

CLINICAL STUDY PROTOCOL

Benzoporphyrin Derivative Monoacid Ring A [BPD-MA (verteporfin)]

BPD OCR 002

A Randomized, Placebo-Controlled, Masked, Multicenter, Phase 3 Study of the Treatment of Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD) Using Photodynamic Therapy (PDT) with Liposomal BPD-MA (verteporfin)

SHORT TITLE: Treatment of AMD with PDT (TAP)

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PROTOCOL SUMMARY

Study Title

A Randomized, Placebo-Controlled, Masked, Multicenter, Phase 3 Study of the Treatment of Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD) Using Photodynamic Therapy (PDT) with Liposomal Benzoporphyrin Derivative Monoacid Ring A (BPD-MA verteporfin).

Study Objectives

Primary

To demonstrate that PDT treatment of patients with CNV secondary to AMD will, with an acceptable safety profile, significantly reduce vision loss compared to placebo (sham treatment).

Secondary

To evaluate the long term safety of PDT treatment.

To compare the effects of PDT treatment with a placebo (sham) regimen on peak-contrast threshold.

Study Design

This will be a masked, multicenter, randomized, Phase 3 study of the treatment of subfoveal choroidal neovascularization (CNV) secondary to Age-Related Macular Degeneration (AMD) using photodynamic therapy (PDT) with liposomal Benzoporphyrin Derivative Monoacid Ring A (BPD-MA verteporfin) compared to placebo. Two studies (A and B) will be conducted under this protocol. Overall, approximately 10 North American and 8 European centers will enroll about 540 patients (30 patients per center) to obtain 450 evaluable patients (225 per study). Approximately equal numbers of centers from each continent will be allocated into each of the two studies.

Patients, treating ophthalmologists, vision examiners and reading center graders will be masked to the identity of the treatment. Sponsor personnel responsible for the conduct and monitoring of the trial will also be masked to the identity of the treatment. The study coordinator from each center will remain unmasked and will be responsible for the randomization of patients using sealed treatment allocation codes and for maintaining the masking of other center staff and the patient. Patients will be randomized to PDT treatment or placebo treatment in a ratio of 2:1. Patient randomization will also be stratified by baseline visual acuity at each center. Vision stratification will be 54-73 letters (approximately 20/40-20/80) and 34-53 letters (approximately 20/100-20/200).

Outpatients with new or recurrent subfoveal CNV secondary to AMD in which laser photocoagulation likely would not be beneficial because the lesion is too large or poorly demarcated will be enrolled in the study. Only one eye per patient will be treated in the study. In cases of two eye involvement the decision of which eye to treat will be between the investigator and patient.

Efficacy will be assessed by comparing the effect of PDT with placebo on both visual acuity using modified ETDRS charts and on contrast threshold using Pelli-Robson charts.

The primary efficacy analysis will be the proportion of patients who are classified as responders based on their best-corrected visual acuity. Two definitions of responder will be used: patients losing less than 3 lines of vision (<15 letters) and less than 6 lines of vision (<30 letters) compared to baseline. As noted in the following table, the study duration will be 24 months. An independent data and safety monitoring committee will monitor the study for safety concerns at 6 month intervals after its initiation. An analysis will be conducted when all patients have completed their 12-month follow-up visit. The sponsor will be unmasked at this point. We will file registration applications with these data if efficacy is proven and the trial will be continued to 24 months to provide additional data on long term safety and efficacy.

	Study Arms	
	PDT	Sham
Drug Dose (mg BPD-MA/m ²)	6	0
Light Dose (J/cm ²)	50	50
Time of Light ^a (min)	15	15
Evaluations ^b	3-month intervals	3-month intervals
Retreatment ^c	3-month intervals	3-month intervals
Interim Safety Analysis	6-month intervals	6-month intervals
Analysis for Registration	Month 12	Month 12
Study Extension	To 2 years	To 2 years

- ^a Time of light administration after the start of a 10-minute drug infusion
- ^b 2-4 days after each treatment a safety assessment will be conducted by telephone.
- ^c Retreatments only if there is angiographic evidence of leakage

Study Procedures

Within 7 days before the initial treatment day, after written informed consent has been obtained, all patients will be screened to determine if they conform to the inclusion and exclusion criteria. Baseline assessments will include a laboratory profile including hematology, serum chemistry and urinalysis; medical history including underlying conditions present and a physical examination including measurement of blood pressure, heart rate and EKG. All patients will have an ophthalmic evaluation including dilated ophthalmoscopy, manifest refraction using modified ETDRS visual acuity charts and protocol, contrast threshold assessment (using the Pelli-Robson chart), standardized colour stereoscopic fundus photography and fluorescein angiography.

The eligibility of the patient for treatment will be initially determined by the treating center. Fluorescein angiograms and fundus photographs of patients who are entered into the trial will be labelled and sent to the Photograph Reading Center for retrospective confirmation of eligibility and grading of lesion characteristics at baseline and all protocol-stipulated follow-up examinations except at month 15 and month 21. Month 15 and month 21 photographs must be sent to the Photograph Reading Center if either specific adverse events occur (see Appendix 8, section 4) or if these visits are the final visits in cases of premature termination of patient's involvement in the study. In the event of any disagreement regarding eligibility based on the fluorescein angiograms and fundus photographs, the Photograph Reading Center's assessment will rule.

On the day of treatment, eligible patients will be assigned randomly to active or placebo treatment after a brief ophthalmological examination justifies proceeding with the treatment as planned. The ophthalmologist and patient will be masked to the identity of the treatment assigned. This will be done by having the study coordinator or study nurse prepare the infusion and by covering the syringe and infusion line with aluminum foil. Vital signs (heart rate and blood pressure) will be assessed prior to the infusion. Patients will be followed 2-4 days and 3 months after each treatment.

Two to four days after initial treatment and any retreatment, patients will be contacted by telephone and undergo a general evaluation of any adverse events. An in-clinic visit to assess safety at this time is optional in which case every attempt must be made by the study coordinator to maintain masking of the treating ophthalmologist. If the patient reports a significant loss of vision in the treated eye within the 2-4 day post-treatment period, the patient will be advised to visit the clinic within 7 days of the treatment and undergo evaluation of best-corrected visual acuity. If, at this follow-up visit, a vision loss of 20 letters (approximately 4 lines) or more since the last assessment is detected in the treated eye, fluorescein angiography will be performed to define the relationship of the vision loss to therapy and the fluorescein angiograms will be sent to the Photograph Reading Center as soon as possible. Vision losses of ≥ 20 letters since the last assessment, that occur within 7 days of the last treatment will be reported on an expedited basis to the sponsors. If any branch retinal artery or vein occlusion is observed after any treatment, the patient will be excluded from further treatment.

Every 3 months, all patients will visit the clinic and will undergo dilated ophthalmoscopy, assessments of visual acuity, contrast threshold, colour fundus photography and fluorescein angiography. Visual acuity and contrast threshold will be determined by a masked vision examiner. Retreatment will be conducted if evidence of CNV leakage is detected by fluorescein angiography. If retreatment on the same day as the follow-up examinations is not feasible it must be conducted within 7 days of the fluorescein angiography.

Each center will evaluate their fluorescein angiograms to determine the eligibility and the need for retreatment, as well as the size of the retreatment spot (i.e., confirmation of leakage and area of the lesion to be treated by the Photograph Reading Center is not required). Subsequently, all angiograms and photographs (except at month 15 and month 21) will be sent within 1 week to the Photograph Reading Center where they will be interpreted by a

masked grader for closure of CNV, adverse events, CNV lesion components and other conditions associated with the natural course of disease or with treatment. Month 15 and month 21 photographs must be sent to the Photograph Reading Center if either specific adverse events occur (see Appendix 8, section 4) or if these visits are the final visits in cases of premature termination of patient's involvement in the study.

The study coordinator will make every reasonable attempt to maintain masking of the ophthalmologist, patient and vision examiner.

Systemic safety will be assessed at the treating centers by laboratory evaluations at intervals of 6 months. A physical examination including an EKG will be conducted at intervals of 12 months. Adverse events and the patient's general health status will be assessed at each visit. Ocular safety will be assessed by the treating center's ophthalmoscopic examinations and the assessment of best-corrected visual acuity and by the Photograph Reading Center's evaluation of the fundus photographs and fluorescein angiograms. The Photograph Reading Center will, in addition to grading the extent of leakage from the CNV lesions, semiquantitatively evaluate any progression of the CNV lesions, fibrosis, RPE atrophy, haemorrhage, and other markers associated with disease progression.

1. INTRODUCTION

1.1 Choroidal Neovascularization Secondary to Age-Related Macular Degeneration

Age-related macular degeneration (AMD) causes severe, irreversible vision loss and is the leading cause of blindness in individuals older than 50 years in the Western World. AMD is a degenerative eye disease with increasing prevalence at older ages. In the Framingham study, AMD was found in 1.6% of the population between 52 and 64, increasing to 27.9% over age 75 (1). The majority of patients have the "dry" form, characterized by drusen and atrophic changes in the retinal pigment epithelium (RPE). However, 80% of the severe vision loss attributable to this disease is related to the "wet" form, characterized by choroidal neovascularization (CNV). CNV leaks blood, lipid and fluid, and leads to rapid loss of central vision. In the United States it is estimated that between 70,000 - 200,000 individuals over the age of 65 develop the wet form of AMD every year (2,3).

1.2 Current Therapy for Age-Related Macular Degeneration

Although the natural history of the disease is eventual quiescence and regression of the neovascularization process, this usually occurs at the cost of subretinal fibrosis and vision loss (4,5). Current treatment relies on occlusion of the vessels using laser photocoagulation (6). Thermal laser photocoagulation is quite non-selective, producing retinal damage to the outer retina, including the photoreceptors, with an atrophic scar and corresponding visual scotoma. Although extensive studies have demonstrated a clinically significant advantage of laser treatment compared to observation for CNV, the treatment benefit is problematic for subfoveal lesions in which immediate visual acuity loss is common (7,8). Also, recurrences are common following standard laser treatment (9). Furthermore, the majority of lesions which have poorly defined boundaries, or that are large, are not amenable to standard laser treatment (10). Results from the Macular Photocoagulation Study (MPS) showed that at the 24 month examination laser treated eyes lost an average of 3.3 lines compared to untreated eyes that lost an average of 4.5 lines. Average visual acuity was 20/320 and 20/400, respectively (7). The percent of patients who lost 6 or more lines of vision was 20% in the treated group and 37% in the untreated group at this time.

1.3 Photodynamic Therapy

Developing strategies have sought more selective closure of the vessels with preservation of the overlying neurosensory retina. One such strategy is photodynamic therapy (PDT), which relies on low intensity light exposure of tissues treated with photosensitizers to produce photochemical effects.

Photodynamic therapy is a two-step process with the first step consisting of intravenous injection of photosensitizer. It is followed by light irradiation that constitutes the second and final step in the therapy (11, 12, 13). Photosensitizing dyes are preferentially retained in

tumours, particularly the neovascular tissue of tumours, which allows for selective treatment of this pathologic tissue (14,15). After exposure to light at an absorption peak of the dye, the activated dye in its triplet state interacts with oxygen and other compounds to form reactive intermediates, such as singlet oxygen, which can then cause disruption of cellular structures (14,16,17). Possible cellular targets include the cell membrane, mitochondria, lysosomal membranes, and the nucleus (18). Evidence from tumour and neovasculature models indicates that occlusion of vasculature is a major mechanism of PDT, which occurs by damage to endothelial cells, with subsequent platelet adhesion and degranulation, and thrombus formation. There is increasing evidence that PDT leads to tumour death via occlusion of the vasculature feeding the tumour, as well as through its direct cytotoxic effect on tumour cells (19,20). This has sparked interest in using PDT to treat ophthalmic diseases characterized by neovascularization.

Previous investigations in PDT have used older photosensitizers such as hematoporphyrin derivative (HPD) or rose bengal, and have been limited by the weaker photosensitizing ability or by prolonged cutaneous photosensitivity. Newer photosensitizing agents have been designed to overcome these difficulties. One of these is Benzoporphyrin Derivative Monoacid Ring A (BPD-MA verteporfin), a synthetic porphyrin with four structural analogs, which absorbs light around 690 nm (21).

1.4 BPD-MA verteporfin (BPD-MA)

BPD-MA verteporfin (BPD-MA) is a potent photosensitizer that is composed of two regioisomers and is being investigated for its antineoplastic and immunomodulatory properties, as well as its potential to stabilize vision in exudative AMD.

BPD-MA is administered intravenously as a liposomal preparation. The liposomes are not in themselves considered a delivery system but a method of solubilizing BPD-MA for intravenous delivery. Immediately after infusion BPD-MA partitions into the lipoprotein phase, particularly the LDL fraction (22). Neoplastic tissues and neovascularization within tumours have been shown to have increased numbers of LDL receptors (23) and this is believed to be a major mechanism of enhanced selectivity of BPD-MA for these tissues. Plasma elimination half-life mean values range from approximately 5 to 6 hours for the two regioisomers of BPD-MA (24). It is cleared primarily via bile and feces (90%), with less than 1% cleared via the kidneys and urine (25).

2. RATIONALE

2.1 Preclinical Summary of PDT with BPD-MA and Light in Ocular Diseases

PDT using intravenously administered BPD-MA has been investigated in a number of animal models. Schmidt-Erfurth et al. have shown in rabbits that PDT with BPD-MA can successfully treat experimental choroidal melanoma and cause choroidal occlusion with minimal retinal damage (26,27) and also that experimental corneal neovascularization can be selectively destroyed (28).

Preclinical investigations demonstrating the effectiveness and safety of PDT with BPD-MA in choroidal neovascularization (CNV) have been conducted by Miller et al. in a primate model of CNV. In these studies, the CNV was induced by laser burns. They have been able to demonstrate effective closure of the CNV, and selectivity of treatment effect. Dosimetry evaluations included BPD-MA dose, irradiance, fluence, and time of irradiation after intravenous bolus injections or infusions of BPD-MA (29, 30, 31). These workers have also demonstrated angiographically that BPD-MA selectively localizes in the CNV (32).

2.2 Clinical Summary of BPD-MA/PDT in the Treatment of CNV

A Phase 1/2 study was initiated in March 1995 to evaluate the safety and maximum tolerated dose of photodynamic therapy (PDT) using intravenous liposomal BPD-MA verteporfin (BPD-MA) administered over 5 or 10 minutes to patients with subfoveal choroidal neovascularization (CNV) and to determine if the CNV could be closed or destroyed in a clinically meaningful way. This original study was primarily designed to assess the safety of PDT. The study was later expanded by a number of treatment amendments to generate enough data to make evaluations on dosimetry. Nearly 140 patients have been treated to date. Five different treatment regimens were examined to assess the safety and efficacy of light dose escalation.

Although complete closure of the CNV could be obtained in the majority of lesions, this was temporary and evidence of leakage, albeit less than pretreatment, was apparent in most lesions by 4 weeks after PDT. By 12 weeks after PDT, some of the lesions had grown beyond that observed before treatment especially in the two treatment regimens in which light was applied 30 minutes after the start of the BPD-MA infusion (Regimens 1 and 3). Greater persistence in the reduction in CNV leakage was found when the light was applied earlier at either 15 (Regimen 4) or 20 minutes (Regimen 2) after the start of the 6 mg/m² BPD-MA infusion. Retreatment of lesions at 2-6 week intervals with Regimens 2 and 4 in nearly 40 patients was effective at closing the CNV leakage that had recurred. However, the persistence of the CNV closure was not found to be any longer than after a single treatment. As seen after single treatments, multiple treatments (up to 4) did not appear to impair the visual acuity relative to that expected in the normal course of the disease progression.

This study defined an excessive light dose as 150 J/cm^2 when applied either 20 minutes after 6 mg/m^2 BPD-MA (Regimen 2) or 30 minutes after 12 mg/m^2 BPD-MA (Regimen 3). At this dose retinal vessel non-perfusion was observed in 5 of 8 patients in addition to the non-perfusion observed in the CNV. This non-selective effect was associated with clinically significant losses of vision in 3 cases. However, at all light doses examined below this (in more than 120 patients), non-perfusion of the CNV could be obtained without impairment of the visual acuity.

Progression of pathologic conditions in the treated eyes which might be associated with CNV were judged either to be unrelated to PDT or not to be clinically significant. Progression or development of pathologic conditions in the treated eyes which likely were not associated with CNV were judged to either be unrelated to PDT or not to be clinically significant at light doses of 100 J/cm^2 or less.

Systemic safety problems were shown to be of little concern with headache (8%) being the most frequently reported event during the 3 month follow-up after dosing.

This study showed that a single course of PDT with BPD-MA can safely stabilize the area and extent of leakage from CNV lesions in a majority of patients with AMD for up to 3 months. Since CNV lesion stabilization is expected to correlate with vision stabilization, these results support our rationale to initiate pivotal studies to evaluate the safety and efficacy of quarterly treatments of CNV secondary to AMD.

2.3 PDT Dosing Rationale

The majority of the CNV lesions had a decreased area of leakage at 12 weeks after a single treatment with Regimens 2 and 4 compared with pretreatment. The data suggest that Regimen 4 (6 mg/m^2 dose of BPD-MA infused intravenously over 10 minutes with light application at 15 minutes after the start of infusion) provided greater persistence of full closure of the CNV lesions to at least 4 weeks. Moreover, the change in visual acuity from baseline to 4 weeks was significantly less in Regimen 4. For this reason Regimen 4 has been chosen as the treatment regimen to be evaluated in this pivotal trial. Of the 3 light doses tested in Regimen 4 ($50, 75$ and 100 J/cm^2) 50 J/cm^2 was chosen for this trial because this dose resulted in the highest incidence of full closure of classic CNV 4 weeks after treatment. Moreover, this dose provides a large margin of safety since no dose-limiting adverse events were observed at 100 J/cm^2 .

2.4 Risk/Benefit

Patients with CNV secondary to AMD usually develop severe, irreversible visual loss. Within two years most affected eyes will have poor central vision ($< 20/200$) without treatment (7). Current treatment with thermal laser photocoagulation is limited to selected cases because it destroys viable photoreceptors overlying the CNV, and results in immediate vision loss. As a

result laser photocoagulation is only applied to small well-demarcated CNV lesions. However, most patients on presentation to the ophthalmologist have CNV lesions that are too large or are poorly demarcated to benefit from intervention with laser photocoagulation. This is the population targeted for inclusion into this study. The only options for these patients are either no treatment or experimental, unproven therapies such as macular surgery, radiation therapy or antiangiogenic therapy.

There is excellent scientific rationale for testing photodynamic therapy, based on both preclinical data and clinical data. PDT has been tested in nearly 140 patients/eyes to evaluate the safety and dose-response characteristics of differing treatment regimens. These data show that the leakage of the CNV lesions assessed by fluorescein angiography can be eliminated completely in the short term (1 week) and reduced in the longer term (12 weeks) compared to pretreatment estimates of leakage, without loss of visual acuity.

Choroidal neovascularization is known to cause accelerated vision loss in AMD. It is considered that stabilizing or reducing the extent of leakage from the CNV may lead to a stabilization in vision or at least a slowing of the rate of vision loss.

3. STUDY OBJECTIVES

Primary

To demonstrate that PDT treatment of patients with subfoveal CNV secondary to AMD will, with an acceptable safety profile, significantly reduce vision loss compared to placebo (sham treatment).

Secondary

To evaluate the long term safety of PDT treatment.

To compare the effects of PDT treatment with a placebo (sham) regimen on peak-contrast threshold.

4. STUDY PLAN

4.1 Overall Design and Plan of Study

The proposed study is entitled "A Randomized, Placebo-Controlled, Masked, Multicenter, Phase 3 Study of the Treatment of Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD) Using Photodynamic Therapy (PDT) with Liposomal BPD-MA verteporfin."

Patients will be randomized to either PDT or placebo in a ratio of 2:1. In case a patient presents with two eligible eyes, only one eye will be treated in the study. The decision of

which eye is treated will be between the patient and physician. Patient randomization will also be stratified by clinical center and by baseline visual acuity at each center. Vision stratification will be 54-73 letters (approximately 20/40-20/80) and 34-53 letters (approximately 20/100-20/200). Each regimen will constitute a single treatment administered every 3 months if evidence of CNV leakage is detected angiographically.

PDT Regimen

- 10-minute infusion of 6 mg/m² BPD-MA
- light application of 50 J/cm² at 15 minutes after the start of infusion.

Placebo regimen

- 10-minute infusion of 5% dextrose in water for injection (D5W)
- light application of 50 J/cm² at 15 minutes after the start of infusion.

Outpatients with new or recurrent subfoveal CNV secondary to AMD in which laser photocoagulation likely would not be beneficial because the lesion is too large or poorly demarcated will be enrolled in the study.

The primary efficacy variable will be the visual acuity responder rate defined as a loss of less than 3 lines (<15 letters) or 6 lines (<30 letters) of vision compared to baseline. An analysis will be conducted when all patients have completed their 12-month follow-up visit. We plan to file registration applications with these data if efficacy is proven and to continue the trial to 24 months to provide additional data on long term safety and efficacy.

A timetable of study procedures is in Appendix 2. A full written description of the procedures can be found in Sections 9 - 13.

4.2 Quality Assurance Measures

All Investigators, study coordinators and photographers will undergo training on all protocol procedures. During the enrollment phase of the study, only investigators who have successfully undergone training by representatives of the Photograph Reading Center and the Sponsors on all protocol procedures may be treating ophthalmologists. During follow-up, certified principal investigators will be responsible for the training of co-investigators on protocol procedures and to carry out retreatment procedures. The principal investigator must act as a preceptor for the first treatment administered by a co-investigator. Only photographers certified by the Photograph Reading Center are allowed to perform the fluorescein angiography and fundus photography. Visual acuity will be measured by individuals who will attend a training session specifically for this study and have been certified by a protocol monitor to measure visual functions.

The Photograph Reading Center will evaluate all stereoscopic colour fundus photographs and fluorescein angiograms except at month 15 and month 21. Month 15 and month 21 photographs must be sent to the Photograph Reading Center if either specific adverse

events occur (see Appendix 8, section 4) or if these visits are the final visits in cases of premature termination of patient's involvement in the study. To assess consistency, ten percent of the fundus photographs and fluorescein angiograms will be regraded by a grader from the Photograph Reading Center.

All investigating centers will undergo site visits by company monitors at intervals of at least 8 weeks to ensure compliance with Good Clinical Research Practices.

4.3 Oversight of Study Ethics and Patient Safety

A Data and Safety Monitoring Committee (DSMC) will review the study data of the entire protocol at 6-month intervals and advise the Sponsor on the safety and ethics of continuing the trial. Unmasking of the committee is warranted only for safety reasons. There is no intention to stop either study (A or B) in the event of overwhelming short term efficacy in favour of PDT since the effects of adverse events on visual acuity loss that may occur on longer follow-up, such as recurrence or atrophy, are unknown.

This committee will be an external and independent organization and consist of internationally recognized experts in ophthalmic clinical research. Current members include the following:

Ophthalmologist, Epidemiologist:	Roy Beck MD, PhD Jaeb Center for Health Research, Inc., Tampa Committee Chairman
Epidemiologist, Retinal Specialist	Ronald Klein, MD University of Wisconsin
Statistician:	Maureen Maguire, PhD Scheie Eye Institute, Philadelphia
Retinal Specialists:	Gabriel Coscas, MD Creteil Hospital, Paris Lee Jampol, MD Northwestern University, Chicago A. F. Deutman, MD Academisch Ziekenhuis Nijmegen, The Netherlands A. C. Bird, M.D. Moorfields Eye Hospital, London, U.K.

4.4 Study Advisory Group

Participating investigators with experience in the application of PDT in AMD have been invited by the company to advise on technical issues in the preparation and conduct of the trial. This group along with company members both oversees the public disclosure of any data generated within the study and reviews and advises on requests for ancillary studies associated with the trial under predefined policies. These policies are made available to all participating centers. Any proposed amendment to the existing protocol will also be discussed with this group.

Current members of the Study Advisory Group are:

External:

Dr. Neil M. Bressler, Committee Chairman, Wilmer Reading Center, Baltimore, USA
Dr. Susan Bressler, Wilmer Reading Center, Baltimore, USA
Dr. Joan Miller, Massachusetts Eye & Ear Infirmary, Boston, USA
Dr. Michel Sickenberg, Hôpital Ophtalmique Jules Gonin, Lausanne, Switzerland
Dr. Ursula Schmidt-Erfurth, Medizinische Universitaet zu Lubeck, Germany

Internal:

Dr. Gustave Huber, CIBA Vision AG, Bülach, Switzerland
Dr. Al Reaves, CIBA Vision Corporation, Duluth, GA, USA
Dr. Andrew Strong, QLT PhotoTherapeutics Inc., Vancouver, Canada
Dr. Ulrike Manjuris, QLT PhotoTherapeutics Inc., Vancouver, Canada

5. STUDY POPULATION

An estimated 18 centers will enroll a minimum of 30 patients per center to obtain 450 evaluable patients for the study. For sample size calculations refer to Section 13.1. Ten North American centers and 8 European Centers will be initiated (See Appendix 10 for list of Investigators).

Two studies will be conducted under this protocol. Approximately equal numbers of North American and European centers will be allocated to each of the two studies (A or B). The allocation of the treating centers to each study is shown in the investigator list (Appendix 10).

The centers must have the ability to enroll these patients within 6 months after their initiation.

5.1 Inclusion Criteria

To be included in the study, outpatients of either sex and of any race must fulfil the following criteria:

1. Have clinical signs of CNV secondary only to Age-Related Macular Degeneration, without any other concurrent retinal disease present that may also be associated with CNV (e.g., myopic degeneration, presumed ocular histoplasmosis syndrome). In case of two-eye eligibility, only one eye will be treated and the decision of which eye will be treated will be made between the patient and physician.
2. Have lesions with the following characteristics determined by fluorescein angiography:

- a) evidence that the classic or occult CNV involves the geometric center of the foveal avascular zone as determined by fluorescein angiography,
 - b) the CNV lesion has a classic component in any proportion to other lesion components, some occult component may be present as well (definitions see Section 9.1.1),
 - c) the area of classic CNV plus occult CNV must occupy at least 50% of the total lesion,
 - d) the greatest linear dimension of the entire CNV lesion must not exceed 5400 μ diameter (equivalent to the diameter of the 9 MPS disc area circle) at the initial treatment,
 - e) if the entire lesion is well-demarcated, the lesion must be > 2 MPS disc areas in size. Smaller well-demarcated lesions may be included only if patients sign additional informed consent items indicating their refusal to submit to laser photocoagulation of these CNV lesions. (See Appendix 14 for the informed consent items [in bold/italics] that must be included in the prior IRB- or Ethics Committee-approved informed consent for individual treating centers).
3. If the lesion is a recurrence after laser photocoagulation, the lesion plus the laser-treated area must be > 6 MPS disc areas in size or not well demarcated. Smaller well-demarcated lesions may be included only if patients sign additional informed consent items indicating their refusal to submit to laser photocoagulation of these CNV lesions. (See Appendix 14 for the informed consent items [in bold/italics] that must be included in the prior IRB- or Ethics Committee-approved informed consent for individual treating centers).
 4. The best-corrected visual acuity of the study eye must be 34-73 letters inclusive using a modified ETDRS chart (approximately 20/40 to 20/200 Snellen Equivalents inclusive). The number of letters will be used to evaluate this inclusion criteria.
 5. Be aged greater than 50 years.
 6. Be considered able to return for all study visits.
 7. Be willing and able to provide written informed consent.

5.2 Exclusion Criteria

Patients may not enter the study if at screening they:

1. Have a tear (rip) of the RPE; a vitelliform-like lesion of the outer retina (e.g. as in pattern dystrophies or basal laminar drusen); or central serous retinopathy.

2. Have any additional ocular diseases which have irreversibly compromised or, during follow-up, could likely compromise the visual acuity of the study eye including amblyopia, uncontrolled glaucoma (intraocular pressure ≥ 30 mmHg), anterior ischemic optic neuropathy, clinically significant diabetic macular edema, severe non-proliferative or proliferative diabetic retinopathy. For cases of cataract refer to Section 7.4.

3. Inability to obtain photographs to document CNV, e.g. due to media opacity, allergy to fluorescein dye or lack of venous access.
4. History of treatment for CNV in the study eye other than confluent laser photocoagulation, such as submacular surgery, radiotherapy or macular scatter ("grid") laser photocoagulation.
5. Are participating in another ophthalmic clinical trial requiring follow-up examinations or are receiving, or have received any experimental systemic treatment for AMD (e.g. retinoic acid, thalidomide) or any other investigational new drug within 12 weeks prior to the start of study treatment.
6. Have 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 be within 20% of the normal range.
7. Have unstable heart disease (Class III or IV disease according to the New York Heart Association's functional criteria, see Appendix 5).
8. Have porphyria or other porphyrin sensitivity or hypersensitivity to sunlight or bright artificial light.
9. Have any acute illness observed during screening or fever or illness observed on the day of treatment prior to infusion. If the illness resolves more than 7 days from the fluorescein angiography the fluorescein angiography has to be repeated and the patient can be randomized and treated at this time. If the illness takes more than 1 week to resolve, the patient must undergo the full screening procedures again.
10. Have uncontrolled hypertension on repeated measurements (SBP > 180 mmHg and DBP > 100 mmHg).
11. Have received prior PDT treatment for CNV.
12. Intraocular surgery within the last 2 months or Nd:YAG capsulotomy within the last month within the treated eye.

6. RANDOMIZATION AND MASKING PROCEDURES

6.1 Randomization

Patients will be randomized in a ratio of 2:1 to PDT treatment or placebo. Randomization must be carried out on the day of the initial treatment by the center study coordinator or

designate (other than the treating ophthalmologists and the vision examiner) with the study patient and treating ophthalmologist present at the center. Since baseline visual acuity is highly predictive of the rate of vision decline in patients with AMD, the randomization process will also include stratification (i.e. 54-73 letters {approximately 20/40-20/80} and 34-53 letters {approximately 20/100-20/200}) for baseline visual acuity of the study eye.

The randomization number is a 5 digit number and will include the center number (01-19), the visual acuity strata with 1 representing the upper strata (54-73 letters) and 2 representing the lower strata (34-53 letters) and the patient number (01-99). For example, the first patient randomized in center 01 that has a visual acuity of 54-73 will receive a randomization number of 01101. The randomization numbers must be allocated sequentially (e.g. first patient: 01101, second patient: 01102 for patients in the upper strata of visual acuity, etc.). The treatment allocated to a specific randomization number will be in a sealed envelope which may only be opened by the study coordinator on the day that a patient who has met all eligibility criteria receives treatment. Allocation of active or placebo treatment will be recorded on a randomization log that must be stored locked with both opened and unopened randomization envelopes.

Immediately after randomization both the Sponsor (clinical monitor) and the Photograph Reading Center will be informed by fax using a "Randomization Alert" form that will be provided to each center.

6.2 Masking

It is the study coordinator's responsibility to make every reasonable attempt to maintain masking of the ophthalmologist, patient, vision examiner and the Photograph Reading Center graders. One of the center personnel (not necessarily the study coordinator), other than the treating ophthalmologist and vision examiner will be responsible for randomization and the infusion procedure.

The best-corrected visual acuity of patients will be measured based on the procedure developed for the Early Treatment Diabetic Retinopathy Study (ETDRS). In order to eliminate bias in measurement of the primary efficacy endpoint, vision examiners will also be masked. The vision examiner must not have any access to any study patient records and must not elicit any historical information from the patient regarding vision or any adverse events experienced. The vision examiner will be given access to prior refractions but should not have access to any prior visual acuity or contrast sensitivity test results.

All fundus photographs and fluorescein angiograms will be coded with labels provided by the study monitor and all except month 15 and month 21 will be forwarded to the Wilmer Photograph Reading Center at The Johns Hopkins University in Baltimore, U.S.A. for masked evaluation of treatment effects. Month 15 and month 21 photographs must be sent to the Photograph Reading Center if either specific adverse events occur (see Appendix 8, section 4) or if these visits are the final visits in cases of premature termination of patient's involvement in the study.

If patients have severe vision losses of 20 letters or more within 7 days after any treatment (this event is expected to be rare) angiography is required to determine any potential

relationship to treatment (see Section 12.6). Such 20 letter or more vision losses must be relative to the visual acuity recorded at the visit immediately before the treatment. Since the review of early (within 1 week) post-treatment angiograms may unmask the treating ophthalmologists it is recommended that angiography should be avoided if at all possible (normal patient care withstanding) in cases of vision losses of less than 20 letters recorded within 7 days after any treatment.

Sponsor personnel responsible for the conduct and monitoring of the trial will also be masked to the identity of the treatment.

7. DRUG AND LIGHT DOSAGE AND ADMINISTRATION

7.1 Test Drug and Placebo

BPD-MA for clinical use will be supplied in clear glass vials of 25 and 15 mg of sterile, liposomal, freeze-dried powder.

Placebo will consist of dextrose 5% in water for injection (D5W). D5W is the major diluent for the BPD-MA infusion. Administration of BPD-MA or placebo is described in Section 7.3 and more fully in Appendix 4.

7.2 Supply, Packaging, Labelling and Storage

Records will be made of the receipt and dispensing of clinical supplies to provide a complete accounting of the disposition of all supplies. The supplies will be stored in the dark at controlled room temperature of 20°C-25°C (68°F-77°F) in a secure locked facility accessible only to the study coordinator or authorized personnel. Used vials will be checked by the Sponsors. At the conclusion of the study, the trial sites will return the supplies to the Sponsor.

7.3 Drug/Light Administration

PDT or placebo treatments must occur within 7 days of fluorescein angiography. Randomization must be on the day of the first treatment. Treatment (PDT or placebo) will be delivered as a two-step process, the first being a 10-minute infusion of 6 mg/m² of BPD-MA or placebo. The second step of light irradiation at a dose rate of 600 mW/cm² will be performed 15 minutes after the start of the 10-minute infusion using red light (689 nm) produced by a diode laser developed specifically for this program. Full instructions on the use of the diode laser are provided in the Operator's manual. Additional details of laser treatment are provided in Appendix 9.

The light dose of 50 J/cm² will be delivered to the CNV lesion from the diode laser as a single circular spot via a fiber optic and a slit lamp using a suitable contact lens. The time to deliver the 50 J/cm² dose is 83 seconds. Light delivery from the diode laser will automatically shut-off once the preset light dose has been delivered. The light delivery can be interrupted using a footswitch if the retinal landmarks are temporarily lost by the treating ophthalmologist. Any interruption in the continuous delivery of the light dose must be recorded in the CRF.

Study Regimens

	Study Regimens	
	PDT	Placebo
Drug Dose (mg BPD-MA/m ²)	6	0
Light Dose (J/cm ²)	50	50
Light Dose Rate (mW/cm ²)	600	600
Time of Light Administration ^a (min)	15	15
Duration of Light Exposure (secs)	83	83

^a Time of light administration after the start of a 10-minute drug infusion

PDT Regimen

For each PDT course a single intravenous infusion of BPD-MA (6 mg/m² body surface area) will be administered over 10 minutes. Refer to Appendix 4 for detailed infusion preparation and instructions. Light doses of 50 J/cm² will be applied 15 minutes after the start of the infusion. Light irradiation will be performed using laser light of 689 ± 3 nm, delivered via a slit lamp, utilising a suitable lens. (See Appendix 9).

Placebo Regimen

For the placebo regimen 30 mL of 5% dextrose in water for injection (D5W) will be administered intravenously over 10 minutes. Light (50 J/cm²) of 689 ± 3 nm will be administered 15 minutes after the start of the infusion.

7.3.1 Determination of Light Treatment Spot Size and Location

The size of the CNV lesion is estimated from the fluorescein angiograms that delineate the classic and occult CNV and any features that block the boundaries of the lesion. Training in identification of the lesion components and estimation of the maximum diameter of the lesion will be given by the Photograph Reading Center before study initiation. A brief synopsis of the identification of lesion components is provided in Section 9.1.1.

The greatest linear dimension of the lesion is determined from the fluorescein angiogram using a reticule with a straight line scale of 20mm subdivided into 200 units. The greatest linear dimension of the lesion on the angiogram is divided by 2.5 to give the actual diameter of the light spot on the retina. 1000 microns is then added to the greatest linear dimension to allow a 500 micron border to ensure full coverage of the lesion. This gives the desired diameter of the light spot size. The laser treatment parameters and the determination of the laser power required for different light spot sizes are described fully in Appendix 9. Conversion tables and examples of laser power calculations for all common contact lenses are also provided in Appendix 9. The reticule can also be used to gauge where the light spot will land on the retina (and retinal landmarks).

The light spot covering the lesion must come no closer than 200 microns to the optic disc. If the lesion or proposed treatment extends closer to the optic disc than 200 microns it is considered appropriate to leave this portion of the CNV lesion untreated.

7.4 Concomitant Treatment

Retrobulbar anesthesia to prevent eye movement is not a requirement but may be administered to the patient at the discretion of the investigator.

Metoclopramide or other agents to prevent nausea induced by fluorescein injection may be administered at the discretion of the investigator.

Any concomitant treatment or investigation for any reason must be recorded on the Case Report Form, including generic name, dose, and duration of therapy.

If the patient has cataract that does not allow visualization of the CNV lesion, cataract surgery should be performed at least 2 months before entering the patient in the study. The patient's vision must be stabilized before considering him/her for treatment in the study. If cataract requiring surgery develops during the study, surgery should be carried out as soon as possible after PDT but no earlier than 1 week after PDT.

8. WARNINGS/PRECAUTIONS

BPD-MA is an experimental drug and the potential exists for unknown serious adverse events to occur. Please refer to the Clinical Data Summary of the Investigator's Brochure and any clinical data provided on the ocular program for additional information and any adverse events reported to date. The major precaution to be taken relates to photosensitivity induced by BPD-MA.

8.1 Precautions for Patients Regarding Photosensitivity

Skin photosensitivity induced by BPD-MA has been tested in early phase safety studies (see section 10.1 of the Investigator Brochure). The results suggest that by 24 hours after a 6 mg/m² dose of BPD-MA the potential for any serious enhancement in the sensitivity of skin to bright light is low. Moreover, studies in dogs using up to 100 times the dose of BPD-MA used in this study showed that there was no detectable ocular toxicity when the dogs were exposed to 6 hours of strong sunlight 24 hours after dosing. The dog study also suggested that any potential ocular photosensitivity was lower than that in skin. No skin or ocular photosensitivity reactions have been reported in 138 patients treated with 6-12 mg/m² BPD-MA in the early phase tests conducted in the ocular program. Our experience to date has led to the following recommendations which are considered to be conservative.

No patient is to expose their skin or eyes to bright light for at least 48 hours post-treatment. This includes but is not limited to bright sunlight, tanning salons, halogen lighting in homes and offices, lighting used in dentists offices or in surgery operating rooms. Dark sunglasses (supplied by the Sponsor) that reduce light transmittance to 4% or less will be required to be worn in bright light conditions for 2 days after BPD-MA administration. The patient will not be required to remain in a darkened room. Exposure to light at low intensities (normal lighting in rooms) is expected to reduce the period of photosensitivity due to photobleaching of the BPD-MA. Patients should be warned that use of sunscreens will not prevent any photosensitivity reaction.

9. PRETREATMENT PROCEDURES

9.1 Observations and Measurements

The following is a descriptive list of the tests and procedures to be performed prior to randomization and treatment. A complete list of Study Procedures is provided in Appendix 2.

Screening/Baseline (Day -7 to Day 0)

- Demographic data including patient's initials, date of birth, sex, race
- Written Informed Consent (Draft provided in Appendix 11)
- Ophthalmic Examination and identification of CNV
 - Best-corrected visual acuity (see Appendix 6)
 - Contrast threshold (see Appendix 7)
 - Colour fundus photography (see Appendix 8)
 - Fluorescein angiography (see Appendix 8)
 - Dilated ophthalmoscopy (see Section 9.1.2)
- Laboratory tests (see Appendix 3)
- Medical History and current medical conditions
- Physical examination

- Blood pressure (sitting), heart rate (sitting)
- 12-lead EKG
- Patient's body weight (kg), height (cm), body surface area (m²)
- Concomitant medications
- Eligibility checks according to the inclusion/exclusion criteria

The fluorescein angiograms and colour photographs will be sent to the Photograph Reading Center within 1 week for retrospective confirmation of eligibility and baseline grading. The Photograph Reading Center evaluates the fluorescein angiogram and photographs in a masked fashion. For details about how to label, store and ship the documents, address, contact person, telephone/fax numbers, etc. please refer to Appendix 8.

9.1.1 Identification of CNV Secondary to Age-Related Macular Degeneration

There must be angiographic evidence of CNV under the geometric center of the foveal avascular zone (FAZ) secondary to Age-Related Macular Degeneration. Although the lesion must have classic CNV, the lesion can include occult CNV, thick contiguous blood or an area of elevated blocked fluorescence corresponding to scar tissue and/or pigment that obscures the boundaries of the neovascular components, or serous detachment of the retinal pigment epithelium. The area of CNV (classic and occult) must be larger than the area of features which obscure the boundaries of CNV such as blood.

Age-Related Macular Degeneration (AMD): AMD's hallmark is drusen, the spectrum of the disorder includes retinal pigment epithelial atrophy, choroidal neovascularization, retinal pigment epithelial detachment (PED), and disciform scars. The latter are important since 90% of the severe blindness in AMD is due to the neovascular form of maculopathy, which is characterized by the presence of choroidal neovascularization, a pigment epithelial detachment, or both.

Lesion: The entire complex of components (e.g., choroidal neovascularization, elevated blocked fluorescence, and thick blood) is considered to constitute the neovascular lesion.

Lesion Component: Area of the retina exhibiting angiographic characteristics such that it is considered part of the choroidal neovascular lesion. Lesion components may include: choroidal neovascularization (classic or occult), thick blood, elevated blocked fluorescence (due to a pigment or scar that obscures the neovascular borders), and serous detachments of the retinal pigment epithelium.

Classic CNV: Classic CNV is defined as a well-demarcated area of bright hyperfluorescence throughout the transit phase of the angiogram with leakage in the mid and late phase frames. Vessels of the neovascular lesion often will be visualized in the early phase of the angiogram but are not required to be identified.

Occult CNV: Occult CNV includes fibrovascular pigment epithelial detachment (a type of occult choroidal neovascularization in which areas of irregular elevation of the retinal pigment epithelium are detectable on stereoscopic angiography and consists of an area of stippled hyperfluorescence noted within 1 to 2 minutes after fluorescein injection). Persistence of fluorescein staining or leakage within this area occurs within 10 minutes after fluorescein injection. These areas are not as discrete or bright as areas of classic choroidal neovascularization or serous detachment of the retinal pigment epithelium in the early phase of the angiogram.

In addition, occult CNV may show late leakage of an undetermined source (a type of occult choroidal neovascularization in which areas of leakage at the level of the retinal pigment epithelium in the late phase of the angiogram are without well-demarcated areas of hyperfluorescence from classic CNV or a fibrovascular pigment epithelial detachment discernible in the early phase of the angiogram that account for the leakage).

Features which can obscure the boundaries of CNV (classic or occult): These include blood which blocks fluorescence through the late phases of the angiogram, elevated blocked fluorescence not corresponding to blood on colour photographs (corresponding to either hyperplastic pigment or fibrin or fibrous tissue or blood not apparent on colour photographs) or serous pigment epithelial detachment (defined as uniform, early, bright hyperfluorescence beneath a smooth dome-shaped elevation of retinal pigment epithelium).

Recurrent CNV lesions result from extrafoveal or juxtafoveal CNV lesions which had standard laser treatment prior to randomization with recurrent CNV (classic or classic and occult) that extends through the foveal center.

9.1.2 Dilated Ophthalmoscopy

A standard examination will be carried out using the indirect stereo ophthalmoscope and a suitable lens. The pupils will be dilated with eye drops (e.g. Tropicamide).

9.2 Informed Consent and Institutional Review

9.2.1 Informed Consent

Draft informed consents are provided in Appendices 11 and 14.

The informed consent form used for the study must comply with the Declaration of Helsinki, federal regulations (U.S. 21 CFR 312 [IND], HPB and EC guidelines) and must have been approved by the Sponsor and the Investigator's Institutional Review Board (IRB). The Investigator or one of his or her associates must explain verbally and in writing the nature of the study and the treatment in such a manner that the subject is aware of potential benefits

and risks. After having been informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice, the patient must sign the IRB- and Sponsor-approved informed consent form in the presence of a witness before screening.

9.2.2 Institutional Review Board (IRB) or Ethics Committee

The appropriate IRB or Ethics Committee must review this protocol and the informed consent form prior to initiating this study. Test medication will not be distributed to an Investigator until the IRB or Ethics Committee has provided written approval of the study and informed consent form to the Investigator and the Sponsor has received a copy of same. A copy of the locally approved informed consent form must be on file with the Sponsor prior to the initiation of the study. A copy of any changes or renewals of the form also must be sent promptly to the Sponsor.

10. TREATMENT DAY PROCEDURES

After the patient arrives at the clinic the study coordinator will check that all eligibility criteria are still in effect before randomizing the patient according to the procedures described in Section 6.

10.1 Observations and Measurements

A list of Study Procedures is provided in Appendix 2.

Pretreatment (before infusion)

- . Ophthalmic examination prior to dosing
- . Assessment of concomitant medications

Treatment

- . Vital signs (heart rate and blood pressure) assessed before the infusion
- . Infusion and light administration (see Section 7.3)
- . Monitoring of adverse events (see Section 12)

11. POST TREATMENT PROCEDURES

A complete list of Study Procedures is provided in Appendix 2.

Two to four days after each treatment all patients will be contacted by telephone to determine if any adverse events have occurred (see Section 12).

If the patient reports a significant loss of vision at or preceding the telephone evaluation the patient will be advised to visit the clinic within 1 week of the treatment and undergo evaluation of best-corrected visual acuity. If, at this follow-up visit, a vision loss of 20 letters or more (³ 4 lines) is detected, fluorescein angiography will be performed to define the relationship of the vision loss to therapy. Vision losses of ≥ 20 letters since the last assessment that occur within 7 days of the last treatment, must be reported on an expedited basis to the Sponsors.

Photographs and angiograms must be sent to the Photograph Reading Center at weekly intervals.

Every 3 months, all patients will visit the clinic and undergo the following procedures:

- . Patient's body weight (kg), height (cm), body surface area (m²)
- . Best-corrected visual acuity (Appendix 6)
- . Assessment of concomitant medications
- . Colour fundus photography (Appendix 8)
- . Contrast threshold (Appendix 7)
- . Fluorescein angiography (Appendix 8)
- . Dilated ophthalmoscopy
- . Monitoring of adverse events (Section 12)

In addition every 6 months:

- . Laboratory assessments (Appendix 3)

In addition every 12 months:

- . 12-lead EKG
- . Physical Examination

11.1 Eligibility for Retreatment

Retreatment will be conducted if evidence of CNV leakage is detected by fluorescein angiography. Retreatments may only be conducted at intervals of 3 months \pm 2 weeks, but no more than 4 treatments per year. Any retreatment must be conducted within 7 days of the fluorescein angiography. Each center will individually evaluate their fluorescein angiograms to determine the need for retreatment and the size of the retreatment spot (ie. confirmation of leakage and area of the lesion to be treated by the Photograph Reading Center is not required).

To be eligible for retreatment, patients must also fulfil the following criteria:

1. Have no additional ocular diseases which have developed and may compromise the visual acuity of the study eye. Cataract which allows visualization and treatment of the CNV is allowed. Cataract that is considered to have significantly compromised the visual acuity should undergo corrective operation (see Section 7.4).
2. It must be possible for the Investigator to visualize the lesion.
3. Have no acute illness or fever observed on the day of treatment prior to infusion. If the illness or fever resolves more than 7 days from the fluorescein angiogram the fluorescein angiography must be repeated before retreatment. In cases where a second fluorescein angiography is required the initial photographs will be used by the Photograph Reading Center to grade the status of the lesion. The photographs from the repeat fluorescein angiography will be used to confirm the location and size of the light spot administered.
4. Have no arteriolar or venular non-perfusion caused by previous treatment in this study.

Every attempt must be made to retreat a patient meeting all retreatment eligibility criteria. If the treatment cannot be carried out, the patient must still be followed according to protocol.

12. EVALUATION AND REPORTING OF ADVERSE EVENTS

The Standard Operating Procedure of QLT will be followed with regard to evaluation and reporting of adverse events.

At each visit, all adverse events either observed by the Investigator or one of his/her professional collaborators, or reported by the patient spontaneously, or in response to the direct question below will be noted in the adverse events section of the patient's case report form. Adverse events in the treated eye which are conditions that may be due to the natural course of the disease and can be observed on the fundus photographs or fluorescein angiograms will be evaluated by the Photograph Reading Center (see Section 12.7).

In an attempt to optimise consistency of adverse event reporting across centers the patient must be asked a standard question to elicit any adverse events. At each in-clinic or telephone evaluation of the patient, study personnel will ask the following:

"Have you had any problems since your last assessment? Please let me know of any kind of event even if you do not think it could be related to the treatment you are receiving, for example problems with your eyes or any other general problems."

If any adverse event is reported, the date of onset, intensity, relationship to study medication or treatment, date of resolution (or the fact that it is still continuing), action taken, and

outcome of the adverse event and whether the adverse event is serious or not will be recorded. The different options for these categories are defined in Sections 12.2-12.5.

For any laboratory abnormality or change in vital signs or ECG that arises after treatment, the clinical Investigator will make a judgement if the value is of any clinical concern. If the finding is felt to be clinically significant and can be verified by a repeat evaluation (when possible) it will be recorded as an adverse event.

12.1 Adverse Event Definitions

12.1.1 Adverse Event (AE)

An **adverse event** is any noxious and unintended experience by a person administered a pharmaceutical product or treated with a device, or by the user of a device, whether or not a causal relationship with the drug or device has been established. An **adverse reaction** is defined as an adverse event that is considered to be related to the treatment.

All **adverse events** occurring during the conduct of a clinical study will be documented in the specific Case Report Forms (CRFs).

12.1.2 Serious Adverse Drug or Device Events (SAEs)

A Serious Adverse Drug or Device Event is any untoward medical occurrence that at any dose:

1. results in death
2. is life threatening
3. requires in-patient hospitalization or prolongation of existing hospitalization;
4. results in persistent or significant disability/incapacity, or
5. results in malignancy or congenital malformation.

Any **serious adverse event** occurring in this study must immediately (within 24 hours) be reported by telefax to one of the people below using the SAE form provided by the Sponsor and confirmed by personal telephone contact within 24 hours of the next business day (i.e. in person and not by voice message). Contacts are:

Ulrike Manjuris

Pilar Escartin

Senior Clinical Research Manager
QLT PhotoTherapeutics Inc.
Canada
Telephone: 416-691-2655
Telefax: 416-691-5066

Clinical Research Monitor
Ciba Vision S.A. Calle Valencia, 307
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Telephone: 0034-3-476-19 07
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Telefax: 41-1-862-0762

Noel Buskard
Medical Director
QLT PhotoTherapeutics Inc.
Canada
Telephone: 604-872-7881
Telefax: 604-875-0001

The trial monitors will inform the medical director at QLT. The telefax should include the initial Serious Adverse Event Report completed in capital letters and in English to the best extent possible given the time constraints. (The Serious Adverse Event Report form will be provided for the study). The Investigator should also inform the Ethics Review Committee of any serious adverse events that occur. The Investigator should provide conventional medical treatment if necessary and monitor the patient's condition until recovery.

12.1.3 Unexpected Adverse Event (UAE)

An adverse drug or device event or reaction, the nature or incidence of which is not consistent with applicable product information, as follows:

1. for investigational drugs, those not described in the current Investigator's Brochure or in the protocol;
2. for devices, any unanticipated effect i.e., not previously identified in nature, severity or incidence in the investigational plan or IND or in the product instructions for use.

12.2 Intensity

The intensity of the adverse clinical event will be characterized as mild, moderate, severe or life-threatening, as follows:

- Mild Usually transient, requiring no special treatment, and does not interfere with the patient's daily activities.
- Moderate Introduces a low level of inconvenience or concern to the patient and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- Severe Interrupts a patient's usual daily activity and requires systemic drug therapy or other treatment.
- Life-Threatening In the opinion of the Investigator, the subject is at immediate risk of death.

12.3 Relationship to Study Treatment

The relationship or association of the study drug or treatment in causing or contributing to the adverse clinical event will be characterized as "none", "unlikely", "possible", "probable", "definite", or, if insufficient data are available to allow a judgement, as "unknown".

- None No relationship to study drug or treatment.
- Unlikely The temporal association, patient history and/or circumstances are such that the study medication and/or light application are not likely to have had an association with the observed event.
- Possible The relationship is assigned when the adverse event:
 - a) Follows a reasonable temporal sequence from treatment, drug and/or light administration but,
 - b) Could have been produced by the patient's clinical state or by other modes of therapy administered to the patient.
- Probable The relationship is assigned when the adverse event:

- a) Follows a reasonable temporal sequence from treatment, drug and/or light administration,
- b) Abates upon discontinuation of the treatment (if applicable),
- c) Cannot be reasonably explained by the known characteristics of the patient's clinical state.

- **Definite** This relationship is assigned when the adverse event:
 - a) Follows a reasonable temporal sequence from treatment, drug and/or light administration,
 - b) Abates upon discontinuation of the treatment (if applicable),
 - c) Cannot be explained by known characteristics of the study patient's clinical state,
 - d) Is confirmed by reappearance of the adverse event on repeat exposure (rechallenge) and the Investigator considers the drug and/or light administration as definitely causing the adverse event.
- **Unknown** Relationships for which a small amount of information exists, but no evaluation as to relationship to study treatment can be made.

12.4 Action taken

- **None** No change in the treatment or study drug dosage was made.
- **Drug or light discontinued permanently** The study drug or light was permanently stopped.
- **Drug or light discontinued and restarted**
- **Other concurrent therapy** To be specified

12.5 Patient Outcome to Date

- **Resolved** The patient has fully recovered from the adverse event with no residual effects observable.
- **Improved** The adverse event is still present and the intensity has lessened.
- **Unchanged** The adverse event itself is still present and observable.

- . Retinal capillary non-perfusion
- . Retinal vascular leakage
- . Choroidal vascular non-perfusion
- . Choroidal vascular staining/leakage
- . Other macular or optic nerve pathology

The evaluation by the Photograph Reading Center will be reported back to the Investigator. A copy of the Reading Center's evaluation will be incorporated into the CRF. The documents used to evaluate these events are described in Appendix 8, Section 2 and Appendix 8, Exhibits.

13. STATISTICAL DESIGN AND ANALYSIS

13.1 Sample Size/Power Considerations

In order to adequately assess the safety of PDT with respect to adverse events, a minimum of 300 patients on active treatment will be required for the entire protocol. For adverse events that have a true rate of occurrence during the treatment period of 1% or greater, 300 patients should provide a 95% chance of detecting at least one of these events during the trial. A 2-to-1 randomization will be utilized, so that a total sample size of 450 patients (300 on PDT and 150 on placebo) who complete two years of treatment is the minimum required for this trial.

The protocol will be divided prospectively in half by center, and analyzed as two "separate" studies. Each study will be split by continent so that an approximate equal number of centers are in both Europe and North America. Within each study, a sample size of 225 patients (150 on PDT and 75 on placebo) who complete 2 years is required.

If we estimate that 50% of the placebo patients will lose less than 3 lines of vision compared to baseline after 1 year, then a total sample size of 225 will provide approximately 94% power to detect a difference from placebo of 25% (50% versus 75%), and 80% power to detect a difference from placebo of 20% (50% versus 70%). This assumes a two-sided significance level (α) of 0.050.

We anticipate ineligibility due to:

1. Misinterpretation of angiographic findings by the treating centers (approximately 4%) (the central photograph reading center will retrospectively determine the final decision on eligibility from the angiograms and photographs).
2. Invalid visits at study endpoint (approximately 3%).
3. Patients lost to follow-up due to death or any other reason (approximately 10%).

If we assume an ineligibility rate of 17%, then in order to have 450 patients complete the protocol, a total of 540 patients will need to be enrolled.

13.2 Statistical and Analytical Plan

The primary set of efficacy analyses will be performed on all available patient data (“intent-to-treat” analyses), where no exclusions will be made from any analyses because of protocol violations. In addition, the data from patients who receive one of the two treatments, who meet the inclusion/exclusion criteria, and who adhere to the protocol, will be considered evaluable for a secondary set of efficacy analyses (“evaluable” patients). Subgroup analyses based on gender, race, and number of treatments required will also be performed. Additional subgroup analyses will be made to evaluate any effect on outcome of CNV lesion size, lesion components and recurrent versus new lesions.

Patient demographic and background characteristics will be summarized and tested for treatment group comparability using appropriate statistical methods. Data from all patients who receive any treatment will be considered evaluable for the safety analysis. All statistical tests in this trial will be two-sided.

13.3 One-year Analysis

The total study duration for each patient will be 24 months, however, the primary analysis of the efficacy data will be based on all patients’ data at 12 months. The 12-month analysis may be used in regulatory submissions to international boards of health. Based on the results at 12 months, the study will not be allowed to be stopped early, if overwhelming short term efficacy in favor of PDT is observed. The DSMC may advise to stop the study due to safety concerns based on this analysis.

13.4 Efficacy Analysis

The primary efficacy variable will be the proportion of patients who are classified as “responders” to treatment, based on their Best Corrected Visual Acuity, as measured using the ETDRS charts (33). The primary assessment of visual acuity will be based on the proportion of patients who are classified as “responders” to treatment. Two separate definitions of a responder will be analyzed:

- (i) A decrease from baseline of less than three lines of vision (<15 letters) in the treated eye. A change of three lines of vision represents a doubling of the visual angle and is considered a clinically significant change.
- (ii) A decrease from baseline of less than six lines of vision (<30 letters) in the treated eye.

Two definitions of responder have been chosen because the baseline visual acuity is so predictive of vision loss. If the majority of patients entered into the trial have relatively good

initial vision at baseline it is possible that most patients in either treatment group might lose 3 or more lines of vision despite there being a 20% significant difference between treatments in the incidence of 6 lines of vision loss. Conversely, if patients entered into the trial had relatively poor vision at baseline very few patients may lose 6 lines even though a significant 20% difference between treatments might exist in the incidence of patients with 3 or more lines of vision loss.

The corresponding null (H_0) and alternative (H_1) hypotheses to be tested for the primary efficacy variable are as follows:

- H_0 : The proportion of patient responders for visual acuity is the same for PDT and placebo.
- H_1 : The proportion of patient responders for visual acuity is different between PDT and placebo.

For the analysis of these responder rates, comparisons between treatment groups will be made using a Cochran-Mantel-Haenszel test. One analysis will adjust for the effects of the stratification variables from the randomization (center and baseline visual acuity category, i.e., 54-73 letters [approximately 20/40-20/80] and 34-53 letters [approximately 20/100-20/200]). Since baseline visual acuity should be correlated with the responder rates, a second analysis will be performed adjusting only for baseline visual acuity. A maximum of 8 stratification levels will be included in this analysis with a total of 5 letters per strata (i.e. 34-38, 39-43, 44-48, etc.).

Secondary efficacy variables will include the following:

1. The proportion of patients whose visual acuity becomes worse than 34 letters read from the ETDRS chart (approximately 20/200) in their treated eye during the first year of treatment.
2. The time until a patient has a decrease from baseline of three or more lines of vision (³15 letters) in the treated eye.
3. The time until a patient has a decrease from baseline of six or more lines of vision (³30 letters) in the treated eye.
4. The mean changes from baseline for visual acuity.
5. The mean changes from baseline for the number of letters read on the Pelli-Robson chart for assessment of contrast sensitivity.
6. The difference between treatments in the CNV lesion closure grades according to the Photograph Reading Center grading system.

For the analysis of the proportions in (1), comparisons between treatment groups will be made using a Cochran-Mantel-Haenszel test, as described above for the primary variable.

Before each Cochran-Mantel-Haenszel test is performed, the Mantel-Fleiss criterion (34) will be checked to determine whether the chi-square approximation with 1 degree of freedom is suitable for the distribution of the Cochran-Mantel-Haenszel statistic. If this criterion is not met, then an exact test will be used.

For the analysis of the time-to-event variables in (2) and (3), life-table techniques will be used to compare the two treatment groups, taking into account the time to "failure". This will be a discrete outcome variable of either 3, 6, 9, or 12 months if the event occurs. If a patient does not have the event occur during the initial 12 months, then this will be considered a censored observation.

For the analysis of the changes from baseline for visual acuity, a method will be used where every letter a patient identifies correctly will be accounted for. In addition, since the height of letters on each line of the ETDRS charts differs geometrically by a factor of 1.2589 (0.1 \log_{10} units), from the height of letters on each adjacent line, a method of converting this nonlinear progression of letter size to a linear scale will be used for the analysis. This conversion is referred to as a logMAR (Logarithm of the Minimum Angle of Resolution) scale, and is obtained by taking the logarithm of the reciprocal of the decimal visual acuity fraction. This decimal fraction is obtained by dividing the numerator of the Snellen fraction by the denominator.

For example, the logMAR value of 20/200 is equal to $\log_{10}(200/20) = \log_{10}(10) = 1.0$, and the logMAR value of 20/20 is equal to $\log_{10}(20/20) = \log_{10}(1) = 0$. This value approximates the logarithm of the minimum angle of resolution. For each line lower on the ETDRS chart (better vision), the logMAR value decreases by 0.1 units. Since lines on the chart are separated by 0.1 logMAR units, each of the 5 letters on a line is assigned 0.02 logMAR units (1/5 of 0.1). These values will be used for all statistical analyses, so that every letter a patient identifies correctly will be accounted for in the analysis.

Change from baseline LogMAR values will be analyzed using a two-factor analysis of covariance (ANCOVA) model, with treatment and study center as factors, and the baseline visual acuity value as the covariate. A treatment-by-center interaction term will be included to test for the homogeneity of treatment effects between centers. In addition, a treatment-by-baseline interaction term will be included to test for the homogeneity of regression slopes between treatments. The baseline lesion size (MPS disc areas) will also be investigated as a possible covariate.

For the analysis of the number of letters read on the Pelli-Robson chart for the assessment of contrast sensitivity, changes from baseline will be analyzed using a two-factor analysis of covariance model, as described above for visual acuity.

As a confirmatory analysis for all dichotomous response variables (primary efficacy and (1) and (2) above), a logistic regression model will be used. This model will look at the relationship between each response variable and a set of explanatory variables that will

include treatment, center, and baseline visual acuity. In addition, a treatment-by-center interaction term will be included.

13.5 Safety Analysis

Safety will be evaluated by tabulating reports of ocular and systemic adverse events. Ocular safety will be assessed by analyzing the changes from baseline for the gradings from the fluorescein angiograms, and by evaluating changes between the pre- and post-treatment ophthalmologic examinations. Systemic safety will be assessed from any adverse events reported by the patients at each follow-up visit and from changes in laboratory parameters (haematology, serum chemistry and urinalysis).

13.6 Evaluation in Case of Discontinued Treatment

For all patients who are discontinued from the trial prematurely, their last visual acuity assessment will be included in a set of "endpoint" analyses, which will include the final assessments from all patients. Both the "responders" analysis and the changes from baseline for visual acuity will be included.

14. ESTIMATED DURATION OF THE STUDY

Initiation of enrolment: Q4/1996

Duration of enrolment: 6 months

1 Year completion: Q2/1998

2 Year completion: Q2/1999

15. PREMATURE TERMINATION OF TREATMENT OR PATIENT IN THE STUDY

Every attempt will be made to complete all follow-up visits.

Premature termination of patient in the study

Patients may be discontinued from the study prior to its completion for the following reasons:

- . Transfer, moved, or otherwise lost to follow-up
- . Patient request (for any reason) to withdraw from the study.
- Gross violation of inclusion/exclusion criteria (e.g. no CNV on retrospective review of baseline angiogram) or noncompliance (e.g. use of nonpermissible concomitant therapy).

In such cases every attempt should be made to conduct safety evaluations (i.e. laboratory evaluations, EKG, physical examination and adverse event assessment) 3 months after the last treatment.

The reason for discontinuation in the study will be documented. These patients will be assessed in the safety analysis and in an efficacy endpoint analysis using the data from the last evaluable visit.

Premature termination of treatment

Patients may be discontinued from further treatments but followed according to protocol for the following reasons:

- Development of a severe adverse event or intercurrent illness which may, in the judgement of the Investigator put the patient at risk if treatment is continued.
- If any arteriolar or venular non-perfusion within the treated area is observed after any treatment.
- Patient refuses retreatment.
- Protocol Violations: The severity of the protocol violation will determine whether the patient can receive additional treatments according to protocol. These cases will be discussed between the Investigator and the Sponsor and documented in a memo to file.

16. RECORD RETENTION

The Investigator must arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice , but not less than 15 years. The Sponsor must retain all other documentation pertaining to the trial for the lifetime of the product. Archived data may be held on microfiche or electronic record, provided that a back-up copy exists and that hard copy can be obtained from it if required.

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APPENDIX 2: Study Procedures Flowchart

Procedure	Screening/ Baseline	0 ^a	Treatment Period (Months)							
			3	6	9	12	15	18	21	24
Demography	x									
Medical History	x									
Informed Consent	x									
Inclusion/Exclusion	x									
Concomitant	x	x	x	x	x	x	x	x	x	x
Physical Examination	x					x				x
Vital Signs ^b	x	x	x	x	x	x	x	x	x	x
EKG	x					x				x
Laboratory Tests	x			x		x		x		x
Best-Corrected Visual	x		x	x	x	x	x	x	x	x
Peak Contrast	x		x	x	x	x	x	x	x	x
Colour Fundus	x		x	x	x	x	x	x	x	x
Fluorescein	x		x	x	x	x	x	x	x	x
Dilated	x	x	x	x	x	x	x	x	x	x
PDT or Placebo ^c		x	x	x	x	x	x	x	x	
Adverse Events		x	x	x	x	x	x	x	x	x

^a Day 0

^b Vital signs must be checked before any infusion of the study drug or its placebo

^c If the CNV is leaking, treatment must be conducted within 7 days of fluorescein angiography

^d 2-4 days after any treatment, all patients will undergo a safety evaluation by telephone

APPENDIX 3: Clinical Laboratory Tests

Haematology

Haematocrit

Total and differential leucocyte count (machine differential leucocyte count)

Red blood cell count

Serum Chemistry

Cholesterol

Creatinine

Sodium

Potassium

Chloride

HCO₃ or CO₂

Albumin

SGOT

SGPT

Alkaline Phosphatase

Total and Direct Bilirubin

Urinalysis (Dip Stick)

pH

Specific Gravity

Protein

Glucose

Ketone

APPENDIX 4: Infusion Instructions

PDT TREATMENT

Drug Dosage and Administration

BPD-MA for clinical use will be supplied in 25 mg and 15 mg vials as sterile, liposomal, freeze-dried powder.

Reconstitution

Reconstitution for 25 mg vials.

To reconstitute: Avoid reconstituting in direct bright light. 11.5 mL of Sterile Water for Injection U.S.P is added to the formulation for a total volume of 12.5 mL of reconstituted drug. The concentration is 2.0 mg/mL of BPD-MA. Care must be taken to gently agitate the solution until it is completely dissolved. Remove foil and check to ensure the solution is uniform with no precipitate.

Reconstitution for 15 mg vials.

To reconstitute: Avoid reconstituting in direct bright light. 7.0 mL of Sterile Water for Injection U.S.P is added to the formulation for a total volume of 7.5 mL of reconstituted drug. The concentration is 2.0 mg/mL of BPD-MA. Care must be taken to gently agitate the solution until it is completely dissolved. Remove foil and check to ensure the solution is uniform with no precipitate.

Precautions: Do not reconstitute with saline solutions. The reconstituted product must be stored in the dark, and must be injected *within 4 hours* as it does not contain an antimicrobial preservative.

After reconstitution replace the vials of BPD-MA in the original packaging to protect the solution from light exposure.

Dilution

The reconstituted BPD-MA has a concentration of 2.0 mg/mL with a volume of 12.5 mL per 25 mg vial and 7.5 mL per 15 mg vial. In order to achieve the desired drug doses of 6 mg/m² body surface area (BSA) further dilution with Dextrose 5% for Injection U.S.P. (D5W) will be required. Each participant will receive a constant total volume of 30 mL by controlled infusion. To determine the required volume of reconstituted drug the desired drug dose and the patient's body surface area is taken into consideration.

EXAMPLE:

Step 1

Drug Dose x Patient BSA = Total Drug Dose

$$6 \text{ mg/m}^2 \times 1.8 \text{ m}^2 = 10.8 \text{ mg}$$

Step 2

Total Dose , Reconstituted Drug Concentration = Volume of Reconstituted Drug

$$10.8 \text{ mg} \div 2.0 \frac{\text{mg}}{\text{mL}} = 5.4 \text{ mL}$$

Step 3

Total Infusion , Volume of Drug = Volume of D5W

$$30.0 - 5.4 = 24.6 \text{ mL}$$

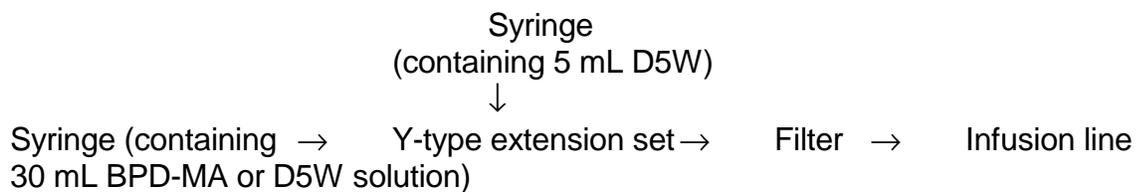
Mix the reconstituted BPD-MA (2.0 mg/mL) together with the required volume of D5W and infusion line in the syringe. The final volume of BPD-MA solution will be 30 mL. Cover the syringe and infusion line with aluminum foil. The colour of the infusate must not be seen by either patient or investigator.

Placebo Administration

30 mL of 5% dextrose in water for injection will be administered intravenously over 10 minutes.

Infusion Procedure

Connect the syringe to a Y-connector, a 1.2 micron filter, and the infusion line in the following manner:



Standard precautions should be taken during infusion of verteporfin to avoid extravasation. A free-flowing IV line should be established before starting the verteporfin infusion and careful monitoring of the infusion line should be followed. Due to the possible fragility of the veins 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 possible. Place the syringe in a programmable syringe pump. Set the infusion rate at 3 mL/min.

Start the infusion pump.

As soon as the syringe is empty, turn off the syringe pump.

Turn the tap on Y-connector to the 5 mL syringe containing D5W. Manually inject the D5W at a rate of approximately 5 mL/min to deliver the residual BPD-MA or D5W placebo solution remaining in the infusion line and filter.

Precautions

Routine precautions must be taken to ensure sterility, exclusion of air and the prevention of extravasation.

Instructions in case of extravasation of BPD / placebo (or for interruption of the infusion due to patient discomfort)

If the patient indicates discomfort or pain at, or near the infusion site, or the nurse/study coordinator notices any extravasation at any time during the infusion the infusion must be stopped immediately.

The investigator, if present, should be asked to leave the room.

The nurse/study coordinator will check the infusion site to confirm that an extravasation has taken place.

1. If extravasation has taken place and **LESS THAN HALF (<15mL)** of the BPD/placebo is estimated to have been administered intravenously follow steps (a) and (b).
 - a) The nurse/coordinator should obtain better venous access as soon as possible.
 - b) The infusion can then be restarted and light application should be carried out 15 minutes (as per the protocol) after the second start of the infusion. If venous access cannot be obtained after several attempts, the patient will either (i) be excluded from further treatments (for patients who have not received any treatments) or (ii) not be treated at that time but scheduled for treatment as soon as possible (but no earlier than 24 hours later) using a new dose of BPD/placebo (for patients who have had one or more previous treatment). The study coordinator should indicate the patient number on the new vial/bag used with a marker and add a comment on the Randomization/Treatment Log that two vials/bags have been used for that particular treatment of this patient.

2. If extravasation has taken place and **MORE THAN ONE HALF (>15mL)** of the BPD/placebo infusate is estimated to have been administered intravenously before stopping the infusion, light application will be carried out 15 minutes after the start of the infusion even if the infusion is now shorter than 10 minutes.

Instructions to the patient after extravasation

Adverse events (pain, swelling etc.) reported by the patient must be treated symptomatically. Immediate application of cold compresses or ice is recommended. The patient's arm should be elevated for 1 day when possible. Pain reliever medication can be prescribed, if needed. The site of extravasation must be protected from light for a minimum of 2 days after the infusion or as long as discoloration of the skin is visible. Once the patient is at home, beginning 24 hours after the event, warm compresses can be used.

Masking

Every attempt should be made to maintain masking of the investigator and patient. The study internist or another physician should be involved in treatment and monitoring of the patient until all symptoms are resolved. There is no need to unmask the physician monitoring the extravasation.

Documentation in CRF

a) "Treatment Dosing" - Page:

Was the study treatment administered according to protocol? Tick "No". In the comment section the extravasation has to be described giving the following details: amount of infusion (mL) administered to the patient; duration of infusion; any interruptions of the infusion and their duration, whether light application has taken place and at what time after the start of the infusion.

b) "Adverse Events (Other Than Study eye)" - Page:

Symptoms of the patient have to be described. (e.g. pain at site of extravasation, swelling etc.). The adverse event has to be evaluated as to its intensity, relationship to treatment = "definite", action taken (e.g. cold compresses, pain medication) and outcome. Extravasation occurred in two out of more than 130 patients in the Phase I/II study and therefore is not considered unexpected. The patient's condition has to be monitored until all symptoms are resolved.

c) "Concomitant Medication" - Page

Any concomitant medication administered to the patient has to be listed on this page.

Infusion Equipment

Syringe: Becton Dickinson 30 mL
Four Way Tap: PCA extension set with backcheck valve-OL, Abbott 6514
Filter: Sterile Acrodisc 1.2T Product # 4190
Infusion Line: IV Angioset with Y Adapter 22GA, Baxter, Catalogue No. 6422

APPENDIX 5: New York Heart Association's Functional Criteria

- Class I No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class IV Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or anginal syndrome may be present even at rest. If any physical activity is undertaken discomfort increases.

APPENDIX 6: Visual Acuity Protocol

1. Visual Acuity Equipment and Facilities

The visual acuity of patients will be measured based on the procedure developed for the Early Treatment Diabetic Retinopathy Study (ETDRS). The following equipment will be used:

- a set of three Lighthouse Distance Visual Acuity Test charts (modified ETDRS Charts 1, 2, and R),
- retroilluminated box providing standardized chart illumination.

The charts and boxes are manufactured by:

Lighthouse Low Vision Products
36-02 Northern Boulevard
Long Island, New York
Tel.: (718) 937-6959

1.1 Visual Acuity Charts

Charts 1 and 2 are used for testing the right and left eye, respectively. Chart R or a Snellen chart will be used for refraction. The features of the charts are 14 lines of letters to be read at a distance of 2 meters, and 3 lines of letters to be read at a distance of 1 meter for patients with reduced vision. Each line shows five high-contrast Sloan letters and has a visual acuity equivalent recorded next to it. The lines are equally difficult and show a geometric progression of letter size (and, thus, an arithmetic progression of the logarithm of minimum angle of resolution) from line to line. Charts 1, 2, and R have different letter sequences. Patients should be prevented from seeing Charts 1 and 2 until refraction has been completed and the visual acuity test begins. The distances must be measured with 1 and 2 meter sticks, with the patient seated in a chair.

1.2 Visual Acuity Box

The dimensions of the light box are 24 and 3/4 inches (62.9 cm) by 25 and 3/4 inches (65.4 cm) by 7 inches (17.8 cm). The box can be mounted on a wall or on a cylindrical stand manufactured by Lighthouse Low Vision Products. The stand is mounted on a five-pronged wheel base, with each prong about 14 inches long (35.6 cm); two of the five wheels are lockable. When the box is mounted on the stand, its height can be varied. The light box should be mounted at a height such that the top of the third row of letters (0.8 LogMAR) is 49 ± 2 (124.5 \pm 5.1 cm) inches from the floor. The rear of the box provides storage space for the two charts not being used.

1.3 Retroilluminated Box

Most of the room lights should be turned off during the visual acuity test. The box itself provides sufficient illumination for the examiner to record the test results. Additional light can have an adverse effect. With the box light off, not more than 15 foot-candles of light (161.4 Lux) should fall on the center of the chart. To measure the amount of light, the room is set up as for the visual acuity test, but with the box lights off. The light meter is placed at the fourth line from the top of the chart, with its back against the chart. The amount of light is measured and the room darkened if necessary.

The visual acuity light box is equipped with two General Electric Cool Daylight 20-watt fluorescent tubes and a ballast. Because the illumination of fluorescent tubes diminishes by 5 percent during the first 100 hours and by another 5 percent during the next 2000 hours,

- new tubes should be kept "on" for 4 days (96 hours) continuously, and
- tubes should be replaced once a year.

The fluorescent tubes should also be checked periodically for proper functioning. A sticker should be placed on the back of the light box, indicating the date on which the present tubes were installed.

Each tube is partly covered by a 14-inch fenestrated sleeve, open in the back, which serves as a baffle to reduce illumination. Each sleeve should be centered on the tube such that an equal length of tube (4 and 3/16 inches, 10.6 cm) is left uncovered to the right and left of the sleeve. The openings in the backs of the sleeves should be oriented to point directly toward the back of the box (e.g., the sleeves should not be tilted up or down). Also, the lower sleeve has a cutout that should point down toward the ballast.

1.4 Visual Acuity Lanes

A distance of exactly 2 meters (78.7 inches) is required between the patient's eyes and the visual acuity chart for the 2-meter test, and a distance of exactly 1 meter (39.37 inches) is required for the 1-meter test. The room must have space for the 2-meter lane, for the visual acuity box (and a stand, if the box is not wall-mounted) and for the patient.

- Wall-mounted box: In addition to the 2-meter lane, 7 inches (17.78 cm) must be allowed for the depth of the box plus space for the patient.
- Stand-mounted box: In addition to the 2-meter lane, 13 inches (33.02 cm) must be allowed for the stand's casters plus space for the patient.

Marking the Distance

The distances are measured from the eye of the patient, seated comfortably in a chair with his or her back firmly placed against the chair's back, to the center of the second (left eye) or fourth letter (right eye) of the third line of the chart. The horizontal distance must be measured individually for each examination. 1- or 2-meter sticks will be used.

1.5 Refraction Technique

All tests of visual function are to be performed after refraction to obtain the best correction. Adjustments to the correction obtained at each visit are specified for each visual function procedure. These adjustments are dependent upon the distance between the patient and the test object as well as the refraction distance.

1.5.1 Equipment

The equipment required for refraction is:

- Retroilluminated Chart R from the ETDRS (modified Bailey-Lovie chart) visual acuity chart set.
- Trial lens frames.
- Wire-rimmed lens set, with positive or negative cylinder lenses.
- +0.37 and -0.37 spherical lenses.
- Jackson cross-cylinders of 0.25, 0.5, and 1.00 diopters.
- Pinhole occluder.
- Tissues.

1.5.2 Beginning Approximate Refraction

At the initial visit, the patient's present glasses (spectacles) for distance viewing (if worn) should be measured with a lensometer, and these measurements used as the beginning approximate refraction. Refractions may be performed with *positive or negative* cylinder power. Each center must designate positive or negative cylinder and must use the same designation throughout the study. If the patient does not wear glasses for distance vision, retinoscopy or autorefractometry should be performed. When no correction is given by any method, the beginning approximate refraction should be no lens correction or plano. The best correction determined from subjective refraction at each visit should be recorded on the *Record of Subjective Refraction* maintained for each patient. At each follow-up visit, the refraction recorded at the previous visit should be used as the beginning approximate refraction for each eye. Only at the baseline examination should the distance prescription worn in glasses be used.

The charts used for measuring distance visual acuity must NOT be used for refraction. Each eye should be refracted at 2 meters unless the visual acuity measured at this distance on the chart used for refraction (Chart R) is worse than 20/320. When visual acuity is worse than 20/320, the eye is refracted at 1 meter with a + 2.00 and - 2.00 sphere only. Whenever a patient cannot read any letters on the top line of Chart R at 1 meter with the *non-study eye* with the beginning approximate refraction, the vision should be checked with a pinhole to see whether reduced vision is due, at least in part, to larger refractive error. If there is no improvement with pinhole, the *non-study eye* is exempt from *refraction*. However, the visual acuity of the *non-study eye* must be measured and recorded in the usual way, beginning at 2 meters first, with the beginning approximate refractive correction.

Patients who arrive for examination wearing contact lenses should be refracted over their lenses starting with plano. The lens correction recorded should be the final correction in the trial frame at the end of refraction and spherical refinement in the visual acuity lane. Corrected aphakic patients, including those with intraocular lenses, should undergo subjective refraction as specified below. For uncorrected aphakic patients, a +10.00 diopter sphere should be added to the trial frame as the beginning approximate refraction.

1.5.3 Procedures for Subjective Refraction

The goal of subjective refraction is to determine the optimum correction to enable the patient to perform the visual function tests at the specified distances. *This process requires skill, patience, and time, particularly for elderly patients who have poor visual acuity and/or central scotomas.* In general, instructions are to "push plus". Add minus diopter spherical corrections only when the visual acuity is thereby improved demonstrably, that is, the patient is able to read at least one more letter on a line or to read at least one letter on a smaller line.

1. Measure and record distance vision of each eye using Chart R. Patients should be encouraged to use eccentric fixation whenever necessary. However, the examiner should make certain that the other eye remains occluded.
2. Seat the patient at 2 meters or 1 meter from Chart R, depending upon the visual acuity determined at 2 meters (see Table 1).
3. Place and adjust the trial frame on the patient's face so that the lens cells are parallel to the anterior plane of the orbit and centered in front of the pupils. Adjust the lens cells for the proper distance from the cornea.
4. Occlude the left eye with lens occluder and tissues or eye patch.
5. Insert the spherical lens correction obtained from the beginning approximate refraction into the trial frame. *The lenses should be positioned as follows:*
 - a. Insert the spherical lens correction in the compartment closest to the eye.
 - b. Place the cylindrical lens correction in the compartment in front of the spherical correction and adjust the axis.

Table 1: Refraction Protocol Summary

Vision with Best Correction (Refraction Distance)	Sphere		Cylinder			Sphere Refinement	
	Power (a)	Increment	Axis (b)	Power (c)	Increment	Power (d)	Increment
20/20 - 20/80 (2 meters)	+0.50 -0.37 +0.50	+0.50 -0.25 +0.50	.50 JCC	.25 JCC	+0.25 -0.25	+0.37 -0.37 +0.37	+0.25 -0.25 +0.25
< 20/80 - 20/160 (2 meters)	+1.00 -1.00 +1.00	+1.00 -1.00 +1.00	1.00 JCC	1.00 JCC	+1.00 -1.00	+0.50 -0.50 +0.50	+0.50 -0.50 +0.50
20/200 - 20/320 (2 meters)	+2.00 -2.00 +2.00	+2.00 -2.00 +2.00	1.00 JCC	1.00 JCC	+1.00 -1.00	+1.00 -1.00 +1.00	+1.00 -1.00 +1.00
< 20/320 (2 meters)	+2.00 -2.00	+2.00 -2.00	No cylinder test			No refinement	

Sequence of Refraction: (a) - (d)

6. *Spherical Correction:* Refract the right eye. The refraction steps below are recommended for visual acuities of 20/20 and 20/80 with the beginning approximate refraction. For visual acuities worse than 20/80, refer to the refraction table for the appropriate sphere and cylinder powers and testing distance (see Table 1) and follow a similar procedure using steps in power that are equal to the power of the lens being presented. *Note: Whenever the visual acuity improves to a higher range by improved correction, for example, from the 20/80 to 20/160 range to the 20/20 to 20/80 range, refinement should be performed with the smaller sphere and cylinder powers given for the better visual acuity.*
 - a. With the patient looking at the visual acuity chart at the smallest line legible, hold a +0.50 spherical lens in front of the right eye. Ask the patient, "Is this better, worse, or no change?". The examiner should state this question with this exact wording.
 - b. Whenever the patient responds that vision is made worse or is blurred, remove the +0.50 spherical lens from in front of the trial frame, record the visual acuity (to the nearest letter), and proceed to Step 6d. Else go to Step 6c.

- c. Remove the +0.50 spherical lens from in front of the trial frame and replace the spherical lens in the trial frame with the spherical lens which is a half diopter more positive. Continue by returning to Step 6a.
- d. Hold a -0.37 spherical lens in front of the right eye and ask the patient, "Is this better, worse (or smaller and darker) or no change?". Whenever the patient says "worse", or "no change" proceed to Step 6f. Whenever the patient says better, hold the -0.37 spherical lens in front of the right eye again and ask whether these letters are easier to read or just smaller and darker. Remove the -0.37 spherical lens from in front of the eye. Whenever the patient says "smaller and darker" proceed to Step 6f.
- e. Whenever the patient responds that the vision is better with this lens, ask the patient to read the visual acuity chart. Whenever the visual acuity is improved, even by one letter, replace the spherical correction in the trial frame with a spherical lens which is a quarter diopter less positive and return to Step 6d. Whenever the visual acuity is not improved, proceed to Step 6f.
- f. Remove the -0.37 spherical lens from in front of the trial frame and hold a +0.50 spherical lens in front of the right eye. Ask the patient, "Is this better, worse, or no change?". Whenever the patient responds that the vision is improved or unchanged, go to Step 6c. Else go to Step 7.

7. *Cylinder Axis:* Determine and refine the cylinder axis, as follows:

- a. Ask the patient to look at a line on the visual acuity chart that is one or two lines larger than the smallest line that the patient can read. Ask the patient to focus on a round letter such a "C", or "O". The patient should focus on the same letter throughout this step.
- b. Whenever a cylinder is present in the beginning approximate refraction, proceed to Step 7c. Otherwise, follow one of the options below to identify a possible need for cylindrical correction.

Option 1:

Place the +0.50 diopter cross-cylinder with the positive axis (white) first at 90°, then at 180°, then 45° and 135°. If the patient states that the vision is improved at any one of these four axis positions, place a +0.50 cylindrical lens in the trial frame at the preferred axis and proceed to Step 7c. If the patient prefers none of the four positions, proceed to Step 9.

Option 2:

Place the +0.50 diopter cross-cylinder with the positive axis (white) first at 90° and then compare to no cylinder; then at 180° and then compare to no cylinder; then at 45° and compare to no cylinder; and then at 135° and compare to no cylinder. If the patient states that the vision is improved at any of these four axis positions, place a +0.50 cylindrical lens at the preferred axis.

If the patient prefers no cylinder over all four cylinder positions, proceed to Step 9.

Option 3:

Place the +0.50 diopter cross-cylinder with the positive axis (white) first at 90° and then at 180° and ask if either position is preferred over no lens. If neither 180° nor 90° is preferred, place the +0.50 diopter cross-cylinder at 45° and 135° and ask if either position is preferred over no lens. If the patient states that the vision is improved at any one of the positions offered, place a +0.50 cylindrical lens at the preferred axis. If the patient prefers no cylinder over all four cylinder positions, proceed to Step 9. If a cylinder correction is found by using either of these three options, proceed to Step 7c.

- c. Position the 0.50 diopter cross-cylinder first with the positive axis 45° to the right of the cylinder axis, and secondly with the positive axis at 45° to the left of the cylinder axis. Ask the patient which position is preferred (position one or position two?). Remember to tell the patient that both positions may blur the vision. Do not offer the choice of "without" a cross-cylinder. The patient must choose the position which is least blurred, position one or position two. The choice of "neither position" is allowed only if both positions are equally blurred or equally good.
- d. If the patient responds that neither position is better and if this was the first test of axis position, move the axis of the cylinder in the trial frame 15° to the right or left and return to Step 7c. Otherwise go to Step 7e.
- e. Whenever the patient prefers one position to the other, rotate the cylinder toward the preferred positive axis of the cross cylinder in the step sizes recommended below and return to Step 7c. (When the patient states that one position of the cross cylinder is no better than the other position, proceed to Step 8).

Axis Step Sizes for Refinement of Cylinder

Cylinder Power	Axis Step Sizes
< 1.00 D	10°
1.00 - <2.00 D	5°
2.00 - <3.00 D	3°
3.00 - <5.00 D	2°
5.00 - < 8.00 D	1°

8. *Cylinder Power:* Refine cylinder power as follows:
 - a. Ask the patient to look at the smallest line on the visual acuity chart that can be read.
 - b. Align the 0.25 diopter cross-cylinder first with the positive axis and then with the negative axis coincident with the cylinder axis. Ask the patient which is better. Do not offer a choice of "without" the cross-cylinder.
 - c. Whenever the patient prefers the negative (red) axis coincident with the cylinder axis, decrease the power of the cylinder in the trial frame by 0.25 diopter and return to step 8b. Whenever a patient indicates a change that would introduce negative cylinder power, remove all cylinder power and continue testing for positive cylinder power at an axis 90° away from the previous axis. Otherwise go to Step 8d.
 - d. Whenever the patient prefers the positive (white) axis coincident with the cylinder axis, increase the power of the trial frame by 0.25 diopters and return to Step 8b. Otherwise go to Step 8e.
 - e. When the patient states that both positions are equally bad or good and the cylinder power in the trial frame has changed by more than 0.50 diopter, return to Step 7c. Otherwise go to Step 9.
9. *Spherical Correction Refinement:* Recheck the power of the sphere in the trial frame by using a +0.37 and -0.37 spheres in front of the right eye as shown on Table 1: Refraction Protocol Summary. Change the spherical power by 0.25 diopter increments of the appropriate sign until the patient is unable to perceive any improvement in vision.
10. Record the lens corrections obtained by subjective refraction for the right eye and the distance at which the eye was refracted on the *Record of Subjective Refraction*. If the corrective power was changed by more than two diopters from the starting refraction, verify that the patient can read at least as well as with the beginning approximate refraction. If not, begin again at Step 1.
11. Repeat the entire process (Steps 1 through 10) for the left eye.

1.6 Testing Best-Corrected Visual Acuity

2-meter Test

Testing of all eyes begins at 2 meters, including those who could not be refracted at 2 meters. For eyes refracted at 1 meter, + 0.50 sphere should be subtracted from the spherical correction before testing vision at 2 meters. First the right eye is tested with Chart 1 and then the left eye is tested with Chart 2. Each chart should remain hidden from view until the eye in question is ready for testing.

The distance from the patient's eyes to the visual acuity chart must be exactly 2 meters. The patient must sit for the 2 meter test. When the patient is seated, his or her back should fit firmly touching the back of the chair. The examiner should ensure that the patient is sitting comfortably, that the head does not move forward or backward during the test, and that the patient's eyes remain at the 2 meter distance.

The testing procedure is based on the principle that the objective is to test visual acuity and not intelligence or the ability to concentrate or follow or remember instructions (although all of these factors are involved). The patient should be told that the chart has letters only and no numbers. If the patient forgets this instruction and reads a number, he or she should be reminded that the chart contains no numbers and the examiner should request a letter in lieu of the number.

The patient should be asked to read slowly (at a rate not faster than about one letter per second) in order to achieve the best identification of each letter and to not proceed until the patient has given a definite response. It may be useful for the examiner to demonstrate the letter-a-second pace by reciting "A,B,C,....". If, at any point, the patient reads quickly, he or she should be asked to stop and read slowly. If the patient loses his or her place in reading or the examiner loses his or her place (possibly because the letters are read too quickly), the examiner should ask the patient to go back to where the place was lost. Examiners should never point to the chart or to specific letters on the chart or read any of the letters during the test.

Each letter is scored as right or wrong. Once a patient has identified a letter with a definite single-letter response and has read the next letter, a correction of the previous letter cannot be accepted. If the patient changes a response aloud (eg, "That was a 'C', not an 'O'") before he or she has read aloud the next letter, then the change should be accepted. If the patient changes a response after beginning to read the next letter, the change is not accepted.

When the patient says he or she cannot read a letter, he or she should be encouraged to guess. If the patient identifies a letter as one of two or more letters, he or she should be asked to choose one letter and, if necessary, to guess even if the next letter has already been read. The examiner may suggest that the patient turn or shake his or her head in any manner if this improves visual acuity. If the patient does this, care must be taken to ensure that the fellow eye remains covered. When it becomes evident that no further meaningful readings can be made, despite urging to read or guess, the examiner should stop the test for that eye.

There are several reasons for encouraging patients to guess:

- patient's statements that they cannot identify a letter are often unreliable,
- encouraging them to guess helps to maximize the patient's effort,
- it helps to assure uniformity among procedures performed in different clinics (inter-center variability) and
- it may help to prevent patient bias (malingering).

1-meter Test

Eyes reading less than 20 letters correctly at 2 meters should be tested at 1 meter. If the trial frame is to be removed when changing the test distance from 2 meters to 1 meter, the chart (Chart 1 or 2) should first be removed from view to prevent the patient from reading the chart with the fellow eye.

Before testing at 1 meter, a +0.50 sphere should be added to the 2 meter correction already in the trial frame to compensate for the closer testing distance. The patient must sit for the 1-meter test. The avoidance of any head movement forward or backward is particularly important during the 1-meter test. The patient should be asked to read only the first 3 lines at 1 meter, making 15 the maximum score attainable at that distance.

After the test of the right eye is completed, occlude the left eye and replace Chart 1 by Chart 2. The test is repeated for the left eye, starting at 2 meters. When testing of the left eye is completed, Chart 2 should be removed from view.

Scoring Best-Corrected Visual Acuity

The examiner records each letter identified correctly by circling the corresponding letter on the Visual Acuity Worksheet. Letters read incorrectly and letters for which no guesses are made are not marked on the form. Each letter read correctly is scored as one point. The score for each line (which is zero if no letters are read correctly) and the total score for each eye are recorded after testing is completed. If testing at 1 meter is not required, 15 points are automatically scored for the 1-meter test. The total combined score (ie, the sum of the 2- and 1-meter scores) and the approximate Snellen fraction, which is determined based on the lowest line read with one or fewer mistakes, are recorded on the Visual Acuity Worksheet.

Light Perception and No Light Perception

If visual acuity is so poor that the patient cannot read any of the largest letters at 1 meter (ie, the number of letters read correctly at 1 meter is zero), light perception should be tested with an indirect ophthalmoscope in a darkened room. The indirect ophthalmoscope light should be in focus at 1 meter or about 3 feet with the rheostat set at maximum voltage. From that distance the beam should be directed in and out of the eye at least four times, and the patient should be asked to respond when he or she sees the light. If the examiner is convinced that the patient perceives the light, vision should be recorded as "light perception"; if not, vision should be recorded as "no light perception".

APPENDIX 7: Protocol for Contrast Sensitivity Testing

1. Introduction

Contrast sensitivity testing is performed after refraction and visual acuity testing. The contrast sensitivity chart used is the Pelli-Robson chart (35,36). The chart is printed on both the front and back. One side is used for testing the right eye and the other side for testing the left eye.

The chart is hung on the wall during testing but must be kept out of sight otherwise. The incident light falling on the charts should be between 75 and 125 foot-candles.

2. Explaining the Test

This test will be unfamiliar to most patients, and patients may cooperate more readily if they understand why it is being performed. Here is one possible set of instructions: "In everyday life we don't just look at small black objects. Contrast sensitivity is a more realistic assessment of how well we see large faint objects around us. This chart is a little different from the regular eye chart. With this chart the letters are uniformly large, and they fade out towards the bottom of the chart. The top line has high-contrast letters, black on white. The letters below them are gray and are difficult to see, very much like looking through a fog or dirty glasses. What you must do is read as many letters as you can. The letters at the bottom of the chart are more difficult for everyone to read, so don't be discouraged." When the patient begins to have trouble, it may be useful to provide some strategies to help him or her make the best attempt at seeing the letters. "Try reading just one letter at a time. Try blinking, or viewing the letter a little eccentrically, moving your head from side to side." Indicate (without touching the chart) the particular letter you want the patient to concentrate on. "Try reading this one. Do you see something against the white background? Is there a smudge? Is it round or square? Does it have corners or lines you can see? Keep trying. The whole letter may suddenly appear to you. Go ahead and guess."

3. Procedure

- Move the patient to 1.0 meter from the contrast sensitivity chart position. The patient may stand for this test, but normally will be seated. Occlude the left eye with lens occluder and eye patch.
- The lens power of the right eye should be increased by +0.50 dioptre from the refraction obtained at 2 meters. If the eye was refracted at 1.0 meter or the visual acuity was measured at 1.0 meter, no change from the correction used at that distance is required. Changing the spherical lens may be easier than adding another lens to the anterior compartment of the trial frame.
- Hang the chart so that the patient's eyes are aligned with the center of the chart. The patient may turn his/her head if this improves the view; however, the fellow eye must remain occluded.
- Explain the test to the patient. Refer to Section 2.

- Explain that the patient should guess once at each letter on the chart, beginning in the upper left hand corner where the highest contrast letters are located.
- The patient should not be coached, but if he/she changes an incorrect response to a correct one, you should count that letter as correct.
- The patient must state one definitive answer per letter.
- Patients should be encouraged to guess even after they believe that the letters have disappeared.
- As the patient reads each letter, mark the Contrast Sensitivity Worksheet indicating each letter identified correctly.
- Stop when the patient states that he/she cannot see anything in the next segment of three letters of any other lighter letter, even after being encouraged to guess. Record the number correct in each segment of three letters on the summary line ("Number Correct" column). Repeat the test on the left eye, using the reverse side of the chart.

Availability of Test Materials

Pelli-Robson Contrast Sensitivity chart

- Printed on both sides
- Order Pelli-Robson chart #7002251 @ \$ 295 from:

Clement Clarke, Inc.
3128 East 17th Avenue
Columbus, OH 43219
1-800-848-8923

APPENDIX 8: Photograph Reading Center Procedures

1. PROCEDURES FOR FUNDUS PHOTOGRAPHY

1.1 Introduction

Determination of patient eligibility requires stereoscopic fluorescein angiography in order to identify the choroidal neovascularization (CNV), the extent of the CNV lesion, and the foveal avascular zone (FAZ). Stereoscopic colour photographs are necessary to describe in further detail the pathology present.

High photographic standards have been established and are to be maintained to prevent otherwise eligible patients from being deemed ineligible because of inability to interpret photographs of poor quality.

To ensure high photographic quality, standardization of camera equipment, film development, and photographic techniques are required. The Photograph Reading Center must be notified of the equipment being used prior to randomizing the first patient. A Photographic Equipment Form (Exhibit A) should be submitted to the Photograph Reading Center to identify which fundus camera will be used for study patients. If more than one model camera is available, it is preferred that a patient be photographed on the same camera at each study visit so that consistent interpretation of the status of the CNV can be made. In addition, the center photographer must satisfy the Fundus Photograph Reading Center that he/she understands the photography protocol and can achieve good quality photography. (See 5. Standardization Procedures for Clinic Personnel.)

1.2 Camera Equipment, Film, and Film Processing

- A 30° or 35° fundus camera with 2.5X magnification is preferred for both colour photographs and fluorescein angiograms. The Zeiss 300 fundus camera is recommended, however, other fundus cameras are acceptable. (A 450 fundus camera is acceptable. Fields of 250 or 600 are not acceptable for the study.)
- Tri-X or Tmax film should be used for fluorescein angiograms. Colour photographs may be taken with either Kodachrome, Ektachrome, or FUJI 50 colour slide film. Since there may be a slight difference in the colour balance of different films, the Photograph Reading Center Investigators recommend that whenever possible the same film type be used at all visits for a patient.
- Delori filters should be used for excitation and barrier filtration: SE-40 Excitation, SB-50 Barrier. These filters should be changed every 24 months, or when inspection proves them to be defective.
- Since the original angiographic negatives are submitted for reading, it is recommended that a high contrast developer be used in order to maximize capillary detail. Kodak D-11, diluted 1:1, should be used at approximately 700 for eight minutes. The exact processing time, temperature, and chemistry can be adjusted by the participating center to

compensate for differences in cameras and to provide negative density acceptable to the Fundus Photograph Reading Center.

1.3 Modification of Photographic Technique

Acceptable results can be obtained with different development techniques and different films. The continuing advancements in hardware make it impossible to say that these recommendations are, in every case, optimal and will remain that way throughout the course of the Study. Therefore, the following provisions are made for exceptions and revisions to this protocol.

- If a photographer at a center believes that there is just cause for deviation from the above protocol, he/she may apply to the Photograph Reading Center for a variance. The application should include a letter of explanation and several sample photographs produced by the proposed method. If the Photograph Reading Center Director agrees that the standards of the Study are upheld, the variance will be granted.
- If the Photograph Reading Center staff identify methods which they consider superior to those in use, those methods will be suggested to or imposed upon the participating photographers.

1.4 Colour Fundus Stereoscopic Photography

1.4.1 Required Fields

The stereoscopic colour photographs of the disc and stereoscopic colour photographs of the macula of both eyes are to meet the criteria described in "Required Fields of the Fundus" (Exhibit B). In cases in which the neovascular lesion is in the far periphery of the photograph of the macula and is likely to be distorted, an additional stereoscopic pair centered on the lesion should be taken. If at the baseline visit a dense cataract precludes good quality photography of the fundus of the non-study eye, a photograph should be taken to document the inability to view the posterior pole and indicate this in "Photographic Inventory Form" (See *Exhibit F-1, Part B.*)

1.5 Fundus Fluorescein Angiography

All fluorescein angiograms should be taken in stereo. An attempt at stereo should be made even if the view of the fundus is obscured by media problems or borderline pupillary dilatation. Use of the stereo separator is permissible providing that it does not diminish the quality of photography.

Unless otherwise specified, the fluorescein angiogram must always have the transit phase photographed on the Study eye. Because the size and relationship of the neovascular lesion to the center of the avascular zone is determined from the fluorescein angiogram, a patient cannot be determined to be eligible if the angiogram is missing or performed earlier than 7 days prior to randomization.

1.5.1 Fluorescein Injection

Five cc of 10% sodium fluorescein should be injected into the antecubital region with a 19 or 21 gauge Butterfly infusion set with a push of 5 seconds in duration.

If any medical condition (such as pregnancy or allergy to fluorescein) develops during follow-up that makes the injection of fluorescein dye for a particular patient inadvisable in the opinion of the ophthalmologist, that patient is exempt from the follow-up angiograms, however, colour fundus photographs still should be obtained.

1.5.2 Required Fields

Prior to fluorescein dye injection, black and white red-free stereoscopic pairs of photographs should be taken of the maculae of both eyes. Photographs of the macula of the Study eye should be taken during the fluorescein dye transit and should include at least one stereoscopic pair. Stereoscopic pairs of the Study eye macula should be taken again at approximately 30, 40, 60, and 90 seconds and at 2, 3, 5, and 10 minutes after injection. The stereoscopic pairs of the macula of the non-study eyes are to be taken after 2 minutes and again at 5 and 10 minutes. Stereoscopic pairs of the optic discs of both eyes can be taken after 2 minutes. If the lesion is in a location which would be distorted or extends beyond the macular photographs, an additional stereoscopic pair centered on the lesion should be taken during or following the transit phase. (See Exhibits C-1 & C-2, Photographic Sequence for Fluorescein Angiography)

1.5.3 Evaluation of Quality

The quality of both the colour photographs and the fluorescein angiograms is assessed as the overall quality of the entire set of photographs. The quality of the photographs submitted for the study eye is first assessed by the grader and reflects the grader's confidence in selecting subsequent answers to specific grading questions. The quality is assessed in the three following categories:

Focus/Clarity:

- Adequate* - Implies all photographic features can be read with great confidence
- Fair* - Implies all or nearly all photographic features can be read, but confidence in gradings is only fair
- Poor* - No photographic features can be read with great confidence and some or all features may not be gradable
- Missing* - No photographs are present.

Stereopsis (facilitates recognition of occult CNV):

- Adequate* - Implies degree of stereopsis obtained is sufficient to identify occult CNV
- Fair* - Implies limited stereopsis present such that occult CNV may escape detection
- Poor* - No stereopsis achieved (includes missing 1/2 of stereo pair)
- Missing* - No photographs are present

Field Definition (to ensure that the entire lesion is visible on all the photographs)

Adequate - Implies field placement is within 1/2 disc diameter of proper placement

Fair - Implies enough of the required photographs are off field by more than 1/2 disc diameter which interferes with the interpretation of the extent of the lesion

Poor - Implies there are not enough photographs with correct field placement to answer questions regarding size and extent of the lesion with confidence.

Missing - No photographs are present

1.6 Photography Schedule by Visit

A complete set of photographs consisting of stereoscopic colour photographs of the disc and stereoscopic colour photographs of the macula of each eye (as specified in 1.4.1, Required Fields) and a fluorescein angiogram (as specified in 1.5.1, Required Fields) should be taken at all study visits:

Screening /Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
---------------------	---------	---------	---------	----------	----------	----------	----------	----------

Photographs for the baseline visit must be taken *within* seven days prior to the day of initial study treatment.

Photographs for follow-up visits should be taken on the day of the scheduled visit. However, when circumstances preclude this (lost picture, camera broken, not taken, etc.) photographs obtained *within three days* of the examination are acceptable. The fluorescein angiogram and the colour photographs must be taken within 72 hours of each other, if not on the same day. If at any time the lesion would be distorted in the macular photographs, additional stereoscopic photographs should be taken, centered on the lesion, both in colour and on the fluorescein angiogram.

1.7 Clinical Center Preparation and Labelling of All Photographs

Using the labels supplied by the Sponsor, colour photographs and fluorescein angiograms should be labelled with the patient's study number, patient's initials, visit, and date of photography. (See *Exhibit D, Instructions for Labeling Photographs.*) The patient's name should *not* appear anywhere on the colour photographs, slide mounts, film, or any materials sent to the Photograph Reading Center. The Photograph Reading Center should not at any time have knowledge of the patient's identity nor randomization assignment.

The colour photographs are placed in clear plastic slide pages (provided by the Sponsor) and the fluorescein negatives are placed in a negative sheet (provided by the Sponsor) as detailed in Exhibit E. Glass slide mounts are not to be used for the color photographs.

The study photographs along with the Photograph Inventory Forms, Photograph Transmittal Form, and Case Report Form grading pages should be sent via courier to the Photograph

Reading Center (*See Exhibit E, Preparation of Photographs for Mailing*) at weekly intervals. The Photograph Reading Center will grade the photographs and send the completed grading forms to the clinical center to be inserted into the case report form.

1.8 Photograph Inventory Forms

Photograph Inventory Form (Exhibit F - 1) is to accompany every set of photographs of enrolled patients submitted to the Photograph Reading Center. The Clinical Center Coordinator is responsible for the information requested in:

- Section A _ Patient Information
- Section B _ Photographs Enclosed
- Section C _ CRF Forms Enclosed
- Section D _ Administrative Information.

Forms containing incomplete information will be returned to the clinical center via FAX for completion. Photographs are not evaluated until all information is complete on the Photograph Inventory Form.

The Photograph Reading Center documents receipt of the photographs and the Photograph Inventory Form in Section E.

1.9 Photograph Transmittal Form

Photograph Transmittal Form (Exhibit F - 2) is to accompany every shipment of photographs submitted to the Photograph Reading Center. This forms provides a list of patients and visits that are included in the shipment. It serves as documentation for both the clinical center and the Photograph Reading Center of what materials have been submitted at a particular time. It also accounts for the contents of the shipment in case the shipment is lost or damaged and there is a question as to the entire contents of the shipment being received.

2. PHOTOGRAPH READING CENTER PROCEDURES

- Baseline study eye photographs will be evaluated for the eligibility status of each patient (Exhibit H - 1).
- Follow-up visit study eye photographs will be evaluated for closure of the CNV, ocular adverse events, and status of the lesion. (Exhibit H - 2).
- Fellow eye photographs at baseline and follow-up visits Month 12 and Month 24 will be evaluated for AMD status. (Exhibit H - 3).
- The completed grading forms (Exhibits H - 1, H - 2 and H - 3) will be sent to the clinical centers to be inserted in the case report forms. A copy will be retained in the Photograph Reading Center patient file.

3. ROLE OF STUDY MONITORS

..It is the monitor*s responsibility to notify the Photograph Reading Center of the number of patients enrolled and the patient's assigned number by faxing the Randomization Alert Form (Exhibit G) to the Photograph Reading Center.

4. DOCUMENTATION OF STUDY EYE OCULAR ADVERSE EVENTS BY INVESTIGATOR & PHOTOGRAPH READING CENTER

- In order to document the presence of specific ocular adverse events, (arteriolar or venular non-perfusion, retinal capillary non-perfusion or vitreous hemorrhage) an Ocular Adverse Events Form (*Exhibit I*) is completed by the Clinical Investigator and submitted to the Photograph Reading Center along with the study photographs, whether or not these adverse events are noted.
- If any of these specific adverse events are noted by the Clinical Investigator, the photographs and Exhibit I must be couriered immediately to the Photograph Reading Center and a copy of Exhibit I must be faxed to the Study Monitor.
- The Photograph Reading Center Investigators review the photographs for these ocular adverse events as described in Section 12.7 and complete the Photograph Reading Center section of the Ocular Adverse Events Form, Exhibit I, Section II.
- When any of these ocular adverse events are identified by the Photograph Reading Center but not identified by the Clinical Center Investigator a copy of the Ocular Adverse Events Form is faxed immediately to the Study Monitor and to the Clinical Center Investigator by the Photograph Reading Center.
- In the event of Photograph Reading Center confirmation of any of these specific adverse events, the Clinical Center Investigator must evaluate the relationship to treatment, any action taken and outcome as described in Section 12.3 - 12.5 and document these in the Case Record Form on Exhibit I.

5. STANDARDIZATION PROCEDURES FOR CENTER PERSONNEL

5.1 Introduction

As in any multicenter study, it is important that procedures be standardized. In fact, the reason for adopting the same prestudy standardization procedures as have been routinely used in multicenter treatment trials in the past is to ensure consistency in interpretation of angiograms, photographs, and the terminology used between centers. Despite the fact that

Investigators may have participated in previous trials for the treatment of CNV, we are still of the opinion

that it is essential to perform prestudy standardization procedures for each new study where the definitions and eligibility criteria differ from previous studies. We also believe that since the clinical centers are both in the US and outside the US, that it is essential to standardize the interpretation and terminology, especially when working with different countries where interpretations and terminology can differ, even though each may be correct.

Standardization procedures for Investigators and photographers are carried out in each center **prior to initiating the study**.

The Photograph Reading Center is responsible for assuring to the Sponsor that Investigators and photographers can apply the protocol for recruiting patients who meet the eligibility criteria and for taking the required photographs, respectively. Documentation that these standardization procedures have been completed are maintained by the Photograph Reading Center with a copy to the Sponsor.

The Principal Investigator of each center should anticipate the need for training and completing standardization procedures for new Study staff as soon as he/she learns of a resignation. The Principal Investigator is also responsible for ensuring that backup staff have completed these procedures. During follow-up, the Principal Investigator of each center is responsible for the training of additional co-investigators on protocol procedures and application of verteporfin treatment. The principal investigator must act as a preceptor for the first treatment administered by the co-investigator.

5.2 Goals of Investigator/Coordinator Training Meeting

The purpose of the training meeting is not limited to the review of procedures regarding the Photograph Reading Center but serves as a supplementary meeting of the Investigators and Sponsor to introduce and explain the Study Protocol.

The goals for the Investigators of the training meeting are:

- Understanding the final protocol.
- Review and clarify terminology used by the Photograph Reading Center for the identification of CNV, its etiology, and its location in relationship to the foveal center.
- Review the procedures for measuring the CNV lesions and determining the spot size to be used for treatment.
- With the use of example cases, apply the eligibility and exclusion criteria.
- Demonstrate knowledge of the eligibility and exclusion criteria by independently reviewing a set of cases. (Each Investigator reviews the same cases.)
- Review and clarify the procedures for submitting photographs and the subsequent procedures, such as for incomplete materials, missed visits, etc.
- Review & clarify the procedures for reporting Adverse Events and to understand the study procedures resulting from any of these adverse events.
- Review the CRFs.

The goals for the Coordinators of the training meeting are:

- Review the final protocol along with the Investigators.
- Attend the session with the Investigators that reviews and clarifies terminology used by the Photograph Reading Center for the identification of CNV, its etiology, and its location in relationship to the foveal center as well as the procedures for measuring the CNV lesions and determining the spot size to be used for treatment.
- Review and clarify the procedures and forms for submitting photographs or other study material to the Photograph Reading Center and the subsequent procedures, such as for incomplete materials, missed visits, etc.
- Review & clarify the procedures for reporting Adverse Events and to understand the study procedures resulting from any of these adverse events.
- Review the photography protocol.
- Review the procedures for standardization of study photographers.
- Review the CRFs.

5.3 Standardization Procedures for Investigators

At the training meeting the Clinical Center Investigators will review the eligibility and exclusion criteria with the Photograph Reading Center Investigators by reviewing examples of both eligible and ineligible cases. Following this review and discussion, the Clinical Center Investigators will independently review 8-10 cases for eligibility. The results of the review will be discussed openly with the Clinical Investigators and the Photograph Reading Center Investigators in order to resolve any continued disagreement of interpretation of the sample cases.

The Investigators will also review the treatment protocol with regard to spot size, location and technique. They will review the procedures to determine the size of the lesion versus the size of the treatment spot by assessing example cases.

Additional Investigators

Additional or replacement clinical center Investigators will need to attend a training meeting at the Photograph Reading Center prior to enrolling patients in the study. The goals and agenda of these meetings will be the same as the initial start-up meeting with clinical center personnel. During follow-up, the Principal Investigator of each center is responsible for the training of additional co-investigators on protocol procedures and application of verteporfin treatment. The Principal Investigator must act as a preceptor for the first treatment administered by a co-investigator. The goals for training a co-investigator are the same as at the initial training meeting (see 5.2) including the review of the eligibility criteria for the fellow eye. The Principal Investigator must confirm by completing a standardization form to the Sponsors that the new co-investigator has been trained according to the protocol before the co-investigator can treat study patients.

BPD OCR 002 AMENDMENT 10

Co-Investigator Training Documentation Form

Purpose: To document training of a new co-investigator
When: A co-investigator has been adequately trained to perform the TAP study procedures
By Whom: Principal investigator
Instructions: Sent to QLT Clinical Department once training of co-investigator has been completed as outlined below. QLT will verify that documentation is complete. This form will be returned to the Investigative Center with confirmation that the co-investigator can perform the delegated duties. A copy is forwarded to the study monitor.

CENTER NO.: _____

DATE: _____

CO-INVESTIGATOR: _____

PHONE: _____

FAX: _____

The above candidate has completed co-investigator training procedures as per TAP study Amendment 10. This is to confirm that Dr. _____ (co-investigator) has been trained on all protocol procedures and will treat study patients at follow-up visits under Principal Investigator supervision.

In detail, the following procedures were reviewed:

- final protocol including all amendments.**
- terminology used by the Photograph Reading Center for the identification of CNV, its etiology, and its location in relationship to the foveal center.**
- procedures for measuring the CNV lesions and determining the spot size to be used for treatment.**
- treatment eligibility and exclusion criteria.**
- procedures for submitting photographs and the subsequent procedures, such as for incomplete materials, missed visits, etc.**
- procedures for recording and reporting Adverse Events and Serious Adverse Events and follow up required from these adverse events.**
- administration of treatment (first treatment by co-investigator under preceptorship of principal investigator)**
- Review the CRFs.**

The following documents are attached:

- revised FDA 1572 to include new co-investigator**
- co-investigator's signed and dated CV**
- copy of revised Study Personnel Identification Log to include new co-investigator**

The documentation listed above must be complete before any new co-investigator is trained to treat patients in the study.

Signature – Co-Investigator

Date

Signature – Principal Investigator

Date

For QLT Clinical Department Use:

Completeness of Documentation verified: _____

Copy to TAP Monitor: _____
Date

5.4 Standardization Procedures for Clinical Center Coordinators

In order to assure that the procedures established by the Photograph Reading Center for the labelling and submission of the photographs to the Photograph Reading Center are understood and followed it is necessary for the Clinical Center Coordinator to attend the Photograph Reading Center training meeting. The goals of the training meeting for the Clinical Coordinator are specified above.

5.5 Standardization Procedures for Photographers

In order to assure that high photographic quality is repeatable rather than present in only isolated cases, standardization procedures for photographers have been established.

The Principal Investigator at each center identifies the photographer(s) at his/her center who will complete these procedures for the study by submitting a Recommendation for Standardization Form (*Exhibit J-1*) to the Photograph Reading Center. This form may be sent along with the standardization photographs prepared by the candidate.

When a photographer who was previously certified or standardized for other studies has been identified to be the photographer for this study, a Photographer Prior Standardization Documentation Form (*Exhibit J - 2*) should be submitted to the Photograph Reading Center. Depending upon which studies they were certified/standardized for, the requirements for submitting photographs may be waived and a standardization number issued.

Candidates must submit required photographs along with a properly completed Photographer Checklist (*Exhibit K*). The required photographs consist of eight recent fluorescein angiogram negatives (taken within the past 6 weeks of submission) with the transit on the macula, according to the Procedures for Fundus Photography. At least one angiogram must be of a patient with age-related macular degeneration with a subfoveal lesion, the remaining patients may have any disease. Stereoscopic colour photographs of the macula and disc of each eye must accompany each angiogram.

All photographs submitted for these standardization procedures will be returned to the clinical center following evaluation. Since the photographs will be returned to the clinical center they may be identified by name or be given a name code. All photographs should be labelled with the date they were taken.

After reviewing the angiograms, the Photograph Reading Center Director will make one of the following judgments:

- (1) the photographs are acceptable - standardization procedures are complete;
- (2) the photographs are marginally acceptable - another 3 to 5 sets of acceptable photographs must be submitted before standardization procedures are complete;
- (3) the quality of the photographs is inconsistent or definite improvements are necessary - the Photograph Reading Center will consult with the photographer, the problems will be analyzed, and the photographer will be notified of possible corrective actions with copies of information sent to the Study Monitor and the Principal Investigator for that center. A second set of eight angiograms will be submitted and if the standardization procedures still are not completed after review of the second set of angiograms, the Photograph Reading Center will arrange a photographic site visit or a telephone conversation with the Principal Investigator so that the problems can be isolated and solved.

APPENDIX 8: EXHIBITS

Exhibit	Name	Description
A	Photography Equipment Form	Provide information to Photograph Reading Center regarding photographic equipment that will be available at clinical center.
B	Required Photographs Fields of the Fundus	Description of photographic fields centered on the disc and centered on the macula.
C - 1 & C - 2	Photographic Sequence for Fluorescein Angiography	Schematic of required frames on fluorescein angiogram.
D	Instructions for Labeling Photographs	Schematic of placement of labels on photographs/angiograms
E	Preparation of All Photographs for Shipping	Placement of slides in slide pages and placement of negative strips in negative sleeves.
F - 1	Photograph Inventory Form	Form to accompany each set of photographs shipped to Photograph Reading Center.
F - 2	Photograph Transmittal Form	Form to accompany each shipment of photographs to the Photograph Reading Center to list the patients and visits that are contained in the shipment.
F - 3	Checklist for Submitting Photographic Materials	Summary of important aspects of preparing and shipping photographic materials
G	Randomization Alert Form	Provides baseline information for each patient enrolled in the study. Coordinator faxes form to Study Monitor. Study Monitor faxes form to Photograph Reading Center.
H - 1	Baseline Consensus Grading Form - Study Eye	Grading Form sent to Photograph Reading Center along with photographs. Completed by graders at Photograph Reading Center. Completed form is returned to clinical center to be inserted in CRF.
H - 2	Follow-up Visit Grading Form - Study Eye	Grading Form sent to Photograph Reading Center along with photographs. Completed by graders at Photograph Reading Center. Completed form is returned to clinical center to be inserted in CRF.
H - 3	Baseline, Visit 12, Visit 24 Grading Form - Fellow Eye	Grading Form sent to Photograph Reading Center along with photographs. Completed by graders at Photograph Reading Center. Completed form is returned to clinical center to be inserted in CRF.
I	Ocular Adverse Events Form	Report of presence or absence of ocular adverse events at all follow-up visits. Completed by investigator and forwarded to Photograph Reading Center along with photographs. Graders complete Reading Center section. Form is returned to clinical center for further completion by investigator and insertion in CRF.

Exhibit	Name	Description
J - 1	Recommendation for Photographer to Initiate Standardization Procedures	Informs Photograph Reading Center of person who will be submitting photographs for review for standardization.
J - 2	Photographer Prior Standardization Documentation Form	Informs Photograph Reading Center of photographers who have been identified to photograph patients in the study and have been previously certified for other studies. Submitted to Reading Center. Standardization is confirmed by Reading Center. Standardization number is assigned. Form is faxed to Study Monitor and clinical center.
K	Photographer Standardization Checklist	Form to accompany photographs submitted for standardization.
L	MPS DA*s Circles Conversion Table	Table of the diameter and area of each disc area circle on the Disc Area Template.

APPENDIX 9: Laser Treatment Parameters

1. Area of Retina to Receive Laser Treatment

Initial Treatment

The largest light treatment spot plus the 500 μm margins will extend no more than 5,500 μm in diameter. Thus the maximum lesion size is 4,500 μm in diameter. The entire lesion (all CNV, blood and/or blocked fluorescence) will be included in the size of the lesion, all of which will be treated. A transparent overlay will be used to judge the lesion's size. It is placed on the 35 mm frame of the angiogram (made using a 30° fundus camera). The Investigator selects the suitable lens and laser link setting for the laser light application. The edge of the light treatment spot must come no closer than 200 μm to the edge of the optic nerve. Thus CNV closer to the optic nerve than 200 μm may remain untreated.

Retreatment

Subsequent retreatments must use a light spot diameter which will cover any leaking CNV and any blood contiguous to that CNV. If there is more than one leaking area, a spot size will be chosen that will cover all areas.

In the event of a lesion being larger than the largest spot size possible with available contact lenses, the largest spot possible will be used to cover the greatest possible area of the lesion.

2. Laser Parameters and Technique

Laser irradiation will be performed using laser light of 689 ± 3 nm, delivered via a slit lamp, and utilising a suitable lens as specified in the laser manual. The dilated pupillary area must be larger than the size of the aiming beam. One of four ophthalmic diode laser systems (i.e., Coherent Ocular Photoactivation Diode Laser [OPDL] and LaserLink® HS Photoactivation Slit Lamp Laser Delivery Adapter, Opal Photoactivator Laser Console and LaserLink® Adapter, Zeiss Visulas PDT Diode Laser and Visulink Adapter, or Zeiss Visulas 690s laser and VISULINK PDT adapter) designed for this application will be used. The diode laser will be loaned to the Investigator by the Sponsor for the duration of the trial. The exact operating conditions of this laser system are too complex to describe here. Refer to the operator's manual accompanying the laser system for instructions on its use.

3. Table of Light Doses and Treatment Times

Light dose (J/cm^2)	Treatment Time (seconds)
50	83

This calculation is based on $\text{Time} = \text{Light Dose} / \text{Dose Rate}$, where dose rate is 600 mW/cm^2 .

4. Spot Size and Laser Treatment Power

The Investigator defines the lesion and specifies its size as the largest linear dimension in microns (μm). To this diameter is added 1000 μm which then defines the proposed treatment diameter. The actual treatment area can be calculated using ($\pi \times [\text{treatment radius}]^2$). One MPS disc area = 1.775 mm^2 .

The treatment area and the fixed dose rate of 600 mW/cm^2 , define the power required from the laser.

$$\begin{aligned} \text{Power (mW)} &= 600 \times \text{treatment area} = 600 \times 3.14 \times \frac{[\text{spot diameter } (\mu\text{m})]^2}{4} \times 10^{-8} \\ &= 4.71 \times 10^{-6} \times [\text{spot diameter } (\mu\text{m})]^2 \end{aligned}$$

To set the slit-lamp adapter (i.e., Coherent LaserLink[®], or Zeiss VisuLink or VISULINK adapters) to the correct spot size, an allowance must be made for the magnification of the contact lens that is used. Different magnification contact lenses are used to allow the full range of lesion sizes to be treated. Thus, the maximum lesion size that can be treated using a single application of laser light is no longer specified. The largest possible treatable lesion dimension is now defined by the characteristics of the laser system and the contact lens magnification used in the procedure. The following tables give the magnification factor for four contact lenses that may be used, as well as the calculated values of treatment area and required laser power. These values are calculated relative to the spot diameter settings that are available on the slit-lamp adapter. For lesions with a proposed treatment spot size between the settings available on the slit-lamp adapter, the next closest setting should be used.

N.B. The following tables are for the Coherent Ocular Photoactivation Diode Laser (OPDL) only. All other laser systems have an in-built calculation of the energy settings with a feedback system to disable the system if there is a discrepancy between the calculated energy and actual energy being delivered.

TABLE 1: MAINSTER LENS $m = x 1.05$

Lens Type: Ocular Inst. Mainster Lens		Magnification: x 1.05	
Diameter of the area to receive laser treatment (retina)	Laser Link® Adapter Setting	Laser Power (mW)	Energy Setting (J)
420	400	0.8	0.07
630	600	1.9	0.16
840	800	3.3	0.28
1050	1000	5.2	0.43
1260	1200	7.5	0.62
1470	1400	10.2	0.85
1680	1600	13.3	1.11
1890	1800	16.8	1.40
2100	2000	20.8	1.73
2310	2200	25.1	2.09
2520	2400	29.9	2.49
2730	2600	35.1	2.93
2940	2800	40.7	3.39
3150	3000	46.7	3.89
3360	3200	53.2	4.43
3570	3400	60.0	5.00
3780	3600	67.3	5.61
3990	3800	75.0	6.25
4200	4000	83.1	6.92

TABLE 2: GOLDMANN 3 MIRROR OR FUNDUS LENS $m = x 1.08$

Lens Type: Goldmann 3 Mirror or Fundus lens Magnification: x 1.08			
Diameter of the area to receive laser treatment (retina)	Laser Link® Adapter Setting	Laser Power (mW)	Energy Setting (J)
432	400	0.9	0.07
648	600	2.0	0.16
864	800	3.5	0.29
1080	1000	5.5	0.46
1296	1200	7.9	0.66
1512	1400	10.8	0.90
1728	1600	14.1	1.17
1944	1800	17.8	1.48
2160	2000	22.0	1.83
2376	2200	26.6	2.22
2592	2400	31.6	2.64
2808	2600	37.1	3.09
3024	2800	43.1	3.59
3240	3000	49.4	4.12
3456	3200	56.3	4.69
3672	3400	63.5	5.29
3888	3600	71.2	5.93
4104	3800	79.3	6.61
4320	4000	87.9	7.32

TABLE 3: MAINSTER WIDE FIELD LENS m = x 1.5

Lens Type: Ocular Inst. Mainster Wide Field Lens Magnification: x 1.5			
Diameter of the area to receive laser treatment (retina)	Laser Link® Adapter Setting	Laser Power (mW)	Energy Setting (J)
600	400	1.7	0.14
900	600	3.8	0.32
1200	800	6.8	0.57
1500	1000	10.6	0.88
1800	1200	15.3	1.27
2100	1400	20.8	1.73
2400	1600	27.1	2.26
2700	1800	34.3	2.86
3000	2000	42.4	3.53
3300	2200	51.3	4.27
3600	2400	61.0	5.09
3900	2600	71.6	5.97
4200	2800	83.1	6.92
4500	3000	95.4	7.95
4800	3200	108.5	9.04
5100	3400	122.5	10.21
5400	3600	137.3	11.45
5700	3800	153.0	12.75
6000	4000	169.6	14.13

TABLE 4: QUADRASPHERIC LENS m = x 2.01

Lens Type: Volk QuadrAspheric Lens		Magnification: x 2.01	
Diameter of the area to receive laser treatment (retina)	Laser Link® Adapter Setting	Laser Power (mW)	Energy Setting (J)
804	400	3.0	0.25
1206	600	6.9	0.57
1608	800	12.2	1.01
2010	1000	19.0	1.59
2412	1200	27.4	2.28
2814	1400	37.3	3.11
3216	1600	48.7	4.06
3618	1800	61.7	5.14
4020	2000	76.1	6.34
4422	2200	92.1	7.67
4824	2400	109.6	9.13
5226	2600	128.6	10.72
5628	2800	149.2	12.43
6030	3000	171.3	14.27
6432	3200	194.9	16.24

EXAMPLE:

Step 1

Largest linear dimension of the lesion: 2200 μm

Margin: + 1000 μm
 —————
 3200 μm
 =====

Step 2

Select lens to be used, eg. Volk QuadrAspheric Lens.

Step 3

Table 4 shows the diameter of the area to receive laser treatment for the next nearest setting as 3216 μm . The corresponding laser link setting can be chosen: 1600 μm . The power to be used is 48.7 mW.

APPENDIX 10: Investigators

Twenty-two centers will participate in the trial. A separate Photograph Reading Center at the Wilmer Ophthalmological Institute of Johns Hopkins University, School of Medicine will confirm eligibility, interpret fundus photographs and fluorescein angiograms following PDT. This will be done in a masked fashion.

Institution	Principal Investigator	Center #	Study A/B
Klinik für Augenheilkunde der Medizinische Universität zu Lubeck Ratzeburger Allee 160 D23538 Lubeck Germany	Dr. Ursula Schmidt-Erfurth Prof. H. Laqua	1	A
Hopital Ophtalmique Universitaire Jules Gonin Av. de France 15 CH 1004 Lausanne Switzerland	Dr. Leonidas Zografos Dr. Michel Sickenberg	2	B
Hopital Cantonal Universitaire de Geneve Departement d'oto-neuro-ophtalmologie Clinique et Policlinique D'Ophtalmologie Rue Michel-du-Crest 24 1211 Geneve 14 Switzerland	Dr. Constantinos Pournaras	3	B
Hopital Intercommunal de Creteil Department of Ophthalmology 40 Avenue de Verdun 94010 Creteil/Paris France	Dr. Giselle Soubrane	4	A
Instituto de Microcirugia ocular de Barcelona Calle Munner 10 08022 Barcelona Spain	Dr. Jordi Mones Dr. Borja Corcostegui	5	B
Allgemeines Krankenhaus Klinik fuer Augenheilkunde Waehringuer Guertel 18-20 8. Stock 1090 Wien Austria	Dr. Michael Stur	6	A

Institution	Principal Investigator	Center #	Study A/B
Eye Outpatients Aberdeen Royal Infirmary Forester Hill AB 92 ZB Aberdeen Scotland	Dr. John Olson	7	B
St. Paul's Eye Unit Royal Liverpool University Hospital Prescot Street L 78 XP Liverpool England	Dr. Simon P. Harding	8	A
Hôpital Bellevue Service Ophtalmologie 42055 Saint Etienne Cedex 2 France	Dr. Françoise Koenig	9	B
Harvard Medical School Massachusetts Eye & Ear Infirmary Department of Ophthalmology 243 Charles Street Boston, Massachusetts 02114, USA	Dr. Joan W. Miller Dr. Evangelos Gragoudas	10	B
The Wilmer Ophthalmological Institute Maumenee 713 600 N. Wolfe Street Baltimore, MD 21287-9275, USA	Dr. Andrew Schachat Dr. Susan Bressler Dr. Neil Bressler	11	A
Cole Eye Institute Cleveland Clinic Foundation 9500 Euclid Avenue, i-22 Cleveland, Ohio 44195, USA	Dr. Hilel Lewis	12	B
Zweng Memorial Retinal Research Foundation 1225 Crane Street Menlo Park, California 94025, USA	Dr. Mark Blumenkranz	13	A
UBC/VH Eye Care Center 2550 Willow Street Vancouver, BC V5Z 3N9 Canada	Dr. Michael Potter	14	B
Texas Retina Associates Suite 400 7150 Greenville Avenue Dallas, Texas 75231, USA	Dr. Gary Fish Dr. Rajiv Anand	15	A

Institution	Principal Investigator	Center #	Study A/B
Vitreous, Retina, Macula Consultants of New York 519 East 72nd Suite 203 New York, NY 10021, USA	Dr. Jason Slakter	16	B
Retina Associates of Cleveland 26900 Cedar Road, Suite 303 Cleveland, Ohio 44122, USA	Dr. Lawrence Singerman	17	A
Associated Retinal Consultants 632 William Beaumont Medical Building 3535 West 13 Miles Royal Oak Medical Center Michigan 48073, USA	Dr. George Williams	18	A
Toronto Western Medical Bldg. 25 Leonard Avenue, Suite 101 Toronto, Ontario M5T 2R2 Canada	Dr. Patricia Harvey	19	B
Bascom Palmer Eye Institute 900 N.W. 17th Street Miami, Florida 33136. USA	Dr. Philip Rosenfeld	20	B
Retina Northwest Lovejoy Medical Building, Suite 300 2525 N.W. Lovejoy Portland, Oregon 97210. USA	Dr. Colin Ma	21	A
Retina Vitreous Consultants Suite 500 3501 Forbes Ave. Pittsburgh, Pennsylvania 15213. USA	Dr. Louis Lobes	22	B
Photograph Reading Center 550 N. Broadway, Room 949 Baltimore, Maryland 21205-2010, USA	Dr. Susan Bressler Dr. Neil Bressler Kelly Manos		

APPENDIX 11: Sample Informed Consent

Title:

Treatment of AMD with PDT (TAP)

Investigator:

Introduction:

This information is given to you so that you can make an informed decision about whether or not to participate in a human research study. Take as much time as you wish to make your decision about signing the Informed Consent. You have the right to ask questions about any procedures before agreeing to be included in this study.

You have been asked to take part in this study because you have choroidal neovascularization (CNV), that is, growth of new, abnormal blood vessels under the retina. Your CNV is due to age-related macular degeneration (AMD). Your ophthalmologist considers you a candidate for this study because your condition is not considered treatable with standard laser surgery. A total of approximately 540 patients will be enrolled into the study world-wide.

BPD-MA is an experimental drug, activated by light, which is being investigated for use in the treatment of ophthalmic diseases characterized by choroidal neovascularization. This treatment modality, called photodynamic therapy (PDT), has been used experimentally to treat AMD as well as skin cancer and psoriasis (a chronic skin condition). The doses used for these conditions are the same as or higher than the dose that will be used in this study. PDT with BPD-MA has been tested extensively in laboratory animals and in more than 200 humans to date. Nearly 140 patients with CNV have been treated at least once. PDT appears to act primarily by closing blood vessels. Treatment will be given, if needed, every 3 months for 2 years.

In this study, two of every three patients will receive the "real" BPD-MA drug before the laser treatment and one of every three will receive a fake drug (placebo) made up of sugar water. It is important to use a placebo for some patients so that there will be a comparison group to allow your doctors eventually to figure out if patients who receive the real drug have a better outcome than patients who do not (and who heal their condition naturally with natural scar formation). It is important that you are not aware if you receive the real medicine or not. For example, if you know that you received the drug you might be more likely to report certain medical problems that may develop during the next year than if you thought you received the placebo. If you know if you received the real drug you may try harder to read the letter chart when you return. By using a placebo and masking the patient to whether they received the real treatment or not, bias and confounding are minimized. Your doctor and other center staff will also not know which treatment you have received.

All study procedures are the same independent of whether you are assigned to active or placebo treatment.

Description and Explanation of Procedures

The study requires your involvement for a period of 2 years. During these 2 years you will be requested to have a check-up visit at the clinic every 3 months. It is expected that you will have active or dummy PDT treatment at or shortly after each of these 3 monthly check-ups. Therefore you should anticipate between 10 and 18 separate visits to the clinic over the 2 year period.

In order to determine your eligibility for the study, you must have a "baseline" (i.e. before treatment) assessment within 7 days before the first treatment. This baseline assessment includes a physical examination, blood tests, and an electrocardiogram (EKG) which tests the electrical function of your heart. You will be asked about your medical history and current medical conditions. You will be asked to disclose any medicines currently being taken. Your family doctor and/or your treating ophthalmologist will be informed about your participation in the study and might be asked to provide additional information on your health. You will also have an eye examination, visual acuity testing, contrast threshold, and photographs and angiography performed. Angiography is a special test in which a dye is injected into a vein in your arm. The dye travels throughout the body, including the eyes. With a special camera and flash, a series of photographs of the retina is taken as the dye passes through it. The photographs will show where and what kind of changes have occurred in the retina.

On the day of the first and subsequent treatments you will receive a 10 minute intravenous (i.v.) infusion of either BPD-MA (6 mg/m² body surface area) or dextrose in water (placebo infusion). An activating light will be shone into your eye shortly after the infusion. This light, delivered by a laser system, is much lower energy than used in conventional laser surgery and has no effect without BPD-MA in the circulation.

YOU MUST REFRAIN FROM EXPOSING YOUR EYES OR SKIN TO BRIGHT LIGHT FOR AT LEAST 48 HOURS POST-TREATMENT. This includes but is not limited to bright sunlight, tanning salons, halogen lighting in homes and offices, lighting used in dentists' offices or in surgery operating rooms. Dark sunglasses will be provided to you and will be required to be worn for 2 days after the infusion. **USE OF SUNSCREENS WILL NOT BLOCK ANY PHOTOSENSITIVITY REACTION.**

Three months after every treatment, the following procedures will be completed: visual acuity testing, fundus photography and angiography, an eye examination, assessment of any adverse events and concomitant medications, vital signs, and contrast threshold. Depending on the condition of your CNV, you may be retreated with PDT after the angiography test.

Two to four days after any treatment we will call you and ask you whether you experienced any changes in vision in the treated eye or any other problems. If you experienced a severe

drop in your vision we will ask you to come to the clinic for a visual acuity examination and possibly ophthalmoscopy, fluorescein angiography and colour photography of your eye.

Every six months additional blood tests will be carried out. Every twelve months a physical examination and an EKG will be performed.

Risks and Discomforts

PDT has been tested in more than 130 patients/eyes with CNV using different doses. These patients have not complained of any immediate discomfort during or shortly after the PDT.

The most common adverse event reported by patients within a 3 month period following treatment has been headache (8% of patients). All adverse events that were considered related to treatment such as headache, dizziness, injection site rash, low blood pressure have occurred at a low incidence of 4% or less.

PDT is an experimental treatment. Although bad effects on the vision at the dose being used in this study are not apparent it is unknown if multiple PDT treatments over a 2 year period could be more harmful than if no treatment was given.

Discomfort and/or a small risk of adverse events may be caused by placing hypodermic needles in your vein. This procedure is required to administer the study drug or its dummy, for administering the dye in the fluorescein angiography tests and for withdrawal of blood for tests required at intervals of 6 months.

Fluorescein angiography is an extremely safe test, although rare patients may have an important reaction to the dye. About 1/225,000 patients may have such a severe reaction that they can have a heart attack or stroke or even die. Fortunately, most reactions are mild, such as temporary nausea or vomiting in a few patients and a rash, hives or wheezing in about 1%. Your doctors have emergency equipment available to help care for you should you have a reaction.

Avoidance of bright light for 48 hours after each treatment may also be considered a discomfort.

Potential Benefits

The most important benefit of participating in this special program is that if this treatment works and is safe, you will have had a two-thirds chance of receiving it before it becomes generally available. The disease you have is the leading cause of vision loss in older people. Helping to show if this treatment works may help many other people preserve vision around the world.

Alternative Treatments

You are not eligible for standard laser therapy because the nature of the CNV lesion in your eye is such that standard laser therapy may lead to a greater loss of vision than using no treatment.

Other than laser, it may be possible to surgically remove the abnormal blood vessel, but this procedure has important risks and is not proven. Some doctors are testing radiation treatment or various drugs for your condition. There is no treatment that is proven to work. Many patients prefer to have no treatment and simply allow a natural scar to form.

Confidentiality

Information derived from this study will be used for research purposes which may include publication and teaching. Your identity will be kept confidential. The drug's manufacturer, QLT PhotoTherapeutics Inc., and CIBA Vision Ophthalmics Inc., the Institutional Review Board of the investigational site, the United States Food and Drug Administration, and possibly other governmental authorities in the United States and Europe may be given access to your records upon request. They are all required to maintain your confidentiality.

Right to Withdraw

Your participation in this study is entirely voluntary, and you may withdraw from the study at any time even after signing this consent. The quality of care you will receive at this clinic will not be affected in any way if you decide not to participate or if you withdraw from the study. At the discretion of the Investigators or Sponsor of the study, it may be necessary to stop your treatment if significant side effects occur, if the protocol is not being followed, or for administrative or other reasons.

Compensation

In the unlikely event that you should be injured as a direct result of this study, you will be provided with emergency medical treatment. This treatment does not imply any negligence on the part of the clinic or any of the physicians involved. When applicable, the clinic reserves the right to bill third party payers for any emergency services rendered, medical treatment will be paid for in excess of insurance payment, by QLT Phototherapeutics Inc. and CIBA Vision Ophthalmics Inc., for any injury that is directly a result of treatment or study procedure in accordance with the protocol. The clinic does not have any program to provide compensation as a result of any injuries. You should be aware that by agreeing to participate in this study, you are not waiving any of your legal rights.

Right to Ask Questions

You are encouraged to ask any questions you may have about the study or your treatment as a research subject. Further information about any aspect of this study, including concerns about side effects, discomfort or injury, is available now or at any time during the

course of the study from the principal Investigator, or from the study coordinator. You will be informed of any new significant findings which may affect your willingness to participate in the study.

Investigator: Phone:

Study Coordinator: Phone:

Consent:

I am aware that the protocol and this Informed Consent has been reviewed and approved by the recognised Institutional Review Board at _____.

I have read or have had read to me the above pages concerning BPD-MA treatment of choroidal neovascularization. The purpose and procedures of this research project with its possible risks and benefits have been fully and adequately explained to me, and I understand them. My questions have been answered, and I voluntarily agree to participate as a subject in the research project under the conditions described. I have been given a copy of this consent form.

Date Name of Subject Signature of Subject

Date Name of Witness Signature of Witness

Date Name of Investigator Signature of Investigator

APPENDIX 12 - ICG ANGIOGRAPHIC ASSESSMENTS

1. INTRODUCTION/RATIONALE

At the request of many of the investigators participating in Study BPD OCR 002 (TAP), and with the approval of the Study Advisory Group and the sponsors, ICG angiographic examination of patients enrolled in the TAP Study has been added as an exploratory ancillary test. Indocyanine green (ICG) angiography has been demonstrated to provide enhanced imaging of the choroidal circulation versus conventional angiography using sodium fluorescein dye. In addition, better delineation of occult choroidal neovascularization is possible utilizing this imaging system. The objectives of incorporating ICG angiography into the evaluation of patients undergoing photodynamic therapy are as follows:

2. STUDY OBJECTIVES (all are secondary to the TAP study objectives)

- a) To study the effects of photodynamic therapy on the choroidal circulation (including large, medium and small choroidal vessels);
- b) To determine the effects of photodynamic therapy on choroidal neovascularization as identified by ICG angiographic examination;
- c) To determine if the outcome of photodynamic therapy (visual acuity outcome and fluorescein angiographic changes) may correlate with ICG findings;
- d) To determine, in a retrospective manner, if ICG angiographic landmarks can help to explain success or failure in selected patients undergoing PDT therapy (specifically, to determine if areas of occult neovascularization identified only on the ICG study were left untreated by the initial or follow-up treatment, or if areas of retina not involved by neovascularization on the ICG study were treated with photodynamic therapy).
- e) In placebo-treated patients to longitudinally determine ICG angiographic patterns over the course of the 2 year trial.

3. STUDY PLAN

Because ICG angiography is an ancillary study, not included in the original Study protocol, a separate Informed Consent and amended IRB approval is required. A sample Informed Consent which can be used and amended as needed at different institutions is attached (Exhibit 12.1). Any center wishing to participate in this ancillary study must supply the IRB letter of approval for this amendment together with the IRB-approved Informed consent to the sponsor.

ICG angiography will be performed at baseline, 3 months, 1 year and 2 years after treatment. ICGs must be performed at least 24 hours before any PDT/placebo treatment. If performed on the same day as the study's fluorescein angiogram, the ICG always will be performed after the fluorescein angiogram. The treating ophthalmologist will not look at any of the ICG images until completion of the TAP investigation so that the ophthalmologist cannot be biased in any way by the ICG findings when determining the management of the patient.

ICG angiography may be performed with one of two systems:

- a) Topcon, or
- b) the Heidelberg Retinal Angiograph (HRA), a scanning ophthalmoscope with confocal mode.

The protocols for obtaining ICG angiograms using the Topcon system and the HRA and 12.3 respectively. scanning laser ophthalmoscope are described in Exhibits 12.2

4. STUDY POPULATION

Patients enrolled in any of the North American or European centers of the BPD OCR 002 clinical study (TAP Study) are eligible to be included in this evaluation. Patients must sign an additional informed consent to participate in this evaluation.

4.1 Exclusion Criteria

Patients with a documented history of allergies to iodides or shellfish.

If a patient develops an allergy to ICG during the follow-up phase, they must be excluded from the follow-up ICG angiographic assessments.

5. STATISTICAL DESIGN AND ANALYSIS

Since this is an exploratory evaluation, statistical analysis of the ICG angiographic interpretation is not planned. A committee of TAP investigators chaired by Dr. Jason Slakter will be responsible for the reading, interpretation and reporting of the angiographic data. The sponsor will conduct comparisons of safety and primary efficacy parameters between the total patient population and the subgroup of patients who had ICG angiographic assessments conducted after randomization into the main study (BPD OCR 002).

6. DATA STORAGE

Data will be stored on optical discs, CD ROM or Zip Drive at the treating center. Data describing which protocol was used, etc., will be recorded on the Photograph Data Form (Exhibit 12.4). The data will be archived centrally on completion of the study at a location to be determined.

EXHIBIT 12.1

Sample Informed Consent ICG Angiography

Purpose of Test

Indocyanine green (ICG) angiography is a form of imaging that gives different information about the choroidal circulation (the vascular circulation beneath the retina) than is possible with conventional fluorescein angiography. By performing this diagnostic test in patients participating in the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) investigation, undergoing photodynamic therapy, we hope to learn more about the response of the retina to treatment, specifically, the response of the choroidal circulation and choroidal neovascularization (the abnormal blood vessels growing beneath the retina) to this form of therapy. This test will be used strictly as a means to better understand the nature of the eye and its response to this treatment, and will not be used in any way for determining your course of treatment, specifically, your eligibility for participating in the study or your need for additional treatment in the future.

Procedure

The ICG angiographic procedure is much like the fluorescein angiogram that you will receive as part of the photodynamic therapy study. You will receive an intravenous injection of indocyanine green dye after which photographs will be taken on a computer-based imaging system. The entire course of the ICG study is approximately 35-40 minutes per test. The test will be performed at your first visit (prior to random assignment in the TAP investigation if this visit has not been completed yet), at three months into the study following initial treatment, one year and two years following initial treatment. The test will be performed on the same day as your other examinations and will not require an additional visit to the office. It can be performed immediately following the fluorescein angiographic examination and should not add significantly to the time needed in the office for participation in the TAP investigation.

Risks

Indocyanine green dye has been utilized as a diagnostic test for over 20 years both in the area of ophthalmology as well as in cardiology. In the course of that time, it has been demonstrated to have fewer side-effects than are exhibited by fluorescein angiography, a test which will be performed as part of the TAP investigation. Patients do occasionally experience mild nausea with the injection. In addition, extravasation of dye (leakage of dye) from a vein can occur causing a slight skin discoloration. This resolves spontaneously without additional therapy. More severe reactions in patients who may be allergic to the dye are possible including allergic phenomenon such as itching, rash or hives. In addition, extremely rarely a patient with severe allergy to this chemical might experience an anaphylactic reaction resulting in heart or respiratory failure, coma or even death.

Alternatives

Your decision to undergo ICG angiography in no way affects your participation in the TAP investigation. The information obtained in this test will be kept in strict confidence along with all of the other material related to this protocol. You have the right to withdraw from undergoing ICG angiography at any time and it will not affect your participation in the photodynamic therapy trial or affect any other care that you are receiving by your doctors. For problems, questions or more information relating to this test, you can contact the principal investigator at your study center or Dr. Jason S. Slakter, Chairman of the ICG Angiography Ancillary Study Committee at (212) 861-9797.

Costs

There is no cost or payment obligation related to this procedure.

EXHIBIT 12.2

ICG Ancillary Study Photographic Protocol for the Topcon System

12.2.1 ICG Injection

Indocyanine green (Cardiogreen, Mynson Wescott and Dunning, Inc., Baltimore, MD) will be dissolved in the manufacturer's supplied aqueous solvent to a concentration of 2 mL of solvent per 25 mg of ICG. All 25 mg of ICG is then injected into an antecubital vein with a 19 or 21 gauge Butterfly infusion set at a rate of approximately 1 cc per second.

If the patient is poorly dilated or darkly pigmented there should be an increase in the amount of dye use-up to 50 mg. of the dye. The amount of dye given should be marked accordingly on the Transfer Disk and Photograph Data Form (Exhibit 12.4).

12.2.2 Guidelines for Performing ICG Videoangiography (ICG-V)

A 50 degree angle will be used for all photographs in the ICG-V except as indicated at 3 and 10 minutes. The field should include the whole optic disc and the macula.

For the green free photograph (deep red) a 640 filter is attached to the filter wheel of the camera. The illumination of the photograph is done by using the illumination light only—no flash.

For the preinjection photo, the exciter and barrier filters should be in place with the gain and flash set to the maximum.

The flash on the Topcon TRC-50IA Camera should then be set at 300 watt•seconds (the highest setting) and the gain on the Kodak Mega Plus control unit should be set at +18 dB.

The timer is started when the ICG injection has begun. Rapid sequence photographs (1 per second) are taken beginning 8-10 seconds after the injection. These filling phase photographs should be taken even before images appear on the alignment monitor.

When the first image of the retinal/choroidal filling is clearly seen on the high resolution monitor, the gain on the Kodak Control Unit should be lowered one step with each of the next four photographs. By turning down the gain on the Kodak Control Unit (+18 dB +12 dB +6 dB 0 dB) one compensates for the increased fluorescence of the retinal/choroidal filling and enables you to take rapid early phase angiograms evenly exposed.

For the rest of the study, the exposure of the photographs should be first adjusted by the flash control on the Topcon 50 IA camera and then by increasing the gain on the Kodak Control Unit. Remember the lower the gain, the higher the resolution.

Images should be saved in their original form with no modifications or enhancements performed.

12.2.3 ICG-V Angiography Sequence

Steps

1. Red Free Stereo Pair of Study Eye
2. Green Free of Study Eye
3. Preinjection image of Study Eye
4. Red Free of Fellow Eye
5. Filling Phase of Study Eye
6. 1 min. Photo of Study Eye
7. 1 min. Photo of Fellow Eye
8. 3 min. stereo pair of Study Eye
9. 3 min. stereo pair of Study Eye - 35°
10. 3 min. stereo pair of Fellow Eye - 35°
11. 3 min. stereo pair of Fellow Eye
12. 5-7 min. photo of Study Eye
13. 5-7 min. photo of Fellow Eye
14. 10-13 min. stereo pair of Study Eye
15. 10-13 min. photo of Study Eye - 35°
16. 10-13 min. photo of Fellow Eye - 35°
17. 10-13 min. stereo pair of Fellow Eye
18. 25-40 min. photo of Study Eye—Late Phase*
19. 25-40 min. photo of Fellow Eye—late Phase*

This is the minimum number of photographs required for the protocol. Please feel free to add stereo pairs or even additional fields that you think would be helpful in the interpretation of the angiogram.

* The late phase photograph is when the dye has left the retinal circulation.

ICG Ancillary Study
Photographic Protocol for the Topcon System

1	2	3	4
Red Free Study Eye Stereo	Pair	Green Free Study Eye	Preinjection photo of Study Eye
5	6	7	8
Red Free Fellow Eye	Filling Phase Study Eye		
9	10	11	12
Filling Phase Study Eye		1 min. Study Eye	1 min. Fellow Eye
13	14	15	16
3 min. Study Eye Stereo	Pair	3 min. Study Eye Stereo 35°	Pair 35°

ICG Ancillary Study
Photographic Protocol for the Topcon System

17 3 min. Fellow Eye Stereo 35°	18 Pair 35°	19 3 min. Fellow Eye Stereo 50°	20 Pair
21 5-7 min. Study Eye	22 5-7 min. Fellow Eye	23 10-13 min. Study Eye Stereo	24 Pair
25 10-13 min. Study Eye 35°	26 10-13 min. Fellow Eye 35°	27 10-13 min. Fellow Eye Stereo	28 Pair
29 25-40 min. Study Eye (Late phase) Stereo	30 Pair	31 25-40 min. Fellow Eye (Late phase) Stereo	32 Pair

EXHIBIT 12.3

ICG Ancillary Study Angiography using the Heidelberg Retina Angiograph (HRA)

Additional information compared to the Topcon system:

- confocal series
- He-/Ne- ophthalmoscopy
- Infrared imaging

12.3.1 ICG Injection Procedure:

- dilute 40 mg of ICG (Cardio Green, Hynson, Westcott & Dunning, Cockeysville, MD) with aqueous solvent to a final volume of 5 ml.
- inject all 40 mg. ICG into cubital vein over 15-20 seconds
- flush with 5 ml of saline

12.3.2 Ophthalmoscopy without ICG:

Take one set of pictures of both maculae at 20° and 30°

- using the He-/Ne- wavelength
- using the infrared wavelength

12.3.3 ICG angiography:

- all single frames should be taken at 30 o (rate 10 images/sec.)
- timing:

early phase: 8-10 pictures during the first min.(AMD eye)

mid phase: at 1 min. post inj. take one confocal series (rate 20 images/sec.) at 4 mm scan depth use 20° frames for lesions smaller than 3 DA at 2 min. one frame of AMD and fellow eye.

late phase: take pictures at 3, 5, 10 and 20 min. post inj. at 20 min. one frame of fellow eye.

EXHIBIT 12.4

**ICG Ancillary Study
Photograph Data Form**

A. Patient Information

Center No. _____

Patient ID# _____

Visit: _____

B. System Used (circle one)

TOPCON

SLO

C. Photography:

Please circle one:

Study Eye: OD/OS

Fellow Eye: OD/OS

Data Storage: Optical disk/CD ROM/Zip Drive

Date of ICG Angiogram

_____ Date

_____ Month

_____ Year

Amount of ICG Dye Given: _____ mg

Complications:

Photographer's Name: _____

APPENDIX 13 - QUALITY OF LIFE
ASSESSING THE HEALTH-RELATED QUALITY-OF-LIFE IMPACT OF
PHOTODYNAMIC THERAPY WITH LIPOSOMAL BENZOPORPHYRIN DERIVATIVE
MONOACID RING A IN A PHASE 3 STUDY (TAP) OF
AGE-RELATED MACULAR DEGENERATION

1. INTRODUCTION

This is an exploratory study which is designed to assess the health-related quality of life (HQL) of individuals with age-related macular degeneration (AMD) participating in an on-going Phase 3 clinical study (Study BPD OCR 002) of photodynamic therapy (PDT) with Liposomal Benzoporphyrin Derivative Monoacid Ring A (BPD-MA verteporfin). While the primary objective of this HQL study is to evaluate the impact of PDT treatment relative to placebo, this study also provides an opportunity to estimate the HQL burden of AMD.

2. RATIONALE

AMD is a progressive disease that results in the loss of central vision. Central vision loss impairs performance of near-vision activities, such as reading, writing, and discriminating colors. In a study of 100 patients with AMD and a visual acuity of 20/100 or worse in at least one eye, Alexander et al. demonstrated significant associations between lower levels of visual acuity and performance on vision-related tasks such as the ability to read titles from a large print *Reader's Digest* and to tell time at a distance of 1.5 meters.¹ The impact of vision loss on overall HQL, however, has not been documented for AMD. HQL is defined in this study as the impact of a disease or its treatment on an individual's usual or expected physical, mental, and social well-being.

QLT PhotoTherapeutics Inc. and Ciba Vision Ophthalmics are co-developing a treatment for AMD, namely PDT with BPD-MA verteporfin that is being evaluated in Clinical Study Protocol BPD OCR 002. The study will enroll approximately 540 patients from at least 11 North American and 9 European centers to obtain 450 evaluable patients. Patients will be randomized to PDT treatment or placebo treatment in a ratio of 2 to 1 and followed for 24 months.

This study provides an opportunity to assess the HQL impact of PDT treatment relative to placebo. This study also provides an opportunity to document the HQL burden of AMD. Baseline HQL assessments will provide estimates of the cross-sectional HQL profile of AMD. Relationships between visual acuity and HQL will enhance our understanding of the impact of visual function on patients' everyday functioning, activities, and feelings.

3. STUDY OBJECTIVES (These objectives are secondary to those of the main BPD OCR 002 Study)

Primary

To assess the HQL impact of PDT treatment relative to placebo (sham treatment) among patients with subfoveal choroidal neovascularization (CNV) secondary to AMD using the National Eye Institute's Visual Functioning Questionnaire-25.

Secondary

To assess the HQL burden of AMD using the National Eye Institute's Visual Functioning Questionnaire-25.*

4. STUDY PLAN

English-speaking patients will be asked to participate in a 10- to 15-minute telephone interview at the time of enrollment in the BPD OCR 002 clinical study and again at months 3, 6, 12, 18, and 24. Specifically, patients will be called at their homes within 1 week prior to randomization and within 2 weeks after the 3-, 6-, 12-, 18-, and 24-month clinical visits. During the interview, patients will be asked to respond to 30 structured questions about multiple areas of HQL (see below: Health-Related Quality-of-Life Assessments).

5. PROCEDURES AND RESPONSIBILITIES

At the initial enrollment visit the study coordinator of the treating center must provide patients with an institutional review board (IRB)-approved informed consent form applicable to the HQL study (Exhibit 13.1 is an example that may be used). Before inclusion in the HQL assessment patients must have had an opportunity to ask the investigator questions about the assessment and must have signed the HQL study informed consent.

The telephone interviews will be conducted by trained staff of Covance Health Economics and Outcomes Services Inc. This consultancy group has also been contracted to manage and analyze the resultant data.

Once a patient has agreed to participate in the HQL assessment the study coordinator at the treating center will immediately fax an Initial HQL Interview Alert form (Exhibit 13.2) to Covance with details of the patients initials, home telephone number, suggested time(s) for contacting the patient and anticipated date of randomization. Covance will call the patient at their home and conduct the initial interview prior to randomization (first treatment). Patients who agree to the initial or follow-up interview may withdraw consent during the interview if they wish. Their medical treatment will not be affected in any way by withdrawal or failure to participate in the interview.

* ©RAND 1996

At subsequent visits, it is the responsibility of the study coordinator at participating treating centers to fax Covance a Follow-up HQL Interview Alert form (Exhibit 13.3) to ensure that an interview is conducted by Covance within 2 weeks after retreatments (if applicable) at relevant follow-up visits described above.

Covance will also track the patients included in the HQL assessment so that if a Follow-up Alert form for any patient does not arrive by a preset time Covance will contact the responsible treating center study coordinator to determine if the patient is still in the study and, if yes, to coordinate the timing of the follow up interview.

Telephone numbers and names used by the interviewer will be held in confidence and destroyed by Covance after the study is completed.

6. STUDY POPULATION

English-speaking patients enrolled in the North American and UK centers of the BPD OCR 002 clinical study are eligible for this HQL study. Therefore, patients must have clinical signs of CNV secondary to AMD and meet all inclusion and exclusion criteria defined in Protocol BPD OCR 002. Since Study BPD OCR 002 is in progress, this study will be comprised only of the subset of patients enrolled in the North American and UK centers on or following the start date of the HQL study at each center. The anticipated size of this subset is 150 to 200 patients.

7. HEALTH-RELATED QUALITY-OF-LIFE ASSESSMENTS

The HQL interview (Exhibit 13.4) consists of the National Eye Institute's (NEI) Visual Functioning Questionnaire-25 (VFQ-25), plus three near-vision questions recommended by the NEI for AMD studies, and two near-vision questions developed specifically for this study. In sum, the interview consists of 30 questions and is expected to last 10 to 15 minutes.

The VFQ-25 was developed as a vision-specific HQL measure relevant to multiple eye conditions. The questions were generated from focus groups among persons with cataract, AMD, glaucoma, diabetic retinopathy, and CMV retinitis. It consists of 25 questions that can be combined into an overall score and 12 subscale scores: general health, general vision, ocular pain, near-vision activities, distance-vision activities, driving, color-vision, peripheral-vision, and vision-specific social function, mental health, role difficulties, and dependency. Scores range from 0 to 100, where 100 represents optimal HQL.

As mentioned above, the near-vision activities subscale was expanded for this study. The three NEI-recommended additional near-vision questions assess degree of difficulty with reading small print, reading bills, and cosmetic activities (shaving, fixing hair, etc.). The additional two questions developed for this study assess difficulty with writing and recreational activities, such as board games or cards.

The VFQ-25 was tested as an interviewer-administered survey among 484 patients with chronic eye conditions and 118 reference group participants with no chronic eye disease.² Internal consistency reliability estimates (Cronbach's alpha) for the subscale and overall scores exceeded 0.70, a level considered appropriate for using a measure in group comparisons.³ VFQ-25 scores for 85 patients with AMD were significantly lower (poorer) than those for the reference group participants except for two subscales, general health and ocular pain. Mean (sd) overall VFQ-25 scores were 68 (20) and 92 (7) for the AMD and reference groups, respectively.

8. STATISTICAL DESIGN AND ANALYSIS

Analyses will be performed on all patients with baseline and at least one follow-up HQL assessment. The sociodemographic and visual acuity characteristics of these patients will be compared to those from all patients in Study BPD OCR 002. Further, sociodemographic data will be summarized and tested for treatment group comparability using appropriate statistical methods.

Responses to VFQ-25 questions will be combined into subscale and overall scores according to the NEI's algorithms. Descriptive statistics (means, standard deviations, ranges) will be computed for scale scores at each assessment. All statistical tests will be two-sided and assessed at the 0.05 significance level.

Primary Objective: To assess the HQL impact of PDT treatment relative to placebo.

Mean HQL change scores from baseline will be computed by treatment group. Change scores will be computed as the HQL score less the baseline score at each time point. The null hypothesis of no change will be assessed by t-tests within each treatment group.

HQL treatment effects across groups will be evaluated using Analysis of Covariance (ANCOVA) models. Each HQL scale change score will be modeled as a function of treatment group, baseline HQL score, study center, and baseline visual acuity. When appropriate, sociodemographic and additional baseline clinical indicators may be included as covariates. Similarly, a repeated measures ANCOVA will be applied to assess trends in treatment effects over time.

Secondary Objective: To assess the HQL burden of AMD using the VFQ-25.

To compare the HQL burden of AMD to other eye conditions, mean baseline VFQ-25 scores for study patients will be compared to those reported by patients with other chronic eye diseases.² To assess how well the VFQ-25 measures the HQL burden of AMD, psychometric statistics will be evaluated. First, the percent of patients scoring at the lowest and highest possible levels at baseline will be computed for each scale score to identify potential floor and ceiling effects. Specifically, patients reporting scores at the lowest level of a scale (floor) can not demonstrate declines in HQL on that scale. Conversely, patients reporting scores at the highest level (ceiling), can not demonstrate

improvements. Second, internal consistency reliability of baseline scale scores will be assessed using Cronbach's alpha. Finally, mean baseline VFQ-25 scores will be compared across visual acuity levels using Analysis of Variance (ANOVA) models to evaluate the cross-sectional relationship between visual acuity and HQL.

9. REFERENCES

Alexander M.F., Maguire M.G., Lietman T.M, et al. "Assessment of visual function in patients with age-related macular degeneration and low visual acuity," *Arch Ophthalmol* 1988; 106:1543-1547.

Mangione CM. "NEI VFQ-25 Scoring Algorithm (2/21/97)," Draft preprint version available from Carol Mangione, MD, UCLA Division of General Internal Medicine.

Nunnally JC. *Psychometric Theory*. New York: McGraw-Hill Book Company, 1978.

Exhibit 13.1

Sample Informed Consent

TITLE: Treatment of AMD with PDT (TAP):Health-Related Quality-of-Life

INVESTIGATORS:

DESCRIPTION AND EXPLANATION OF PROCEDURES:

You are invited to participate in a study of health-related quality of life issues in patients with macular degeneration. The study will assess factors, including general health and vision, difficulty with activities and responses to vision problems.

You will be asked to participate in a 10- to 15- minute telephone interview at the time of your enrollment in the TAP clinical study and again at months 3, 6, 12, 18, and 24. If you prefer not to answer a question for any reason whatsoever, you may simply tell the interviewer and go on to the next question.

Initially, you will be called at your home at a time agreed to by you within one week before randomization into the study. Next you will be called at your home at a time agreed to by you within two weeks after each of the 3, 6, 12, 18, and 24 month follow-up visits. The total number of telephone contacts will be 6.

During the telephone interview, you will be asked to answer 30 questions about areas of health-related quality of life. We expect this to take from 10 to 15 minutes. No questions of a personal or sensitive nature (for example, related to sexual behaviour, suicide or illicit activities) are included in the questionnaire.

POTENTIAL BENEFITS:

Although we do not expect you to benefit directly from this study, we may learn about the impact of PDT treatment on the quality of life for those with AMD as well as the impact of AMD itself on the quality of life. This knowledge may be of help for others in the future.

CONFIDENTIALITY:

Information derived from this study may be used for research purposes which may include publication and teaching. Your identity will be kept confidential. In any report or papers from the study, no one will be identified by name. The answers you give us via the telephone interview and analyzed by statisticians will be kept separate from information that identifies you.

RIGHT TO WITHDRAW:

Your participation in this study is entirely voluntary, and you may withdraw from this study even after signing the consent. The quality of the care you will receive at the (name of institution) will not be affected in any way if you decide not to participate or if you withdraw from this study.

RIGHT TO ASK QUESTIONS:

You are free to ask questions about this study or your treatment as a research subject. Further information about any aspect of this study is available now, or at any time during the course of the study from the principal investigator, (name/number of investigator) Additionally, you may contact (name/number senior institutional Research Administrator) if you have any questions or concerns about your treatment as a research subject.

THE PURPOSE AND PROCEDURES OF THIS RESEARCH PROJECT HAVE BEEN FULLY EXPLAINED TO ME, AND I UNDERSTAND THEM. I VOLUNTARILY AGREE TO PARTICIPATE AS A SUBJECT IN THIS RESEARCH PROJECT, AND UNDERSTAND THAT BY SIGNING THIS CONSENT FORM, I AM INDICATING THAT AGREEMENT. I HAVE BEEN GIVEN A COPY OF THIS CONSENT FORM.

_____	_____	_____
Date	Name of Subject	Signature of Subject
_____	_____	_____
Date	Name of Witness	Signature of Witness
_____	_____	_____
Date	Name of Investigator	Signature of Investigator

Exhibit 13.2

INITIAL HQL INTERVIEW ALERT

Fax to: <i>Paola Murphy</i>	Fax from:
Location: <i>Covance Clinical & Periapproval Services, One Radnor Corporate Center, Radnor, PA 19087</i>	Center Code:
Fax No.: (610) 687-4344	Telephone No.
Telephone No.: (610) 975-5326	

Clinical Center:

Principal Investigator:

Patient Date of Birth:

(Use alpha characters for month, e.g. 3 MAR 97)

Patient Initials: _____

Patient's First Name: _____

PROPOSED RANDOMIZATION

Date:

(Use alpha characters for month, e.g. 3 MAR 97)

Home Telephone No.:

Best contact dates/times:

Date	Time(s)

Exhibit 13.3

FOLLOW-UP HQL INTERVIEW ALERT

Fax to: <i>Paola Murphy</i>	Fax from:
Location: <i>Covance Clinical & Periapproval Services, One Radnor Corporate Center, Radnor, PA 19087</i>	Center Code:
Fax No.: (610) 687-4344	Telephone No.
Telephone No.: (610) 975-5326	

Clinical Center:

Principal Investigator:

Patient No.:

Patient Initials: _____

Follow-up visit: Month

Date:

(Use alpha characters for month, e.g. 3 MAR 97)

Home Telephone No.:

Best contact dates/times:

Date

Time(s)

Exhibit 13.4

Health-Related Quality-of-Life Interview

Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible.

Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

PART 1 - GENERAL HEALTH AND VISION

In general, would you say your overall health is:

READ CATEGORIES:

Excellent 1
Very Good 2
Good 3
Fair 4
Poor 5

At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

READ CATEGORIES:

Excellent 1
Good 2
Fair 3
Poor 4
Very Poor 5
Completely Blind 6

How much of the time do you worry about your eyesight?

READ CATEGORIES:

None of the time 1
A little of the time 2
Some of the time 3
Most of the time 4
All of the time 5

How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

READ CATEGORIES:

None 1
Mild 2
Moderate 3
Severe, or 4

Very severe? 5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

How much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?

(READ CATEGORIES AS NEED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

Because of your eyesight, how much difficulty do you have writing checks or filling out forms?

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools?

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

Because of your eyesight, how much difficulty do you have doing recreational activities that require you to see well up close, such as board games or cards?

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

How much difficulty do you have reading street signs or the names of stores?

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(READ CATEGORIES AS NEEDED)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

Yes 1 Skip To Q 20C

No 2

20a. IF NO, ASK: Have you never driven a car or have you given up driving?

Never drove 1 Skip To Part 3, Q 22

Gave up 2

20b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

Mainly eyesight 1 Skip To Part 3, Q22

Mainly other reasons 2 Skip To Part 3, Q22

Both eyesight and other reasons 3 Skip To Part 3, Q22

20c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

No difficulty at all 1

A little difficulty 2

Moderate difficulty 3

Extreme difficulty 4

How much difficulty do you have driving at night? Would you say you have:
(READ CATEGORIES AS NEEDED)

No difficulty at all 1

A little difficulty 2

Moderate difficulty 3

Extreme difficulty 4

Have you stopped doing this because
of your eyesight 5

Have you stopped doing this for other reasons or
are you not interested in doing this 6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

READ CATEGORIES:	All of the time	of Most of the time	Some of the time	A little of the time	None of the time
<u>Do you accomplish less</u> than you would like because of your vision?	1	2	3	4	5
<u>Are you limited</u> in how long you can work or do other activities because of your vision?	1	2	3	4	5
How much does pain or discomfort <u>in or around your eyes</u> , for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

	(Circle One On Each Line)				
	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
I <u>stay home most of the time</u> because of my eyesight.	1	2	3	4	5
I feel <u>frustrated</u> a lot of the time because of my eyesight.	1	2	3	4	5
I have <u>much less control</u> over what I do, because of my eyesight.	1	2	3	4	5
Because of my eyesight, I have to <u>rely too much on what other people tell me</u> .	1	2	3	4	5
I <u>need a lot of help</u> from others because of my eyesight.	1	2	3	4	5
I worry about <u>doing things that will embarrass myself or others</u> , because of my eyesight.	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Items	Item Source	Copyright	Copyright Date
1-5, 9, 11, 13-30	NEI VFQ-25	Rand	1996
6, 7, 12	NEI VFQ Optional Additional Questions	Rand	1996
8, 10	Developed for this study		

APPENDIX 14

INFORMED CONSENT FOR PATIENTS WHO REFUSE THERMAL LASER FOR CHOROIDAL NEOVASCULAR LESIONS IN WHICH THERMAL LASER HAS BEEN SHOWN TO BE BENEFICIAL COMPARED TO NO TREATMENT

Title:

Treatment of AMD with PDT (TAP)

Investigator:

Introduction:

This information is given to you so that you can make an informed decision about whether or not to participate in a human research study. Take as much time as you wish to make your decision about signing the Informed Consent. You have the right to ask questions about any procedures before agreeing to be included in this study.

You have been asked to take part in this study because you have choroidal neovascularization (CNV), that is, growth of new, abnormal blood vessels under the retina. Your CNV is due to age-related macular degeneration (AMD). ***Thermal (heat) laser treatment (called laser photocoagulation) is recommended for your condition. If you have this photocoagulation, the thermal laser treatment will immediately cause a reduction in vision corresponding to the area that receives this thermal laser. This laser treatment is considered beneficial compared to no treatment at all because, for most patients like you, the amount of destruction that occurs by leaving these blood vessels untreated eventually (after about 1 year), becomes greater than the amount caused by the laser. You have told your eye doctor that you understand the risks and benefits of thermal laser photocoagulation compared with no treatment for your eye condition and that you do not want to have this thermal laser treatment.***

Recent research has suggested that a special kind of non-thermal laser treatment called photodynamic therapy may lead to less damage in the retina than no treatment without causing an immediate reduction in vision as would occur with thermal laser photocoagulation. Your ophthalmologist considers that you are a candidate for this study because you do not want to have thermal laser treatment for your abnormal blood vessels.

BPD-MA is an experimental drug, activated by light, which is being investigated for use in the treatment of ophthalmic diseases characterized by choroidal neovascularization. This treatment modality, called photodynamic therapy (PDT), has been used experimentally to treat AMD as well as skin cancer and psoriasis (a chronic skin condition). The doses used for these conditions are the same as or higher than the dose that will be used in this study. PDT with BPD-MA has been tested extensively in laboratory animals and in more than 200 humans to date. Nearly 140 patients with CNV have been treated at least once. PDT

appears to act primarily by closing blood vessels. Treatment will be given, if needed, every 3 months for 2 years.

In this study, two of every three patients will receive the "real" BPD-MA drug before the laser treatment and one of every three will receive a fake drug (placebo) made up of sugar water.

It is important to use a placebo for some patients so that there will be a comparison group to allow your doctors eventually to figure out if patients who receive the real drug have a better outcome than patients who do not (and who heal their condition naturally with natural scar formation). It is important that you are not aware if you receive the real medicine or not.

For example, if you know that you received the drug you might be more likely to report certain medical problems that may develop during the next year than if you thought you received the placebo. If you know if you received the real drug you may try harder to read the letter chart when you return. By using a placebo and masking the patient to whether they received the real treatment or not, bias and confounding are minimized. Your doctor and other center staff will also not know which treatment you have received.

All study procedures are the same independent of whether you are assigned to active or placebo treatment.

Description and Explanation of Procedures

The study requires your involvement for a period of 2 years. During these 2 years you will be requested to have a check-up visit at the clinic every 3 months. It is expected that you will have active or dummy PDT treatment at or shortly after each of these 3 monthly check-ups. Therefore you should anticipate between 10 and 18 separate visits to the clinic over the 2 year period.

In order to determine your eligibility for the study, you must have a "baseline" (i.e. before treatment) assessment within 7 days before the first treatment. This baseline assessment includes a physical examination, blood tests, and an electrocardiogram (EKG) which tests the electrical function of your heart. You will be asked about your medical history and current medical conditions. You will be asked to disclose any medicines currently being taken. Your family doctor and/or your treating ophthalmologist will be informed about your participation in the study and might be asked to provide additional information on your health. You will also have an eye examination, visual acuity testing, contrast threshold, and photographs and angiography performed. Angiography is a special test in which a dye is injected into a vein in your arm. The dye travels throughout the body, including the eyes. With a special camera and flash, a series of photographs of the retina is taken as the dye passes through it. The photographs will show where and what kind of changes have occurred in the retina.

On the day of the first and subsequent treatments you will receive a 10 minute intravenous (i.v.) infusion of either BPD-MA (6 mg/m^2 body surface area) or dextrose in water (placebo infusion). An activating light will be shone into your eye shortly after the infusion. This light, delivered by a laser system, is much lower energy than used in conventional laser surgery and has no effect without BPD-MA in the circulation.

YOU MUST REFRAIN FROM EXPOSING YOUR EYES OR SKIN TO BRIGHT LIGHT FOR AT LEAST 48 HOURS POST-TREATMENT. This includes but is not limited to bright sunlight, tanning salons, halogen lighting in homes and offices, lighting used in dentists' offices or in surgery operating rooms. Dark sunglasses will be provided to you and will be required to be worn for 2 days after the infusion. USE OF SUNSCREENS WILL NOT BLOCK ANY PHOTOSENSITIVITY REACTION.

Three months after every treatment, the following procedures will be completed: visual acuity testing, fundus photography and angiography, an eye examination, assessment of any adverse events and concomitant medications, vital signs, and contrast threshold. Depending on the condition of your CNV, you may be retreated with PDT after the angiography test.

Two to four days after any treatment we will call you and ask you whether you experienced any changes in vision in the treated eye or any other problems. If you experienced a severe drop in your vision we will ask you to come to the clinic for a visual acuity examination and possibly ophthalmoscopy, fluorescein angiography and colour photography of your eye.

Every six months additional blood tests will be carried out. Every twelve months a physical examination and an EKG will be performed.

Risks and Discomforts

If you are assigned randomly to placebo, the amount of damage to your vision over the next several years may be greater than if standard thermal laser treatment were used. PDT is an experimental treatment. Although harmful effects on the vision at the dose being used in this study have not been apparent, it is not known if multiple PDT treatments over a 2-year period could be more harmful than if no treatment was given or if standard thermal laser treatment were given.

PDT has been tested in more than 130 patients/eyes with CNV using different doses. These patients have not complained of any immediate discomfort during or shortly after the PDT.

The most common adverse event reported by patients within a 3 month period following treatment has been headache (8% of patients). All adverse events that were considered related to treatment such as headache, dizziness, injection site rash, low blood pressure have occurred at a low incidence of 4% or less.

Discomfort and/or a small risk of adverse events may be caused by placing hypodermic needles in your vein. This procedure is required to administer the study drug or its dummy, for administering the dye in the fluorescein angiography tests and for withdrawal of blood for tests required at intervals of 6 months.

Fluorescein angiography is an extremely safe test, although rare patients may have an important reaction to the dye. About 1/225,000 patients may have such a severe reaction that they can have a heart attack or stroke or even die. Fortunately, most reactions are mild, such as temporary nausea or vomiting in a few patients and a rash, hives or wheezing in about 1%. Your doctors have emergency equipment available to help care for you should you have a reaction.

Avoidance of bright light for 48 hours after each treatment may also be considered a discomfort.

Potential Benefits

The most important benefit of participating in this special program is that if this treatment works and is safe, you will have had a two-thirds chance of receiving it before it becomes generally available. The disease you have is the leading cause of vision loss in older people. Helping to show if this treatment works may help many other people preserve vision around the world.

Alternative Treatments

You are eligible for standard thermal laser treatment; if you are assigned randomly to placebo, the amount of damage to your vision over the next several years may be greater than if standard thermal laser treatment were used. If you choose not to participate in this investigation, you and your ophthalmologist will discuss your further care which may include reconsideration of thermal laser treatment now or in the future.

Other than laser, it may be possible to surgically remove the abnormal blood vessel, but this procedure has important risks and is not proven. Some doctors are testing radiation treatment or various drugs for your condition. There is no treatment that is proven to work. Many patients prefer to have no treatment and simply allow a natural scar to form.

Confidentiality

Information derived from this study will be used for research purposes which may include publication and teaching. Your identity will be kept confidential. The drug's manufacturer, QLT PhotoTherapeutics Inc., and CIBA Vision Ophthalmics Inc., the Institutional Review Board of the investigational site, the United States Food and Drug Administration, and possibly other governmental authorities in the United States and Europe may be given access to your records upon request. They are all required to maintain your confidentiality.

Consent:

I am aware that the protocol and this Informed Consent has been reviewed and approved by the recognized Institutional Review Board at _____.

I have read or have had read to me the above pages concerning BPD-MA treatment of choroidal neovascularization. The purpose and procedures of this research project with its possible risks and benefits have been fully and adequately explained to me, and I understand them. My questions have been answered, and I voluntarily agree to participate as a subject in the research project under the conditions described. I have been given a copy of this consent form.

_____	_____	_____
Date	Name of Subject	Signature of Subject

_____	_____	_____
Date	Name of Witness	Signature of Witness

_____	_____	_____
Date	Name of Investigator	Signature of Investigator

APPENDIX 15

Benzoporphyrin Derivative Monoacid Ring A [BPD-MA (verteporfin)]

BPD OCR 002

A Randomized, Placebo-Controlled, Masked, Multicenter, Phase 3 Study of the Treatment of Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD) Using Photodynamic Therapy (PDT) with Liposomal BPD-MA (verteporfin)

SHORT TITLE: Treatment of AMD with PDT (TAP)

STATISTICAL ANALYSIS PLAN

[25-SEPTEMBER-98]

CONFIDENTIAL

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The document is a confidential communication of QLT PhotoTherapeutics Inc. and CIBA Vision Corporation. Acceptance of the document constitutes agreement by the recipient that the contents will not be disclosed to any unauthorized personnel, without prior written authorization from QLT PhotoTherapeutics Inc. or CIBA Vision Corporation.

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STATISTICAL ANALYSIS PLAN
PDT - CLINICAL PROTOCOL BPD OCR 002 (TAP TRIAL)

1. INTRODUCTION

Age-related macular degeneration (AMD) causes severe, irreversible vision loss and is the leading cause of blindness in individuals older than 50 years of age in the Western world. AMD is a degenerative eye disease with increasing prevalence at older ages. The majority of patients have the nonneovascular form of the disease, characterized by drusen and atrophic abnormalities in the retinal pigment epithelium. However, 80% of the severe vision loss attributable to this disease is related to the neovascular form, characterized by choroidal neovascularization (CNV). CNV leaks blood, lipid and fluid, and often leads to rapid loss of central vision.

Although the natural history of the disease is eventual quiescence and regression of the neovascularization process, this usually occurs at the cost of subretinal fibrosis and vision loss. Current treatment relies on destruction of the vessels using thermal laser photocoagulation. This procedure is quite non-selective, producing damage to the outer retina, including the photoreceptors, with an atrophic scar and corresponding visual scotoma. Although extensive studies have demonstrated a clinically significant advantage of laser treatment compared with observation in selected cases, the treatment benefit is problematic for subfoveal lesions.

Developing strategies have sought more selective treatment of the new vessels with preservation of the overlying neurosensory retina. One such strategy is photodynamic therapy (PDT), which relies on low intensity light exposure of tissues treated with photosensitizers to produce photochemical effects. Photodynamic therapy is a two-step process. The first step consists of intravenous injection of a photosensitizer. The second step is light irradiation. After exposure to light at an absorption peak of the dye, the activated dye interacts with oxygen and other compounds to form reactive intermediates which can then cause disruption of cellular structures and neovascular shutdown.

Study Objectives

The primary objective of this study is to determine if PDT treatment of patients with CNV secondary to AMD will, with an acceptable safety profile, significantly reduce vision loss compared with placebo (sham treatment). Secondary objectives include the comparison of the effects of PDT treatment with placebo on peak-contrast threshold, and the evaluation of the long-term safety of PDT treatment.

Study Design

This is a masked, multicenter, randomized, placebo-controlled, Phase 3 study of the treatment of subfoveal CNV secondary to AMD using photodynamic therapy. Two studies are being conducted under this protocol in North America and Europe. Approximately equal numbers of centers from each continent have been allocated into each study. The primary analysis of the efficacy data will be based on data obtained at the 12-month follow-up visit.

Analysis of the results through the first 12 months will be used in regulatory submissions to international boards of health.

Patients, treating ophthalmologists, vision examiners and Photograph Reading Center graders are masked to the identity of the treatment. Sponsor personnel responsible for the conduct and monitoring of the trial are also masked to the identity of the treatment. The study coordinator from each center will remain unmasked, and is responsible for the randomization of patients using sealed treatment allocation codes, and for maintaining the masking of other center staff and the patient. Patients are randomized to PDT or placebo treatment in a ratio of 2-to-1, respectively. Patient randomization is stratified by center and by two levels of baseline visual acuity.

Outpatients with new or recurrent subfoveal CNV secondary to AMD are enrolled in the study. Only one eye per patient is being treated in the study. Efficacy will be assessed by comparing the effect of PDT with placebo on best-corrected visual acuity using modified ETDRS charts, on contrast threshold using Pelli-Robson charts, and on the extent of CNV closure as assessed by fluorescein angiography.

Study Procedures

Within 7 days before the initial treatment day, all patients are screened to determine if they conform to the inclusion and exclusion criteria. Baseline assessments include a laboratory profile, medical history, and a physical examination. All patients have an ophthalmic evaluation including manifest refraction using modified ETDRS visual acuity charts, contrast threshold assessment (using the Pelli-Robson chart), standardized color stereoscopic fundus photography and fluorescein angiography.

At screening and every 3 months, all patients visit the clinic and undergo dilated ophthalmoscopy, assessments of visual acuity, contrast threshold, color fundus photography and fluorescein angiography. Best-corrected visual acuity and contrast threshold are determined by a masked vision examiner using a standardized protocol refraction and vision measurement. Retreatment will be conducted if evidence of CNV leakage is detected by fluorescein angiography.

Systemic safety is being assessed by laboratory evaluations at intervals of 6 months. A physical examination including an EKG is being conducted at intervals of 12 months. Adverse events and the patient's general health status is being assessed at each visit. Ocular safety is being assessed by the treating center's ophthalmoscopic examinations and the assessment of best-corrected visual acuity, and by the Photograph Reading Center's evaluation of the fundus photographs and fluorescein angiograms.

2. SAMPLE SIZE/POWER CONSIDERATIONS

In order to adequately assess the safety of PDT with respect to adverse events, a minimum of 300 patients on active treatment are required for the entire trial from both

studies. For adverse events that have a true rate of occurrence during the treatment period of 1% or greater, 300 patients should provide a 95% chance of detecting at least one of these events during the trial. A 2-to-1 randomization is being used, so that a total sample size of 450 patients (300 on PDT and 150 on placebo) who complete two years of treatment is the minimum required.

The protocol is conducted and will be analyzed as two “separate” studies, referred to as studies “A” and “B.” Each study is split by continent so that an approximate equal number of centers are in both Europe and North America. Within each study, a minimum sample size of 225 patients (150 on PDT and 75 on placebo) who complete 2 years is required. The data from both studies will also be combined in order to generate integrated summaries.

It is estimated that 50% of the placebo patients will be “responders” at the 1-year follow-up visit. A responder is defined as someone who loses less than 15 letters of visual acuity compared with baseline. Based on this estimate, a total sample size of 225 within each study will provide approximately 94% power to detect an absolute difference of 25% between PDT and placebo (Placebo=50% versus PDT=75%). In addition, this sample size will provide 80% power to detect an absolute difference from placebo of 20% (Placebo=50% versus PDT=70%). This assumes a two-sided significance level (α) of 0.050.

If it is assumed that up to 17% of the randomized patients will not have data available at the end of the trial because of death, loss to follow-up, and gross ineligibility, then a total of 540 patients (270 per study) need to be randomized to have 450 eligible patients (225 per study) complete the 2-year trial.

The patient randomization is stratified with respect to both study center and the patient’s baseline vision level, based on their best-corrected visual acuity (BCVA). Two levels of vision are defined within each center, i.e., 54-73 letters scored on the ETDRS chart (approximately 20/40-20/80), and 34-53 letters scored on the ETDRS chart (approximately 20/100-20/200). The stratification of the randomization with respect to study center and baseline BCVA ensures a 2-to-1 balance between treatment groups within each center and within each level of baseline BCVA. The randomization is stratified on baseline vision level because of the high likelihood that the treatment response will be correlated with the baseline BCVA.

3. SCHEDULE OF ANALYSIS

The total planned study duration for each patient will be 24 months; however, the first analysis (primary analysis) of the efficacy data will be based on the data obtained after all patients have completed their 12-month follow-up visit. Analysis of the results through the first 12 months will be used in regulatory submissions to international boards of health. At the time of these submissions, many patients will have data beyond 12 months. For these regulatory submissions, available data from patients beyond the first 12 months will be included. The amount of data submitted to regulatory authorities will be based on the cut-off date (September 25, 1998) when all patients have completed their 12-month visit.

The second analysis will be performed after all patients have completed their 24-month follow-up visit. The purpose of this analysis will be to confirm the durability of effect and long-term safety of photodynamic therapy. All analyses will be performed using the same data sets and methods used for the 12-month analysis.

All statistical tests in this trial will be two-sided, and all p-values ≤ 0.050 will be considered statistically significant. All statistical analyses for this trial will be performed using the SAS® system.

4. DATA SETS TO BE ANALYZED

4.1 Intent-to-Treat Data Set

The primary set of efficacy analyses will be performed on the intent-to-treat data set (for all randomized patients), which will include all available efficacy data collected during the trial, and data substituted for all missing values. These analyses will be referred to as the “intent-to-treat” analyses. For each patient, missing efficacy values will be substituted by carrying forward the last observed data point prior to the missing value. This method will be referred to as “last observation carried forward” or “LOCF”. For the first analysis at Month 12, patients who were early dropouts will have their last value carried forward through Month 12, and through any additional visits that would have occurred as of the data cut-off date defined above. For the second analysis at Month 24, all patients who were early dropouts at any time during the study will have their last value carried forward through Month 24. The LOCF method will also be used for patients who have one or more missing values followed by an observed value. These missing “interim” value(s) will be replaced by carrying forward the observed value immediately prior to the missing value(s).

4.2 Evaluable-Patients Data Set

A secondary set of efficacy analyses will be performed on the “evaluable-patients” (i.e., “per-protocol”) data set, which will include all efficacy data from patients who receive either of the two treatments, meet the inclusion/exclusion criteria without significant deviation, and adhere to the protocol procedures without any significant deviation. The data set will include only the “observed cases”, i.e., only the data that was actually collected. No data will be substituted for missing values. These analyses will be referred to as the “evaluable-patients” analyses.

Patient Exclusions

Patients who deviate from the protocol in a significant manner during the course of the trial will have either all or part of their efficacy data excluded from the “evaluable-patients” analysis. Reasons for excluding data from these analyses follow; however, this list may not be exhaustive because of possible unforeseen protocol violations and/or deviations. If additional criteria are appended to the following list, it will be done prior to the unmasking of the treatment codes.

1. Patients whose CNV lesions deviate significantly from the protocol-defined inclusion criteria will have all of their efficacy data excluded. These deviations will include the following:
 - Extrafoveal CNV
 - CNV not due to AMD
 - CNV lesion larger than maximum linear dimension of 12 MPS disc area circle
 - Baseline visual acuity >73 letters or <34 letters (ETDRS)
2. Patients who have two visits with at least one of the following protocol deviations in the treatment administration will have partial data excluded. For these patients, any efficacy data collected following the second deviation will be excluded from all analyses.
 - Duration of light administration <50 seconds
 - Amount of drug given estimated to be <4mg/m²
 - Light administration >30 minutes from the start of the infusion
3. Patients who drop out of the study and are no longer being treated according to the protocol, but who are still being followed for safety reasons, will have partial data excluded. Any efficacy data collected at the first visit after a patient's last scheduled treatment will be included in all analyses; however, additional measurements will be excluded.
4. Patients who deviate by more than 21 days from the intended treatment visit date will only have the efficacy data at that visit excluded.

4.3 Safety Data Set

The analysis of the safety variables will be performed on all patients who receive at least one treatment and who have at least one safety variable recorded on the case report form following treatment. These analyses will be referred to as the "safety" analyses. No data will be excluded from these analyses because of protocol violations.

5. BASELINE COMPARABILITY

Patient demographic and background characteristics (e.g., gender, age, race, smoking history, AMD disease history, vital signs, visual acuity, CNV location, lesion components, area of lesion) will be summarized and tested for treatment group comparability. These analyses will be performed on both the intent-to-treat and evaluable-patients data sets. Continuous-type variables (e.g., age) and ordered categorical variables (e.g., area of lesion) will be analyzed using a Wilcoxon rank sum test. Binary-response variables (e.g., gender) and unordered categorical variables (e.g., race) will be analyzed using a chi-square or Fisher's exact test.

6. EFFICACY ANALYSIS

6.1 Primary Efficacy Variable

The primary efficacy variable will be the proportion of patients who are classified as a “responder” to treatment, based on their BCVA, as measured using the ETDRS charts. Every letter that a patient identifies correctly on the ETDRS chart will be reflected in their BCVA score and thus factored into the determination of whether or not they are a responder. Patients who are not responders to treatment will be considered “non-responders” or “failures”.

In the analyses, two separate definitions of a responder will be used which are based on the severity of vision loss:

- (i) A decrease from baseline of less than 15 letters of vision (approximately 3 lines) in the treated eye. A change of three lines of vision represents a doubling of the visual angle and is considered a clinically significant change.
- (ii) A decrease from baseline of less than 30 letters of vision (approximately 6 lines) in the treated eye.

The primary analysis for establishing efficacy will be based on the 15-letter responder rates at the 12-month visit. The 15-letter responder rates at the 24-month visit will be used for confirming the durability of effect. Therefore, if the difference in 15-letter responder rates at the 12-month visit is statistically significant between treatment groups favoring PDT at the 0.050 level (2-sided), then the study will be judged as having provided pivotal evidence of efficacy for the primary variable.

The corresponding null (H_0) and alternative (H_1) hypotheses to be tested for the primary efficacy variable are as follows:

- H_0 : The proportion of patient responders is the same for PDT and placebo.
 H_1 : The proportion of patient responders is different between PDT and placebo.

For the analysis of the responder rates at 12 and 24 months, comparisons between treatment groups will be made using a chi-square test. A 95% confidence interval around the difference in these proportions between groups will be calculated.

As a confirmatory analysis of patient responder rates, a logistic regression model will be used. This model will be used to examine the relationship between responder rates and a set of explanatory variables that will include treatment, baseline visual acuity, and other clinically significant baseline variables. An odds ratio with a 95% confidence interval will be calculated for the treatment effect.

Patient responder rates will also be analyzed using a repeated-measures analysis. For this analysis, the method of weighted-least squares will be used for parameter estimation and hypothesis testing. Factors in the model will include treatment, visit, and treatment-

by-visit interaction, as well as other possible factors. For the 12-month analysis, the responder rates at 3, 6, 9, and 12 months will be included. For the 24-month analysis, the responder rates at 3, 6, 9, 12, 15, 18, 21, and 24 months will be included.

6.2 Secondary Efficacy Variables

Secondary efficacy variables will include the following:

- a) The time until a patient has a “moderate” loss of vision, i.e., a decrease from baseline of 15 or more letters in the treated eye, based on the patient’s BCVA.
- b) The time until a patient has a “severe” loss of vision, i.e., a decrease from baseline of 30 or more letters in the treated eye, based on the patient’s BCVA.
- c) The proportion of patients whose visual acuity score in their treated eye becomes less than 34 letters (approximately 20/200).
- d) The time until a patient’s visual acuity score in their treated eye becomes less than 34 letters.
- e) Visual acuity score (number of letters read on the ETDRS chart).
- f) The number of letters scored from the Pelli-Robson chart for assessment of contrast sensitivity.
- g) Evidence of increase/decrease in classic and occult CNV compared with baseline (fluorescein angiography gradings).

For the analysis of the proportions in (c), the same methods will be used as will be done for the responder rates.

Time-to-Event Analysis

It is expected that normal fluctuations in visual acuity may show a patient initially losing 15 (or 30) letters of BCVA from baseline at various times early on in the study, and at later visits show less than a 15 (or 30) letter decrease or even improvement in BCVA. To adjust for this fluctuation, a treatment failure or “event” will be defined for the time-to-event analysis as a patient who demonstrates a 15 (or 30) letter loss of BCVA from baseline at two or more consecutive visits that are at least 45 days apart. Consecutive visits for the purpose of this analysis means consecutive completed visits by the patient, not necessarily protocol-specified visits. If a patient misses a visit, it is the consecutive visits that the patient completes that are used. Therefore, the time intervals in (a) and (b) will be calculated from the study entrance to the first of two consecutive losses of 15 (or 30) letters of BCVA from baseline.

If the first loss of 15 (or 30) letters occurs at the patient’s last available measurement, then the time intervals in (a) and (b) will be calculated from the study entrance to this first loss. If

the patient is lost to follow-up and the event has not yet occurred, then the observation will be considered censored at the time of loss to follow-up.

Life-table techniques and the associated methods for presentation of data (e.g., survival curves) will be used to describe the event-free distribution of the two treatment groups. The event-free distributions will be compared between the two treatment groups using a log-rank test. Life-table estimates of the hazard¹ and survival functions for each group will be plotted to assess the level to which the two hazards deviate from proportionality. In addition, a Cox proportional hazards model will be used to confirm the treatment effect and to adjust for predefined stratification variables, possible treatment-by-center interaction, and other clinically significant baseline variables.

If the hazards for the two treatment groups are shown to deviate significantly from proportionality, then either a Cox model with a time dependent covariate(s), or some other model may need to be evaluated.

For secondary variable (d), the time until a patient's visual acuity score in their treated eye becomes less than 34 letters, the same analysis methods will be used as described above (e.g., two or more consecutive visits with less than 34 letters, life-table analysis, etc.).

Visual Acuity Score

Visual acuity scores [secondary variable (e)] will be summarized descriptively at each visit and analyzed at Months 12 and 24 using an analysis of covariance (ANCOVA) model, with treatment and study center included as factors. The covariate will be the baseline visual acuity score. A treatment-by-center interaction term will be included to test for the homogeneity of treatment effects between centers. In addition, a treatment-by-baseline interaction term will be included to test for the homogeneity of regression slopes between treatments. The baseline lesion size (MPS disk areas) will also be investigated as a possible covariate.

Contrast Sensitivity

The number of letters read on the Pelli-Robson chart for the assessment of contrast sensitivity [secondary variable (f)] will be summarized descriptively and analyzed using an analysis of covariance model, as described above for visual acuity.

CNV Closure

The evidence of increase/decrease in classic and occult CNV compared with baseline [secondary variable (g)] will be based on the fluorescein angiography gradings as made by the Photograph Reading Center. The extent of closure is graded on a 4-point ordered categorical scale, with a fifth category for photographs that can't be graded:

- A) No CNV or 100% Closed & No Recurrence
- B) Partial Closure $\geq 50\%$ to $< 100\%$ Closed & No Recurrence

¹ The probability that an individual experiences a failure at time t conditional on that they have not experienced the event (failure) up until time t . The hazard represents an instantaneous failure rate for an individual not experiencing the event up until time t .

- C) Less than 50% Closed & No Recurrence
- D) Recurrence (New CNV)
- E) Can't Grade

Frequency distributions of these closure grades will be summarized at each visit. Analyses comparing the two treatment groups will be made at Months 12 and 24 using a Mantel-Haenszel chi-square test. Photographs that can't be graded, i.e., category "E", will be counted as missing and will not be included in the tests. These summaries and statistical tests will be done separately for classic and occult CNV.

6.3 Subgroup Analyses

Subgroup analyses will be performed on the responder rates for visual acuity to determine if the response to treatment is consistent across the subgroup levels. Responder rates will be given by treatment group at each visit, with statistical tests provided at the 12- and 24-month visits. Analyses will be based on the following subgroups:

- 1.
2. Age (<75 Years vs. ≥75 Years)
3. Gender (Male vs. Female)
4. Race (Caucasian vs. Others)
5. Iris Color (Dark vs. Light)
6. Initial Visual Acuity (Stratum 1 vs. Stratum 2)
7. Size of Lesion at Baseline in MPS Disk Areas (≤3, >3 to ≤6, >6 to ≤9, >9)
8. Percent of Classic CNV at Baseline (≥50%, <50%, Questionable, No)
9. Presence of Occult CNV at Baseline (Yes + Questionable vs. No)
10. Presence of Blood at Baseline (Yes + Questionable vs. No)
11. Percent of Fibrosis at Baseline (0-25%, 26-50%, >50%)
12. Baseline Hypertension (Definite vs. All Others)
13. Cigarette Smoking (Past, Current, Never)
14. Lesion (New vs. Recurrent, as assessed by the Photograph Reading Center only)

In #12, Definite Hypertension will be defined as:

- Systolic BP ≥ 160 mmHg, or
- Diastolic BP ≥ 95 mmHg, or
- Systolic BP = 140-159 mmHg, and either history of hypertension, or currently on anti-hypertension medication, or
- Diastolic BP = 90-94 mmHg, and either history of hypertension, or currently on anti-hypertension medication.

7. SAFETY ANALYSIS

Ocular safety will be assessed by evaluating ocular adverse events that occur during the trial, and by evaluating changes between the pre- and post-treatment ophthalmologic examinations. Systemic safety will be assessed by evaluating systemic adverse events

that occur during the trial, and by evaluating changes in vital signs and laboratory parameters (hematology, serum chemistry and urinalysis).

7.1 Adverse Events

To help facilitate the summarizing of adverse events, reported adverse-event terms will be coded to a standardized set of “preferred terms” as defined in the COSTART dictionary. These preferred terms will then be categorized into one of twelve body systems as defined in the dictionary. Adverse events will be summarized in the following two sets of tables based on their relationship to the trial medication/ procedure:

- 1) All events regardless of their relationship to the trial medication/procedure.
- 2) Only events which are felt by the investigator to be potentially related to the trial medication/procedure (i.e., relationship listed as “possible,” “probable,” “definite,” or “unknown”).

For each preferred term, summaries by treatment group will be made with respect to the proportion of patients having at least one occurrence of that event during the first year of the trial (plus during any additional visits that occur prior to the data cut-off date), and then again during the entire 2 years of the trial. In addition, the total number of occurrences of each adverse event will be reported for the same time periods. For differences between treatment groups that are felt to be clinically significant, statistical tests will be performed on the proportions using either a chi-square test or a Fisher’s exact test.

7.2 Laboratory Data

For each laboratory variable measured every 6 months, both within- and between-group comparisons will be summarized and analyzed as follows:

Within-Group Changes from Baseline

A 2x2 square “shift table” will be created for each variable within each treatment group to summarize the distribution of clinically significant lab abnormalities, as indicated on the CRF:

		<u>Posttreatment Lab</u> Clinically Significant Abnormality?	
		Yes	No
<u>Baseline</u> <u>Lab</u> Clinically Significant Abnormality?	Yes	Y-Y	Y-N
	No	N-Y	N-N

Each cell of the table will include the frequency count and the corresponding percentage of the whole table, and each table will include marginal totals. To test for a significant shift in the distribution of values from baseline, a McNemar's test for matched pairs will be used. This test compares the "discordant pairs" which are counted in the two cells off the main diagonal (upper right and lower left corners of table).

Scatterplots of each variable comparing baseline to post-treatment will also be created. Since decentralized laboratories will result in different sets of normal ranges, each variable will be normalized as follows:

$$\text{Relative Value} = (\text{Measured Value} - \text{Lower Limit}) / (\text{Upper Limit} - \text{Lower Limit}),$$

where "Lower Limit" and "Upper Limit" refer to the lower and upper limits of the normal range. Thus, relative values less than 0 correspond to measured values below the normal range, relative values greater than 1 correspond to measured values above the normal range, and relative values between 0 and 1 correspond to measured values within the normal range. For each variable, a scatterplot of the baseline versus post-treatment values will be generated and visually assessed.

Between-Group Changes From Baseline

For each variable assessed at each visit, a summary of the distribution of the changes from baseline will be made based on clinically significant abnormalities. The 4 categories of shifts, as defined above, will be summarized as follows:

8. REFERENCES

- 1) Allison P.D., *Survival Analysis Using the SAS® System: A Practical Guide*, Cary, NC: SAS Institute Inc., 1995. 292 pp.
- 2) Collett D., *Modelling Survival Data In Medical Research*, London: Chapman & Hall, 1994.
- 3) Ferris F.L. III, Kassoff A., Bresnick G.H., Bailey I. "New visual acuity charts for clinical research," *Am J Ophthalmol* 1982; 94: 91-96.
- 4) Fleiss J.L., *Statistical Methods for Rates and Proportions*, New York: John Wiley & Sons, 1981.
- 5) Hosmer D.W., Lemeshow S., *Applied Logistic Regression*, New York: John Wiley & Sons, 1989.
- 6) SAS Institute Inc. SAS® Procedures Guide, Version 6, Third Edition, Cary, NC: SAS Institute Inc., 1990. 705 pp.
- 7) SAS Institute Inc. SAS/STAT® User's Guide, Version 6, Forth Edition, Volume 1, Cary, NC: SAS Institute Inc., 1989. 943 pp.
- 8) SAS Institute Inc. SAS/STAT® User's Guide, Version 6, Forth Edition, Volume 2, Cary, NC: SAS Institute Inc., 1989. 846 pp.
- 9) Stokes, M.E., Davis C.S., Koch G.G., *Categorical Data Analysis Using the SAS® System*, Cary, NC: SAS Institute Inc., 1995. 499 pp.

APPENDIX 16

TAP Study Extension for Study Eye and Fellow Eye

In order to participate in the TAP extension, a patient must be enrolled in TAP at time of the Month 24 visit.

Neither the investigator nor the patient will be unmasked as to the identity of previous treatment assignment of the study eye during the double masked randomized study until all patients have completed the Month 24 visit and statistical analyses are completed.

Any patient reaching the Month 24 visit will be offered active treatment in their study eye if the patient meets the retreatment criteria in TAP and the treating ophthalmologist considers that there may be treatment benefit. Patients who do not require retreatment in their study eye at the Month 24 visit due to absence of CNV leakage may be included unless this is due to endstage of the disease. Any patient reaching the Month 24 visit will be offered active treatment in their fellow eye if the fellow eye meets the eligibility criteria listed below. Active treatment will be provided to either eye or both eyes every 3 months thereafter for an additional 24 months.

If the study eye is no longer eligible for retreatment at Month 24, and the fellow eye has no CNV lesion at Month 24 which meets the fellow eye inclusion/exclusion criteria, the patient is discontinued from the study. If the patient discontinued treatment in the study, and neither the study nor fellow eye meets the inclusion/exclusion criteria at M24, the patient is discontinued from the study.

The fellow eye will be treated with the same verteporfin and light dosing parameters as the study eye (6 mg/m², 50 J/cm² 15 min after the start of the infusion). When both study and fellow eye require treatment, only one verteporfin infusion will be administered. The study eye will receive light application first, 15 min after the start of the infusion, the fellow will receive light application immediately thereafter and no later than 20 min after the start of the infusion.

In order to determine eligibility and retreatment criteria for both eyes e.g. size of the lesion, fluorescein angiography (early and late frames) must be performed. It is the responsibility of the investigator in cooperation with their photographers to determine whether the appropriate views can be achieved in one fluorescein angiography setting or whether two separate angiograms are needed. This might require a separate visit by the patient and should be discussed with the patient before enrollment in the extension.

An informed consent must be signed for the study extension providing the patients with the latest safety information (see sample informed consent form attached).

Study procedures that should be done at the 3-monthly follow up visits according to the detailed descriptions of the protocol dated May 5, 1997 include best-corrected visual acuity, peak contrast threshold, color fundus photography, fluorescein angiography, dilated ophthalmoscopy, assessment of concomitant medication and adverse events (as

defined in Amendment #8). PDT treatments are to be carried out at 3-month intervals if all criteria are met. If the patient receives PDT treatment to either eye at the Month 48 visit, a telephone follow up call must be made 2-4 days and 1 month post treatment to assess any possible adverse events. For any patient who discontinues the study prematurely (before Month 48), telephone follow up calls, 2-4 days and 1 month post treatment, must take place after the last PDT treatment to either eye to assess any possible adverse events.

Adverse Event procedures should be followed as outlined in section 12.

General Eligibility Criteria for the TAP Extension

To include either the study or the fellow eye in the TAP Study extension, outpatients of either sex and of any race must be on the TAP study at the Month 24 follow-up visit.

Eligibility Criteria of the Study Eye in the TAP Extension

Retreatment will be conducted if evidence of CNV leakage is detected by fluorescein angiography. Retreatments may only be conducted at intervals of 3 months \pm 2 weeks. Any retreatment must be conducted within 7 days of the fluorescein angiography. Each center will individually evaluate their fluorescein angiograms to determine the need for retreatment and the size of the retreatment spot (i.e. confirmation of leakage and area of the lesion to be treated by the Photograph Reading Center is not required).

To be eligible for retreatment, patients must also fulfil the following criteria:

1. Have no additional ocular diseases, which have developed and may compromise the visual acuity of the study eye. Cataract, which allows visualization and treatment of the CNV, is allowed. Cataract that is considered to have significantly compromised the visual acuity should undergo corrective operation (see Section 7.4).
2. It must be possible for the Investigator to visualize the lesion.

3. Have no acute illness or fever observed on the day of treatment prior to infusion. If the illness or fever resolves more than 7 days from the fluorescein angiogram the fluorescein angiography must be repeated before retreatment.

Continuation Criteria for patients who discontinued treatment of their study eye but are being followed

Patients who discontinued treatment of their study eye for any reason, will not be offered active treatment in the study eye but could be included for fellow-eye treatment if they fulfill the fellow-eye inclusion criteria.

Inclusion Criteria of the Fellow Eye in the TAP Extension

1. The fellow eye must have clinical signs of CNV secondary only to Age-Related Macular Degeneration, without any other concurrent retinal disease present that may also be associated with CNV (e.g., myopic degeneration, presumed ocular histoplasmosis syndrome).
2. The fellow eye must have a lesion with the following characteristics determined by fluorescein angiography:
 - a) evidence that the classic or occult CNV involves the geometric center of the foveal avascular zone as determined by fluorescein angiography,
 - b) the CNV lesion has a classic component in any proportion to other lesion components, some occult component may be present as well (definitions see Section 9.1.1),
 - c) the area of classic CNV plus occult CNV must occupy at least 50% of the total lesion,
 - d) the greatest linear dimension of the entire CNV lesion must not exceed 5400 μ diameter (equivalent to the diameter of the 9 MPS disc area circle) at the initial treatment,
3. The best-corrected visual acuity of the fellow eye must be 24 - 73 letters inclusive using a modified ETDRS chart (approximately 20/40 to 20/320 Snellen Equivalents inclusive). The number of letters will be used to evaluate this inclusion criterion

Exclusion Criteria of the Fellow Eye in the TAP Extension

Patients may not enter the TAP study extension for the fellow eye if they:

1. Have a tear (rip) of the RPE; a vitelliform-like lesion of the outer retina (e.g. as in pattern dystrophies or basal laminar drusen); or central serous retinopathy.

2. Have any additional ocular diseases which have irreversibly compromised or, during follow-up, could likely compromise the visual acuity of the fellow eye including amblyopia, uncontrolled glaucoma (intraocular pressure ≥ 30 mmHg), anterior ischemic optic neuropathy, clinically significant diabetic macular edema, severe non-proliferative or proliferative diabetic retinopathy. For cases of cataract refer to Section 7.4 of the original TAP protocol dated May 5, 1997

Retreatment Criteria of the Fellow Eye in the TAP Extension

Retreatment will be conducted if evidence of CNV leakage is detected by fluorescein angiography. Retreatments may only be conducted at intervals of 3 months \pm 2 weeks. Any retreatment must be conducted within 7 days of the fluorescein angiography. Each center will individually evaluate their fluorescein angiograms to determine the need for retreatment and the size of the retreatment spot (i.e. confirmation of leakage and area of the lesion to be treated by the Photograph Reading Center is not required).

To be eligible for retreatment, patients must also fulfil the following criteria:

1. Have no additional ocular diseases, which have developed and may compromise the visual acuity of the study eye. Cataract, which allows visualization and treatment of the CNV, is allowed. Cataract that is considered to have significantly compromised the visual acuity should undergo corrective operation (see Section 7.4).
2. It must be possible for the Investigator to visualize the lesion.
3. Have no acute illness or fever observed on the day of treatment prior to infusion. If the illness or fever resolves more than 7 days from the fluorescein angiogram the fluorescein angiography must be repeated before retreatment.

Sample Patient Information Letter for TAP Extension

This letter can be sent to the patients before their Month 24 visit as an introduction to the TAP extension.

Dear Patient:

During the past two years it has been our privilege to have you as a participant in the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) investigation. With this visit, you have completed the two-year commitment you originally made to the investigation. This letter has been prepared to tell you how much we appreciate your participation, to review the care you have received as a participant in the investigation and to clarify what you can expect from us in the future.

Your participation has enabled us to follow the condition of your eyes according to a fixed schedule. At each visit to the clinic your eyes have been examined, vision has been measured and photographs of the back of the eye have been taken. You may have been interviewed regarding your health status. You may have been retreated (after being given either placebo [sugar water] or the investigational verteporfin) at your follow-up visits according to a protocol followed by your study ophthalmologist.

Your contribution has been invaluable in helping the ophthalmologists interested in macular diseases to evaluate the effects of photodynamic therapy with verteporfin for treating new blood vessels in the center of vision. More than 600 other patients are taking part in this investigation. The TAP physicians are still collecting data from patients who enrolled in the investigation after you and will be doing so until late 1999.

Results of the TAP investigation, which comprises of two randomized, double-masked, placebo-controlled trials involving 609 patients at 22 centers in North America and Europe, showed that patients treated with verteporfin treatment were less likely to have loss of vision and more likely to have improved vision compared to placebo-treated patients at 12-month follow-up. The study remains ongoing in order to determine longer-term effectiveness and safety. As this therapy is still investigational, only patients who are currently enrolled in these clinical trials are eligible for treatment at this time.

In the current ongoing TAP study, analysis of data from the first 12 months of the study showed that 402 of the 609 patients were treated with verteporfin. Notable adverse events that occurred at a greater percentage on verteporfin versus placebo included vision disturbances (6% more on verteporfin), injection site events (10% more on verteporfin), back pain during infusion (2.2% more on verteporfin), and sunburn like reactions (2.5% more on verteporfin).

Collectively, about 700 patients have received verteporfin treatment in two masked clinical studies (TAP and VIP studies). In these studies, a few AMD patients have noticed in their study eye a significant decrease in vision soon after treatment that may be associated with photodynamic therapy with verteporfin or placebo. Of the 402 patients in the TAP studies

who have been treated with verteporfin through February 1999, 3 patients (<1%) have experienced a significant decrease in vision in the study eye shortly after verteporfin treatment. In the on-going VIP trial of approximately 226 verteporfin treated patients and 113 placebo treated patients who have a less advanced stage of AMD, this significant decrease in vision in the study eye shortly after treatment has occurred in 8 patients (<3%). At this time, we do not know if the affected patients in the VIP trial were treated with verteporfin or placebo. In most cases, this significant decrease in vision has partially resolved. In all but one case these significant vision decreases occurred after the first treatment. This significant decrease in vision in your study eye shortly after treatment is a possible complication that may or may not be permanent.

Since photodynamic therapy with verteporfin is an experimental treatment it cannot be made generally available until regulatory authorities have reviewed the data and given approval if it is found to be safe and effective. The sponsors are able to provide the active treatment to you if you are willing to continue to be assessed under a protocol. We would like you to consider continuing to be followed by us in an extension to the TAP investigation. This will enable us to obtain additional information on safety and effectiveness of treatment with the active verteporfin.

You must decide whether to participate in the extension to the TAP investigation for the next two years or not at the time of your last follow-up visit (Month 24)

You will be evaluated every 3 months for another period of up to 24 months and then if your ophthalmologist considers that there is any potential benefit to be gained by treatment of your study eye or your other eye, you will be offered active treatment during this additional period of 24 months whether or not you have been receiving active treatment or the placebo (sugar water) treatment for your study eye.

Neither you nor your ophthalmologist will know which treatment was given up until now, but both of you will be informed when all patients have completed the masked investigation in late 1999. If you do consent to continue in this study and receive verteporfin treatment, the procedures that will be followed at each of the 3 monthly clinic visits will be similar to those you have undergone in the masked TAP investigation, except that there will be no further requirement for routine laboratory testing (blood, urine, EKG), physical examinations and measurement of your blood pressure, heart rate and temperature. If both of your eyes need treatment, you will receive one infusion of verteporfin and light application to your study eye 15 minutes after the start of the infusion followed by light application to your other eye no later than 20 minutes after the start of the infusion.

If you are willing to continue in the extension of this TAP investigation, you will be given a consent form for your review and signature before entering the extension of the TAP investigation. This information will be reviewed with you to ensure that you fully understand the potential risks, discomforts and benefits, the availability of alternative treatments, that your identity will be kept confidential, that your participation is voluntary

and you have the right to withdraw from the investigation at any time without affecting the quality of your care, what compensation will occur if you are injured as a direct result of this investigation, and your right to ask questions at any time about the investigation.

If you do not wish to receive verteporfin treatment, or do not wish to continue follow up with us, it is important to remember that you should continue to follow your doctor's advice with respect to monitoring the vision in each of your eyes. We want to make sure that you receive continuing care for your eyes. In the event that you return to the exclusive care of the eye doctor who referred you to us, a summary of the information about your eyes which we have collected in this clinic, will be made available to your doctor.

Regardless of where you choose to go for your future eye examinations, our interest in you, your eyes and your vision does not end with this visit. We may be in contact with you from time to time. We may want to tell you about findings from this investigation and any subsequent study, as these become available. We may want to examine your eyes again if there is any new information that may apply to you. Please continue to notify us of any changes in your address and telephone number, even if you plan to be away for only a few months.

We will discuss with you the current status of your eyes and your vision. We will be happy to answer any questions you have about the TAP investigation or about your future eye care.

All of us in the TAP investigation – doctors, nurses, scientists, technicians, photographers and secretaries – are sincerely grateful and appreciate your participation, cooperation and contribution to the TAP investigation.

Sincerely,

Dr. _____
TAP Ophthalmologist

Phone: _____

TAP Clinic Coordinator

Phone: _____

SAMPLE INFORMED CONSENT FORM FOR EXTENSION TO TAP INVESTIGATION

Investigator:

Introduction:

This information is given to you so that you can make an informed decision about whether or not to participate in the extension to the TAP research study. Take as much time as you wish to make your decision about signing the Informed Consent. You have the right to ask questions about any procedures before agreeing to be included in this study.

You have been asked to take part in the study extension because you have choroidal neovascularization (CNV), that is, growth of new, abnormal blood vessels under the retina in one or both eyes. Your CNV is due to age-related macular degeneration (AMD).

As you have been informed at the beginning of the study, BPD-MA is an experimental drug, activated by light, which is being investigated for use in the treatment of ophthalmic diseases characterized by choroidal neovascularization. This treatment modality, called photodynamic therapy (PDT), has been used experimentally to treat AMD in the TAP and VIP investigations as well as skin cancer and psoriasis (a chronic skin condition). More than 500 patients with CNV have been treated at least once. Treatment will be given, if needed, every 3 months for up to 2 years.

Description and Explanation of Procedures

The study requires your involvement for a period of up to 2 years. During these 2 years you will be requested to have a check-up visit at the clinic every 3 months. It is expected that you will have active PDT treatment of one or both eyes at or shortly after each of these 3 monthly check-ups. Therefore you should anticipate between 8 and 16 separate visits to the clinic over the 2-year period.

In order to determine your eligibility for the study extension, your TAP study eye and your other eye will be assessed as part of your Month 24 TAP study visit. You will have an eye examination, visual acuity testing, contrast threshold, and photographs and angiography performed as per the TAP study protocol. Angiography is a special test in which a dye is injected into a vein in your arm. The dye travels throughout the body, including the eyes. With a special camera and flash, a series of photographs of the retina is taken as the dye passes through it. The photographs will show where and what kind of changes has occurred in the retina. You will be asked to disclose any medicines currently being taken as well as any change in use during the study. Your family doctor and/or treating ophthalmologist will be informed about your participation in this study extension and termination from the study, unless you object.

On the day of treatments you will receive a 10-minute intravenous (I.V.) infusion of BPD-MA (6 mg/m² body surface area). An activating light will be shone into your eye shortly after the infusion. This light, delivered by a laser system, is much lower energy than used in conventional laser surgery and has no effect without BPD-MA in the circulation. Your other eye, if it requires treatment and is eligible, will be treated with the same verteporfin and light dosing parameters as your study eye (6 mg/m², 50 J/cm² 15 min after the start of the infusion). When both your initial study eye and your other eye require treatment, only one verteporfin infusion will be administered. The study eye will receive light application first, 15 min after the start of the infusion, the other eye will receive light application immediately thereafter and no later than 20 min after the start of the infusion.

YOU MUST REFRAIN FROM EXPOSING YOUR EYES OR SKIN TO BRIGHT LIGHT FOR AT LEAST 48 HOURS POST-TREATMENT. This includes but is not limited to bright sunlight, tanning salons, halogen lighting in homes and offices, lighting used in dentists' offices or in surgery operating rooms. Dark sunglasses will be provided to you and will be required to be worn for 2 days after the infusion. **USE OF SUNSCREENS WILL NOT BLOCK ANY PHOTSENSITIVITY REACTION.**

Three months after every treatment, the following procedures will be completed: visual acuity testing, fundus photography and angiography, an eye examination, assessment of any adverse events and concomitant medications, and contrast threshold. Depending on the condition of your CNV, you may be retreated with PDT after the angiography test.

Two to four days and one month after your last treatment we will call you and ask you whether you experienced any changes in vision in the treated eye or any other problems. If you experienced a severe drop in your vision we will ask you to come to the clinic for a visual acuity examination and possibly ophthalmoscopy, fluorescein angiography and color photography of your eye.

Risks and Discomforts

Verteporfin is an experimental treatment and there may be unforeseen risks. Although harmful effects on the vision at the dose being used in this study have not been apparent, it is not known if multiple verteporfin treatments over a 2-year period or more could be more harmful than if no treatment was given or if standard thermal laser treatment were given.

Verteporfin was initially tested in 142 patients/eyes with CNV using different doses. These patients did not complain of any immediate discomfort during or shortly after verteporfin. The most common adverse event reported by these patients within a 3-month period following treatment was headache (8% of patients). All adverse events that were considered related to treatment such as headache, dizziness, injection site rash, low blood pressure occurred at a low incidence of 4% or less.

In the current ongoing TAP study, analysis of data from the first 12 months of the study showed that 402 of the 609 patients were treated with verteporfin. Notable adverse events that occurred at a greater percentage on verteporfin versus placebo included vision

disturbances (6% more on verteporfin), injection site events (10% more on verteporfin), back pain during infusion (2.2% more on verteporfin), and sunburn like reactions (2.5% more on verteporfin).

Collectively, about 700 patients have received verteporfin treatment in two masked clinical studies (TAP study and VIP trial). In these studies, a few AMD patients have noticed in their study eye a significant decrease in vision soon after treatment that may be associated with photodynamic therapy with verteporfin or placebo. Of the 402 patients in the TAP study who have been treated with verteporfin through February 1999, 3 patients (<1%) have experienced a significant decrease in vision in the study eye shortly after verteporfin treatment. In the on-going VIP trial of approximately 226 verteporfin treated patients and 113 placebo treated patients who have a less advanced stage of AMD, this significant decrease in vision in the study eye shortly after treatment has occurred in 8 patients (<3%). At this time, we do not know if the affected patients in the VIP trial were treated with verteporfin or placebo. In most cases, this significant decrease in vision has partially resolved. This significant decrease in vision in your study eye shortly after treatment is a possible complication that may or may not be permanent. In all but one case these significant vision decreases occurred after the first treatment.

Discomfort and/or a small risk of adverse events may be caused by placing hypodermic needles in your vein. This procedure is required to administer the study drug, for administering the dye in the fluorescein angiography tests and for withdrawal of blood for tests in case of infusion related back pain. Injection site reactions reported with administration of drug included but are not limited to injection site pain, swelling, and inflammation.

Fluorescein angiography is an extremely safe test, although rare patients may have an important reaction to the dye. About 1/225,000 patients may have such a severe reaction that they can have a heart attack or stroke or even die. Fortunately, most reactions are mild, such as temporary nausea or vomiting in a few patients and a rash, hives or wheezing in about 1%. Your doctors have emergency equipment available to help care for you should you have a reaction.

Avoidance of bright light for 48 hours after each treatment may also be considered a discomfort.

Potential Benefits

Results of the TAP investigation showed that patients treated with verteporfin therapy were less likely to have loss of vision and more likely to have improved vision compared to placebo-treated patients at 12-month follow-up. This effect might have the potential to continue beyond 12 months.

Alternative Treatments

Your investigator told you whether one or both of your eyes are eligible for standard laser therapy. Your eye(s) are not eligible for standard laser therapy if the nature of the CNV lesion in your eye(s) is such that standard laser therapy may lead to a greater loss of vision than using no treatment.

If your eye(s) are eligible for standard laser thermal therapy and you choose not to participate in this investigation for either one or both eyes, you and your ophthalmologist will discuss your further care which may include thermal laser treatment now or in the future. If you have thermal laser treatment, the treatment will immediately cause a reduction in vision corresponding to the area that receives this thermal laser. This laser treatment is considered beneficial compared to no treatment at all because, for most patients like you, the amount of destruction that occurs by leaving these blood vessels untreated eventually (after about 1 year), becomes greater than the amount caused by the laser. Laser treatment has not been compared to verteporfin therapy in a research study. If you want to participate in the TAP study extension, you have told your eye doctor that you understand the risks and benefits of thermal laser photocoagulation and that you do not want to have this thermal laser treatment.

Other than laser, it may be possible to surgically remove the abnormal blood vessel, but this procedure has important risks and is not proven. Some doctors are testing radiation treatment or various drugs for your condition. There is no treatment that is proven to work. Many patients prefer to have no treatment and simply allow a natural scar to form.

Confidentiality

Information derived from this study will be used for research purposes which may include publication and teaching. Your identity will be kept confidential. The drug's manufacturer, QLT PhotoTherapeutics Inc., and CIBA Vision Ophthalmics Inc., the Institutional Review Board of the investigational site, the United States Food and Drug Administration, and possibly other governmental authorities in the United States and Europe may be given access to your records upon request. They are all required to maintain your confidentiality.

Right to Withdraw

Your participation in the study and its extension is entirely voluntary, and you may withdraw from the study/study extension at any time even after signing this consent. The quality of care you will receive at this clinic will not be affected in any way if you decide not to participate or if you withdraw from the study. At the discretion of the Investigators or Sponsor of the study, it may be necessary to stop your treatment if significant side effects occur, if the protocol is not being followed, or for administrative or other reasons.

Compensation

In the unlikely event that you should be injured as a direct result of this study, you will be provided with emergency medical treatment. This treatment does not imply any negligence on the part of the clinic or any of the physicians involved. When applicable, the clinic reserves the right to bill third party payers for any emergency services rendered, medical treatment will be paid for in excess of insurance payment, by QLT PhotoTherapeutics Inc. and CIBA Vision Ophthalmics Inc., for any injury that is directly a result of treatment or study procedure in accordance with the protocol. The clinic does not have any program to provide compensation as a result of any injuries. You should be aware that by agreeing to participate in this study, you are not waiving any of your legal rights.

Right to Ask Questions

You are encouraged to ask any questions you may have about the study or your treatment as a research subject. Further information about any aspect of this study, including concerns about side effects, discomfort or injury, is available now or at any time during the course of the study from the principal Investigator, or from the study coordinator. You will be informed of any new significant findings which may affect your willingness to participate in the study.

Investigator: Phone: _____

Study Coordinator: Phone: _____

24h emergency contact or to obtain information:

Name: Phone: _____

Consent:

I am aware that the protocol and this Informed Consent has been reviewed and approved by the recognized Institutional Review Board at _____.

I have read or have had read to me the above pages concerning BPD-MA treatment of choroidal neovascularization. The purpose and procedures of this research project with its possible risks and benefits have been fully and adequately explained to me and I understand them. My questions have been answered to my satisfaction, and I voluntarily agree to participate as a subject in the research project under the conditions described. I understand that I have the right to withdraw from the study at any time without affecting the quality of care that I will receive. I have been given a copy of this consent form.

Date Name of Subject _____
Signature of Subject

Date Name of Witness _____
Signature of Witness

Date Name of Investigator _____
Signature of Investigator

ADDENDUM TO SAMPLE INFORMED CONSENT FORM FOR EXTENSION TO TAP INVESTIGATION

Investigator:

Risks and Discomforts

Collectively, about 700 patients have received verteporfin treatment in two masked clinical studies (TAP and VIP studies). Analysis of data from the first 24 months of the TAP study and the first 12 months of the VIP study have provided updated information on the safety of verteporfin therapy. In the ongoing TAP study, analysis of data from the first 24 months of the study showed that 402 of the 609 AMD patients were treated with verteporfin.

The following reports on adverse events reflect the package insert of the United States of America.

The most frequently reported adverse events to verteporfin are headaches, injection site reactions (including leaking of verteporfin into the skin and rashes) and visual disturbances (including blurred vision, decreased vision and spots in vision). These events occurred in approximately 10-20% of patients.

The following events, listed by where they occurred, were reported more frequently with verteporfin therapy than with placebo therapy and occurred in 1-10% of patients:

- In the Eye (cataracts, inflammation of the eye, dry eyes, itching, severely decreased vision, double vision, tearing and bleeding inside the eye)
- Other (weakness, back pain usually during drug infusion, fever, flu, sunburn, irregular heart beat, high blood pressure, blood circulation problems, varicose veins, skin problems, constipation, gastrointestinal cancers, nausea, anemia, too many or too few white blood cells, abnormal liver blood tests, protein in urine, elevated creatinine, joint disorder and pain, muscle weakness, abnormal sensations in the arm or leg, problems sleeping, dizziness, inflamed or sore throat, pneumonia, problems hearing, and prostate gland problems).

In the ongoing VIP study, analysis of data from the first 12 months of the study showed that 306 of the 459 patients (AMD or PM) were treated with verteporfin. Overall, the most frequently reported adverse events to verteporfin were visual disturbances (including decreased vision, blurred vision, and spots in vision) in 34% of VIP patients.

Severe vision loss (decrease in reading ability of 4 lines or more on the TAP/VIP eye chart) within 7 days of being treated has been reported in about 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 verteporfin group occurred primarily during infusion.

I am aware that this Addendum to the Informed Consent has been reviewed and approved by the recognized Institutional Review Board at _____.

I have read or have had read to me the above pages concerning the safety of verteporfin treatment of choroidal neovascularization. The possible risks and benefits have been fully and adequately explained to me, and I understand them. My questions have been answered to my satisfaction, I voluntarily agree to continue to participate as a subject in the research project under the conditions described. I understand that I have the right to withdraw from the study at any time without affecting the quality of care that I will receive. I understand that confidentiality and other information contained in the original consent form signed at the start of the TAP study remain in effect. I have been given a copy of the most current complete informed consent and of this addendum to the consent form.

Date Name of Subject Signature of Subject

Date Name of Witness Signature of Witness

Date Name of Investigator Signature of Investigator

APPENDIX 17

TAP Study Extension for Study Eye and Fellow Eye

TAP Study Extension M48 to M60

In order to participate in the fifth year of the TAP extension, a patient must be enrolled in TAP at the time of the Month 48 visit.

TAP Study Extension: Long-Term Safety Assessment at M60

An informed consent addendum has to be signed for the fifth year of the study extension (see sample informed consent addendum attached). The original informed consent document, that the patient signed at the beginning of the TAP Investigation and the most current safety information must be reviewed with the patient.

Any patient reaching the Month 48 visit will be asked to come back for a safety assessment visit at the Month 60 time point. It is the responsibility of the investigator to decide whether follow-up assessments of the patient any time prior to M60 are indicated depending on the stage of the disease. Between M48 and M60, no protocol specific study procedures are required. Active treatment in either eye can be offered between M48 and M60 at any time (but there will be no treatment at the Month 60 visit) at the discretion of the investigator.

A final visit should be conducted at the Month 60 visit, or earlier, if the patient discontinues the study prematurely. Study procedures required at the Month 60 visit, or the final visit, should be done according to the detailed descriptions of the TAP protocol dated May 5, 1997. These include visual acuity, peak contrast threshold, color fundus photography, fluorescein angiography, dilated ophthalmoscopy, assessment of concomitant medications and adverse events. There will be no active treatment provided at any final visit.

Where a patient discontinues the study prematurely and the patient received a PDT treatment to either eye as part of a final visit, a telephone follow up call must be made 2-4 days and 1 month post treatment to assess any possible adverse events.

Adverse Event procedures should be followed as outlined in section 12 of the TAP protocol.

Data Collection:

A CRF module for the final visit (M60) and a Last Visit module will be completed, including the following information:

- all adverse events (updates to ongoing AEs and new AEs) experienced during the fifth year of the extension using the AE page and Exhibit I, if required,
- all concomitant medications (updates to ongoing concomitant medications and new concomitant medications) used during the fifth year of the extension,

- Each treatment the patient received in the fifth year of the extension, will be recorded on a separate treatment page,
- The remaining assessments will be completed for the day of the final visit.

Sample Informed Consent Addendum

Investigator:

Introduction:

This information is given to you so that you can make an informed decision about whether or not to participate in the fifth year to the TAP research study. Take as much time as you wish to make your decision about signing the Informed Consent. You have the right to ask questions about any procedures before agreeing to be included in this study.

You have been asked to take part in the study extension because you have choroidal neovascularization (CNV), that is, growth of new, abnormal blood vessels under the retina in one or both eyes. Your CNV is due to age-related macular degeneration (AMD).

As you have been informed at the beginning of the study, verteporfin is an experimental drug, activated by light, which is being investigated for use in the treatment of ophthalmic diseases characterized by choroidal neovascularization. This treatment modality, called photodynamic therapy (PDT), has been used experimentally to treat AMD as well as skin cancer and psoriasis (a chronic skin condition). The treatment is now commercially available in more than 20 countries worldwide as Visudyne™ therapy to treat a certain type of CNV due to AMD.

In this extension, treatment will be given, at the discretion of your doctor, if needed, for up to 1 additional year.

Description and Explanation of Procedures:

The study requires your involvement for an additional period of up to 1 year. During that year, your eye doctor will determine when you will have check-up visits at the clinic. Routine follow-up assessments will be conducted during these check-up visits. If necessary, you will have Visudyne™ therapy to one or both eyes at or shortly after each of these check-ups. A final visit will be required at the end of that year (Month 60).

If you discontinue the study early and you received Visudyne™ therapy to either eye at a last study visit, a telephone follow up call will be made 2-4 days and 1 month post treatment to assess any possible adverse events.

If you experienced a severe drop in your vision after any treatment, we will ask you to come to the clinic for a visual acuity examination and possibly ophthalmoscopy, fluorescein angiography and color photography of your eye as described previously.

Right to Ask Questions

You are encouraged to ask any questions you may have about the study or your treatment as a research subject. Further information about any aspect of this study, including

concerns about side effects, discomfort or injury, is available now or at any time during the course of the study from your doctor or from the study coordinator. You will be informed of any new significant findings, which may affect your willingness to participate in the study.

Doctor: Phone:

Study Coordinator: Phone:

24 hour emergency contact or to obtain information

Name: Phone:

Consent

I am aware that this Addendum to the Informed Consent has been reviewed and approved by the recognized Institutional Review Board at _____.

I have read or have had read to me the above pages concerning the additional follow-up assessment at Month 60 and the care I will receive during this additional year in the TAP study. My questions have been answered to my satisfaction, I voluntarily agree to continue to participate as a subject in the research project under the conditions described. I understand that I have the right to withdraw from the study at any time without affecting the quality of care that I will receive. I understand that confidentiality and other information contained in the original consent form signed at the start of the TAP study, and any informed consent forms or addenda signed during the study remain in effect. I have been given a copy of the most current complete informed consent and of this addendum to the consent form.

Date	Name of Subject	Signature of Subject
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Date	Name of Witness	Signature of Witness
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Date	Name of Investigator	Signature of Investigator
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