

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**21-119/S-001**

**MEDICAL REVIEW**



**Study Title:** BPD OCR 003 PM: A Randomized, Placebo-Controlled, Masked, Multicenter, Phase IIIB Study of the Treatment of New Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration or Pathologic Myopia Using Photodynamic Therapy with Verteporfin for Injection

**Objectives**

**Primary:** To determine if verteporfin PDT of new subfoveal choroidal neovascularization will significantly improve or retain visual function compared to placebo (sham treatment), and to evaluate the safety of verteporfin PDT.

**Secondary:** To determine if verteporfin PDT-induced improvements of visual function are associated with a better health-related quality of life compared to placebo (sham treatment).

To determine if verteporfin PDT reduces the risk of developing classic choroidal neovascularization (CNV) in lesions that present as occult CNV with no classic CNV (AMD only).

The Quality of Life (HQL) study results are to be provided in a separate report after Month 24.

Date of First Patient Enrolled:	February 26, 1998
Date of Last Patient Enrolled:	September 25, 1998
Date of Last Patient Completed 12-month Follow-up:	October 7, 1999
Data Cutoff:	October 29, 1999

**Reviewer's Comments:** *The 24 month follow-up should have been available by the 120 day safety update. These results were not provided in the safety update.*

**Design:** Masked, multicenter, randomized, parallel group, Phase 3B study comparing verteporfin PDT treatment to placebo. Since pathologic myopia (PM) and age-related macular degeneration (AMD) patients were allowed to participate under this protocol, two separate study reports were prepared. The PM population is described herein. The study used a 2:1 (verteporfin:placebo) randomization ratio. Patients were stratified by study center and etiology of CNV (PM or AMD). Analysis was planned after 12-month and 24-month follow-up. This report presents the 12-month analysis results for the PM population.

**Reviewer's Comments:** *Acceptable.*

## Study Investigators

Country	Investigator(s)	Study Center	Site Identification and Number	Number of PR Patients Enrolled
Austria	Michael Stur, MD <sup>a</sup>	Allgemeines Krankenhaus Klinik für Augenheilkunde Währinger Gürtel 18-20, 8. Stock 1090 Vienna	VIE 06	3
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France	Gisèle Soubrane, MD <sup>a</sup> Dagmar Kühn, MD Maddalena Quaranta, MD	Hôpital Intercommunal de Créteil Département d'Ophtalmologie 40 Avenue de Verdun F-94010 Créteil	PAR 04	7
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Germany	Bernhard Jurklies, MD <sup>a</sup> Daniel Pauleikhoff, MD <sup>b</sup>	University of Essen Department of Ophthalmology Hufslandstrasse 55 D-45147 Essen	ESS 28	6
Italy	Ugo Menchini, MD <sup>a</sup> Gianni Virgili, MD Francesco Bandello, MD	University of Udine Department of Ophthalmology Viale Venezia 410 I-33100 Udine	UDI 26	12
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Switzerland	Constantinos Pourmaras, MD <sup>a</sup> Guy Donati, MD	Hôpital Cantonal Universitaire de Geneva Département d'oto-neuro-ophtalmologie Clinique et Policlinique d'Ophtalmologie Rue Micheli-du-Crest 24 CH-1211 Geneva 14	GEN 03	5
Switzerland	Michel Sickenberg, MD <sup>a</sup>	Hôpital Ophtalmique Universitaire Jules Gonin Av. de France 15 CH-1004 Lausanne	LAU 02	9
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United States	Hunter Little, MD <sup>a</sup> Mark Blumenkranz, MD Robert Jack, MD	Zweng Memorial Retinal Research Foundation 1225 Crane Street Menlo Park, California 94025	MEN 13	3
United States	Gary Fish, MD <sup>a</sup> Bradley Jost, MD Rajiv Anand, MD David Callanan, MD	Texas Retina Associates Suite 400 7150 Greenville Avenue Dallas, Texas 75231	TEX 15	5
United States	Hilel Lewis, MD <sup>a</sup>	Cleveland Clinic Eye Institute	CCE	0

Country	Investigator	Study Center	Site Identification and Number	Number of PM Patients Enrolled
	Peter Kaiser, MD	9500 Euclid Avenue, Desk A31 Cleveland, Ohio 44195	12	
United States	Jennifer Lim, MD <sup>a</sup> Christina Flaxel, MD	University of Southern California Doheny Eye Institute 1450 San Pablo Street Los Angeles, California 90033	USC 25	1
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United States	Colin Ma, MD <sup>a</sup> Richard Dreyer, MD	Devers Eye Institute 1040 N.W. 22nd Avenue N200 Portland, Oregon 97210	POR 21	1
United States	Raymond Margherio, MD <sup>a</sup> George Williams, MD	Associated Retinal Consultants, PC William Beaumont Medical Building 3535 West 13 Mile Road Royal Oak, Michigan 48073	ROY 18	3
United States	Travis Meredith, MD <sup>a</sup>	Barnes Retina Institute Suite 17413 East Pavilion One Barnes Hospital Plaza St. Louis, Missouri 63110	STL 23	1
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United States	Robert Rosa, MD <sup>c</sup> Phillip Rosenfeld, MD <sup>c</sup> Mary-Lou Lewis, MD	Bascom Palmer Eye Institute 900 N.W. 17th Street Miami, Florida 33136	MIA 20	7
United States	David Saperstein, MD <sup>a</sup> Thomas M. Aaberg, Sr, MD	Emory Eye Center 1365-B Clifton Road Atlanta, Georgia 30322	ATL 24	5
United States	Andrew Schachat, MD <sup>a</sup> Neil Bressler, MD Susan Bressler, MD	The Wilmer Ophthalmological Institute Johns Hopkins University Maumenee Building 600 N. Wolfe Street Baltimore, Maryland 21287-9275	BAL 11	7
United States	Jason Slakter, MD <sup>a</sup> John Sorenson, MD	Vitreous-Retina-Macula Consultants of New York 519 East 72 <sup>nd</sup> Street New York, New York 10021	NEW 16	6
United States	Lawrence Singerman, MD <sup>a</sup> Hernando Zegarra, MD Michael Novak, MD	Retina Associates of Cleveland 26900 Cedar Road, #303 Cleveland, Ohio 44122	RAC 17	3
			<b>Total Patients</b>	<b>120</b>

<sup>a</sup> Indicates Principal Investigator

<sup>b</sup> Additional location - St. Franziskus Hospital, Augenabteilung, Hohenzollertring, Munster

<sup>c</sup> Co-Principal Investigators

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**Patient Population:** The study was to enroll approximately 400 patients (110 PM patients; 290 AMD patients).

### **Patient Inclusion Criteria**

Patients of either gender and any race were eligible provided they fulfilled all of the following criteria:

1. Had subfoveal CNV secondary to pathologic myopia alone or new subfoveal CNV secondary to age-related macular degeneration alone.
2. Lesions with occult CNV but no classic CNV must have contained blood or shown progression of disease within the preceding 3 months before randomization to treatment.
 

Disease progression was defined as either:

  - a. documented loss of  $\geq 6$  letters on a best-corrected visual acuity score, or
  - b. documented fluorescein angiographic evidence of  $\geq 10\%$  increase in the lesion's greatest linear dimension.
3. All study eyes must have had a best-corrected visual acuity score  $\geq 50$  letters or approximately 20/100 or better on ETDRS chart except eyes with new classic CNV-containing lesions secondary to AMD which must have had a best-corrected visual acuity score  $\geq 70$  letters (better than approximately 20/40).
4. If subfoveal CNV was a recurrence after prior laser photocoagulation, the laser photocoagulation must have been conducted within the past 3 months (90 days) before enrollment into the VIP trial. (This criterion was deleted by Amendment No. 2, dated July 16, 1998.)
5. If subfoveal CNV was due to pathologic myopia there had to be fundus manifestations consistent with this diagnosis (e.g. lacquer cracks), and at least one of the following had to apply:
  - a. the spherical equivalent had to be equal to or more negative than -6 diopters, or
  - b. the axial length had to be  $\geq 26.5$  mm.
6. Were considered able to return for all study visits.
7. Females of childbearing potential had to have a negative pregnancy test (blood) before inclusion in the study and had to use an effective method of contraception during the study. Negative pregnancy tests (urine) were required before any retreatment.
8. Were willing and able to provide written informed consent. Patients who were eligible for laser photocoagulation, or who enrolled in the HQL or other ancillary studies, had to sign the respective informed consent.
9. Were 18 years or older with pathologic myopia or 50 years or older with AMD.

Inclusion Criteria letters 1, 3, 6, 7, 8, and 9 applied to all patients while Criterion 5 applied only to PM patients and Criterion 2 applied only to AMD patients.

### **Patient Exclusion Criteria**

Patients were not eligible for enrollment if at screening they had any of the following:

1. Color photography and fluorescein angiography showed:
  - a. CNV did not involve the geometric center of the foveal avascular zone.
  - b. the area of CNV (classic plus occult) was less than 50% of the total lesion (not including areas of prior laser treatment).
  - c. the greatest linear dimension of the entire CNV lesion exceeded 5400  $\mu\text{m}$  diameter (approximately equivalent to the diameter of a 9 Macula Photocoagulation Study [MPS] disc area circle) at the initial treatment.
2. patient met criteria for subfoveal confluent laser photocoagulation but was not willing or able to sign an additional informed consent indicating refusal to submit to laser photocoagulation.

3. the study eye had a tear (rip) of the retinal pigment epithelium (RPE); a vitelliform-like lesion of the outer retina (e.g., in pattern dystrophies or basal laminar drusen); idiopathic parafoveal telangiectasis, central serous retinopathy, or serous pigment epithelial detachment without CNV.
4. Any additional ocular diseases which would have irreversibly compromised or, during follow-up, could likely have compromised the visual acuity of the study eye including amblyopia, uncontrolled glaucoma, anterior ischemic optic neuropathy, clinically significant diabetic macular edema, severe nonproliferative, or proliferative diabetic retinopathy.
5. Subfoveal CNV secondary to ocular histoplasmosis syndrome (OHS), pseudo OHS, multifocal choroiditis (including punctate inner choroidopathy), angoid streaks or idiopathic CNV.
6. Inability to obtain photographs to document CNV e.g. due to media opacity, allergy to fluorescein dye, or lack of venous access.
7. Patients with cataract which, in the Investigator's opinion, would progress during the course of the study and would affect central vision in the study eye. Such cataracts could be removed at least 2 months before entering the patient in the study.
8. History of treatment for CNV or other confluent laser photocoagulation in the study eye such as PDT, submacular surgery, radiotherapy or macular scatter ("grid") laser photocoagulation (including prophylactic macular scatter ["grid"]).
9. Been participating in another ophthalmic clinical trial requiring follow-up examinations or were receiving, or had received any experimental systemic treatment for CNV (e.g., retinoic acid, thalidomide) or any other investigational new drug within 12 weeks prior to the start of study treatment.
10. Active hepatitis or clinically significant liver disease with abnormal liver function tests in at least two of the following: SGOT, SGPT, alkaline phosphatase >3 times upper limit of normal range, bilirubin >1.5 times upper limit of normal range; albumin must have been within 20% of the normal range.
11. Unstable heart disease (Class III or IV disease according to the New York Heart Association's functional criteria).
12. Porphyria or other porphyrin sensitivity or hypersensitivity to sunlight or bright artificial light.
13. Any acute illness observed during screening which was undiagnosed or had any diagnosed illness whose presence was considered to be a safety risk for treatment to be administered.
14. Uncontrolled hypertension on repeated measurements (SBP >180 mmHg and DBP >100 mmHg).
15. Intraocular surgery within the last 2 months or Nd:YAG capsulotomy within the last month in the study eye.

**Reviewer's Comments:** *Acceptable.*

**Treatment:** Consistent with other Visudyne studies, Verteporfin 6 mg/m<sup>2</sup>, diluted to 30 mL with Dextrose 5% in Water (D5W), or placebo (D5W, 30 mL), was administered intravenously as a 10-minute infusion. Batch numbers for verteporfin were TC0715, TC0992, and TC1019; for placebo, commercially available D5W was used.

Patients received either verteporfin or placebo followed by light exposure. Only one eye per patient was treated. Treatment was delivered as (1) a 10-minute infusion of either verteporfin or placebo and (2) light administration 15 minutes after the start of the infusion using red laser (diode) light (689 ± 3 nm), 50 J/cm<sup>2</sup> delivered at 600 mW/cm<sup>2</sup> over 83 seconds. Retreatment of eligible patients was recommended every 3 months through Month 21, if CNV leakage was observed on the fluorescein angiogram.

Retreatment was to be given if evidence of CNV leakage was detected by fluorescein angiography. Retreatments were done at intervals of 90 days  $\pm$  2 weeks relative to the initial treatment, each time within 7 days of fluorescein angiography. Patients could receive no more than 4 treatments per year. Each center evaluated their own fluorescein angiograms to determine the need for retreatment and the size of the retreatment spot. Confirmation of leakage and area of the lesion to be treated were not required by the Photograph Reading Center. However, the Photograph Reading Center retrospectively confirmed the presence of leakage and eligibility for retreatment by fluorescein angiograms taken at Months 12 and 24, and at any visit considered to be a final assessment (in the event that a patient discontinued early).

In addition to presence of CNV leakage, patients were required to fulfill the following criteria to be eligible for retreatment:

1. Had no additional ocular diseases which developed since the last visit and could compromise visual acuity of the study eye. Cataracts, which did not interfere with visualization and treatment of the CNV, were allowed. Cataracts that affected visual acuity were to undergo corrective operation.
2. Had a lesion that could be visualized by the Investigator.
3. Had no undiagnosed acute illness or no diagnosed illness whose presence was considered to be a safety risk for retreatment. If an illness resolved more than 7 days since the fluorescein angiogram, fluorescein angiography and color fundus photographs were repeated before retreatment. In cases where a second fluorescein angiogram was required, the initial photographs were used by the Photograph Reading Center to grade the status of the lesion. The photographs from the repeat fluorescein angiography were used to confirm the location and size of the light spot administered.
4. Had no arteriolar or venular nonperfusion caused by previous treatment in this study.
5. Females of childbearing potential had to have a negative pregnancy test (urine) within 3 days of any retreatment and had to be using an effective method of contraception during the study.
6. Had no confirmed decrease from pretreatment of 20 or more letters of best-corrected visual acuity in the study eye on Days 1 through 4 after treatment (following Amendment No. 2).

Every attempt was made to retreat each patient meeting all retreatment eligibility criteria. If the treatment could not be carried out, the patient was nonetheless followed according to the protocol. Retreatment used a light spot diameter that covered any leaking CNV and any blood contiguous to that CNV. If there was more than one leaking area, a spot size was chosen that covered all areas. In the event of a lesion being larger than the largest spot size possible with available contact lenses, the largest spot possible was used to cover the greatest area of the lesion.

**Reviewer's Comments:**     *Acceptable.*

NDA 21-119 Visudyne (verteporfin for injection) Supplement 1

## Schedule of Study Procedures

	Screening/ Baseline <sup>a</sup>	Day 0	Treatment Period (Months)							
			3	6	9	12	15	18	21	24
Demography	X									
Medical History	X									
Informed Consent	X									
Inclusion/Exclusion	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Physical Examination	X									
Vital Signs <sup>b</sup>	X	X	X	X	X	X	X	X	X	X
Laboratory Tests	X									
Pregnancy Tests <sup>c</sup>	X		X	X	X	X	X	X	X	X
Best-Corrected Visual Acuity	X		X	X	X	X	X	X	X	X
Contrast Sensitivity	X		X	X	X	X	X	X	X	X
Color Fundus Photography	X		X	X	X	X	X	X	X	X
Fluorescein Angiography	X		X	X	X	X	X	X	X	X
Optional ICG Angiography <sup>d</sup>	X		X	X	X	X	X	X	X	X
Dilated Ophthalmoscopy	X	X	X	X	X	X	X	X	X	X
Verteporfin or Placebo <sup>e</sup>		X	X	X	X	X	X	X	X	
Subjective visual performance <sup>f</sup>	X		X	X	X	X	X	X	X	X
Adverse Events <sup>g</sup>		X	X	X	X	X	X	X	X	X
HQL <sup>h</sup>	X			X		X		X		X

a Day -7 to 0.

b Vital signs were checked before each infusion of study drug.

c Negative blood test required within 7 days of initial treatment and a negative urine test was required within 3 days of any retreatment in females of childbearing potential.

d Optional procedure and assessment.

e If CNV leakage was present, treatment was conducted within 7 days of fluorescein angiography.

f Patient's subjective visual performance scores were obtained in the clinic at baseline and at each follow-up visit and by telephone 4 weeks after each follow-up visit through Month 21.

g A safety assessment was conducted by telephone 2-4 days after each treatment.

h HQL interviews were conducted within 2 weeks after the assigned study visit (6, 12, 18, and 24 month visits).

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Summary of Baseline Characteristics

Characteristic	Number (%) of Patients					
	ITT Patients			Evaluable Patients at Month 12		
	Verteporfin N=81	Placebo N=39	P value	Verteporfin N=69	Placebo N=31	P value
Gender			.223			.654
Women	57 (70.4)	23 (59.0)		46 (66.7)	19 (61.3)	
Men	24 (29.6)	16 (41.0)		23 (33.3)	12 (38.7)	
RACE			1.000			1.000
Caucasian	74 (91.4)	36 (92.3)		65 (94.2)	29 (93.5)	
Black	0 ( 0.0)	0 ( 0.0)		0 ( 0.0)	0 ( 0.0)	
Asian	3 ( 3.7)	2 ( 5.1)		2 ( 2.9)	1 ( 3.2)	
Hispanic	4 ( 4.9)	1 ( 2.6)		2 ( 2.9)	1 ( 3.2)	
AGE (Years) <sup>a</sup>						
< 30	4 ( 4.9)	1 ( 2.6)		2 ( 2.9)	1 ( 3.2)	
30-39	10 (12.3)	12 (30.8)		9 (13.0)	9 (29.0)	
40-49	22 (27.2)	10 (25.6)		19 (27.5)	9 (29.0)	
50-59	25 (30.9)	12 (30.8)		21 (30.4)	9 (29.0)	
60-69	13 (16.0)	2 ( 5.1)		11 (15.9)	2 ( 6.5)	
≥70	7 ( 8.6)	2 ( 5.1)		7 (10.1)	1 ( 3.2)	
Mean	51.3	47.3	.063	52.3	46.7	.037
STD	12.7	12.7		12.6	11.9	
Median	51.0	46.0		51.0	45.0	
Minimum	19.0	27.0		19.0	27.0	
Maximum	77.0	84.0		77.0	78.0	
DEFINITE HYPERTENSION			.466			.788
Yes	14 (17.3)	9 (23.1)		13 (18.8)	7 (22.6)	
No	67 (82.7)	30 (76.9)		56 (81.2)	24 (77.4)	
MEDICAL HISTORY			.749			1.000
Yes	72 (88.9)	36 (92.3)		63 (91.3)	29 (93.5)	
No	9 (11.1)	3 ( 7.7)		6 ( 8.7)	2 ( 6.5)	
IRIS COLOR (STUDY EYE)			.150			.378
Dark	35 (43.2)	11 (28.2)		30 (43.5)	10 (32.3)	
Light	45 (55.6)	28 (71.8)		39 (56.5)	21 (67.7)	
Unknown	1 ( 1.2)	0 ( 0.0)		0 ( 0.0)	0 ( 0.0)	
VISUAL ACUITY (STUDY EYE) <sup>a</sup>			.073			.179
Mean	62.0	60.0		62.3	60.8	
STD	6.6	8.6		6.3	9.1	
Median						
Minimum						
Maximum						
CONTRAST SENSITIVITY (STUDY EYE) <sup>a</sup>			.053			.067
Mean	27.2	28.9		27.1	28.9	
STD	4.4	4.8		4.1	3.7	
Median						
Minimum						
Maximum						
PRIOR TREATMENT FOR PM			1.000			.605
No	63 (77.8)	31 (79.5)		55 (79.7)	23 (74.2)	
Yes						
Laser Photocoagulation <sup>b</sup>	9 (11.1)	6 (15.4)		9 (13.0)	6 (19.4)	
Interferon	1 ( 1.2)	0 ( 0.0)		1 ( 1.4)	0 ( 0.0)	
Other	9 (11.1)	3 ( 7.7)		5 ( 7.2)	3 ( 9.7)	
SMOKING HISTORY			.392			.452
Never smoked	43 (53.1)	26 (66.7)		37 (53.6)	21 (67.7)	
Current smoker	15 (18.5)	6 (15.4)		12 (17.4)	4 (12.9)	
Previous smoker	23 (28.4)	7 (17.9)		20 (29.0)	6 (19.4)	

<sup>a</sup> Parameters are presented as number and percentage of patients. Age is also presented as mean and standard deviation. Visual acuity and contrast sensitivity are presented only as mean and standard deviation.

<sup>b</sup> Denotes prior laser photocoagulation that was administered in the study eye, as reported by the Treating Center.

Baseline Disease and Lesion Characteristics - Number (%) of Patients

Characteristic	ITT Patients			Evaluable Patients at Month 12		
	Verteporfin N=81	Placebo N=39	P value	Verteporfin N=69	Placebo N=31	P value
<b>EVIDENCE OF CNV</b>			.466			NA <sup>a</sup>
≥50% <sup>b</sup>	77 (95.1)	35 (89.7)		69 (100.0)	31 (100.0)	
<50% <sup>b</sup>	2 (2.5)	2 (5.1)		0 (0.0)	0 (0.0)	
No evidence	1 (1.2)	2 (5.1)		0 (0.0)	0 (0.0)	
Can't grade	1 (1.2)	0 (0.0)		0 (0.0)	0 (0.0)	
<b>CNV LOCATION</b>			.808			.578
Subfoveal	50 (61.7)	27 (69.2)		45 (65.2)	20 (64.5)	
Probably subfoveal	15 (18.5)	7 (17.9)		15 (21.7)	7 (22.6)	
Not subfoveal	11 (13.6)	3 (7.7)		9 (13.0)	3 (9.7)	
No CNV	1 (1.2)	1 (2.6)		0 (0.0)	0 (0.0)	
Can't grade	4 (4.9)	1 (2.6)		0 (0.0)	1 (3.2)	
<b>LESION COMPONENTS CLASSIC CNV</b>			.585			1.000
≥50%	69 (85.2)	31 (79.5)		62 (89.9)	28 (90.3)	
<50%	9 (11.1)	5 (12.8)		7 (10.1)	3 (9.7)	
No evidence	1 (1.2)	2 (5.1)		0 (0.0)	0 (0.0)	
Can't grade	2 (2.5)	1 (2.6)		0 (0.0)	0 (0.0)	
<b>OCCULT CNV</b>			1.000			.772
No	67 (82.7)	33 (84.6)		58 (84.1)	27 (87.1)	
Yes	12 (14.8)	5 (12.8)		11 (15.9)	4 (12.9)	
Can't grade	2 (2.5)	1 (2.6)		0 (0.0)	0 (0.0)	
<b>LASER RX AREA</b>			.747			.735
No	74 (91.4)	35 (89.7)		62 (89.9)	27 (87.1)	
Yes	7 (8.6)	4 (10.3)		7 (10.1)	4 (12.9)	
<b>BLOOD</b>			.014			.050
No	42 (51.9)	11 (28.2)		36 (52.2)	9 (29.0)	
Yes	37 (45.7)	28 (71.8)		33 (47.8)	22 (71.0)	
Can't grade	2 (2.5)	0 (0.0)		0 (0.0)	0 (0.0)	
<b>BLOCKED</b>			.743			.828
No	31 (38.3)	18 (46.2)		27 (39.1)	13 (41.9)	
Yes	48 (59.3)	20 (51.3)		42 (60.9)	18 (58.1)	
Can't grade	2 (2.5)	1 (2.6)		0 (0.0)	0 (0.0)	
<b>CNV SECONDARY TO:</b>			1.000			1.000
PM only	78 (96.3)	39 (100.0)		68 (98.6)	31 (100.0)	
PM + OHS <sup>a</sup>	1 (1.2)	0 (0.0)		1 (1.4)	0 (0.0)	
OHS	2 (2.5)	0 (0.0)		0 (0.0)	0 (0.0)	
<b>LESION SIZE (MPS DA<sup>b</sup>)</b>			.292			.861
No lesion	1 (1.2)	0 (0.0)		0 (0.0)	0 (0.0)	
≤1	51 (63.0)	22 (56.4)		44 (63.8)	18 (58.1)	
>1 to ≤2	14 (17.3)	9 (23.1)		13 (18.8)	9 (29.0)	
>2 to ≤3	9 (11.1)	3 (7.7)		9 (13.0)	2 (6.5)	
>3	4 (4.9)	4 (10.3)		3 (4.3)	2 (6.5)	
Can't grade	2 (2.5)	1 (2.6)		0 (0.0)	0 (0.0)	
<b>GREATEST LINEAR</b>			.646			.320
Mean	2011.7	1995.4		2020.4	1840.9	
STD	857.5	1112.9		849.3	930.6	
Median						
Minimum						
Maximum						
No lesion	1 (1.2)	1 (2.6)		0 (0.0)	0 (0.0)	
Probably ≤ 5400	1 (1.2)	0 (0.0)		0 (0.0)	0 (0.0)	
Probably ≥ 5400	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Can't grade	3 (3.7)	1 (2.6)		0 (0.0)	0 (0.0)	

<sup>a</sup> OHS = Ocular histoplasmosis syndrome

<sup>b</sup> MPS DA = Macular Photocoagulation Study disc areas

**Reviewer's Comments:** *There are no significant differences between groups. The population is predominately patients with classic CNV features.*

### Assessments

- Best-corrected visual acuity: measured using the procedure developed for the ETDRS, which was performed at baseline and at 3, 6, 9, 12, 15, 18, 21, and 24 months.
- Contrast sensitivity: measured on a Pelli-Robson chart at baseline and at 3, 6, 9, 12, 15, 18, 21, and 24 months.
- Fluorescein leakage from CNV and lesion size: measured by a central Photograph Reading Center from fluorescein angiograms and color fundus photographs at baseline and at 12 and 24 months.
- Adverse events were collected at each follow-up visit.
- Other safety assessments (concomitant medications, vital signs, best-corrected visual acuity, color fundus photographs, fluorescein angiograms, and dilated ophthalmoscopy) were performed at screening and each follow-up visit.

**Protocol Deviations** No patients were excluded from the ITT analysis. At Month 12, 12 (15%) verteporfin and 8 (20%) placebo patients were excluded from the evaluable analysis.

Since there was little known about the specific time-course of this disease, an interim evaluation of unmasked visual acuity data was planned in the protocol to assess the accuracy of the initial assumptions used in the sample size calculation. However, because the patient accrual was much faster than expected and the originally planned sample size was achieved by the time of the planned interim evaluation, the evaluation of unmasked visual acuity data was not performed.

### Discontinued Patients

Patient Number	Treatment Group	Total Number of Treatments Received	Reason for Discontinuation
<b>Patients who discontinued treatment but continued follow-up</b>			
V28P53	Verteporfin	0	(Adverse Event). Patient experienced dyspnea and flushing (allergic reaction) during the infusion at baseline. Infusion was stopped, and light treatment was not administered. The patient did not receive any additional study treatment.
<b>Patients who discontinued permanently from study</b>			
V13P51 <sup>a</sup>	Verteporfin	2	(Patient Request). Patient requested withdrawal, as she was unable to attend study visits due to intercurrent illness (cancer).
V15P53	Verteporfin	2	(Lost to Follow-up). Patient expressed difficulty in travel to Dallas.
V01P55	Placebo	3	(Patient Request). Personal reasons
V03P52	Placebo	2	(Patient Request). Patient refused to continue in the study.

<sup>a</sup> Reported by the Investigator as patient request, but analyzed in the safety results as withdrawal due to adverse events.

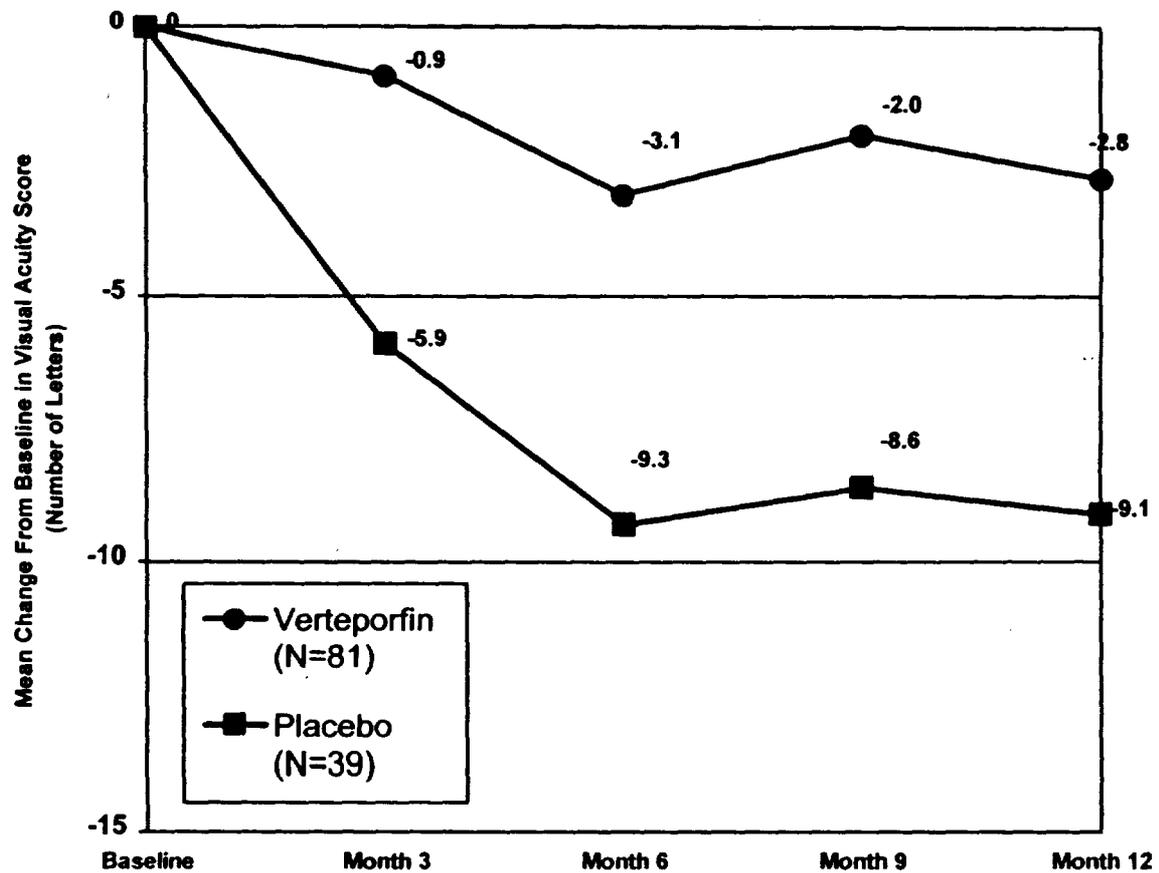
**Patient Responders<sup>a</sup> (<15-Letter Decrease in Visual Acuity)  
(Intent-to-Treat)**

Visit	Number (%) of Patients				
	Verteporfin N=81	Placebo N=39	Difference <sup>b</sup> (Percent)	95% C.I. of Difference	P value <sup>c</sup>
Month 3	76 (93.8)	31 (79.5)	(14.3)	[ 0.6, 28.1]	
Month 6	68 (84.0)	30 (76.9)	( 7.0)	[-8.4, 22.5]	
Month 9	71 (87.7)	26 (66.7)	(21.0)	[ 4.5, 37.4]	
<b>Month 12</b>	<b>70 (86.4)</b>	<b>26 (66.7)</b>	<b>(19.8)</b>	<b>[ 3.2, 36.3]</b>	<b>.011</b>

<sup>a</sup> A responder was a patient who had a decrease from baseline of <15 letters in VA.

<sup>b</sup> Proportion of verteporfin responders minus the proportion of placebo responders.

<sup>c</sup> Chi-square used to test significance between the proportion of patient responders for verteporfin treatment versus placebo at Month 12.



**Reviewer's Comments:** *The study demonstrates clinical efficacy of verteporfin for injection in the treatment of predominately classic choroidal neovascularization secondary to high myopia.*

**Patient Responders at Month 12 (<15 letters) by Pooled Study Center  
(Intent-to-Treat)**

Study Center	Number (%) of Patients						
	Verteporfin			Placebo			Difference (Percent)
	N	n	(%)	N	n	(%)	
Center 1 (Lübeck, Germany)	6	4	( 66.7)	4	2	( 50.0)	16.7
Center 2 (Lausanne, Switzerland)	6	4	( 66.7)	3	2	( 66.7)	0.0
Center 3 (Geneva, Switzerland)	4	2	( 50.0)	1	1	(100.0)	-50.0
Center 4 (Créteil, France)	5	5	(100.0)	2	1	( 50.0)	50.0
Center 5 (Barcelona, Spain)	3	3	(100.0)	1	1	(100.0)	0.0
Center 6 (Vienna, Austria)	2	2	(100.0)	1	1	(100.0)	0.0
Center 7 (Aberdeen, UK)	0			0			
Center 8 (Liverpool, UK)	1	1	(100.0)	0			
Center 9 (Cedex, France)	8	7	( 87.5)	2	1	( 50.0)	37.5
Center 10 (Boston, USA)	1	1	(100.0)	1	1	(100.0)	0.0
Center 11 (Baltimore, USA)	5	5	(100.0)	2	2	(100.0)	0.0
Center 12 (Cleveland, USA)	0			0			
Center 13 (Menlo Park, USA)	2	2	(100.0)	1	1	(100.0)	0.0
Center 14 (Vancouver, Canada)	1	1	(100.0)	1	1	(100.0)	0.0
Center 15 (Dallas, USA)	3	2	( 66.7)	2	2	(100.0)	-33.3
Center 16 (New York City, USA)	4	4	(100.0)	2	1	( 50.0)	50.0
Center 17 (Cleveland, USA)	2	2	(100.0)	1	1	(100.0)	0.0
Center 18 (Royal Oak, USA)	2	2	(100.0)	1	0	( 0.0)	100.0
Center 19 (Toronto, Canada)	3	3	(100.0)	2	0	( 0.0)	100.0
Center 20 (Miami, USA)	5	4	( 80.0)	2	2	(100.0)	-20.0
Center 21 (Portland, USA)	1	1	(100.0)	0			
Center 22 (Pittsburgh, USA)	0			1	1	(100.0)	
Center 23 (St. Louis, USA)	0			1	1	(100.0)	
Center 24 (Atlanta, USA)	3	3	(100.0)	2	1	( 50.0)	50.0
Center 25 (Los Angeles, USA)	0			1	0	( 0.0)	
Center 26 (Udine, Italy)	8	7	( 87.5)	4	2	( 50.0)	37.5
Center 27 (Örebro, Sweden)	1	1	(100.0)	0			
Center 28 (Essen, Germany)	5	4	( 80.0)	1	1	(100.0)	-20.0

**Reviewer's Comments:** *There are no significant differences between Centers. The impact of those investigators with financial interests is negligible since they could be eliminated from the study without causing a significant change in the percentage of responders in each treatment group.*

**Absence of CNV Leakage**

Visit	Number (%) of Patients			
	Treating Centers		Photograph Reading Center	
	Verteporfin	Placebo	Verteporfin	Placebo
Month 12	32(40.5)	16(44.4)	28(35.4)	11(30.6)

**Reviewer's Comments:** *The Reading Center identified additional patients with leakage.*

**Unmasked Patients**

REASON FOR POTENTIAL UNMASKING	Number (%) of Patients	
	Verteporfin N=78	Placebo N=78
REASON FOR POTENTIAL UNMASKING	5 (6.2)	1 (2.6)
Safety concern (allergic reaction)	1 (1.2)	0 (0.0)
Photosensitivity reaction within a few days of treatment	3 (3.7)	1 (2.6)
Severe vision decrease within 7 days of treatment	1 (1.2)	0 (0.0)

**Withdrawals Due to Adverse Events**

Patient V13P51, Verteporfin; Metastatic Colon Cancer

Patient V28P53, Verteporfin; Dyspnea, Flushing

**Reviewer's Comments:** *Gastrointestinal cancers were reported in a significant number of patients in the original Age Related Macular Degeneration Study. The applicant should monitor all gastrointestinal cancers observed in all studies.*

Adverse Events reported in  $\geq 2.0\%$  of Patients in Either Treatment Group

<b>BODY SYSTEM Adverse Event</b>	<b>Verteporfin N=81</b>	<b>Placebo N=39</b>
Total patients with at least one adverse event	50 (61.7)	24 (61.5)
<b>TREATMENT SITE — OCULAR</b>	29 (35.8)	12 (30.8)
Cataract	2 ( 2.5)	1 ( 2.6)
Conjunctivitis	4 ( 4.9)	1 ( 2.6)
Dry eyes	2 ( 2.5)	1 ( 2.6)
Eye disorder	4 ( 4.9)	0 ( 0.0)
Eye pain	2 ( 2.5)	1 ( 2.6)
Face edema	0 ( 0.0)	1 ( 2.6)
Glaucoma	1 ( 1.2)	1 ( 2.6)
Visual Disturbance	17 (21.0)	8 (20.5)
Vision abnormal	7 ( 8.6)	1 ( 2.6)
Vision decreased	11 (13.6)	7 (17.9)
Visual field defect	3 ( 3.7)	2 ( 5.1)
Vitreous disorder	2 ( 2.5)	0 ( 0.0)
<b>SPECIAL SENSES</b>	16 (19.8)	3 ( 7.7)
Conjunctivitis	3 ( 3.7)	1 ( 2.6)
Dry eyes	1 ( 1.2)	1 ( 2.6)
Eye disorder	3 ( 3.7)	0 ( 0.0)
Eye pain	2 ( 2.5)	0 ( 0.0)
Glaucoma	1 ( 1.2)	2 ( 5.1)
Retinal disorder	1 ( 1.2)	1 ( 2.6)
Visual Disturbance	3 ( 3.7)	0 ( 0.0)
Vision abnormal	2 ( 2.5)	0 ( 0.0)
Vision decreased	1 ( 1.2)	0 ( 0.0)
Visual field defect	1 ( 1.2)	0 ( 0.0)
Vitreous disorder	1 ( 1.2)	1 ( 2.6)
<b>BODY AS A WHOLE</b>	28 (34.6)	14 (35.9)
Abdominal pain	4 ( 4.9)	0 ( 0.0)
Accidental injury	2 ( 2.5)	1 ( 2.6)
Allergic reaction	3 ( 3.7)	1 ( 2.6)
Asthenia	4 ( 4.9)	0 ( 0.0)
Chest pain substernal	0 ( 0.0)	1 ( 2.6)
Face edema	1 ( 1.2)	1 ( 2.6)
Fever	0 ( 0.0)	1 ( 2.6)
Flu syndrome	6 ( 7.4)	1 ( 2.6)
Headache	8 ( 9.9)	3 ( 7.7)
Infection	4 ( 4.9)	2 ( 5.1)
Injection Site Adverse Events	6 ( 7.4)	2 ( 5.1)
Inject. Site discoloration	1 ( 1.2)	0 ( 0.0)
Inject. Site edema	2 ( 2.5)	0 ( 0.0)
Inject. Site extravasation	1 ( 1.2)	1 ( 2.6)
Inject. Site hemorrhage	1 ( 1.2)	0 ( 0.0)
Inject. Site inflammation	2 ( 2.5)	0 ( 0.0)
Inject. Site pain	4 ( 4.9)	1 ( 2.6)

<b>BODY SYSTEM Adverse Event</b>	<b>Verteporfin N=81</b>	<b>Placebo N=39</b>
Pain	3 ( 3.7)	3 ( 7.7)
Photosensitivity reaction	3 ( 3.7)	1 ( 2.6)
<b>CARDIOVASCULAR</b>	<b>4 ( 4.9)</b>	<b>8 (20.5)</b>
Hemorrhage	0 ( 0.0)	1 ( 2.6)
Hypertension	3 ( 3.7)	4 (10.3)
Migraine	0 ( 0.0)	1 ( 2.6)
Palpitation	0 ( 0.0)	1 ( 2.6)
Vascular disorder	0 ( 0.0)	1 ( 2.6)
Vasodilatation	0 ( 0.0)	1 ( 2.6)
<b>DIGESTIVE</b>	<b>12 (14.8)</b>	<b>6 (15.4)</b>
Diarrhea	1 ( 1.2)	1 ( 2.6)
Dry mouth	0 ( 0.0)	1 ( 2.6)
Gastrointestinal disorder	1 ( 1.2)	1 ( 2.6)
Nausea	3 ( 3.7)	3 ( 7.7)
Tooth disorder	2 ( 2.5)	1 ( 2.6)
Vomiting	0 ( 0.0)	1 ( 2.6)
<b>HEMIC AND LYMPHATIC</b>	<b>0 ( 0.0)</b>	<b>1 ( 2.6)</b>
Leukocytosis	0 ( 0.0)	1 ( 2.6)
<b>METABOLIC AND NUTRITIONAL</b>	<b>1 ( 1.2)</b>	<b>1 ( 2.6)</b>
Hemochromatosis	0 ( 0.0)	1 ( 2.6)
<b>MUSCULOSKELETAL</b>	<b>3 ( 3.7)</b>	<b>3 ( 7.7)</b>
Arthralgia	0 ( 0.0)	3 ( 7.7)
<b>NERVOUS</b>	<b>7 ( 8.6)</b>	<b>2 ( 5.1)</b>
Ataxia	0 ( 0.0)	1 ( 2.6)
Depression	3 ( 3.7)	0 ( 0.0)
Dizziness	2 ( 2.5)	0 ( 0.0)
Libido decreased	0 ( 0.0)	1 ( 2.6)
Paresthesia	1 ( 1.2)	1 ( 2.6)
<b>RESPIRATORY</b>	<b>14 (17.3)</b>	<b>8 (20.5)</b>
Bronchitis	2 ( 2.5)	1 ( 2.6)
Cough increased	2 ( 2.5)	0 ( 0.0)
Dyspnea	1 ( 1.2)	1 ( 2.6)
Pharyngitis	5 ( 6.2)	2 ( 5.1)
Sinusitis	4 ( 4.9)	4 (10.3)
<b>SKIN AND APPENDAGES</b>	<b>5 ( 6.2)</b>	<b>3 ( 7.7)</b>
Alopecia	1 ( 1.2)	1 ( 2.6)
Dry skin	0 ( 0.0)	1 ( 2.6)
Pruritus	2 ( 2.5)	2 ( 5.1)
Skin disorder	2 ( 2.5)	0 ( 0.0)
<b>UROGENITAL</b>	<b>4 ( 4.9)</b>	<b>2 ( 5.1)</b>
Uterine fibroids enlarged	0 ( 0.0)	1 ( 2.6)
Vaginal hemorrhage	1 ( 1.2)	1 ( 2.6)

**Title:** BPD OCR 004 (OHS, 9 Months): An Open-Label, Multicenter, Safety and Effect on Visual Acuity Study of the Treatment of Subfoveal Choroidal Neovascularization Secondary to Ocular Histoplasmosis Syndrome (OHS) Using Photodynamic Therapy with Verteporfin for Injection

**Primary Objective:** To evaluate the safety and effects on visual acuity of verteporfin used in photodynamic treatment of subfoveal CNV in patients with OHS.

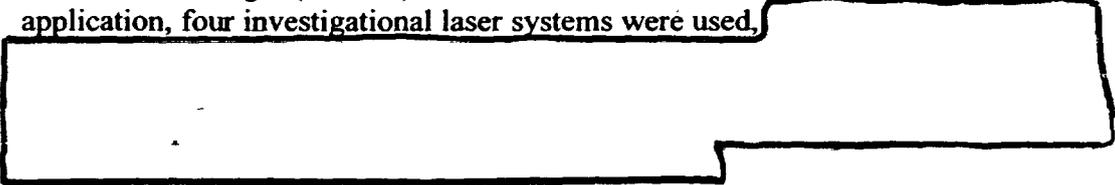
**Study Design:**

Clinical Study BPD OCR 004 was an open-label, multicenter, Phase 1/2 study of the treatment of subfoveal choroidal neovascularization secondary to OHS using verteporfin PDT treatment. Four centers were to enroll approximately 20 patients, (5-10 patients per center).

**Reviewer's Comments:** *The study design is flawed. In the absence of a control group, it is not possible to determine whether patients are benefited or harmed by treatment. There are potential control groups available from the literature. A control group must be included to establish safety and efficacy in this population.*

**Treatment:**

Consistent with other Visudyne studies, treatment consisted of an infusion over 10 minutes of verteporfin (6 mg/m<sup>2</sup>), followed by an application of 50 J/cm<sup>2</sup> of nonthermal red light (689 nm) initiated 15 minutes after the start of the infusion. For light application, four investigational laser systems were used.



**Analysis Plan:**

“The primary analysis was prospectively planned to be after 12 months of follow-up. Due to the timing of regulatory submissions, the Sponsors considered it important to submit available data from this study, and therefore, this clinical summary provides the results of all 9-month data and 65% of the 12-month data. The cutoff date for this clinical summary was May 31, 2000. The total study follow-up will be 24 months. The Sponsors are currently considering an extension of the study to 48 months, which would result in additional analyses at 36 and 48 months.”

**Reviewer's Comments:** *Strongly disagree. From a regulatory prospective, the study should not have been submitted early and it is inappropriate to have changed original analysis plan without a good scientific rationale.*

**Inclusion Criteria**

Patients who were willing to sign an informed consent; were 18 years of age or older, male or female (with documentation of negative pregnancy test), and any race were eligible provided they fulfilled all of the following criteria:

1. In at least one eye, had subfoveal CNV secondary to ocular histoplasmosis alone.
2. Evidence of classic or occult CNV extending through the geometric center of the foveal avascular zone (FAZ). (Feeder vessels to recurrent CNV that extended through the geometric center of the FAZ did not exclude the patient.)
3. Study eye had to have a best-corrected visual acuity score between 34 and 73 (approximately equal to or worse than 20/40 on ETDRS chart but equal to or better than 20/200).

**Exclusion Criteria**

Patients were not eligible for enrollment if the following were present:

1. Color photography and fluorescein angiography showed:
  - a. CNV did not involve the geometric center of the foveal avascular zone. (Whenever depigmentation from earlier laser treatment extended through the geometric center of the FAZ, the patient was not eligible.)
  - b. The area of CNV (classic plus occult) was less than 50% of the total lesion (not including areas of prior laser treatment).
  - c. The greatest linear dimension of the entire CNV lesion exceeded 5400  $\mu\text{m}$  diameter (approximately equivalent to the diameter of a 9 Macula Photocoagulation Study [MPS] disc area circle) at the initial treatment.
  - d. The study eye had a tear (rip) of the retinal pigment epithelium (RPE); a vitelliform-like lesion of the outer retina (e.g., as in pattern dystrophies or basal laminar drusen); idiopathic parafoveal telangiectasis, central serous retinopathy, or serous pigment epithelial detachment without CNV.

**APPEARS THIS WAY  
ON ORIGINAL**

## Schedule of Study Procedures

Procedure	Screening/ Baseline <sup>a</sup>	Day 0	Treatment Period (Months)							
			3	6	9	12	15	18	21	24
Demography, Medical History, Inclusion/Exclusion	X									
Informed Consent	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Physical Exam, Laboratory Test	X									
Vital Signs <sup>b</sup>	X	X	X	X	X	X	X	X	X	X
Pregnancy Tests <sup>c</sup>	X		X	X	X	X	X	X	X	X
Best-Corrected Visual Acuity	X		X	X	X	X	X	X	X	X
Contrast Sensitivity	X		X	X	X	X	X	X	X	X
Color Fundus Photography	X		X	X	X	X	X	X	X	X
Fluorescein Angiography	X		X	X	X	X	X	X	X	X
Dilated Ophthalmoscopy	X	X	X	X	X	X	X	X	X	X
Verteporfin <sup>d</sup>		X	X	X	X	X	X	X	X	
Subjective visual performance <sup>e</sup>	X		X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X

- a Day -7 to 0.
- b Vital signs were checked before each infusion of study drug.
- c Negative blood test required within 7 days of initial treatment and a negative urine test was required within 3 days of any retreatment in females of childbearing potential.
- d If CNV leakage was present, treatment was conducted within 7 days of fluorescein angiography.
- e Patient's subjective visual performance scores were obtained in the clinic at screening and each visit and by telephone 4 weeks after each follow-up visit through Month 21.

## List of Study Investigators

Country	Investigator	Study Center	Site Identification and Number	Patients Enrolled
Switzerland	Michel Sickenberg, MD	Hôpital Ophthalmique Universitaire Jules Gonin Av. de France 15 CH-1004 Lausanne	LAU 02	1
United States	Robert Rosa, MD Phillip Rosenfeld, MD Mary-Lou Lewis, MD	Bascom Palmer Eye Institute 900 N.W. 17th Street Miami, Florida 33136	MIA 20	8
	David Saperstein, MD* Thomas M. Aaberg, Sr, MD	Emory Eye Center 1365-B Clifton Road Atlanta, Georgia 30322	ATL 24	17

\* David Saperstein, MD was the Principal Investigator from the beginning of the study to January 2000. Thomas M. Aaberg, Sr, MD became the Principal Investigator in January 2000.

APPEARS THIS WAY  
ON ORIGINAL

## Summary of Baseline Characteristics

Characteristic	Number (%) of Patients	
	Verteporfin (N=26)	
<b>GENDER</b>		
Women	16	(61.5)
Men	10	(38.5)
<b>AGE (Years)<sup>a</sup></b>		
30-39	5	(19.2)
40-49	8	(30.8)
50-59	10	(38.5)
60-69	2	(7.7)
≥70	1	(3.8)
Mean		49.3
<b>VISUAL ACUITY (STUDY EYE)<sup>a</sup></b>		
Mean Score (letters)		56.1
<b>CONTRAST SENSITIVITY (STUDY EYE)<sup>a</sup></b>		
Mean Score (letters)		29.1
<b>ASSESSED BY THE PHOTOGRAPH READING CENTER</b>		
<b>LESION COMPONENTS</b>		
Evidence of CNV in ≥50% of lesion	23	(88.5)
CNV Location (Subfoveal or Probably Subfoveal)	24	(92.3)
Classic CNV		
≥50%	18	(69.2)
<50%	5	(19.2)
Occult CNV <sup>b</sup>	9	(34.6)
Blood	10	(38.5)
Blocked fluorescence	6	(23.1)
CNV Secondary to OHS Alone	24	(92.3)
<b>LESION SIZE (MPS DA)</b>		
≤1	8	(30.8)
>1 to 2	4	(15.4)
>2 to 3	10	(38.5)
>3	3	(11.5)
Can't grade	1	(3.8)
<b>GREATEST LINEAR DIMENSION (GLD) OF LESION (microns)<sup>a</sup></b>		
Mean <sup>c</sup>		2,583.3

<sup>a</sup> Parameters are presented as number and percentage of patients. Age is also presented as mean. Visual acuity, contrast sensitivity, and GLD are presented as mean only.

<sup>b</sup> Includes 1 patient who was graded as questionable.

<sup>c</sup> Sample size for GLD was 24 patients.

MPS DA = Macular Photocoagulation Study disc areas

**Reviewer's Comments:** *The demographics will need to be compared to a control group when the control group is identified.*

**APPEARS THIS WAY  
ON ORIGINAL**

**Patient Responders**

	Number (%) of Patients			
	Verteporfin			N=26
	<15 letters			
Visit	N	n	(%)	95% C.I.
Month 3	26	24	(92.3)	[73.4, 97.0]
Month 6	25	22	(88.0)	[67.7, 94.7]
Month 9	24	22	(91.7)	[71.5, 96.7]
Month 12	17	17	(100.0)	N/A

C.I.=Confidence Interval

N/A=not available

**Reviewer's Comments:** *Safety and efficacy cannot be determined without a control group.*

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

## Adverse Experiences

	Number (%) of Patients Total (N=26)	
Total patients with at least one adverse event	20	(76.9)
<b>TREATMENT SITE — OCULAR (Study Eye Events)</b>	14	(53.8)
Blepharitis	1	(3.8)
Cataract	4	(15.4)
Conjunctivitis	3	(11.5)
Corneal lesion	1	(3.8)
Corneal opacity	1	(3.8)
Eye disorder	1	(3.8)
Eye hemorrhage	1	(3.8)
Eye pain	1	(3.8)
Glaucoma	1	(3.8)
Retinal disorder	1	(3.8)
Visual Disturbance <sup>a</sup>	5	(19.2)
Vision abnormal	3	(11.5)
Vision decreased	1	(3.8)
Visual field defect	2	(7.7)
<b>SPECIAL SENSES</b>	15	(57.7)
Blepharitis	1	(3.8)
Cataract	4	(15.4)
Conjunctivitis	4	(15.4)
Corneal lesion	1	(3.8)
Corneal opacity	1	(3.8)
Eye disorder	1	(3.8)
Glaucoma	1	(3.8)
Otitis media	1	(3.8)
Scleritis	1	(3.8)
Visual Disturbance <sup>a</sup>	1	(3.8)
Vision abnormal	1	(3.8)
<b>BODY AS A WHOLE</b>	13	(50.0)
Abdominal pain	1	(3.8)
Accidental injury	1	(3.8)
Allergic reaction	1	(3.8)
Asthenia	1	(3.8)
Chills and fever	1	(3.8)
Cyst	1	(3.8)
Fever	1	(3.8)
Flu syndrome	3	(11.5)
Headache	5	(19.2)
Infection	5	(19.2)
Injection Site Adverse Events <sup>a</sup>	4	(15.4)
Injection site edema	1	(3.8)
Injection site extravasation	2	(7.7)

	<b>Number (%) of Patients Total (N=26)</b>	
Injection site inflammation	1	(3.8)
Injection site pain	2	(7.7)
Injection site reaction	1	(3.8)
Neck pain	1	(3.8)
Neck rigidity	1	(3.8)
Pain	2	(7.7)
Photosensitivity reaction	1	(3.8)
<b>CARDIOVASCULAR</b>	<b>4</b>	<b>(15.4)</b>
Cardiovascular disorder	1	(3.8)
Hypertension	1	(3.8)
Syncope	2	(7.7)
<b>DIGESTIVE</b>	<b>6</b>	<b>(23.1)</b>
Cholecystitis	1	(3.8)
Constipation	1	(3.8)
Diarrhea	1	(3.8)
Gastroenteritis	1	(3.8)
Gingivitis	1	(3.8)
Nausea	1	(3.8)
Proctitis	1	(3.8)
<b>MUSCULOSKELETAL</b>	<b>2</b>	<b>(7.7)</b>
Arthralgia	1	(3.8)
Joint disorder	1	(3.8)
Tendon disorder	1	(3.8)
<b>NERVOUS</b>	<b>4</b>	<b>(15.4)</b>
Anxiety	1	(3.8)
Depression	2	(7.7)
Insomnia	1	(3.8)
<b>RESPIRATORY</b>	<b>7</b>	<b>(26.9)</b>
Bronchitis	2	(7.7)
Cough increased	3	(11.5)
Lung disorder	1	(3.8)
Pharyngitis	1	(3.8)
Rhinitis	2	(7.7)
Sinusitis	2	(7.7)
<b>SKIN AND APPENDAGES</b>	<b>4</b>	<b>(15.4)</b>
Contact dermatitis	1	(3.8)
Pruritus	1	(3.8)
Rash	2	(7.7)
Skin discoloration	1	(3.8)
<b>UROGENITAL</b>	<b>1</b>	<b>(3.8)</b>
Cystitis	1	(3.8)

page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

## Ocular Adverse Events

BODY SYSTEM Adverse Event	PM		Histo		AMD		PM		AMD	
	Verteporfin N=81		Verteporfin N=26		Verteporfin N=627		Placebo N=39		Placebo N=321	
TREATMENT SITE — OCULAR (Study Eye)	33	(41)	17	(65)	317	(51)	15	(38)	141	(44)
AMD progression	1	(1)			9	(2)	0		4	(1)
Blepharitis	3	(4)			19	(3)	1	(3)	5	(2)
Cataract	5	(6)	7	(27)	90	(15)	3	(8)	41	(13)
Conjunctivitis	4	(5)	4	(15)	39	(6)	1	(3)	22	(7)
Corneal lesion	2	(2)	2	(8)	16	(3)	0		13	(4)
Corneal ulcer	1	(1)					0			
Diplopia	1	(1)					0			
Dry eyes	2	(2)			15	(3)	1	(3)	11	(3)
Eye disorder <sup>b</sup>	5	(6)	2	(8)	9	(1)	0		8	(2)
Eye itching	1	(1)			20	(3)	1	(3)	7	(2)
Eye pain	2	(2)			35	(6)	2	(5)	24	(7)
Face Edema	0						1	(3)		
Glaucoma	1	(1)			10	(2)	1	(3)	7	(2)
Keratitis	1	(1)					0			
Lacrimation disorder	1	(1)			13	(2)	1	(3)	6	(2)
Photophobia	3	(4)			7	(1)	0		5	(2)
Retinal disorder					4	(1)			10	(3)
Subretinal hemorrhage					13	(2)			9	(3)
Visual Disturbance <sup>c</sup>	18	(22)	6	(23)	182	(29)	8	(20)	58	(18)
Vision abnormal	7	(9)	3	(11)	103	(17)	3	(8)	27	(8)
Vision decreased	12	(15)	1	(4)	106	(17)	5	(13)	31	(10)
Visual field defect	3	(4)	3	(11)	73	(12)	0		20	(6)
Vitreous disorder	3	(4)			9	(1)	0		7	(2)
Vitreous hemorrhage					11	(2)			4	(1)
SPECIAL SENSES (Including Nonstudy Eye) <sup>d</sup>	19	(23)	17	(65)	210	(33)	5	(13)	110	(34)
AMD progression	2	(2)			16	(3)	1	(3)	15	(5)
Blepharitis	2	(2)			16	(3)	1	(3)	5	(1)
Cataract	3	(4)	5	(19)	51	(8)	1	(3)	22	(7)
Conjunctivitis	3	(4)	5	(19)	30	(5)	1	(3)	21	(6)
Corneal lesion	2	(3)			14	(2)	0		9	(3)
Dry eyes	1	(2)			13	(2)	0		12	(4)
Eye disorder <sup>b</sup>	3	(4)	2	(8)	12	(2)	0		11	(3)
Eye itching					16	(3)			5	(2)
Eye pain	2	(3)			17	(3)			11	(3)
Glaucoma	1	(2)			9	(1)	2	(5)	7	(2)
Lacrimation disorder	0						1	(3)		
Otitis media	2	(3)					1	(3)		
Photophobia	3	(4)					0			
Retinal disorder	1	(1)					1	(3)		
Visual Disturbance <sup>c</sup>	4	(5)			55	(9)	1	(3)	33	(10)
Vision abnormal	2	(3)			28	(4)	1	(3)	18	(6)
Vision decreased	2	(3)			29	(4)	0		13	(4)
Visual field defect	1	(2)			7	(1)	0		6	(2)
Vitreous disorder	1	(2)					1	(3)		

<sup>a</sup> Adverse events that were reported at an incidence of at least 1.0% (study eye) or 2.0% (nonstudy eye) in either treatment group in Studies OCR 002 A+B and OCR 003 AMD combined.

<sup>b</sup> The preferred term of eye disorder is nonspecific and includes reported terms such as "entropion of the right eye", "eyes tired in evening when reading", dermatochalasis, and pterygium.

<sup>c</sup> Visual disturbance is a summary term; individual terms are indented below it. Visual disturbance events were from subjective spontaneous reporting by patients. All individual terms included in the 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>d</sup> The total number of patients with at least one event under "Special Senses" also included the non-ocular events of deafness, ear pain, otitis externa, otitis media, tinnitus, and taste perversion, each occurring at an incidence of  $< 2.0\%$ .

## Non-ocular events

BODY SYSTEM Adverse Event	AMD		Histo		PM		PM		AMD	
	Verteporfin N=627		Verteporfin N=26		Verteporfin N=81		Placebo N=39		Placebo N=321	
BODY AS A WHOLE	356	(57)	14	(54)	34	(42)	16	(41)	171	(53)
Abdominal pain	22	(3.5)	2	(7)	5	(6)	1	(3)	12	(3.7)
Accidental injury	64	(10.2)	5	(19)	3	(4)	2	(5)	35	(10.9)
Allergic reaction	11	(1.8)			3	(4)	3	(8)	10	(3.1)
Asthenia	34	(5.4)			5	(6)			10	(3.1)
Back pain	37	(5.9)			3	(4)			24	(7.5)
Chest pain	24	(3.8)					1	(3)	15	(4.7)
Face edema					1	(1)	1	(3)		
Fever	19	(3.0)					1	(3)	6	(1.9)
Flu syndrome	49	(7.8)	3	(11)	7	(9)	2	(5)	16	(5.0)
Headache	61	(9.7)	5	(19)	8	(10)	4	(10)	43	(13.4)
Hernia	9	(1.4)							8	(2.5)
Infection	63	(10.0)	5	(19)	7	(9)	3	(8)	36	(11.2)
Infusion related back pain	15	(2.4)							0	(0.0)
Injection Site Adverse Events <sup>b</sup>	82	(13.1)	4	(15)	8	(10)	2	(5)	18	(5.6)
Inj. site discoloration	4	(0.6)			1	(1)			0	(0.0)
Inj. site edema	34	(5.4)	1	(4)	2	(2)			1	(0.3)
Inj. site extravasation	35	(5.6)	2	(7)	1	(1)	1	(3)	10	(3.1)
Inj. site fibrosis	1	(0.2)							0	(0.0)
Inj. site hemorrhage	10	(1.6)			1	(1)			4	(1.2)
Inj. site hypersensitivity	8	(1.3)							1	(0.3)
Inj. site inflammation	17	(2.7)	2	(7)	2	(2)			2	(0.6)
Inj. site pain	54	(8.6)	3	(11)	5	(6)	1	(3)	2	(0.6)
Inj. Site reaction	1	(0.2)	1	(4)	1	(1)			0	(0.0)
Neoplasm							1	(3)		
Pain	58	(9.3)	4	(15)	3	(4)	3	(8)	25	(7.8)
Photosensitivity reaction	16	(2.6)			3	(4)	1	(3)	1	(0.3)
CARDIOVASCULAR	180	(28.7)	4	(15)	4	(5)	10	(26)	92	(28.7)
Angina pectoris	12	(1.9)							10	(3.1)
Atrial fibrillation	15	(2.4)					1	(3)	15	(4.7)
Cardiovascular disorder	18	(2.9)							9	(2.8)
Coronary artery disorder	14	(2.2)							8	(2.5)
Hemorrhage							1	(3)		
Hypertension	1	(0.2)			3	(4)	5	(13)	28	(8.7)
Migraine							1	(3)		
Myocardial infarction	12	(1.9)							9	(2.8)
Palpitation							1	(3)		
Syncope	9	(1.4)	2	(7)					7	(2.2)
Vascular disorder							1	(3)		
Vasodilation							1	(3)		
DIGESTIVE	159	(25.4)			16	(20)	6	(15)	85	(26.5)
Constipation	15	(2.4)							1	(0.3)
Diarrhea	26	(4.1)			1	(1)	1	(3)	17	(5.3)
Dry Mouth							1	(3)		
Dyspepsia	11	(1.8)							9	(2.8)
Gastrointestinal disorder	17	(2.7)			2	(2)	1	(3)	12	(3.7)
Nausea	44	(7.0)			4	(5)	3	(8)	18	(5.6)
Tooth disorder					2	(2)	1	(3)		
Vomiting	15	(2.4)			1	(1)	1	(3)	8	(2.5)

BODY SYSTEM Adverse Event	AMD		Histo		PM		PM		AMD	
	Verteporfin N=627		Verteporfin N=26		Verteporfin N=81		Placebo N=39		Placebo N=321	
ENDOCRINE SYSTEM	13	(2.1)							9	(2.8)
Hypothyroidism	8	(1.3)							7	(2.2)
HEMIC AND LYMPHATIC	70	(11.2)			1	(1)	1	(3)	28	(8.7)
Anemia	26	(4.1)							14	(4.4)
Echymosis	14	(2.2)							8	(2.5)
Leukocytosis							1	(3)		
METABOLIC/NUTRITIONAL	137	(21.9)			3	(5)	2	(5)	89	(27.7)
Creatinine increased	15	(2.4)							5	(1.6)
Glycosuria	21	(3.3)							12	(3.7)
Hemochromatosis							1	(3)		
Hypercholesteremia	41	(6.5)							27	(8.4)
Hypokalemia	8	(1.3)							7	(2.2)
Ketosis	12	(1.9)							8	(2.5)
Peripheral edema	33	(5.3)							16	(5.0)
MUSCULOSKELETAL	110	(17.5)			6	(7)	3	(8)	58	(18.1)
Arthralgia	28	(4.5)					3	(8)	15	(4.7)
Arthritis	28	(4.5)							20	(6.2)
Arthrosis	18	(2.9)							4	(1.2)
Bone disorder	10	(1.6)							7	(2.2)
Osteoporosis	13	(2.1)							7	(2.2)
NERVOUS	158	(25.2)	4	(15)	8	(10)	2	(5)	76	(23.7)
Anxiety	15	(2.4)							5	(1.6)
Ataxia							1	(3)		
Depression	31	(4.9)	2	(8)	3	(4)			19	(5.9)
Dizziness	30	(4.8)			2	(2)			15	(4.7)
Insomnia	16	(2.6)	3	(11)					7	(2.2)
Libido decreased							1	(3)		
Paresthesia	4	(0.6)			1	(1)	1	(3)	7	(2.2)
Vertigo	15	(2.4)							7	(2.2)
RESPIRATORY	149	(23.8)	7	(27)	18	(22)	9	(23)	78	(24.3)
Bronchitis	31	(5.3)	2	(8)	5	(6)	1	(3)	16	(5.0)
Cough increased	31	(6.1)	3	(11)					15	(4.4)
Dyspnea	22	(3.5)					1	(3)	12	(3.7)
Lung disorder	13	(2.1)							7	(2.2)
Pharyngitis	23	(3.7)			6	(7)	3	(8)	12	(3.7)
Pneumonia		(3.7)							10	(3.1)
Rhinitis	20	(3.2)	2	(8)					16	(5.0)
Sinusitis	15	(2.4)	2	(8)	5	(6)	4	(10)	5	(1.6)
SKIN AND APPENDAGES	102	(16.3)	5	(19)	7	(9)	3		50	(15.6)
Alopecia					1	(1)	1	(3)		
Pruritus	12	(1.9)			2	(2)	2	(5)	9	(2.8)
Rash	25	(4.0)	2	(8)					14	(4.4)
Skin Disorder										
UROGENITAL	100	(15.9)			6	(7)	3		57	(17.8)
Cystitis	20	(3.2)					1	(3)	11	(3.4)
Prostatic disorder	19	(3.0)							8	(2.5)
Uterine fibroids enlarged							1	(3)		
Urinary tract infection	20	(3.2)							13	(4.0)
Vaginal Hemorrhage					1	(1)	1	(3)		

15 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

**Deficiencies**

1. An incomplete listing of Adverse Reactions was provided in the original supplement submission. Specifically, Table 47, Page 5 of 5 is missing. (Page 149). The complete listing should be submitted.
2. The 24 month visual acuity data for study OCR 003 PM should have been available and submitted in the Safety Update. This information should be submitted.
3. The study OCR 004 was prematurely reported. The 12 month results should be reported and should include an appropriate control group. Any differences in the inclusion criteria for the study group and the control group should be clearly identified.
4. Gastrointestinal cancers were reported in a significant number of patients in the original Age Related Macular Degeneration Studies. Gastrointestinal cancers should be monitored in all studies, and a summary should be reported.

**Conclusions and Recommendations:**

NDA 21-119, Visudyne (verteporfin for injection) in conjunction with the [REDACTED]

[REDACTED] for the treatment of macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization is deferred until the deficiencies identified above have been resolved.

The financial disclosure statements have been reviewed and found to be unlikely to have an impact on the reported results.

Final labeling decisions will be deferred until the application is otherwise approvable.

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

cc: Orig NDA 21-119

[REDACTED]

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

NDA 21-119 Visudyne (verteporfin for injection) Supplement 1

Medical Officer's Review of NDA 21-119/SE1-001  
Supplement 1

NDA #21-119	Submission dates:	8/20/01
M.O. Suppl 1, Review #3	Received dates:	8/21/01
	Review date:	8/21/01

Proposed Trade name: Visudyne

Generic name: Verteporfin for injection

Sponsor: QLT PhotoTherapeutics Inc.  
887 Great Northern Way  
Vancouver, BC Canada V5T 4T5  
(604) 872-7881

Proposed Indication(s): The treatment of patients with predominantly classic subfoveal choroidal neovascularization due to macular degeneration, pathologic myopia or presumed ocular histoplasmosis.

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*Executive Summary*

I. Recommendations

A. Recommendation on Approvability

*NDA 21-119, Visudyne (verteporfin for injection) with the labeling submitted on August 20, 2001, in conjunction with the [redacted] is recommended for approval for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age related macular degeneration, pathologic myopia or presumed ocular histoplasmosis.*

B. Recommendation on Phase 4 Studies and Risk Management Steps  
*No additional Phase 4 studies are recommended at this time.*

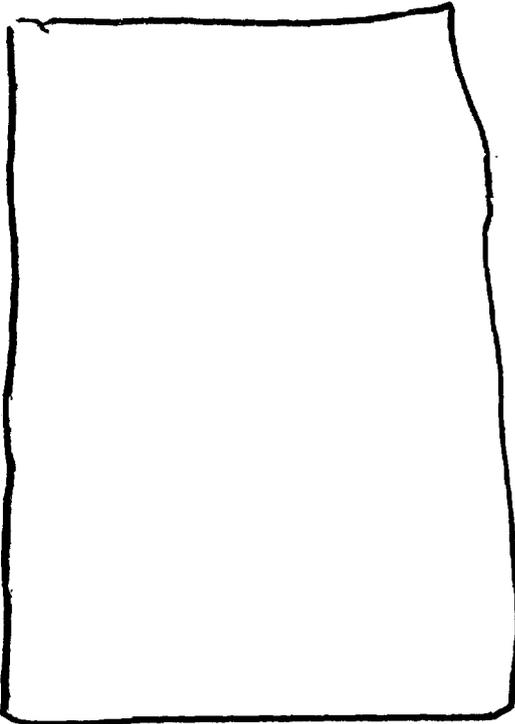
II. Summary of Clinical Findings

*See previous reviews.*

III. Labeling

[redacted]

12 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.



**Reviewer's Comments:**     *The proposed labeling is acceptable.*

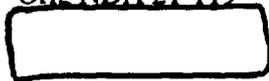
**Conclusions and Recommendations:**

NDA 21-119, Visudyne (verteporfin for injection) with the labeling submitted on August 20, 2001, and listed above, in conjunction with the

[redacted] is recommended for approval for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age related macular degeneration, pathologic myopia and presumed ocular histoplasmosis.

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

cc:    Orig NDA 21-119



**Medical Officer's Review of NDA 21-119/SE1-001  
Supplement 1**

NDA #21-119	Submission dates:	1/29/01, 2/19/01, 2/23/01 & 4/13/01
M.O. Suppl 1, Review #2	Received dates:	1/31/01, 2/21/01, 2/26/01 & 4/16/01
	Review date:	8/20/01

Proposed Trade name: Visudyne

Generic name: Verteporfin for injection

Sponsor: QLT PhotoTherapeutics Inc.  
887 Great Northern Way  
Vancouver, BC Canada VST 4TS  
(604) 872-7881

Proposed Indication(s): The treatment of patients with predominantly classic subfoveal choroidal neovascularization.

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## **Executive Summary**

### **I. Recommendations**

#### **A. Recommendation on Approvability**

*NDA 21-119, Visudyne (verteporfin for injection) with the labeling changes noted in this review, in conjunction with the*

*[REDACTED] is recommended for approval for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age related macular degeneration, pathologic myopia or presumed ocular histoplasmosis.*

#### **B. Recommendation on Phase 4 Studies and Risk Management Steps**

*The expansion of the indication to include predominantly classic subfoveal choroidal neovascularization due to pathologic myopia and presumed ocular histoplasmosis represents a relatively small addition to the population. The risks do not appear to differ from the original indication. No additional Phase 4 studies are recommended at this time.*

### **II. Summary of Clinical Findings**

#### **A. Brief Overview of Clinical Program**

*Adequate and well controlled studies in subfoveal choroidal neovascularization due to age related macular degeneration, an adequate and well controlled study in patients with subfoveal choroidal neovascularization due to pathologic myopia and an open label, historically controlled study was performed in patients with subfoveal choroidal neovascularization due to presumed ocular histoplasmosis.*

#### **B. Efficacy**

*The Visudyne treatment group demonstrated statistically significant decreases in the likelihood of a three line loss of best corrected visual acuity in patients with predominately classic subfoveal choroidal neovascularization due to pathologic myopia at the 3, 9 and 12 month time points. The 12 month time point was the predetermined primary efficacy endpoint.*

*Compared to historical controls, the Visudyne treatment group demonstrated significant decreases in the likelihood of a six line loss of best corrected visual acuity in patient with subfoveal choroidal neovascularization due to ocular histoplasmosis at the 12 month time point.*

C. Safety

*No new safety findings were observed with these additional indications.*

D. Dosing

*No changes in the dosing schedule were made in the clinical studies or are proposed in the revised labeling.*

E. Special Populations

*The proposed additional indications represent an expansion into special populations. No additional populations have been studied.*

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

**Background:**

Visudyne (verteporfin for injection) is approved for the treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization. This supplement proposes to expand the indication by providing studies in patients with subfoveal choroidal neovascularization due to pathologic myopia and presumed ocular histoplasmosis.

The addition of a claim for predominately classic subfoveal choroidal neovascularization due to either pathologic myopia or presumed ocular histoplasmosis would be acceptable based on a controlled study in either of these indications demonstrating superiority of Visudyne over the control group. An additional claim for predominantly classic subfoveal choroidal neovascularization (without regard to specific cause) would require positive results from controlled studies in each of three causes of predominately classic subfoveal choroidal neovascularization provided the diseases after treatment appear to behave similarly.

**Deficiencies Noted in the December 2000 Approvable Letter:**

The supplement was not approved after its initial submission because:

1. An incomplete listing of Adverse Reactions was provided in the original supplement submission. Specifically, Table 47, Page 5 of 5 is missing. (Page 149).

**Reviewer's Comments:** *The typographical error in Table 47 was corrected.*

2. The 24 month visual acuity data for study OCR 003 PM should have been available and submitted in the Safety Update.

**Reviewer's Comments:** *This information has been submitted and is included below.*

3. The study OCR 004 was prematurely reported. The 12 month results should be reported and should include an appropriate control group.

**Reviewer's Comments:** *The 12 month results have now been reported and are listed below.*

**APPEARS THIS WAY  
ON ORIGINAL**

4. Gastrointestinal cancers were reported in a significant number of patients in the original Age Related Macular Degeneration Studies. Gastrointestinal cancers should have been monitored in all studies, and a summary should have been reported.

**Reviewer's Comments:** *A summary of all gastrointestinal cancers was submitted and is provided below.*

Review of safety data from all ocular and non-ocular verteporfin studies (controlled and uncontrolled) as of January 16, 2001, a total of 14 verteporfin-treated patients had gastrointestinal cancer (including 1 esophageal, 2 gastric, 1 pancreatic, 1 unspecified digestive cancer, and 9 colorectal cancers). These cases occurred in only 6 of the 29 verteporfin studies conducted. The total number of patients exposed to verteporfin in all studies as of September 29, 2000, was 5741. No more than 70 additional patients were treated with verteporfin in clinical trials up to December 15, 2000. Therefore, using the conservative exposure number from the end of September, the incidence of all gastrointestinal cancers in verteporfin-treated patients was 0.24% (14/5741 patients). The incidence of colorectal cancer was 0.16% (9/5741 patients). One of the 9 colorectal cancers was almost certainly a pre-existing condition since the diagnosis was made 10 days after the first verteporfin treatment (Patient 04114 in Study OCR 002 A). As of January 16, 2001, no gastrointestinal cancer was reported in post-marketing surveillance data. As of December 15, 2000, approximately 20,000-40,000 patients were treated with commercially available verteporfin (VISUDYNE™).

**Incidence of Gastrointestinal Cancer and Colorectal Cancer in Placebo-Controlled Studies (2 Years Follow-up)<sup>a</sup>**

	Number (%) of Patients	
	Verteporfin n N=708	Placebo N=360
Gastrointestinal Cancer <sup>b,c</sup>	9 (1.3)	3 (0.8)
Colorectal Cancer <sup>b</sup>	7 (1.0)	1 (0.3)

a Studies OCR 002 A+B and OCR 003 AMD+PM combined.

b Includes Patient 04114 (verteporfin), who most likely had pre-existing colon cancer (not treatment-emergent).

c Includes patients with colorectal cancer.

**Patients with the Preferred Term of Gastrointestinal Carcinoma from all Studies**

Patient Number	Age <sup>a</sup> / Sex	Course/Day	Reported Term	Gastrointestinal Medical History
<b>VERTEPORFIN PATIENTS (Total 5741 Verteporfin Patients Treated)</b>				
<b>Study OCR 002 A (Total 204 Verteporfin Patients Treated)</b>				
01217	75/M	C3 D68	Cancer sigmoid colon	Hypercholesterolemia; latent diabetes mellitus; antral gastritis; duodenal ulcer; esophageal diverticulum
01233	69/F	C5 D153	Gastric cancer	Cholecystectomy; appendectomy
04114 <sup>d</sup>	78/M	C1 D10	Cancer of the colon	Colonopathy
15204	89/M	C3 D214	Adenocarcinoma of cecum	Chronic cholecystitis with cholelithiasis
18123	74/M	C2 D62	Cancer of colon	None
<b>Study OCR 002 B (Total 198 Verteporfin Patients Treated)</b>				
12203	73/F	C7 D86	Colon cancer	Esophagitis
19209	69/M	C2 D505	Colon cancer with metastases to liver and bone	Hypercholesterolemia
<b>Study OCR 003 AMD (Total 225 Verteporfin Patients Treated)</b>				
V01A11	79/M	C5 D65	Gastric stump cancer	Biliary calculus; Perforation of the stomach due to ulcer with 2/3 resection of the stomach; Bladder tumor.
<b>Study OCR 003 PM (Total 81 Verteporfin Patients Treated)</b>				
V13P51	60/F	C2 D66	Metastatic colon cancer	None
<b>Study OCR 002 Extension (Uncontrolled Study) (Total 127 Verteporfin Patients Treated<sup>e</sup>)</b>				
02104	77/M	C4 D106	Probable digestive <sup>f</sup> carcinoma	Duodenal ulcer
13105	79/F	C11 D303	Colon cancer	None
<b>Study OCR 005 (Uncontrolled Study) (Total 4295 Verteporfin Patients Treated)</b>				
093 14	79/F	C2 D75	Esophageal cancer	Hiatal hernia
124 08	87/F	C1 D17	Pancreatic cancer	None
179 11	80/F	C1 D74	Rectal cancer	Colitis

<sup>a</sup> Age at study entry.

<sup>b</sup> Start Day since last course of treatment ("C3 D68" indicates that the adverse event started 68 days after the patient received their third course of treatment).

<sup>c</sup> As reported by the Investigator.

<sup>d</sup> This colorectal cancer is most likely not treatment-emergent (diagnosis 10 days after first verteporfin treatment).

<sup>e</sup> Includes only patients who were first exposed to verteporfin in the extension study (i.e., patients previously randomized to placebo in the controlled trial). Patients randomized to verteporfin in the controlled trial are already counted in Studies OCR 002 A and B.

<sup>f</sup> This event was reported with episodes of melena, suggesting an upper gastrointestinal origin.

**APPEARS THIS WAY  
ON ORIGINAL**

If Patient 04114 is excluded because he had pre-existing colon cancer, only 6 verteporfin patients had treatment-emergent colorectal cancer in the 2-year controlled studies (0.8% over 2 years; or 0.4% annual incidence). The 6 verteporfin patients with colorectal cancer in placebo-controlled trials ranged in age from 60 to 89 years; 4 are men and 2 are women. The mean age of the 627 verteporfin patients in controlled studies OCR 002 A+B and OCR 003 AMD was 75 years, while the mean age of the 81 verteporfin patients in controlled study OCR 003 PM was 51 years.

Colorectal cancer is one of the most common malignancies in old age and increases markedly with advancing age. The American Cancer Society annual incidence rate for a 75-year-old is slightly more than 0.3% for women and nearly 0.5% for men. The annual incidence of 0.4% for treatment-emergent colorectal cancer in the controlled studies falls within the range of the natural annual incidence of colorectal cancer. The incidence of treatment-emergent colorectal cancer in all verteporfin studies (0.14%) is notably less than the natural annual incidence.

Colorectal cancer develops with a natural history of 10-15 years. All patients who were diagnosed with new colorectal cancer while participating in clinical trials first received verteporfin  $\leq 3.5$  years before the cancer was diagnosed. Most of the patients (7 of 9) who developed colorectal cancer received  $\leq 3$  verteporfin treatments before diagnosis. Of these 7 patients, 5 developed colorectal cancer  $< 3$  months from their last verteporfin treatment. A cause-effect relationship between verteporfin treatment and these cases is extremely unlikely because of the small number of treatments and the short time interval between treatment and diagnosis of colorectal cancer. Therefore, verteporfin exposure is unlikely to have been a factor in the genesis of the disease. Furthermore, there is no known mechanism of action by which verteporfin would lead to colorectal cancer. The COSTART term of gastrointestinal carcinoma is a summary term grouping different types of cancer. The only gastrointestinal cancer with several events in verteporfin controlled studies is colorectal cancer. The incidence of treatment-emergent colorectal cancer in verteporfin patients over 2 years is  $< 1\%$  and is well within the expected natural incidence.

**Reviewer's Comments:** *Gastrointestinal cancer and colorectal cancer remain a concern; however, a clear causal relationship cannot be established at this time.*

**APPEARS THIS WAY  
ON ORIGINAL**

**Study Title:** BPD OCR 003 PM: A Randomized, Placebo-Controlled, Masked, Multicenter, Phase IIIB Study of the Treatment of New Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration or Pathologic Myopia Using Photodynamic Therapy with Verteporfin for Injection

**Reviewer's Comments:** *Details of this study are listed in Medical Officer Review #1 of this Supplement and are not repeated here. Data through Month 24 is now available and is listed below.*

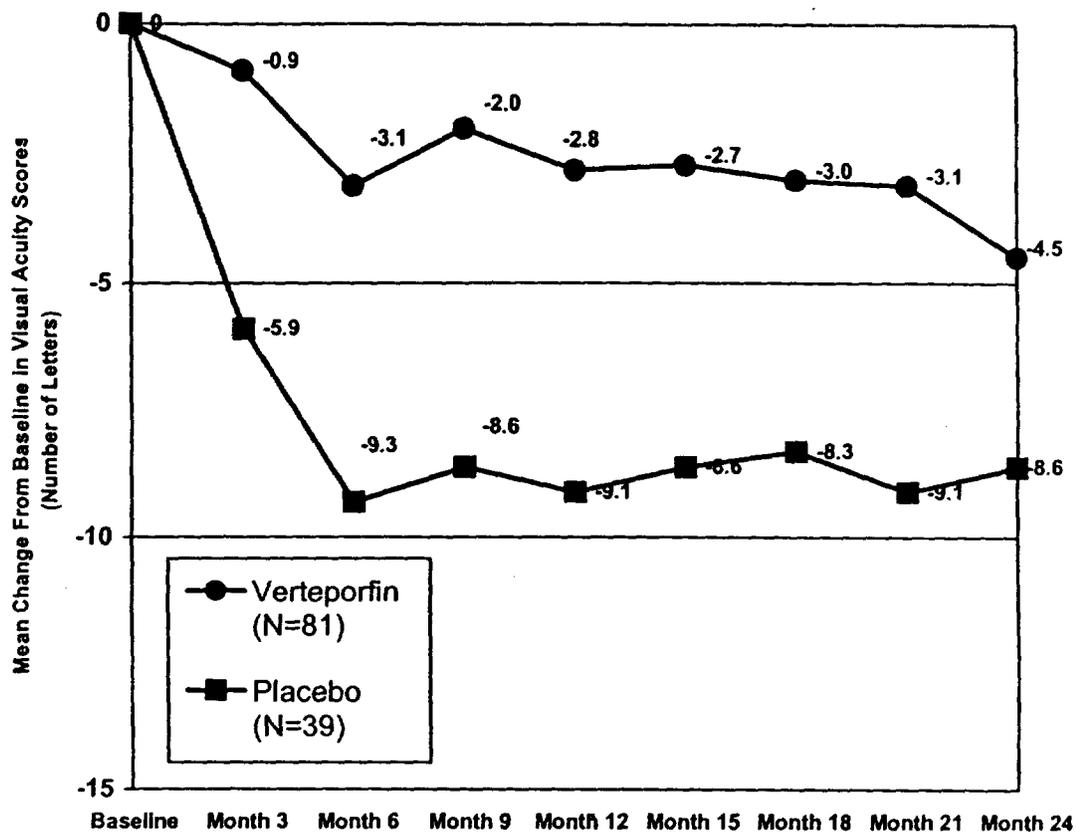
**Patient Responders<sup>a</sup> (<15-Letter Decrease in Visual Acuity)  
(Intent-to-Treat)**

Month	Verteporfin (n/N)	Placebo (n/N)	Difference (Percent)	95% CI (Difference)	P value <sup>c</sup>
Month 3	76 (93.8)	31 (79.5)	(14.3)	[ 0.6, 28.1]	
Month 6	68 (84.0)	30 (76.9)	( 7.0)	[-8.4, 22.5]	
Month 9	71 (87.7)	26 (66.7)	(21.0)	[ 4.5, 37.4]	
Month 12	70 (86.4)	26 (66.7)	(19.8)	[ 3.2, 36.3]	.011
Month 15	66 (81.5)	29 (74.4)	( 7.1)	[-9, 23.2]	
Month 18	65 (80.2)	29 (74.4)	( 5.9)	[-10.3, 22.1]	
Month 21	67 (82.7)	26 (66.7)	(16.0)	[-0.9, 33.0]	
Month 24	64 (79.0)	28 (71.8)	( 7.2)	[-9.5, 23.9]	.381

- <sup>a</sup> A responder was a patient who had a decrease from baseline of <15 letters in VA.  
<sup>b</sup> Proportion of verteporfin responders minus the proportion of placebo responders.  
<sup>c</sup> Chi-square used to test significance between the proportion of patient responders for verteporfin treatment versus placebo at Month 12.

**Reviewer's Comments:** *The difference between groups is statistically significant only at Months 9 and 12. Month 12 was defined as the primary endpoint, however, the lack of a statically significant effect is of concern.*

**APPEARS THIS WAY  
ON ORIGINAL**



**Reviewer's Comments:** *The study demonstrates clinical efficacy of verteporfin for injection in the treatment of predominately classic choroidal neovascularization secondary to high myopia, however, the groups are slowly converging.*

APPEARS THIS WAY  
ON ORIGINAL

**Title:** BPD OCR 004 (OHS, 12 Months): An Open-Label, Multicenter, Safety and Effect on Visual Acuity Study of the Treatment of Subfoveal Choroidal Neovascularization Secondary to Ocular Histoplasmosis Syndrome (OHS) Using Photodynamic Therapy with Verteporfin for Injection

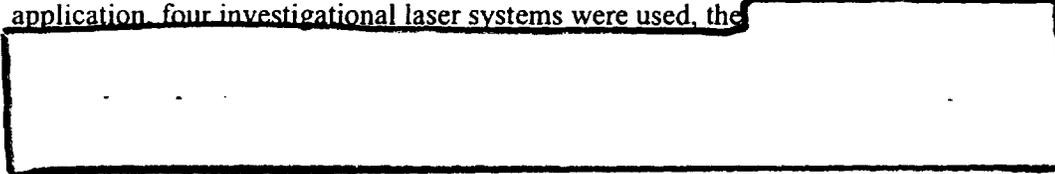
**Primary Objective:** To evaluate the safety and effects on visual acuity of verteporfin used in photodynamic treatment of subfoveal CNV in patients with OHS.

**Study Design:**

Clinical Study BPD OCR 004 was an open-label, multicenter, Phase 1/2 study of the treatment of subfoveal choroidal neovascularization secondary to OHS using verteporfin PDT treatment. Four centers were to enroll approximately 20 patients (5-10 patients per center).

**Treatment:**

Consistent with other Visudyne studies, treatment consisted of an infusion over 10 minutes of verteporfin ( $6 \text{ mg/m}^2$ ), followed by an application of  $50 \text{ J/cm}^2$  of nonthermal red light (689 nm) initiated 15 minutes after the start of the infusion. For light application, four investigational laser systems were used, the



**Inclusion Criteria**

Patients who were willing to sign an informed consent, were 18 years of age or older, male or female (with documentation of negative pregnancy test), and any race were eligible provided they fulfilled all of the following criteria:

1. In at least one eye, had subfoveal CNV secondary to ocular histoplasmosis alone.
2. Evidence of classic or occult CNV extending through the geometric center of the foveal avascular zone (FAZ). (Feeder vessels to recurrent CNV that extended through the geometric center of the FAZ did not exclude the patient.)
3. Study eye had to have a best-corrected visual acuity score between 34 and 73 (approximately equal to or worse than 20/40 on ETDRS chart but equal to or better than 20/200).

**Exclusion Criteria**

Patients were not eligible for enrollment if the following were present:

1. Color photography and fluorescein angiography showed:
  - a. CNV did not involve the geometric center of the foveal avascular zone. (Whenever depigmentation from earlier laser treatment extended through the geometric center of the FAZ, the patient was not eligible.)
  - b. The area of CNV (classic plus occult) was less than 50% of the total lesion (not including areas of prior laser treatment).
  - c. The greatest linear dimension of the entire CNV lesion exceeded 5400  $\mu\text{m}$  diameter (approximately equivalent to the diameter of a 9 Macula Photocoagulation Study [MPS] disc area circle) at the initial treatment.
  - d. The study eye had a tear (rip) of the retinal pigment epithelium (RPE); a vitelliform-like lesion of the outer retina (e.g., as in pattern dystrophies or basal laminar drusen); idiopathic parafoveal telangiectasis, central serous retinopathy, or serous pigment epithelial detachment without CNV.

**Schedule of Study Procedures**

Procedure	Screening Baseline	Day -7	Treatment Period (Months)										
			0	3	6	9	12	15	18	21	24		
Demography, Medical History, Inclusion/Exclusion	X												
Informed Consent	X												
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam, Laboratory Test	X												
Vital Signs <sup>b</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Tests <sup>c</sup>	X		X	X	X	X	X	X	X	X	X	X	X
Best-Corrected Visual Acuity	X		X	X	X	X	X	X	X	X	X	X	X
Contrast Sensitivity	X		X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photography	X		X	X	X	X	X	X	X	X	X	X	X
Fluorescein Angiography	X		X	X	X	X	X	X	X	X	X	X	X
Dilated Ophthalmoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X
Verteporfin <sup>d</sup>		X	X	X	X	X	X	X	X	X	X	X	X
Subjective visual performance <sup>e</sup>	X		X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X

<sup>a</sup> Day -7 to 0.

<sup>b</sup> Vital signs were checked before each infusion of study drug.

<sup>c</sup> Negative blood test required within 7 days of initial treatment and a negative urine test was required within 3 days of any retreatment in females of childbearing potential.

<sup>d</sup> If CNV leakage was present, treatment was conducted within 7 days of fluorescein angiography.

<sup>e</sup> Patient's subjective visual performance scores were obtained in the clinic at screening and each visit and by telephone 4 weeks after each follow-up visit through Month 21.

## List of Study Investigators

Country	Investigator	Study Center	Site Identification and Number	Patients Enrolled
Switzerland	Michel Sickenberg, MD	Hôpital Ophthalmique Universitaire Jules Gonin Av. de France 15 CH-1004 Lausanne	LAU 02	1
United States	Robert Rosa, MD Phillip Rosenfeld, MD Mary-Lou Lewis, MD	Bascom Palmer Eye Institute 900 N.W. 17th Street Miami, Florida 33136	MIA 20	8
	David Saperstein, MD * Thomas M. Aaberg, Sr, MD	Emory Eye Center 1365-B Clifton Road Atlanta, Georgia 30322	ATL 24	17

\* David Saperstein, MD was the Principal Investigator from the beginning of the study to January 2000.  
Thomas M. Aaberg, Sr, MD became the Principal Investigator in January 2000.

## Summary of Baseline Characteristics

Characteristic	Number	% of Patients
Verteporfin (N=26)		
<b>GENDER</b>		
Women	16	(61.5)
Men	10	(38.5)
<b>AGE (Years)<sup>a</sup></b>		
30-39	5	(19.2)
40-49	8	(30.8)
50-59	10	(38.5)
60-69	2	(7.7)
≥70	1	(3.8)
Mean		49.3
VISUAL ACUITY (STUDY EYE) <sup>a</sup> Mean Score (letters)		56.1
CONTRAST SENSITIVITY (STUDY EYE) <sup>a</sup> Mean Score (letters)		29.1
ASSESSED BY THE PHOTOGRAPH READING CENTER		
<b>LESION COMPONENTS</b>		
Evidence of CNV in ≥50% of lesion	23	(88.5)
CNV Location (Subfoveal or Probably Subfoveal)	24	(92.3)
Classic CNV		
≥50%	18	(69.2)
<50%	5	(19.2)
Occult CNV <sup>b</sup>	9	(34.6)
Blood	10	(38.5)
Blocked fluorescence	6	(23.1)
CNV Secondary to OHS Alone	24	(92.3)
<b>LESION SIZE (MPS DA)</b>		
≤1	8	(30.8)
>1 to 2	4	(15.4)
>2 to 3	10	(38.5)
>3	3	(11.5)
Can't grade	1	(3.8)
GREATEST LINEAR DIMENSION (GLD) OF LESION (microns) <sup>a</sup> Mean <sup>c</sup>		2,583.3

<sup>a</sup> Parameters are presented as number and percentage of patients. Age is also presented as mean. Visual acuity, contrast sensitivity, and GLD are presented as mean only.

<sup>b</sup> Includes 1 patient who was graded as questionable.

<sup>c</sup> Sample size for GLD was 24 patients.

MPS DA = Macular Photocoagulation Study disc areas

**Reviewer's Comments:** *The demographics will need to be compared to a control group when the control group is identified.*

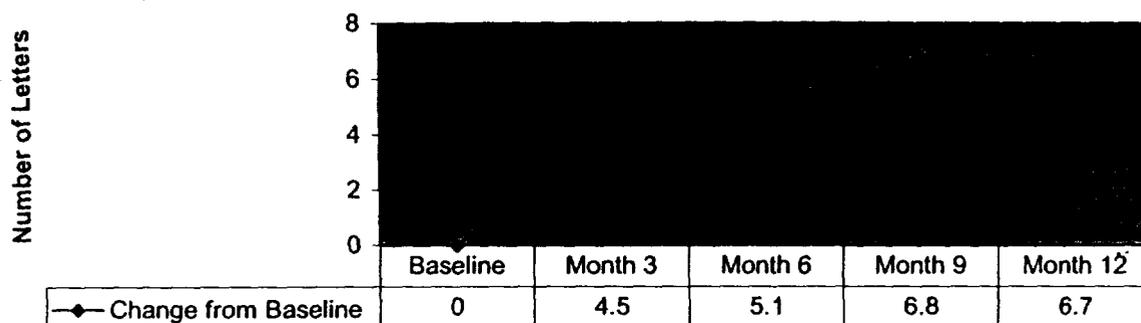
**Patient Responders**

Visit	Number (%) of Patients			
	Verteporfin N=26			
	<15 letters			
	N	n	(%)	95% C.I.
Month 3	26	24	(92.3)	[73.4, 97.0]
Month 6	25	22	(88.0)	[67.7, 94.7]
Month 9	24	22	(91.7)	[71.5, 96.7]
Month 12	25	23	(92.0)	[72.5, 96.8]

C.I.=Confidence Interval

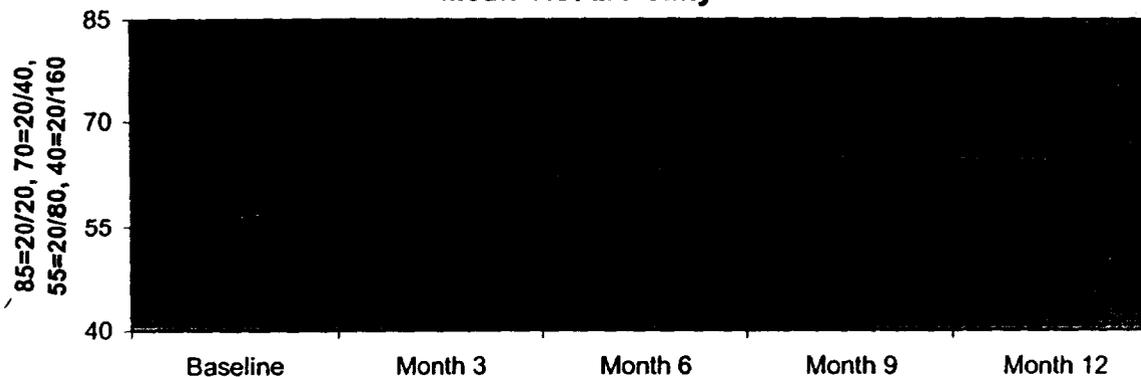
**Reviewer's Comments:** *Safety and efficacy cannot be determined without a control group.*

**Change in Visual Acuity**

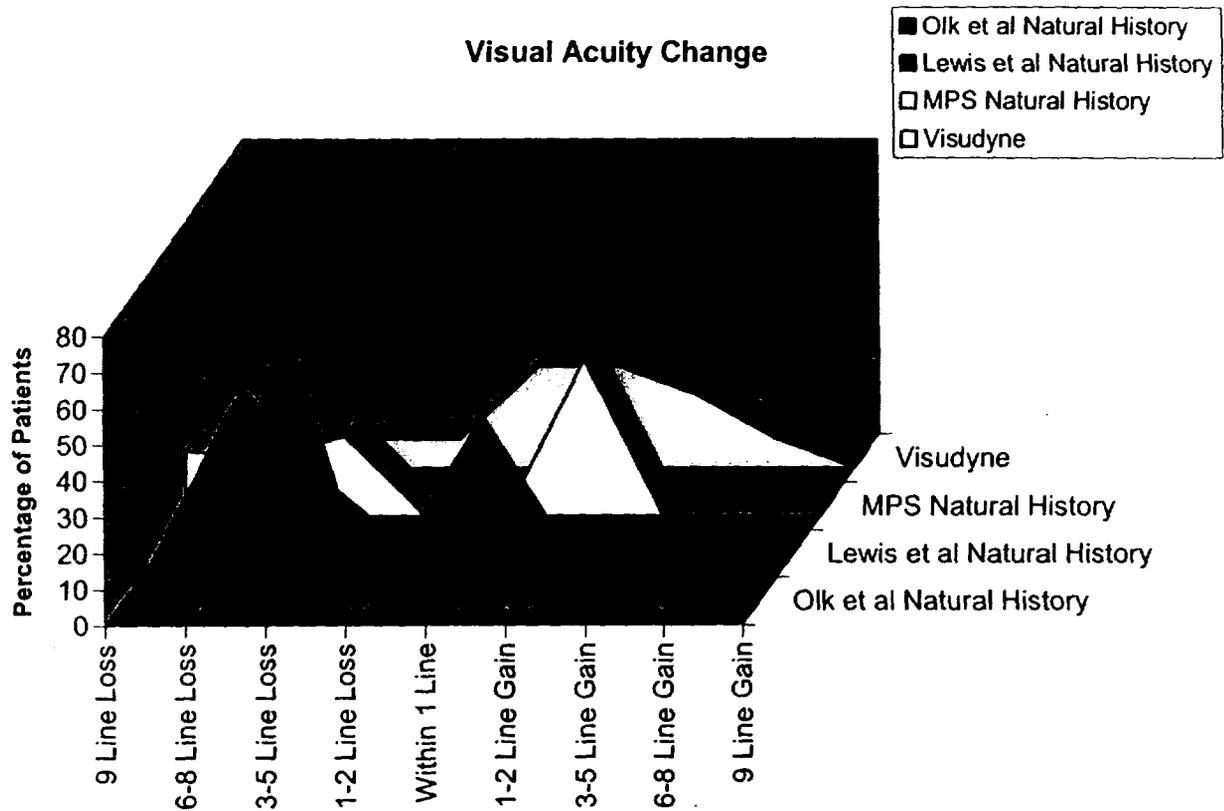


**Reviewer's Comments:** *The improvement listed is not considered clinically significant. As noted below, there is very little change in mean visual acuity.*

**Mean Visual Acuity**



## Comparison to Natural History



Olk RJ, Burgess DB, McCormick PA. Subfoveal and Juxtafoveal Subretinal Neovascularization in the Presumed Ocular Histoplasmosis Syndrome. *Ophthalmology* 91: 1592-1602, 1984.

Lewis ML, Van NewKirk MR, Gass JD. Follow-up Study of Presumed Ocular Histoplasmosis Syndrome. *Ophthalmology* 87:390-399, 1980.

Macular Photocoagulation Study Group. Argon Laser Photocoagulation for Ocular Histoplasmosis. *Arch Ophthalmol.* 101:1347-1357, 1983.

**Reviewer's Comments:** *In comparison to historical controls, Visudyne therapy offers a moderate improvement in visual acuity outcome, particular in the reduction of visual loss (3-6 lines).*

**Adverse Experiences**

	Number (%) of Patients Total (N=26)	
Total patients with at least one adverse event	21	(81)
<b>TREATMENT SITE — OCULAR (Study Eye Events)</b>	17	(65)
Blepharitis	1	(4)
Cataract	7	(27)
Conjunctivitis	4	(15)
Corneal lesion	2	(8)
Corneal opacity	1	(4)
Eye disorder	2	(8)
Eye hemorrhage	1	(4)
Eye pain	1	(4)
Glaucoma	1	(4)
Retinal disorder	1	(4)
Vision abnormal	3	(12)
Vision decreased	1	(4)
Visual field defect	3	(12)
<b>SPECIAL SENSES</b>	17	(65)
AMD Progression	1	(4)
Blepharitis	1	(4)
Cataract	5	(19)
Conjunctivitis	5	(19)
Corneal lesion	1	(4)
Corneal opacity	1	(4)
Eye disorder	2	(8)
Glaucoma	1	(4)
Keratitis	1	(4)
Otitis media	1	(4)
Scleritis	1	(4)
Vision abnormal	1	(4)
Vision decreased	1	(4)
<b>BODY AS A WHOLE</b>	13	(50)
Abdominal pain	2	(8)
Accidental injury	5	(19)
Allergic reaction	1	(4)
Asthenia	1	(4)
Chills and fever	1	(4)
Cyst	1	(4)
Fever	1	(4)
Flu syndrome	3	(11)
Headache	5	(19)
Infection	5	(19)
Injection Site Adverse Events <sup>a</sup>	4	(15)
Injection site edema	1	(4)

	Number (%) of Patients Total (N=26)	
Injection site extravasation	2	(8)
Injection site inflammation	2	(8)
Injection site pain	3	(11)
Injection site reaction	1	(4)
Neck pain	1	(4)
Neck rigidity	1	(4)
Pain	4	(15)
Photosensitivity reaction	1	(4)
<b>CARDIOVASCULAR</b>	4	(15)
Cardiovascular disorder	1	(4)
Hypertension	1	(4)
Syncope	2	(8)
<b>DIGESTIVE</b>	6	(23)
Cholecystitis	1	(4)
Constipation	1	(4)
Diarrhea	1	(4)
Gastroenteritis	1	(4)
Gingivitis	1	(4)
Nausea	1	(4)
Proctitis	1	(4)
<b>MUSCULOSKELETAL</b>	2	(8)
Arthralgia	1	(4)
Joint disorder	1	(4)
Tendon disorder	1	(4)
<b>NERVOUS</b>	4	(15)
Anxiety	1	(4)
Depression	2	(8)
Insomnia	3	(11)
<b>RESPIRATORY</b>	7	(27)
Bronchitis	2	(8)
Cough increased	3	(11)
Lung disorder	1	(4)
Pharyngitis	1	(4)
Rhinitis	2	(8)
Sinusitis	2	(8)
<b>SKIN AND APPENDAGES</b>	5	(19)
Contact dermatitis	1	(4)
Pruritus	1	(4)
Rash	2	(8)
Skin discoloration	1	(4)
<b>UROGENITAL</b>	1	(4)
Cystitis	1	(4)

## Summary of Adverse Experiences – All indications

Ocular Adverse Events	PM		HbE		AMD		PM		AMD	
BOI	Verteporfin		Verteporfin		Verteporfin		Placebo		Placebo	
Adverse Event	N=31	N=10	N=26	N=26	N=62	N=62	N=39	N=39	N=321	N=321
TREATMENT SITE — OCULAR (Study Eye)	33	(41)	17	(65)	317	(51)	15	(38)	141	(44)
AMD progression	1	(1)	1	(4)	9	(2)	0		4	(1)
Blepharitis	3	(4)	1	(4)	19	(3)	1	(3)	5	(2)
Cataract	5	(6)	5	(19)	90	(15)	3	(8)	41	(13)
Conjunctivitis	4	(5)	5	(19)	39	(6)	1	(3)	22	(7)
Corneal lesion	2	(2)	1	(4)	16	(3)	0		13	(4)
Corneal ulcer	1	(1)					0			
Diplopia	1	(1)					0			
Dry eyes	2	(2)			15	(3)	1	(3)	11	(3)
Eye disorder <sup>b</sup>	5	(6)	2	(8)	9	(1)	0		8	(2)
Eye itching	1	(1)			20	(3)	1	(3)	7	(2)
Eye pain	2	(2)			35	(6)	2	(5)	24	(7)
Face Edema	0						1	(3)		
Glaucoma	1	(1)			10	(2)	1	(3)	7	(2)
Keratitis	1	(1)	1	(4)			0			
Lacrimation disorder	1	(1)			13	(2)	1	(3)	6	(2)
Photophobia	3	(4)			7	(1)	0		5	(2)
Retinal disorder			1	(4)	4	(1)			10	(3)
Subretinal hemorrhage					13	(2)			9	(3)
Visual Disturbance <sup>c</sup>	18	(22)	6	(23)	182	(29)	8	(20)	58	(18)
Vision abnormal	7	(9)	3	(11)	103	(16)	1	(3)	37	(11)
Vision decreased	12	(15)	1	(4)	106	(17)	7	(18)	28	(9)
Visual field defect	3	(4)	3	(11)	58	(9)	2	(5)	14	(4)
Vitreous disorder	3	(4)			9	(1)	0		7	(2)
Vitreous hemorrhage					11	(2)			4	(1)
SPECIAL SENSES (Including Nonstudy Eye) <sup>d</sup>	19	(23)	17	(65)	210	(33)	5	(13)	110	(34)
AMD progression	2	(2)			16	(3)	1	(3)	15	(5)
Blepharitis	2	(2)	1	(4)	16	(3)	1	(3)	3	(1)
Cataract	3	(4)	5	(19)	51	(8)	1	(3)	22	(7)
Conjunctivitis	3	(4)	5	(19)	30	(5)	1	(3)	21	(6)
Corneal lesion	2	(3)			14	(2)	0		9	(3)
Dry eyes	1	(2)			13	(2)	0		12	(4)
Eye disorder <sup>b</sup>	3	(4)	2	(8)	12	(2)	0		11	(3)
Eye itching					16	(3)			6	(2)
Eye pain	2	(3)			17	(3)	0		8	(2)
Glaucoma	1	(2)	1	(4)	9	(1)	2	(5)	7	(2)
Lacrimation disorder	0						1	(3)		
Otitis media	2	(3)					1	(3)		
Photophobia	3	(4)					0			
Retinal disorder	1	(1)					1	(3)		
Visual Disturbance <sup>c</sup>	4	(5)			55	(9)	1	(3)	33	(10)
Vision abnormal	2	(3)	1	(4)	28	(4)	1	(3)	18	(6)
Vision decreased	2	(3)	1	(4)	29	(4)	0		13	(4)
Visual field defect	1	(2)			7	(1)	0		6	(2)
Vitreous disorder	1	(2)					1	(3)		

<sup>a</sup> Adverse events that were reported at an incidence of at least 1.0% (study eye) or 2.0% (nonstudy eye) in either treatment group in Studies OCR 002 A+B and OCR 003 AMD combined.

<sup>b</sup> The preferred term of eye disorder is nonspecific and includes reported terms such as "entropion of the right eye", "eyes tired in evening when reading", dermatochalasis, and pterygium.

<sup>c</sup> Visual disturbance is a summary term. All individual terms included in the summary term are presented here, whether or not they occurred in ≥1.0% (study eye) or ≥2.0% (nonstudy eye) of patients.

<sup>d</sup> The total number of patients with at least one event under "Special Senses" also included the non-ocular events of deafness, ear pain, otitis externa, otitis media, tinnitus, and taste perversion, each occurring at an incidence of <2.0%.

Non-ocular events	AMD		Hist		PM		PM		AMD	
BODY SYSTEM	Verteporfin		Verteporfin		Verteporfin		Placebo		Placebo	
Adverse Events	N=627		N=26		N=1		N=39		N=321	
<b>BODY AS A WHOLE</b>	356	(57)	14	(54)	34	(42)	16	(41)	171	(53)
Abdominal pain	22	(3.5)	2	(7)	5	(6)	1	(3)	12	(3.7)
Accidental injury	64	(10.2)	5	(19)	3	(4)	2	(5)	35	(10.9)
Allergic reaction	11	(1.8)			3	(4)	3	(8)	10	(3.1)
Asthenia	34	(5.4)			5	(6)			10	(3.1)
Back pain	37	(5.9)			3	(4)			24	(7.5)
Chest pain	24	(3.8)					1	(3)	15	(4.7)
Face edema					1	(1)	1	(3)		
Fever	19	(3.0)					1	(3)	6	(1.9)
Flu syndrome	49	(7.8)	3	(11)	7	(9)	2	(5)	16	(5.0)
Headache	61	(9.7)	5	(19)	8	(10)	4	(10)	43	(13.4)
Hernia	9	(1.4)							8	(2.5)
Infection	63	(10.0)	5	(19)	7	(9)	3	(8)	36	(11.2)
Infusion related back pain	15	(2.4)							0	(0.0)
<b>Injection Site Adverse Events<sup>b</sup></b>	82	(13.1)	4	(15)	8	(10)	2	(5)	18	(5.6)
Inj. site discoloration	4	(0.6)			1	(1)			0	(0.0)
Inj. site edema	34	(5.4)	1	(4)	2	(2)			1	(0.3)
Inj. site extravasation	35	(5.6)	2	(7)	1	(1)	1	(3)	10	(3.1)
Inj. site fibrosis	1	(0.2)							0	(0.0)
Inj. site hemorrhage	10	(1.6)			1	(1)			4	(1.2)
Inj. site hypersensitivity	8	(1.3)							1	(0.3)
Inj. site inflammation	17	(2.7)	2	(7)	2	(2)			2	(0.6)
Inj. site pain	54	(8.6)	3	(11)	5	(6)	1	(3)	2	(0.6)
Inj. Site reaction	1	(0.2)	1	(4)	1	(1)			0	(0.0)
Neoplasm							1	(3)		
Pain	58	(9.3)	4	(15)	3	(4)	3	(8)	25	(7.8)
Photosensitivity reaction	16	(2.6)			3	(4)	1	(3)	1	(0.3)
<b>CARDIOVASCULAR</b>	180	(28.7)	4	(15)	4	(5)	10	(26)	92	(28.7)
Angina pectoris	12	(1.9)							10	(3.1)
Atrial fibrillation	15	(2.4)					1	(3)	5	(1.6)
Cardiovascular disorder	18	(2.9)							9	(2.8)
Coronary artery disorder	14	(2.2)							8	(2.5)
Hemorrhage							1	(3)		
Hypertension	61	(9.7)	1	(4)	3	(4)	5	(13)	28	(8.7)
Migraine							1	(3)		
Myocardial infarction	12	(1.9)							9	(2.8)
Palpitation							1	(3)		
Syncope	9	(1.4)	2	(7)					7	(2.2)
Vascular disorder							1	(3)		
Vasodilation							1	(3)		
<b>DIGESTIVE</b>	159	(25.4)			16	(20)	6	(15)	85	(26.5)
Constipation	15	(2.4)	1	(4)					1	(0.3)
Diarrhea	26	(4.1)	1	(4)	1	(1)	1	(3)	17	(5.3)
Dry Mouth							1	(3)		
Dyspepsia	11	(1.8)							9	(2.8)
Gastrointestinal disorder	17	(2.7)			2	(2)	1	(3)	12	(3.7)
Nausea	44	(7.0)			4	(5)	3	(8)	18	(5.6)
Tooth disorder					2	(2)	1	(3)		
Vomiting	15	(2.4)			1	(1)	1	(3)	8	(2.5)
<b>ENDOCRINE SYSTEM</b>	13	(2.1)							9	(2.8)

Non-ocular events	AMD		Hist		PM		PM		AMD	
	Verteporfin N=62		Verteporfin N=25		Verteporfin N=81		Placebo N=39		Placebo N=321	
<b>BODY SYSTEM</b>										
<b>Adverse Event</b>										
Hypothyroidism	8	(1.3)							7	(2.2)
<b>HEMIC AND LYMPHATIC</b>	70	(11.2)			1	(1)	1	(3)	28	(8.7)
Anemia	26	(4.1)							14	(4.4)
Ecchymosis	14	(2.2)	1	(4)					8	(2.5)
Leukocytosis							1	(3)		
<b>METABOLIC/NUTRITIONAL</b>	137	(21.9)			3	(5)	2	(5)	89	(27.7)
Creatinine increased	15	(2.4)							5	(1.6)
Glycosuria	21	(3.3)							12	(3.7)
Hemochromatosis							1	(3)		
Hypercholesteremia	41	(6.5)							27	(8.4)
Hypokalemia	8	(1.3)							7	(2.2)
Ketosis	12	(1.9)							8	(2.5)
Peripheral edema	33	(5.3)							16	(5.0)
<b>MUSCULOSKELETAL</b>	110	(17.5)			6	(7)	3	(8)	58	(18.1)
Arthralgia	28	(4.5)	1	(4)			3	(8)	15	(4.7)
Arthritis	28	(4.5)							20	(6.2)
Arthrosis	18	(2.9)							4	(1.2)
Bone disorder	10	(1.6)							7	(2.2)
Osteoporosis	13	(2.1)							7	(2.2)
<b>NERVOUS</b>	158	(25.2)	4	(15)	8	(10)	2	(5)	76	(23.7)
Anxiety	15	(2.4)							5	(1.6)
Ataxia							1	(3)		
Depression	31	(4.9)	2	(8)	3	(4)			19	(5.9)
Dizziness	30	(4.8)			2	(2)			15	(4.7)
Insomnia	16	(2.6)	3	(11)					7	(2.2)
Libido decreased							1	(3)		
Paresthesia	4	(0.6)			1	(1)	1	(3)	7	(2.2)
Vertigo	15	(2.4)							7	(2.2)
<b>RESPIRATORY</b>	149	(23.8)	7	(27)	18	(22)	9	(23)	78	(24.3)
Bronchitis	33	(5.3)	2	(8)	5	(6)	1	(3)	16	(5.0)
Cough increased	38	(6.1)	3	(11)					14	(4.4)
Dyspnea	22	(3.5)					1	(3)	12	(3.7)
Lung disorder	13	(2.1)							7	(2.2)
Pharyngitis	23	(3.7)			6	(7)	3	(8)	12	(3.7)
Pneumonia	23	(3.7)							10	(3.1)
Rhinitis	20	(3.2)	2	(8)					16	(5.0)
Sinusitis	15	(2.4)	2	(8)	5	(6)	4		5	(1.6)
<b>SKIN AND APPENDAGES</b>	102	(16.3)	5	(19)	7	(9)	3		50	(15.6)
Alopecia					1	(1)	1	(3)		
Pruritus	12	(1.9)	1	(4)	2	(2)	2	(5)	9	(2.8)
Rash	25	(4.0)	2	(8)					14	(4.4)
Skin Disorder										
<b>UROGENITAL</b>	100	(15.9)			6	(7)	3		57	(17.8)
Cystitis	20	(3.2)	1	(4)			1	(3)	11	(3.4)
Prostatic disorder	19	(3.0)							8	(2.5)
Uterine fibroids enlarged							1	(3)		
Urinary tract infection	20	(3.2)							13	(4.0)
Vaginal Hemorrhage					1	(1)	1	(3)		

14 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

**Conclusions and Recommendations:**

NDA 21-119, Visudyne (verteporfin for injection) with the labeling changes noted above, in conjunction with the [REDACTED]

[REDACTED] recommended for approval for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age related macular degeneration, pathologic myopia and presumed ocular histoplasmosis.

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

cc: Orig NDA 21-119

[REDACTED]

- 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