0
UROGENITAL SYSTEM				
BLADDER NEOPLASM	0	0	1	1.0
BREAST CARCINOMA	1	0.5	0	0
BREAST NEOPLASM	0	0	1	1.0
CYSTITIS	4	2.0	1	1.0
DYSURIA	1	0.5	1	1.0
HEMATURIA	1	0.5	4	4.0
HYDRONEPHROSIS	1	0.5	0	0
KIDNEY CALCULUS	1	0.5	1	1.0
KIDNEY SYS KIDNEY FAILURE	1	0.5	0	0
KIDNEY FUNCTION ABN	1	0.5	0	0
KIDNEY PAIN	1	0.5	0	0
METrorrhagia	1	0.5	0	0
PROSTATIC CARCINOMA	3	1.5	3	3.0
PROSTATIC DISORDER	4	2.0	3	3.0
URINARY FREQUENCY	2	1.0	1	1.0
URINARY RETENTION	3	1.5	1	1.0
URINARY TRACT DISORDER	1	0.5	2	2.0
URINARY TRACT INFECTION	4	2.0	4	4.0
UTERINE DISORDER	1	0.5	0	0
VAGINAL MONILIASIS	1	0.5	0	0
VAGINITIS	1	0.5	0	0

**Reviewer's Comments:**

*The adverse experiences highlighted above occurred more frequently in the verteporfin group.*

APPEARS THIS WAY  
ON ORIGINAL

**Gastrointestinal Cancer**

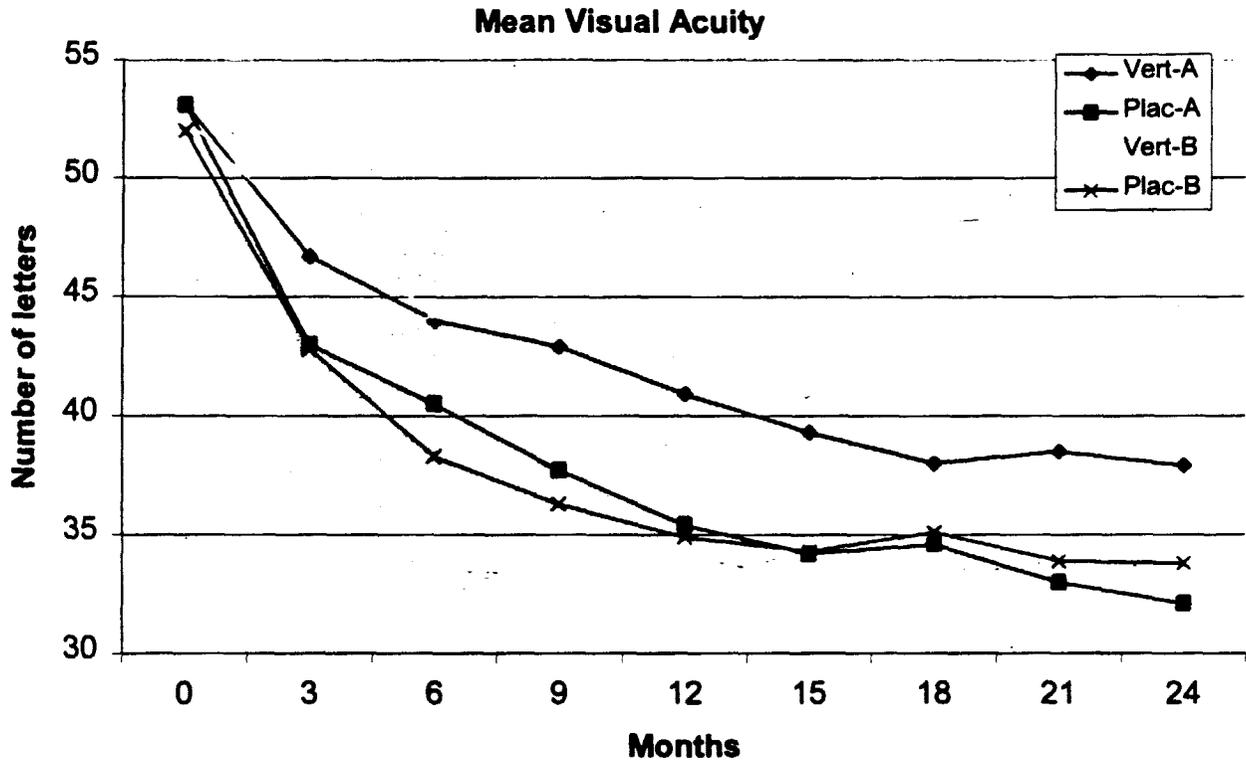
*Seven patients were reported to have developed gastrointestinal cancers. All patients were in the verteporfin group. The cases are listed below and represent a higher frequency than would have been expected based purely on age. There is no clear mechanism of action to attribute these cases to verteporfin.*

Study A	Age/Gender	Course/Day at Event	Reported Term
01217	75/M	C3 D68	Cancer sigmoid T4N0M0
01233	69/F	C5 D153	Gastric cancer
04114	78/M	C1 D10	Cancer of the colon
15204	89/M	C3 D214	Adenocarcinoma of cecum
18123	74/M	C2 D62	Cancer of colon
 Study B			
12203	73/F	C7 D86	Colon cancer
19209	69/M	C2 D505	Colon cancer

**Reviewer's Comments:** *The time course of some of these events makes verteporfin unlikely although not impossible to be the cause of the cancer.*

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

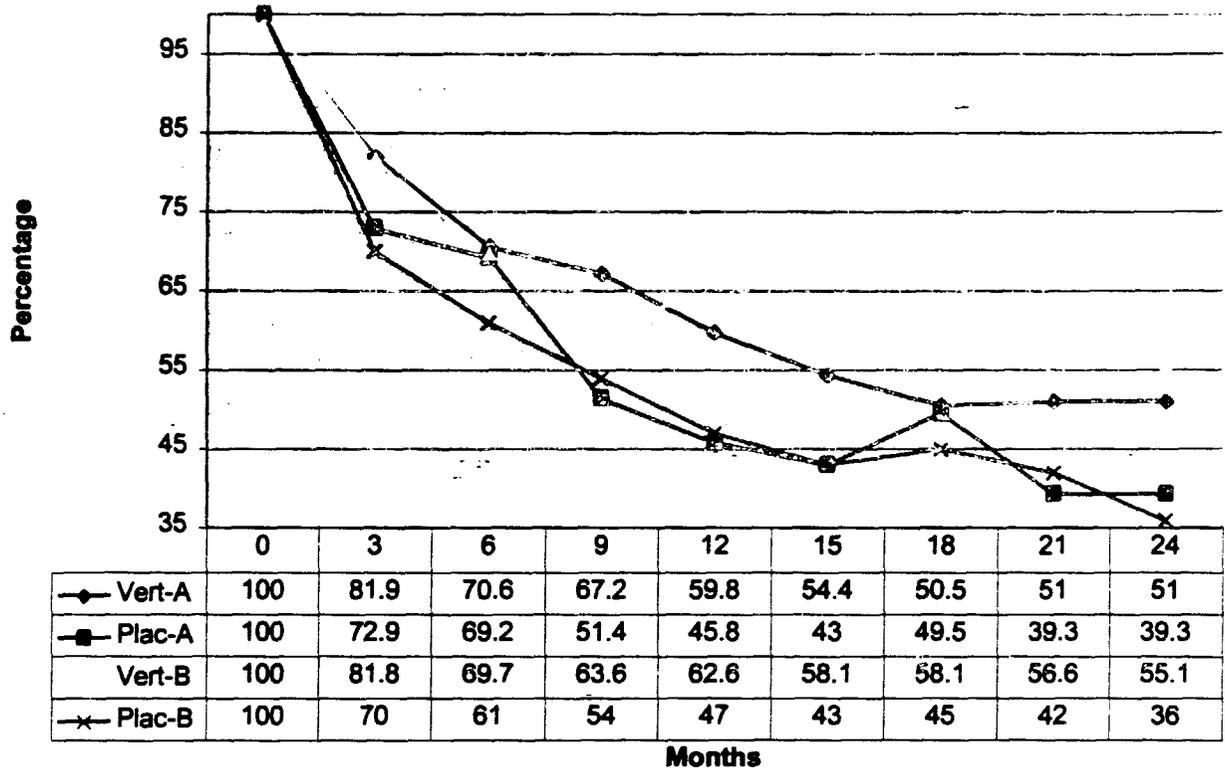


**Reviewer's Comments:**

*There is a continued decrease in visual acuity over the two year period in all groups. The Verteporfin groups continue to have better visual acuity than the placebo groups at all time points.*

APPEARS THIS WAY  
ON ORIGINAL

**Percentage of Responders (LOCF)**



**Reviewer's Comments:**

*The percentage of responders continues to decrease over time in all groups. When adjusted for the multiple "looks" performed on the 2-year data, only study B is statically significant at 21 and 24 months.*

APPEARS THIS WAY  
ON ORIGINAL