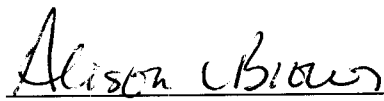



PROTOCOL No.: BPD OCR 003 AMENDMENT NO. 6 DATED 09 July 2002  
SPONSOR NAME: QLT Inc. and Novartis Ophthalmics  
DRUG NAME: VISUDYNE® (Verteporfin for Injection)  
PROTOCOL TITLE: A Randomized, Placebo-Controlled, Masked, Multicenter, Phase IIIB Study of the Treatment of New Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration or Pathologic Myopia using Photodynamic Therapy with Liposomal BPD-MA (verteporfin) DATED 19-DECEMBER, 1997

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PREPARED BY:

  
Alison L. Brown  
(Associate Director, Clinical Operations)

9 July 02  
Date


  
Jestina Doe-Anderson, PhD  
(Principal Clinical Scientist)

9 July 02  
Date


APPROVED BY:

The undersigned attest to the following:

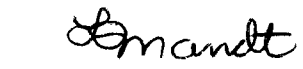
1. Reviewed the protocol amendment
2. Agree to its contents

  
Al Reaves, PhD  
(Therapeutic Head, Clinical Research)

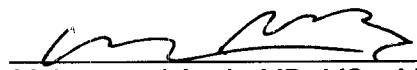
9 July 2002  
Date

  
Noel Buskard, MD, FRCP, FACP  
(Safety Officer)

July 15, 2002  
Date

  
Lawrence D. Mandt  
(Head, Quality and Regulatory Affairs)

15 July 02  
Date

  
Mohammad Azab, MD, MSc, MBA  
(Senior Vice President, Clinical Research & Medical Affairs and PRC Chairman)

11 JULY 2002  
Date

<b>PROTOCOL No.:</b>	<b>BPD OCR 003 AMENDMENT NO. 6 DATED 09 July 2002</b>
<b>SPONSOR NAME:</b>	QLT Inc. and Novartis Ophthalmics
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<b>REVISION NO. 1:</b>	Extend study duration
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Reason for Revision:	To extend the study duration for an additional 12 months (60 months total duration) so that long-term safety follow-up information can be obtained after open-label verteporfin treatment of patients with Pathologic Myopia (PM). If the patient requires a visit or treatment at a time other than the protocol required Month 48, 54, or 60 follow-up visits, a visit can be scheduled at the discretion of the investigator and an enrolled patient can be treated with study drug, if necessary (Note that no treatment is to be given at Month 60). These visits that are scheduled at the discretion of the investigator do not have to follow the requirements of the VIP protocol.
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**PROTOCOL No.:** BPD OCR 003 AMENDMENT NO. 6 DATED 09 July 2002

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Amendment:

## APPENDIX 2: STUDY PROCEDURES FLOWCHART FOR THE FIFTH-YEAR EXTENSION

Procedure	Treatment Period (Months)		
	48*	54	60
Medical History**		X	
Informed Consent	X	If not done at M48	
Inclusion/Exclusion <sup>a</sup>	X	If not done at M48	
Concomitant Medications	X	X	X
Pregnancy Tests <sup>b</sup>	X	X	
Best-Corrected Visual Acuity	X	X	X
Color Fundus Photography	X	X	X
Fluorescein Angiography	X	X	X
Dilated Ophthalmoscopy	X	X	X
PDT <sup>c</sup>	X	X	
Telephone Contact 2-4 days after treatment	X	X	
Adverse Events Assessment	X	X	X
<p>* The month 48 visit can take place only if IRB/EEC approval is granted prior to the patient completing the Month 48 Visit of the original extension.</p> <p>** Collect a medical history update (at Month 54 only) if the patient exited the study at Month 48 and re-entered the continuation.</p> <p><sup>a</sup> When a patient enters the extension study, the patient must meet the extension inclusion/exclusion criteria as defined in Amendment 6, dated 09 July 2002.</p> <p><sup>b</sup> A negative urine test is required within 3 days of any re-treatment in females of childbearing potential.</p> <p><sup>c</sup> Treatment must be conducted within 7 days of fluorescein angiography at scheduled follow-up visits, if protocol requirements are met. The Month 48 treatment can occur only if IRB approval is granted prior to the patient completing the Month 48 visit of the original extension and if informed consent and inclusion/exclusion criteria are met.</p>			

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## APPENDIX 19

### VIP Trial Open-Label Continuation of Extension Study

#### General Description

To participate in the extension study for an additional 12 months, the patients must have not been discontinued prematurely from the initial extension study and must meet the inclusion/exclusion criteria for the continuation of the extension study. With IRB approval, open-label treatment with verteporfin will be provided at Month 48 and at Month 54 to qualified eyes with CNV leakage as assessed by fluorescein angiography. No treatment will be administered at the 60-month visit.

Some PM patients may complete the 48-month visit and exit the VIP PM extension prior to approval of this amendment. Those patients will be allowed to enter the extension study at the Month 54 visit if they can satisfy the inclusion/exclusion criteria.

#### Informed Consent

The informed consent addendum must be signed prior to continuing in the extension to provide patients with the latest safety information (sample informed consent addendum is included).

#### Study Procedures

Routine study procedures should be performed during follow-up visits at 6-month intervals through the 60-month visit as described in the revised Appendix 2. The required procedures include the following: medical history update (if the patient exited the study at Month 48 and re-entered the continuation), best-corrected visual acuity, color fundus photography, fluorescein angiography, dilated ophthalmoscopy, pregnancy test (if required), telephone contact 2 to 4 days after treatment, and assessment of concomitant medication and adverse events. Vital signs, HQL assessments, subjective visual performance ratings, peak contrast threshold, and ICG angiography will not be done in the extension study. Verteporfin PDT treatment of qualified eyes should be performed at Month 48 and Month 54 if all criteria are met. At the first visit (48-month visit or later) for a patient with two qualified eyes that require treatment and neither eye has received prior open-label verteporfin treatment, only one eye (jointly decided between the investigator and the patient) can be treated at that visit. If no significant safety issues are identified, the second eye can be treated 4 to 14 days later following another infusion. At all subsequent visits when both eyes require treatment, one infusion of verteporfin should be administered and laser light should be applied first to the

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study eye and then to the fellow eye. For bilateral treatment, laser light should be applied to the second eye no later than 20 minutes from the start of the infusion. The document flow for reporting and evaluating ocular adverse events in either eye remains as described in the masked study. Serious Adverse Event procedures should be followed as outlined in section 12 of the VIP protocol. These procedures will be done at the last scheduled visit (month 60), but no treatment will be provided.

#### Inclusion Criteria for the Continuation of the Extension Study

To participate in the continuation of the extension study, a patient must have been enrolled in the extension study.

##### A. Study Eye

To qualify the study eye for continuing in the extension study, the patient must fulfill the following criteria at the first continuation visit:

1. Study eye was previously enrolled in the extension.

##### B. Fellow Eye

To qualify the fellow eye for the continuation of the extension study, the patient must have been previously enrolled in the extension and the fellow eye must fulfill the following criteria at or after the 48-month visit:

Previously enrolled fellow eye:

1. Fellow eye was enrolled in the extension study.

Never enrolled fellow eye:

1. Has a CNV lesion secondary to PM that involves the geometric center of the foveal avascular zone as determined by the investigator using fluorescein angiography.
2. Has potential for treatment benefit in their fellow eye according to their treating ophthalmologist even if there is an absence of CNV leakage.

#### Exclusion Criteria for the Extension Study

##### A. Study Eye

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The study eye does not qualify if any of the following criteria are met prior to continuing into the extension study:

1. Patient discontinued study eye treatment for any reason.
2. Patient received any surgical (submacular surgery, retinal translocation, etc.), radiation or subfoveal laser (photocoagulation) treatment of the study eye CNV lesion since completing the VIP 48-month visit.
3. Patient received any medicinal treatment of the study eye CNV lesion since completing the VIP 48-month visit. [Note: Open-label treatment with Visudyne PDT is allowed.]
4. Patient has participated in a clinical study other than VIP since completing the VIP 48 month visit.

**B. Fellow Eye**

The fellow eye does not qualify for continuing in the extension if any of the following criteria are met prior to enrolling into the continuation of the extension study:

1. Patient discontinued previously enrolled fellow eye treatment for any reason.
2. Patient received any surgical (submacular surgery, retinal translocation, etc.), radiation or subfoveal laser (photocoagulation) treatment of the previously enrolled fellow eye CNV lesion since completing the VIP 48-month visit.
3. Patient received any medicinal treatment of the previously enrolled fellow eye CNV lesion since completing the VIP 48-month visit.
4. Patient has participated in a clinical study other than VIP since discontinuing the Month 48 visit.
5. Has any of the following in the fellow eye: a tear (rip) of the RPE; any vitelliform-like lesion of the outer retina (e.g. as in pattern dystrophies or basal laminar drusen), any idiopathic parafoveal telangiectasis, any central serous retinopathy, or any serous pigment epithelial detachment without CNV. [Note: This exclusion is not applicable to a fellow eye that qualified and received treatment in VIP prior to the 48-month visit.]
6. Has any of the following conditions in the fellow eye: uncontrolled glaucoma, anterior ischemic optic neuropathy, clinically significant diabetic macular edema, severe non-proliferative or proliferative diabetic retinopathy. [Note: This exclusion is not

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applicable to a fellow eye that qualified and received treatment in VIP prior to the 48-month visit.]

7. Has subfoveal CNV in the fellow eye secondary only to any of the following conditions: ocular histoplasmosis syndrome (OHS), pseudo OHS, multifocal choroiditis (including punctate inner choroidopathy), angioid streaks or idiopathic CNV. [Note: This exclusion is not applicable to a fellow eye that qualified and received treatment in VIP prior to the 48-month visit.]
8. Fellow eye experienced severe vision loss from Visudyne fellow eye treatment prior to the 48-month visit.

#### Treatment and Retreatment Criteria

Once an eye is qualified for the continuation of the extension study, treatment and retreatment eligibility must be established by fluorescein angiography (early and late frames) to determine if CNV leakage is present and the size (GLD) of the CNV lesion. When both eyes are treatment candidates, it is the responsibility of the investigators in cooperation with their photographers to determine whether the appropriate fluorescein angiographic views can be achieved for both eyes during one visit or whether a separate visit will be required to capture the required angiographic information.

The initial extension treatment and any retreatment should be performed if evidence of CNV leakage is detected by fluorescein angiography. As described in the VIP protocol, each treatment or retreatment should be conducted within 7 days of the most recent fluorescein angiogram.

To be eligible for extension treatment or retreatment, patients must also fulfill the following criteria:

1. The investigator must consider that a qualified eye(s) has potential for treatment benefit. Each qualified eye must be considered independently.
2. Have no additional ocular disease that has developed and may compromise the safety of the eye(s). Cataract, that does not obscure visualization and treatment of the CNV, is allowed. Cataract that is considered to have significantly compromised the visual acuity should undergo corrective operation (see protocol Section 7.4).
3. It must be possible for the Investigator to visualize the lesion in the eye(s) considered for treatment.

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4. Have no retinal arteriolar or retinal venular non-perfusion caused by previous treatment to the eye(s) considered for treatment.
5. Women of childbearing potential must have a negative pregnancy test (urine) within 3 days of any retreatment and must use an effective method of contraception during the extension study.
6. Following the previous treatment, have no confirmed decrease in vision relative to pretreatment in either eye considered for treatment on Day 1 to Day 4 after treatment, of 20 letters or more in best-corrected visual acuity.

Every attempt should be made to re-treat a qualified eye(s) if it meets the retreatment eligibility criteria. If an eye qualifies for treatment but the treatment cannot be carried out, that eye must still undergo routine study procedures according to protocol.

#### Review and Retention of Photographs

Each center will individually evaluate their photographs (fluorescein angiograms and color fundus photographs) to determine if either eye qualifies (leakage, GLD, etc.) for treatment or retreatment. Confirmation of the investigator's angiographic findings by the Photograph Reading Center is not required prior to continuing a patient in the extension study. All photographs should be labeled as described in the VIP protocol and retained at the site. No photographs taken during the continuation of the extension study will be required for submission to the Photograph Reading Center unless needed to substantiate a serious ocular adverse event (Exhibit I) or unless specifically requested by the Photograph Reading Center or Sponsor.

#### Recording Extension Study Information

New worksheets and CRF pages specific to the extension study will be provided to record relevant information pertaining to the study.

Some patients may exit the VIP PM extension prior to the approval of the continuation of the extension study by their investigator's ethics committee. If any of those patients later qualify and continue in the extension study, their open-label treatment(s) with Visudyne PDT that occurred after exiting VIP PM extension should be recorded in the extension CRF as a concomitant medication. Additions or changes in significant medical history, underlying medical conditions and concomitant medications since exiting VIP PM extension should also be recorded. Adverse events that were ongoing when the patient exited VIP PM extension should be recorded and/or updated in the extension CRF.



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The visit month recorded on the initial extension continuation CRF should reflect the 6-month cycle of visits as continued from when the patient first entered the original VIP study.

#### Order of Treatments and Retreatments

All qualified eyes will be treated with verteporfin-PDT in open-label fashion using the same treatment parameters for verteporfin infusion and light application as described in the VIP protocol (6 mg/m<sup>2</sup>, 50 J/cm<sup>2</sup> beginning 15 minutes after starting the infusion). At the first visit where both eyes require treatment and neither eye has previously received open-label verteporfin treatment, the investigator and the patient should jointly decide which eye to treat first as described in the "Study Procedures" section of this amendment. At all other visits where both eyes require treatment at the same visit, one infusion will be administered and laser light should be applied first to the study eye and then to the fellow eye. For bilateral treatment, laser light should be applied to the second eye beginning no later than 20 minutes from the start of the infusion.

#### Termination From the Extension Study

The 60-month visit will be considered as the last possible visit in the extension study. Any patient who experiences a decrease in vision within 4 days of treatment in either treated eye of 20 letters or more in best-corrected visual acuity relative to pre-treatment must be discontinued from further treatment to either eye. These patients should be scheduled for follow-up evaluation at least until vision in that eye(s) returns to the pre-treatment level or until the investigator establishes that additional improvement in vision is unlikely.

#### Data Handling

Data obtained from the extension study will be summarized descriptively without formal statistical analyses. For the study eye, visual acuity scores will be summarized separately for patients who switch from placebo to active treatment during the extension, and for patients who continue on active treatment during the extension. Visual acuity scores for any fellow eyes that receive active treatment will be summarized beginning at the visit they were first treated.

All non-ocular adverse events that occur during the extension while patients are on open-label verteporfin treatment will be pooled and summarized with all adverse events from the verteporfin treatment group of the 2-year masked study. The ocular events will be summarized separately by study eye and by fellow eye, and, separately by masked treatment and by open-label treatment.

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#### Sample Addendum to Informed Consent

### SAMPLE INFORMED CONSENT FORM ADDENDUM FOR THE VIP EXTENSION CONTINUATION STUDY

#### Introduction:

This addendum is to provide you with information about a 12-month continuation of the 2-year extension to the VIP study and to provide you with updated safety information on the study drug (verteporfin). If you agree to continue to participate in the extension study, one or both of your eyes may be treated with active drug (verteporfin). During the extension study, your eye that was treated with masked medication in VIP will continue to be referred to as your 'study eye' while your other eye will be referred to as your 'fellow eye.'

If you require a visit or treatment at a time other than at your Month 48, 54, or 60 follow-up visits, another visit can be scheduled at the discretion of your investigator. At that visit, you and your doctor may choose to have your eye(s) retreated with study drug, if necessary. However, because Month 60 is your last visit, you will not receive treatment at this visit.

#### The VIP Extension Study:

If you participated in the VIP PM extension study, you will be examined to determine if you qualify for continuing in the extension study. Your fellow eye may also qualify if your doctor determines that it has CNV due to PM that might respond to treatment in the extension study. If you choose to participate and your study eye and/or fellow eye qualify for treatment, you will be examined every 6 months and treated with active drug (verteporfin) when necessary. All VIP procedures except for vital signs, quality of life interviews, visual performance ratings, peak contrast threshold and the ICG angiography will be done in the extension study. At the 60-month visit, you will be examined and you will not receive any treatment and the study will end.

#### Updated Safety Information on Verteporfin:

#### Risks and Discomforts

The following adverse events are from the US package insert for verteporfin.

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 10-30% of patients.

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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).

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 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 VIP 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

**PROTOCOL No.:** BPD OCR 003 AMENDMENT NO. 6 DATED 09 July 2002

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**REVISION NO. 2:** Administrative wording changes.

**Reason for Revision:** Administrative and/or wording changes were made to provide greater clarity to the protocol procedures.

**Amendment:** CIBA Vision changed to Novartis Ophthalmics throughout the protocol and appendices. QLT PhotoTherapeutics changed to QLT, Inc. throughout the protocol and appendices.

**REVISION NO. 3:** Contact information

**Reason for Revision:** To provide the investigational site with the most current contact information.

**Amendment:** Updated contact names and numbers as appropriate.

	Ronald Alder
	Clinical Research Monitor
	CIBA Vision AG, Hettlingen
	Grenzstrasse 10
	Bülach, Switzerland
	Telephone: 41 1 864 1552
	Telefax: 41 1 862 0762
Juho Peters	Sonja Bangerter
Medical Monitor	Clinical Research Monitor
CIBA Vision AG, Hettlingen	CIBA Vision AG, Hettlingen
Grenzstrasse 10	Grenzstrasse 10
Bülach, Switzerland	Bülach, Switzerland
Telephone: 41 1 864 1542	Telephone: 41 1 864 1542
Telefax: 41 1 862 0762	Telefax: 41 1 862 0762

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Telefax: 0034 3 246 54 22  
**Alison L. Brown**  
**Associate Director, Clinical Operations**  
**Novartis Ophthalmics, Inc.**  
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**Duluth, Georgia 30097**  
**Telephone: 770-905-1866**  
**Telefax: 770-905-1966**  
**E-Mail: alisonl.brown@pharma.novartis.com**  
Al Reaves  
Head, Clinical Project Management  
Novartis Ophthalmics, Inc.  
11695 Johns Creek Parkway  
Duluth, Georgia 30097  
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E-Mail: al.reaves@pharma.novartis.com

# **CLINICAL STUDY PROTOCOL**

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

**BPD OCR 003**

**“A Randomized, Placebo-Controlled, Masked, Multicenter, Phase IIIB Study of the Treatment of New Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration or Pathologic Myopia using Photodynamic Therapy with Liposomal BPD-MA (verteporfin).”**

**SHORT TITLE:            Verteporfin In Photodynamic Therapy (V.I.P.)**

**CONFIDENTIAL**

**QLT Inc.  
887 Great Northern Way  
Vancouver, British Columbia  
Canada V5T 4T5**

**Novartis Ophthalmics AG  
Grenzstrasse 10  
CH-8180 Bülach  
Switzerland**

**Novartis Ophthalmics Corporation  
11460 Johns Creek Parkway  
Duluth, Georgia 30097**

**REVISED PROTOCOL (Including Amendment 6): JULY 9, 2002**

**Original, dated December 19, 1997**

**Includes Amendment 1, dated February 23, 1998**

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## SIGNATURE PAGE FOR FINAL PROTOCOL

PROTOCOL NO.: BPD OCR 003

DATED: December 19, 1997

TITLE OF PROTOCOL: A Randomized, Placebo-Controlled, Masked, Multicenter, Phase IIIB Study of the Treatment of New Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration or Pathologic Myopia using Photodynamic Therapy with Liposomal BPD-MA (verteporfin).

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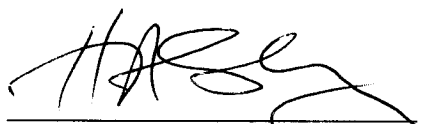
  
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Director, Clinical Research

Dec 19/1997  
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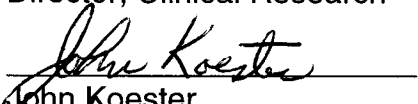
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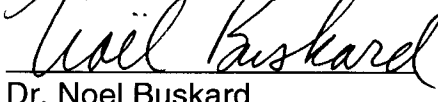
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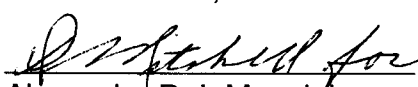
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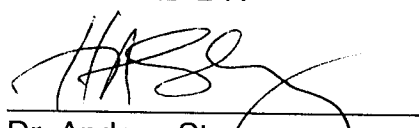
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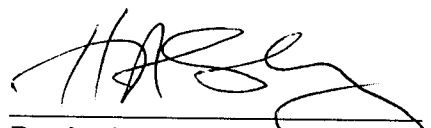
  
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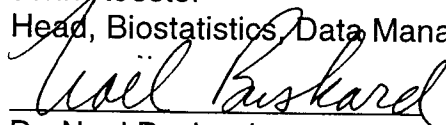
  
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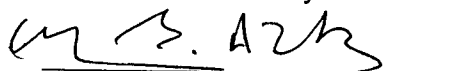
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## PROTOCOL SUMMARY

### **Study Title**

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

### **Study Objectives**

#### *Primary:*

To demonstrate that PDT of new subfoveal CNV will significantly improve or retain visual function compared to placebo (sham treatment).

To evaluate the safety of PDT.

#### *Secondary:*

- (1) To determine if PDT-induced improvements of visual function are associated with a better health-related quality of life (HQL) compared to placebo (sham treatment).
- (2) To determine if PDT reduces the risk of developing classic CNV in lesions that present as occult CNV with no classic CNV.

### **Study Design**

This will be a masked, multicenter, randomized, Phase IIIB study of the treatment of new subfoveal choroidal neovascularization (CNV) secondary to Age-Related Macular Degeneration (AMD) or Pathologic Myopia (PM) using photodynamic therapy (PDT) with liposomal Benzoporphyrin Derivative Monoacid Ring A (BPD-MA verteporfin) compared to placebo in patients with a relatively good best-corrected visual acuity (visual acuity score  $\geq 50$ , or approximately 20/100 or better on the ETDRS chart).

A stratification based on the etiology of the CNV (AMD versus PM) will occur prior to randomization. Overall, approximately 16 North American and 12 European centers will enroll about 400 of these patients (about 15 patients per center) to obtain 240 evaluable patients with CNV secondary to AMD and up to 90 patients with CNV secondary to PM.

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 or designate 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 center.

Outpatients with new subfoveal CNV secondary to AMD (aged 50 years or older) or to PM (aged 18 years or older) 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 best-corrected visual acuity using modified ETDRS charts and on contrast threshold using Pelli-Robson charts.

The primary efficacy analysis will be the proportion of patients with new subfoveal CNV secondary to AMD or to PM who are classified as responders based on their best-corrected visual acuity. Three definitions of responder will be used in both AMD and PM groups: (i) patients whose vision is better than baseline or stable ( $< 8$  letters loss) relative to baseline, (ii) patients losing less than 3 lines of vision ( $< 15$  letters) compared to baseline, and (iii) patients losing less than 6 lines of vision ( $< 30$  letters) compared to baseline. The primary efficacy criteria in PM will be (i) while the primary efficacy criteria in AMD will be (ii). 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. The primary analysis will be conducted when all patients have completed their 12-month follow-up visit. Although the sponsor will be unmasked at this point, the patients, treating ophthalmologists, vision examiners and Reading Center graders will remain masked unless the study is terminated based on this analysis. The trial will be continued to 24 months to provide additional data on long term safety and efficacy. For PM patients only, an interim evaluation of responder rate in each treatment group will be conducted either at the time when at least 10 patients are considered treatment failures (non-responders) according to efficacy criterion (i) or, when 60 patients have completed at least the 3-month visit, whichever is sooner. On the basis of this interim evaluation, the PM sample size may be changed.



	Study Arms	
	PDT	Sham
Drug Dose (mg BPD-MA/m <sup>2</sup> )	6	0
Light Dose (J/cm <sup>2</sup> )	50	50
Time of Light <sup>a</sup> (min.)	15	15
Evaluations	3-month intervals	3-month intervals
Retreatment <sup>b</sup>	3-month intervals	3-month intervals
Interim Safety Analysis	6-month intervals	6-month intervals
Interim Efficacy Analysis	PM only <sup>c</sup>	PM only <sup>c</sup>
Primary Analysis	Month 12	Month 12
Study Extension	To 2 years	To 2 years

<sup>a</sup> Time of light administration after the start of a 10-minute drug infusion

<sup>b</sup> Retreatments if there is fluorescein angiographic evidence of leakage

<sup>c</sup> The interim efficacy analysis in PM will be conducted when at least 10 patients are considered failures, or when 60 patients have completed at least 3-month visit, whichever is sooner.

## Study Procedures

Within 7 days before the initial treatment day, after informed consent has been signed and dated by the patient, all patients will be screened to determine if they conform to the inclusion and exclusion criteria. Baseline assessments will include an interview to determine patients HQL (using the NEI-VFQ-25 in French- German- and English-speaking patients only) a laboratory profile including hematology and serum chemistry; pregnancy test (where required); medical history including underlying conditions present and a physical examination including measurement of blood pressure and heart rate. All patients will have an ophthalmic evaluation including manifest refraction using modified ETDRS visual acuity charts and protocol, contrast threshold assessment (using the Pelli-Robson chart), dilated ophthalmoscopy, standardized color stereoscopic fundus photography and fluorescein angiography.

If available, an ICG angiography can also be performed as an ancillary study in combination with the fluorescein angiography but the ICG data may not be used as the basis for treatment decisions.

All patients will subjectively assess their visual performance of the study eye by grading it on a 0 to 100 points scale, where 0 would be considered as blind in the study eyes and 100 as perfect vision in the study eyes.

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 labeled and sent to the Photograph Reading Center for retrospective confirmation of eligibility and grading of lesion characteristics at baseline and 12- and 24-month follow-up examinations. Any ICG angiograms collected at these times will also be sent to the Photograph Reading Center. If patients are prematurely lost to follow-up, the angiograms

from the last visit will also be sent to the Photograph Reading Center. In the event of any disagreement regarding eligibility, the Photograph Reading Center's assessment will rule.

On the day of randomization, eligible patients will be allocated to one of two possible strata : AMD or PM. They will be assigned randomly within each strata to active or placebo treatment in a ratio of 2:1 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 designate 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 3 months after each treatment.

Two to four days after each treatment, all patients will be contacted by telephone to determine if any adverse event has occurred. If the patient reports a significant loss of vision in the treated eye within 4 days after treatment, the patient will be advised to visit the clinic as soon as possible or at least 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, ICG angiography (if available), color fundus photography and ophthalmoscopy will be performed to help define the relationship of the vision loss to therapy and angiograms/photographs will be sent to the Photograph Reading Center as soon as possible. The patient will be asked to return for re-evaluation (best corrected visual acuity with the ETDRS charts, contrast sensitivity, fluorescein angiography, color fundus photography and ophthalmoscopy) at week 2 and at week 4 after their last treatment to monitor the progress of their condition. Vision losses of  $\geq 20$  letters since the last assessment, that occur within 7 days of the last treatment, will be reported on an expedited basis to the sponsors as a serious adverse event. If any treatment-related branch retinal artery or vein occlusion is observed after any treatment, the patient will be excluded from further treatment but will continue to return for vision and HQL assessments. Likewise, patients experiencing significant vision decreases in their treated eye of 20 letters or more in best-corrected visual acuity that was confirmed 1 to 4 days (Day 1 to Day 4) after treatment (Day 0) relative to pre-treatment will be excluded from further treatment but will continue to return for vision and HQL assessments.

The patient will be phoned by the investigator or study coordinator or designate  $4 \pm 1$  weeks after each treatment in order to record the patient's subjective score of the visual performance of the study eye (0 to 100 scale).

Every 3 months, all patients will visit the clinic and will undergo dilated ophthalmoscopy, assessments of visual acuity, contrast threshold, color fundus photography and fluorescein angiography (ICG angiography is optional). Visual acuity and contrast threshold will be determined by a masked vision examiner. At each follow-up visit, the patients will also provide their subjective score of the visual performance of the study eye. Retreatment will be conducted if evidence of CNV leakage is detected by fluorescein angiography providing the patient has not experienced a significant decrease in vision in the treated eye of 20 letters or more in best-corrected visual acuity that was confirmed 1 to 4 days (Day 1 to Day 4) after treatment (Day 0) relative to pre-treatment. 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, the 12 and 24 month angiograms and photographs 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. Angiography and photography conducted at visits other than baseline, 12 and 24 months must be conducted to the same high standards outlined in this protocol, but records will be maintained at the treating centers. If patients are lost to follow-up, the angiograms/photographs from the last visit will be sent to the Photograph Reading Center.

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

HQL interviews with English- French- and German-speaking patients will be conducted within 2 weeks after the 6, 12, and 18 month follow-up visits, and, within 28 days before the 24-month visit.

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, hemorrhage, and other markers associated with disease progression.

# **1. INTRODUCTION**

## **1.1 Public Health Importance**

### **1.1.1 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).

### **1.1.2 Choroidal Neovascularization Secondary to Pathologic Myopia.**

#### **Public Health Impact of Pathologic Myopia**

Pathologic myopia has been reported to be the seventh leading cause of blindness in the United States (4) and is often associated with the development of choroidal neovascularization (5). The importance of CNV in pathologic myopia may be of even greater impact where pathologic myopia is endemic, such as in certain Asian populations in the United States, Canada, and Asia.

## **1.2 Current Therapy**

### **1.2.1 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 (6,7). Current treatment relies on occlusion of the vessels using laser photocoagulation (8). 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 (9,10). Also, recurrences are common following standard laser treatment (11). Furthermore, the majority of lesions which have poorly defined boundaries, or that are large,

are not amenable to standard laser treatment (12). 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 (9). 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.

### **1.2.2 Pathologic Myopia**

#### **Treatment of CNV in Pathologic Myopia**

Extrapolating from successful treatment of CNV for extrafoveal and juxtafoveal lesions due to AMD, OHS, or idiopathic lesions, several reports have described stabilization of vision following laser photocoagulation of these lesions (5,13,14). Unfortunately, the benefits of this treatment have not been shown to persist beyond one to two years, predominantly because of the development of subfoveal recurrent CNV (14). Furthermore, laser photocoagulation has not been recommended for CNV lesions due to pathologic myopia that extend into the foveal center because the amount of iatrogenic visual loss from laser photocoagulation might be greater than the amount of visual loss from no treatment in some cases. Nevertheless, many cases left untreated still will develop significant visual loss; treatment for these new or recurrent subfoveal lesions require an intervention not as rapidly destructive as laser photocoagulation. Submacular surgery has not been shown to produce any beneficial results in selected cases reported to date (15). Therefore, there is no proven treatment for subfoveal CNV from pathologic myopia 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 (16, 17, 18). Photosensitizing dyes are preferentially retained in tumors, particularly the neovascular tissue of tumors, which allows for selective treatment of this pathologic tissue (19, 20). After exposure to light at a wavelength absorbed by 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 (19, 21, 22). Possible cellular targets include the cell membrane, mitochondria, lysosomal membranes, and the nucleus (23). Evidence from tumor and neovascularity 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 tumor death via occlusion of the vasculature feeding the tumor, as well as through its direct cytotoxic effect

on tumor cells (24,25). 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 (26).

#### **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 neovascular 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 (27). Neoplastic tissues and neovascularization within tumors have been shown to have increased numbers of LDL receptors (28) and this is believed to be a major mechanism of enhanced selectivity of BPD-MA for these tissues. Terminal plasma elimination half-life mean values range from approximately 5 to 6 hours for the two regioisomers of BPD-MA (29). It is cleared primarily via bile and feces (90%), with less than 1% cleared via the kidneys and urine (30).

## **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 (31,32) and also that experimental corneal neovascularization can be selectively destroyed (33).

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 (34,35,36). These workers have also demonstrated angiographically that BPD-MA selectively localizes in the CNV (37).

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

A Phase I/II 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) secondary to any cause 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 were treated using five different treatment regimens to assess the safety and efficacy of light dose escalation.

Although complete absence of fluorescein dye leakage 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 of 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/m<sup>2</sup> BPD-MA infusion. Twelve weeks after PDT treatment, the extent of leaking CNV was less than at baseline in the majority of patients treated with either Regimen 2 or 4. Retreatment of lesions at 2-6 week intervals with Regimens 2 and 4 in nearly 40 patients was effective at stopping the CNV leakage that had recurred. However, the persistence of absence of CNV leakage 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<sup>2</sup> when applied either 20 minutes after 6 mg/m<sup>2</sup> BPD-MA (Regimen 2) or 30 minutes after 12 mg/m<sup>2</sup> BPD-MA (Regimen 3). At this dose inner 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.

The pattern of CNV non-perfusion induced by PDT and the subsequent recurrence of perfusion of the CNV, as determined by fluorescein angiography, appeared to be similar whether the CNV was secondary to AMD or PM. However, the average visual acuity improvement that was observed 1 week after PDT was larger in the eyes (n= 11) with CNV secondary to PM. Also, this average visual acuity improvement was sustained throughout the 3 months of follow-up only in the eyes with CNV secondary to PM.

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<sup>2</sup> 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.

#### **Phase IIIA:**

The Phase I/II 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 supported our rationale to initiate pivotal Phase IIIA studies to evaluate the safety and efficacy of quarterly treatments of CNV secondary to AMD. Two Phase IIIA studies (TAP) were initiated in December 1996. Enrollment was closed recently during September 1997. 609 patients were randomized to treatment, of which two-thirds received active PDT. To date, there have been no safety concerns raised by an independent committee of ophthalmologists and statisticians who are monitoring safety issues.

### **2.3 Rationale for this Phase IIIB study (VIP)**

#### **2.3.1 CNV Secondary to AMD**

The patient inclusion criteria in Phase IIIA (TAP) studies were designed to include patients with CNV lesions secondary to AMD associated with a rapid progression of vision loss (i.e. lesions containing at least some classic CNV and patients who still had significant vision to lose in the study eye), thereby increasing the probability of demonstrating a clinically and statistically significant benefit of PDT intervention.

The pathogenesis of AMD is poorly understood, especially in the neovascular stages. The CNV lesions included in the TAP study were of unknown age and therefore many may have progressed to a late stage that may not have been optimally amenable to treatment with PDT. The time course of progression from newly developed fibrovascular CNV to a mature scar is highly variable (usually 3 to 36 months). In most cases, the mature scar and leveling off of visual loss will develop within 2 to 3 years, although some cases may continue to grow and scar and have continued visual loss beyond 5 years after presentation. It is evident that many of the photoreceptors overlying the CNV lesions are still functional during this time (relatively good central vision can often be found for considerable time in some eyes with very large CNV lesions). However, the fibrovascular tissue in long-standing CNV lesions may have caused irreversible disruption of the normal anatomy that, in time, likely will lead to irreversible photoreceptor atrophy and vision loss. Therefore if there has been a CNV-induced irreversible change in the anatomy, PDT may be unable to preserve significant affected macula from the destructive effects of long-standing CNV even though it might have destroyed the CNV lesion without significant



iatrogenic damage. Therefore, in VIP, we aim to select CNV lesions that are considered to be in an early stage of the disease progression.

Although lesions with occult component of CNV were allowed in TAP, occult CNV lesions with no classic CNV were not selected for the TAP investigation because the natural history of vision loss associated with some occult only lesions is slower than that in classic CNV-containing lesions. At present, these occult only CNV lesions do not have any treatment options. However, as many as 60% of patients with wet AMD present with occult only CNV. While the results of the TAP investigation may adequately show that primarily occult lesions respond well to verteporfin-PDT, there is a clinical interest in studying PDT in occult only lesions. PDT with verteporfin is theoretically an appropriate treatment to administer to these occult only CNV lesions types. The long wavelength (690 nm) that is used to activate verteporfin adequately penetrates through blood whose absorption cuts off at about 650 nm and there is no reason to suspect that the 690 nm wavelength cannot penetrate through the RPE layer.

The intent of the VIP trial is to broaden our experience of PDT both in new occult-only CNV lesion types that were excluded from TAP, and in new CNV lesions with classic CNV and visual acuity better than 20/40 who were also excluded from the TAP studies.

The average best-corrected visual acuity (better than 20/100) in VIP will be much better than that in TAP. The TAP study required a visual acuity range from 20/40-20/200 for inclusion, so the vision loss from normal vision (20/20 or better) was already significant, ranging from 3 to  $\geq 10$  lines. It is known from previous studies that patients with better baseline vision will lose more vision than those with worse baseline vision. Therefore beneficial effects of PDT on vision preservation may be more pronounced in VIP than in TAP. The positive effect of treatment-induced vision preservation on health-related quality of life and overall subjective visual performance also may be easier to demonstrate.

### **2.3.2 CNV Secondary to Pathologic Myopia**

Results from the Phase I/II study in a limited number of eyes with CNV secondary to Pathologic Myopia were very promising with respect to visual acuity improvement. Independent of the treatment regimen tested, the visual acuity improved in all eyes tested when assessed at 1 week after PDT and these improvements were generally sustained throughout the 12 weeks of follow-up. Repeat treatments in a subset of these patients also appeared effective at reclosing the CNV and safe with respect to the visual acuity. Another significant objective of the VIP trial is to broaden our experience of PDT in subfoveal CNV secondary to Pathologic Myopia.

## **2.4 Risk/Benefit**

Patients with subfoveal CNV secondary to AMD usually develop severe, irreversible visual loss. Within two years most affected eyes will have poor central vision (worse than 20/200) without treatment (7). Current treatment with thermal laser photocoagulation is limited to a small minority of cases because it destroys viable photoreceptors overlying the CNV, and results in immediate vision loss. Thermal laser photocoagulation cannot be used at all in subfoveal occult CNV lesions. The only options for the majority of patients are either no treatment or experimental, unproven therapies such as macular surgery, radiation therapy or antiangiogenic therapy.

Patients with subfoveal CNV secondary to PM have, overall, a slower course of central vision loss than AMD patients with subfoveal CNV. Visual acuity can wax and wane over many years although in general the long-term prognosis is poor. Currently, there are no proven, acceptable treatments for subfoveal CNV secondary to PM. PDT has the potential to significantly improve the visual acuity in these eyes by reducing the subretinal CNV-induced fluid and resulting metamorphopsia.

## **3. STUDY OBJECTIVES**

### *Primary:*

To determine if PDT of new subfoveal CNV will significantly improve or retain visual function compared to placebo (sham treatment).

To evaluate the safety of PDT.

### *Secondary:*

- (1) To determine if PDT-induced improvements of visual function are associated with a better health-related quality of life compared to placebo (sham treatment).
- (2) To determine if PDT reduces the risk of developing classic CNV in lesions that present as occult CNV with no classic CNV.

## **4. STUDY PLAN**

### **4.1 Overall Design and Plan of Study**

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

Patients who meet all the inclusion criteria will be randomized to either PDT or placebo in a ratio of 2:1 in 1 of the 2 strata: AMD or PM. 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 be stratified by clinical center. Each regimen will constitute a single treatment administered every 3 months if evidence of CNV leakage is detected on fluorescein angiography.

#### PDT Regimen

- 10-minute infusion of 6 mg/m<sup>2</sup> BPD-MA
- light application of 50 J/cm<sup>2</sup> 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/cm<sup>2</sup> at 15 minutes after the start of infusion.

Outpatients with new subfoveal CNV and vision  $\geq$  50 letters (approximately 20/100 or better on the ETDRS chart) will be enrolled in the study.

The primary efficacy variable for AMD patients will be the visual acuity responder rate defined as a loss of less than 3 lines (<15 letters) of vision compared to baseline. The primary efficacy variable for PM patients will be the visual acuity responder rate defined as a loss of less than 8 letters compared to baseline. For PM patients only, an interim evaluation of responder rate will be conducted when at least 10 patients are considered treatment failures (non-responders) to the primary responder criterion or 60 patients have completed 3 months follow-up, whichever is sooner. Primary analyses will be conducted when all patients have completed their 12-month follow-up visit. We plan to publish the findings of this 12-month analysis and may continue the trial to 24 months to provide additional data on long term safety and efficacy.

Health-related quality of life interviews will be conducted before treatment and within 2 weeks after the 6, 12, and 18 month visits, and, within 28 days before the 24-month visit.

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 coordinator or designates and photographers will undergo training on all protocol procedures. During the enrollment phase of the study, only investigators who have successfully been certified as treating ophthalmologists for the TAP study or for this protocol 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, ICG 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. Visual acuity examiners certified for the TAP study will also be eligible to conduct vision measurements in this study.

The Photograph Reading Center will evaluate the baseline, 12 and 24-month stereoscopic color fundus photographs, fluorescein and ICG angiograms. To assess consistency, ten percent of the fundus photographs, fluorescein and ICG angiograms will be regraded by a grader from the Photograph Reading Center. To assess consistency in grading within each investigative site, centers may be asked to send selected photographs from visits at 3, 6, 9, 15, 18 and 21 months to the Photograph Reading Center for quality assurance checks including leakage and size of retreatment. The necessity of these additional quality assurance checks will be based primarily but not exclusively on observations from the baseline and the 12 month visit photographs provided to the Photograph Reading Center.

For AMD patients that were judged to be eligible because of anatomic deterioration, centers may be asked to send the pre-study FA photographs to the Photograph Reading Center to document the anatomic deterioration that occurred within 3 months of screening.

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.

QLT Standard Operating Procedures will be followed by the sponsor staff in the conduct and reporting of this study.

## **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 the study in the event of overwhelming short term efficacy in favor 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:

<b>Ophthalmologist, Epidemiologist:</b>	Roy Beck MD, Ph.D. Jaeb Center for Health Research, Inc., Tampa Committee Chairman
<b>Epidemiologist, Retinal Specialist</b>	Ronald Klein, MD University of Wisconsin
<b>Biostatistician:</b>	Maureen Maguire, Ph.D. Scheie Eye Institute, Philadelphia
<b>Retinal Specialists:</b>	Gabriel Coscas, MD Creteil Hospital, Paris  Lee Jampol, MD Northwestern University, Chicago  A. F. Deutman, MD Academisch Ziekenhuis Nijmegen, The Netherlands  A. C. Bird, MD 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 (Appendices 15 and 16). Any proposed amendment to the existing protocol will also be discussed with this group.

Current full-time members of the Study Advisory Group are:

##### *External:*

Dr. Neil M. Bressler, Committee Chairman, Wilmer Ophthalmological Institute, Baltimore, USA  
Dr. Susan Bressler, Wilmer Photograph 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. Andrew Strong, QLT Inc., Vancouver, Canada  
Dr. Ulrike Manjuris, QLT Inc., Toronto, Canada  
Dr. Al Reaves, Novartis Ophthalmics, Atlanta, USA  
Dr. Gustave Huber, Novartis Ophthalmics, Bülach, Switzerland

Additional investigators and study coordinators are invited to participate in the Study Advisory Group. These additional members will act as rotating members to represent the VIP SAG with a 1 year tenure.

## **5. STUDY POPULATION**

An estimated 28 centers will enroll approximately 400 patients to obtain 240 evaluable AMD patients and up to 90 evaluable PM patients for the study. For sample size calculations refer to Section 13.1. Approximately 16 North American centers and 12 European Centers will be initiated (See Appendix 10 for list of Investigators).

Each center must have the ability to enroll 15 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 fulfill the following criteria during the screening assessments: (Note: Criteria 1, 3, 6, 7, 8, and 9 apply to all patients while criterion 2 applies only to AMD patients and criterion 5 applies only to PM patients)

1. Have subfoveal CNV secondary to Pathologic Myopia alone or new subfoveal CNV secondary to Age-Related Macular Degeneration alone.
2. Lesions with occult CNV but no classic CNV must either contain blood or must have shown a progression of the disease within the preceding 3 months before randomization to treatment.

For the purpose of this study, disease progression is defined as either:

- i) a documented loss of 6 or more letters of vision using best-corrected visual acuity assessments with the ETDRS chart (VIP protocol)

or:

- ii) documented fluorescein angiographic evidence of a  $\geq 10\%$  increase in the lesion's greatest linear dimension.

3. All study eyes must have a best-corrected visual acuity score  $\geq 50$  or approximately 20/100 or better on ETDRS chart except eyes with new classic CNV-containing lesions secondary to AMD which must have a best-corrected visual acuity score  $\geq 70$  (better than approximately 20/40).
4. (This criterion was deleted by Amendment No. 2, dated July 16, 1998.)
5. If subfoveal CNV is due to Pathologic Myopia there must be fundus manifestations consistent with this diagnosis (e.g. lacquer cracks) and at least one of the following must apply.
  - a) the spherical equivalent must be equal to or more negative than -6 diopters.
  - b) the axial length must be  $\geq 26.5$  mm
6. Be considered able to return for all study visits.
7. Females of childbearing potential must have a negative pregnancy test (blood) before inclusion in the study and must use an effective method of contraception during the study. Negative pregnancy tests (urine) will be required before any retreatment.
8. Be willing and able to provide written informed consent. Patients who are eligible for laser photocoagulation, or who will be enrolled into the HQL, or other ancillary studies, should sign the respective informed consent.
9. Be aged 18 years or greater with Pathologic Myopia or 50 years or older with AMD.

## 5.2 Exclusion Criteria

Patients may not be randomized to treatment if:

1. Color photography and fluorescein angiography shows :
  - a) CNV does not involve the geometric center of the foveal avascular zone.
  - b) the area of CNV (classic plus occult) is less than 50% of the total lesion, (not including areas of prior laser treatment).
  - c) the greatest linear dimension of the entire CNV lesion exceeds 5400 $\mu$  diameter (approximately equivalent to the diameter of the 9 MPS disc area circle) at the initial treatment,
  - d) patient meets criteria for subfoveal confluent laser photocoagulation but is not willing/able to sign an additional informed consent indicating refusal to submit to laser photocoagulation.
  - e) the study eye has a tear (rip) of the RPE; a vitelliform-like lesion of the outer retina (e.g. as in pattern dystrophies or basal laminar drusen), idiopathic

parafoveal telangiectasis, central serous retinopathy, or serous pigment epithelial detachment without CNV.

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, anterior ischemic optic neuropathy, clinically significant diabetic macular edema, severe non-proliferative or proliferative diabetic retinopathy.
3. Subfoveal CNV secondary to ocular histoplasmosis syndrome (OHS), pseudo OHS, multifocal choroiditis (including punctate inner choroidopathy), angioid streaks or idiopathic CNV.
4. Inability to obtain photographs to document CNV, e.g. due to media opacity, allergy to fluorescein dye or lack of venous access.
5. Patients with cataract which, in the investigator's opinion, would progress during the course of the study and would affect central vision in the study eye. Such cataracts may be removed at least 2 months before entering the patient in the study.
6. History of treatment for CNV other than confluent laser photocoagulation in the study eye such as PDT, submacular surgery, radiotherapy or macular scatter ("grid") laser photocoagulation (including prophylactic macular scatter ("grid")).
7. Are participating in another ophthalmic clinical trial requiring follow-up examinations or are receiving, or have received any experimental systemic treatment for the CNV (e.g. retinoic acid, thalidomide) or any other investigational new drug within 12 weeks prior to the start of study treatment.
8. 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.
9. Have unstable heart disease (Class III or IV disease according to the New York Heart Association's functional criteria).
10. Have porphyria or other porphyrin sensitivity or hypersensitivity to sunlight or bright artificial light.
11. Have any acute illness observed during screening which is undiagnosed. Have any diagnosed illness whose presence is considered to be a safety risk for treatment to be administered.
12. Have uncontrolled hypertension on repeated measurements (SBP > 180 mmHg and DBP > 100 mmHg).



13. 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.

The randomization number is a 6 digit number and will include the letter V as the first digit, the center number (01-28) as the second and third digits, the strata (A = AMD, P = PM) as the fourth digit, and the patient number (01-98) as the last 2 digits. Within each center, patients with AMD will be sequentially assigned patients numbers between 01 and 49 while those with PM will be sequentially assigned numbers between 50 and 98. For example, the first patient with AMD randomized in center 01 will receive a randomization number of V01A01. The randomization numbers must be allocated sequentially within each strata (e.g. first AMD patient: V01A01, second AMD patient: V01A02). The treatment allocated to a specific randomization number will be in a sealed envelope which may only be opened by the study coordinator or designate/nurse preparing the infusion after all verification checks (material and patients) 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 or designate'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 or designate), 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) and used in the TAP investigation. In order to eliminate bias in measurement of the primary efficacy endpoint, vision examiners will also be masked. The vision examiner will 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. In order to maintain masking and avoid bias in angiographic evaluation, Investigators should not examine the follow-up ICG angiograms.

Fundus photographs, fluorescein and ICG angiograms from baseline, 12-month and 24-month visits (or any last visit for patients lost to follow-up) will be coded with labels provided by the study monitor and forwarded to the Wilmer Photograph Reading Center at The Johns Hopkins University in Baltimore, U.S.A. for masked evaluation of patient eligibility and treatment effects.

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 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, Labeling 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 designate or authorized personnel. Used vials will be checked by the Sponsors. At the conclusion of the study, the trial sites will return the supplies (used and unused vials) 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/m<sup>2</sup> of BPD-MA or placebo. The second step of light irradiation at a dose rate of 600 mW/cm<sup>2</sup> 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/cm<sup>2</sup> 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/cm<sup>2</sup> 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 <sup>2</sup> )	6	0
Light Dose (J/cm <sup>2</sup> )	50	50
Light Dose Rate (mW/cm <sup>2</sup> )	600	600
Time of Light Administration <sup>a</sup> (min)	15	15
Duration of Light Exposure (secs)	83	83

<sup>a</sup> 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/m<sup>2</sup> body surface area) will be administered over 10 minutes. Refer to Appendix 4 for detailed infusion preparation and instructions. Light doses of 50 J/cm<sup>2</sup> 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, utilizing 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/cm<sup>2</sup>) 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. An ICG angiogram can be performed if available as an ancillary study to the fluorescein angiography. The information from the ICG angiogram may not be used to determine the size of the treatment spot. Training in identification of the lesion components and estimation of the maximum diameter of the lesion by fluorescein angiography 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.

Cataract surgery should be performed at least 2 months before entering the patient in the study if the patient has cataract that does not allow visualization of the CNV lesion at the time of screening, or early cataract which, in the investigator's opinion, will naturally progress during the study and affect central vision and visualization of the CNV lesion. 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/m<sup>2</sup> 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 mucosal membranes. No skin or ocular photosensitivity reactions have been reported in 138 patients treated with 6-12 mg/m<sup>2</sup> 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 24 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 1 day 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.

In case of extravasation, to prevent any direct skin photosensitivity, the site of extravasation will be covered by the unmasked study personnel for at least 48 hours. (Additional instructions in case of extravasation can be found in Appendix 4).

## **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)**

- Written Informed Consent (Drafts provided in Appendix 11 [laser ineligible] and Appendix 12 [laser eligible], ICG angiography [Appendix 13], HQL [Appendix 14] as appropriate).
- Demographic data including patient's initials, date of birth, sex, race.
- Health-related quality of life interview (see Appendix 14)
- Ophthalmic Examination and identification of CNV
  - Subjective Visual performance (0 to 100 scale)
  - Best-corrected visual acuity (see Appendix 6)
  - Contrast threshold (see Appendix 7)
  - Color fundus photography (see Appendix 8)
  - Fluorescein angiography (see Appendix 8)
  - Optional ICG angiography (see Appendix 13)
  - 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)
- Patient's body weight (kg), height (cm), body surface area (m<sup>2</sup>)
- Concomitant medications
- Eligibility checks according to the inclusion/exclusion criteria
- Pregnancy test (blood test for females of childbearing potential)

The fluorescein and ICG angiograms and color 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 angiograms 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.

ICG Angiographic assessments may be conducted at the discretion of the investigator under the ancillary protocol in Appendix 13 but may not be used as a basis for treatment decisions.

### 9.1.1 Identification of CNV Secondary to Age-Related Macular Degeneration or Pathologic Myopia

There must be angiographic evidence of CNV under the geometric center of the foveal avascular zone (FAZ) secondary to Age-Related Macular Degeneration or Pathologic Myopia. The area of CNV 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 where the greatest linear dimension of at least one druse is > 63 microns, 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.

**Pathologic Myopia (PM):** CNV in PM is often associated with lacquer cracks. Fuch's spots are also prevalent in PM. Similar disorders of the outer retina as those seen in AMD are observed.

**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 color photographs (corresponding to either hyperplastic pigment or fibrin or fibrous tissue or blood not apparent on color 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**

Samples of draft informed consents are provided in Appendices 11 (laser ineligible lesions) and 12 (laser eligible lesions).

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 and ICH 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 date and sign the IRB- and Sponsor-approved informed consent form in the presence of a witness when applicable before conducting non-standard tests (e.g., laboratory examinations) at screening. If a patient is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion and, then, sign and date the consent form.



### **9.2.2 Institutional Review Board (IRB) or Ethics Committee**

The appropriate IRB or Ethics Committee must review this protocol and the informed consent forms of the different ancillary studies, if applicable, 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 copies of the IRB approval and approved informed consent. 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 or designate 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 event has occurred (see Section 12). If the patient reports a significant loss of vision in the treated eye within 4 days after treatment, the patient will be advised to visit the clinic as soon as possible or at least 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 ( $\geq 4$  lines) is detected, fluorescein angiography, ICG angiography (if available), color fundus photography and ophthalmoscopy will be performed to help define the relationship of the vision loss to therapy and the patient will be asked to return for re-evaluation (best corrected visual acuity with the ETDRS charts, contrast sensitivity,

fluorescein angiography, color fundus photography and ophthalmoscopy) at week 2 and at week 4 after their last treatment to monitor the progress of their condition. Vision losses of  $\geq 20$  letters since the last assessment that occur within 7 days of the last treatment, must be reported on an expedited basis to the Sponsors as a serious adverse event.

Four weeks ( $\pm 1$  week) after the initial treatment and each scheduled follow-up visit (regardless of whether treatment occurred at follow-up), all patients will be contacted by telephone to provide a subjective assessment of the visual performance of the study eye. A standard question will be asked "At the present time, how would you rate your eye sight in the study eye (with glasses or contact lenses, if you wear them) on a scale of 0 to 100, 0 being totally blind and 100 having perfect eyesight?" The patients will be provided with their previous score before they are asked this question. For consistency, the same study individual should ask this question at follow-up and at in-clinic visits.

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

- Patient's body weight (kg), height (cm), body surface area ( $m^2$ )
- Best-corrected visual acuity (Appendix 6)
- Subjective visual performance score (0 to 100)
- Assessment of concomitant medications
- Color fundus photography (Appendix 8)
- Contrast threshold (Appendix 7)
- Fluorescein angiography (Appendix 8)
- Dilated ophthalmoscopy
- Monitoring of adverse events (Section 12)

Photographs and angiograms from baseline, 12-month and 24-months and any other visit requiring shipments of photographs and angiograms must be sent to the Photograph Reading Center within 1 week of the test.

ICG angiographic assessments may be conducted at the discretion of the investigator at each retreatment decision time point (Appendix 13) but may not be used as a basis for treatment decisions.

Health-related quality of life interviews will be conducted within 2 weeks after the 6, 12 and 18 month visits, and, within 28 days before the 24-month visit (see Appendix 14).

### **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. For the purpose of this protocol, 3 months is considered to be 90 days. Retreatments can therefore be conducted only at  $90 \pm 14$ ,  $180 \pm 14$ ,  $270 \pm 14$ ,  $360 \pm 14$ ,  $450 \pm 14$ ,  $540 \pm 14$ , and  $630 \pm 14$  days after the initial treatment. 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). Females of childbearing potential must undergo urine pregnancy testing and test negative within 3 days of each retreatment.

To be eligible for retreatment, patients must also fulfill 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 undiagnosed acute illness. Have no diagnosed illness whose presence is considered to be a safety risk for retreatment to be administered.
4. Have no retinal arteriolar or retinal venular non-perfusion caused by previous treatment in this study.
5. Females of childbearing potential must have a negative pregnancy test (urine) within 3 days of any retreatment and must use an effective method of contraception during the study.
6. Have no confirmed decrease in vision in the treated eye relative to pre-treatment, on Day 1 to Day 4 after treatment, of 20 letters or more in best-corrected visual acuity.

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 optimize 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.

## **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 the assigned Monitor and 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:

Andrew Strong  
Director, Clinical Research  
QLT Inc.  
887 Great Northern Way  
Vancouver, B.C. V5T 4T5, Canada  
Telephone: 604-707-7322  
Telefax: 604-707-7269  
E-Mail: astrong@qltinc.com

Alison L. Brown  
Associate Director, Clinical Operations  
Novartis Ophthalmics, Inc.  
11695 Johns Creek Parkway  
Duluth, Georgia 30097  
Telephone: 770-905-1866  
Telefax: 770-905-1966  
E-Mail: alisonl.brown@pharma.novartis.com

Noel Buskard  
Medical & Safety Officer  
QLT Inc.  
887 Great Northern Way  
Vancouver, B.C. V5T 4T5, Canada  
Telephone: 604-707-7407  
Telefax: 604-873-4192  
Pager: 604-877-5974  
E-mail: nbuskard@qltinc.com

Al Reaves  
Head, Clinical Project Management  
Novartis Ophthalmics, Inc.  
11695 Johns Creek Parkway  
Duluth, Georgia 30097  
Telephone: 770-905-1860  
Telefax: 770-905-1260  
E-Mail: al.reaves@pharma.novartis.com

The trial monitors will inform the Medical and Safety Officer 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 judgment, 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.
- Worsened The adverse event is still present and the intensity has increased.
- Prolonged hospitalization The patient's hospital stay was extended beyond that anticipated for this procedure.
- Death

- Lost to follow-up (unknown)

## **12.6 Reporting and Evaluation of Severe Vision Loss**

Vision loss of 20 letters or more (approximately 4 lines) in the treated eye, relative to the last pretreatment vision, detected within 7 days after treatment will be reported immediately (within 24 hours) to the sponsor as a serious adverse event. In such cases fluorescein angiography (ICG angiography optional) and fundus photography must be performed as soon as possible and all angiograms and photographs must be sent immediately to the Photograph Reading Center.

## **12.7 Reporting and Evaluation of Ocular Adverse Events in the Treated Eye**

The Sponsor will be informed immediately on the serious adverse event form (within 24 hours) about the following 3 specific events that can be associated with severe vision loss (for full details of document flow see Appendix 8, Section 4). Angiograms and photographs will be forwarded to the Photograph Reading Center immediately. The Photograph Reading Center evaluation will be mailed to the treating center and inserted into the CRF.

- Arteriolar or venular non-perfusion
- Extensive retinal capillary non-perfusion ( $\geq 1$  MPS disc area)
- Vitreous hemorrhage

Ocular adverse events which can only be detected by ophthalmological examination and are not visible on any angiograms or color fundus photographs that have been sent to the Photograph Reading Center (such as peripheral retinal detachment) will be documented and evaluated by the Investigator in the adverse event section of the CRF.

Events which are conditions that may be due to the natural course of the disease will be reported and semiquantitatively evaluated by the Photograph Reading Center based on their review of the 12 and 24 month (or final visit, if patient drops out) fluorescein angiograms, ICG angiograms and the color photographs compared to baseline. Conditions that will be evaluated are noted below:

- Increased size of lesion
- Increased areas of RPE atrophy
- Subretinal or intraretinal hemorrhage
- Increased fibrosis
- Retinal capillary non-perfusion
- Retinal vascular leakage
- Choroidal vascular non-perfusion
- Choroidal vascular staining/leakage



- Other macular or optic nerve pathology

Therefore, the events listed above should not be recorded by the treating center at any visit in the adverse event section of the CRF.

When the photographs are not sent to the Photograph Reading Center any adverse events other than those listed above that are visible on angiograms or fundus photographs, will be documented and evaluated by the Investigator in the adverse event section of the CRF.

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

The following table summarizes sample size estimates based on various responder rates within the two treatment groups. Patients will be randomized in a 2-to-1 ratio, where two PDT patients will be randomized to every one placebo patient. The sample sizes needed to detect differences statistically with 80%, 85%, 90%, and 95% power are given. These estimates are based on a two-group, continuity-corrected chi-square test. A two-sided significance level of 0.050 is assumed.

TOTAL SAMPLE SIZE NEEDED TO DETECT DIFFERENCE STATISTICALLY  
ASSUMING A 2-TO-1 RANDOMIZATION

Responder Rate			Statistical Power			
Placebo	PDT	$\Delta$	80%	85%	90%	95%
50%	70%	20%	233	263	302	367
	75%	25%	149	167	191	230
	80%	30%	103	115	130	156
	85%	35%	75	83	93	110
60%	80%	20%	209	234	268	323
	85%	25%	131	146	166	198
	90%	30%	88	98	110	130
	95%	35%	62	68	76	88

### Intent-to-Treat Efficacy Analysis

The intent-to-treat analysis will include all available data from patients who have evidence of CNV in their lesion at baseline as assessed by the Photograph Reading Center. For the AMD patients, we estimate that 60% of those who receive placebo will be “responders” after 1 year, and will lose less than 3 lines of visual acuity compared to baseline. If approximately 290 patients are enrolled and 270 patients (PDT=180, Placebo=90) have data available for the intent-to-treat analysis at 1 year, then this sample size will provide approximately 90% power to detect a difference from placebo of 20% (Placebo=60% vs. PDT=80%). In addition, this sample size will provide approximately 99% power to detect a difference from placebo of 25% (Placebo=60% vs. PDT=85%). This assumes a two-sided significance level ( $\alpha$ ) of 0.050.

For the PM patients, we estimate that 50% of those who receive placebo will be “responders” after 1 year and remain stable, i.e., lose less than 1.5 lines of visual acuity (< 8 letters) compared to baseline. If approximately 110 patients are enrolled and 102 patients (PDT=68, Placebo=34) have data available for the intent-to-treat analysis at 1 year, then this sample size will provide approximately 80% power to detect a difference from placebo of 30% (Placebo=50% vs. PDT=80%). Based on the interim evaluation (see Section 13.3), this sample size for the PM group may need to be adjusted.

### Evaluable-Patients Analysis

The evaluable-patients analysis will include all available data from patients who follow the protocol without significant deviation. Inevaluability of patients and/or visits is anticipated due to:

- (1) Significant 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 the primary timepoint (1 year) due to significant protocol deviations (approximately 5%).
- (3) Patients lost to follow-up due to death or any other reason (approximately 8%).
- (4) Patient did not receive the randomized study treatment.

If we assume that 17% of the enrolled AMD and PM patients (total ~400) will not be evaluable for efficacy at one year, then approximately 240 AMD patients and 90 PM patients will be available for the evaluable-patients analysis. For the AMD group, a sample size of 240 patients (PDT=160, Placebo=80) will provide approximately 86% power to detect a difference from placebo of 20% (Placebo=60% vs. PDT=80%), and approximately 98% power to detect a difference from placebo of 25% (Placebo=60% vs. PDT=85%). For the PM group, a sample size of 90 patients (PDT=60, Placebo=30) will provide approximately 80% power to detect a difference from placebo of 32%

(Placebo=50% vs. PDT=82%). These calculations assume a two-sided significance level ( $\alpha$ ) of 0.050.

The randomization will be stratified with respect to both study center and disease etiology (AMD or PM). This stratification of the randomization will ensure a 2-to-1 balance between treatment groups within each level of these two factors.

### **13.2 Statistical and Analytical Plan**

All analyses will be conducted separately for the two CNV etiologies studied (i.e., separate analyses for the AMD and PM populations).

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 except where there is no evidence of CNV on the baseline lesion as assessed by the Photograph Reading Center. 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, cigarette smoking, systemic hypertension, initial visual acuity 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, visual acuity and evidence of CNV in fellow-eye, use of ICG 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 Interim Evaluation in Pathologic Myopia**

Since there is little known about the specific time-course of this disease, an administrative interim evaluation will be performed on the pathologic myopia patients. This evaluation will be performed when either (1) ten overall treatment failures (non-responders) have occurred, i.e., a decrease in vision of 8 or more letters in the treated eye, or (2) at least 60 patients have completed their 3-month evaluation, whichever is sooner. No formal statistical analysis will be done between the treatment groups as part of this interim look at the data. Instead, the results of this evaluation of responder rate will be used to determine if the initial assumptions of responder rate used to calculate the sample size were accurate. On the basis of this interim evaluation, the PM sample size may be changed by a formal protocol amendment. Since no formal statistical analysis will be done between the 2 treatment groups, there will be no planned adjustment of the P-value at the primary efficacy analysis at one year. The results of the interim evaluation will be presented to the DSMC but will not be communicated to the investigators who will remain masked.

### 13.4 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 AMD portion of the study may be allowed to be stopped early, if statistically significant efficacy in favor of PDT is observed. There is no intention of stopping the PM portion of the study based on efficacy results at 12 months. The DSMC may advise to stop the study due to safety concerns based on the 12-month analysis.

### 13.5 Efficacy Analysis

All efficacy analyses will be conducted separately for the two CNV etiologies studied (i.e., separate analyses for the AMD and PM populations). 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 (38). The primary assessment of visual acuity will be based on the proportion of patients who are classified as "responders" to treatment. Three separate definitions of a responder will be analyzed:

- (i) A decrease from baseline of less than 1.5 lines of vision (< 8 letters) in the treated eye. The ophthalmic community generally considers that a vision change within an eye of 1.5 lines or more is required for them to consider the change as clinically significant.
- (ii) A decrease from baseline of less than 3 lines of vision (<15 letters) in the treated eye. A change of 3 lines of vision represents a doubling of the visual angle and is considered a clinically significant change within the individual eye.
- (iii) A decrease from baseline of less than 6 lines of vision (<30 letters) in the treated eye.

The primary efficacy criterion in PM will be (i) while the primary efficacy criteria in AMD will be (ii). The responder definition in (iii) will be used as a secondary efficacy criterion.

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.

Secondary efficacy variables will include the following:

1. The proportion of patients who have an improvement from baseline in vision of  $\geq 1.5$  lines ( $\geq 7$  letters) in the treated eye.
2. The proportion of patients whose visual acuity becomes worse than 34 letters read from the ETDRS chart (approximately 20/200) in their treated eye.
3. The time until a patient has a decrease from baseline of 8 or more letters in the treated eye.
4. The time until a patient has a decrease from baseline of 3 or more lines of vision ( $\geq 15$  letters) in the treated eye.
5. The time until a patient has a decrease from baseline of 6 or more lines of vision ( $\geq 30$  letters) in the treated eye.
6. The mean changes from baseline for visual acuity.
7. The mean changes from baseline for the number of letters read on the Pelli-Robson chart for assessment of contrast sensitivity.
8. The proportion of patients whose subjective vision score is better than or equal to baseline.
9. The proportion of patients whose subjective vision score declines by less than or equal to 25% compared to the baseline vision score.
10. The mean changes from baseline in the patient's subjective vision score.
11. The difference between treatments in the CNV lesion closure grades according to the Photograph Reading Center grading system.
12. To assess the HQL impact of PDT treatment relative to placebo using the VFQ-25.
13. To assess the HQL burden of AMD and PM using the VFQ-25.

For the analysis of the proportions in (1), (2), (8) and (9), comparisons between treatment groups will then 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 (39) 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 (3), (4) and (5), 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, 12 months or longer. For the primary analysis at one year, patients who discontinued the visual evaluation will be censored at the time of their last visual evaluation.

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.

## **13.6 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.

### **13.7 Evaluation in Case of Discontinued Treatment**

Patients who are discontinued from treatment during the trial, or who decide to discontinue, will continue to be followed for safety and efficacy. If they are followed, then they will have their visual acuity measured at their regularly scheduled visits. For the first visit following the visit on which they are discontinued, their visual acuity value will be included in all efficacy analyses (intent-to-treat and evaluable patients).

For the analysis of the responder rates, all patients who are discontinued from the trial prematurely and have incomplete follow-up data will contribute information to the evaluation of responder rates at each visit. Patients who are treatment failures (e.g., lost > 3 lines of VA) at their last follow-up visit, will be considered treatment failures through the end of the trial. Patients who are not treatment failures will be considered to have the same risk of failure, based on their amount of follow-up time completed, as the patients who completed the follow-up.

## **14. ESTIMATED DURATION OF THE STUDY**

Initiation of enrollment:	Q1/1998
Duration of enrollment:	6 months
12 months completion:	Q3/1999
2 Year completion:	Q3/2000

## **15. PREMATURE TERMINATION OF TREATMENT OR PATIENT IN THE STUDY**

Every attempt will be made to complete all follow-up visits. If a patient drops out or refuses further treatment, the patient should be encouraged to return for assessment at least at the 12-month visit.

### **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., adverse event assessment) 3 months after the last treatment.

### **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 judgment 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 FOR THE FIFTH-YEAR EXTENSION

Procedure	Treatment Period (Months)		
	48*	54	60
Medical History**		X	
Informed Consent	X	If not done at M48	
Inclusion/Exclusion <sup>a</sup>	X	If not done at M48	
Concomitant Medications	X	X	X
Pregnancy Tests <sup>b</sup>	X	X	
Best-Corrected Visual Acuity	X	X	X
Color Fundus Photography	X	X	X
Fluorescein Angiography	X	X	X
Dilated Ophthalmoscopy	X	X	X
PDT <sup>c</sup>	X	X	
Telephone Contact 2-4 days after treatment	X	X	
Adverse Events Assessment	X	X	X
<p>*The month 48 visit can take place only if IRB/EEC approval is granted prior to the patient completing the Month 48 Visit of the original extension.</p> <p>**Collect a medical history update (at Month 54 only) if the patient exited the study at Month 48 and re-entered the continuation.</p> <p><sup>a</sup>When a patient enters the extension study, the patient must meet the extension inclusion/exclusion criteria as defined in Amendment 6, dated 09 July 2002.</p> <p><sup>b</sup>A negative urine test is required within 3 days of any re-treatment in females of childbearing potential.</p> <p><sup>c</sup>Treatment must be conducted within 7 days of fluorescein angiography at scheduled follow-up visits, if protocol requirements are met. The Month 48 treatment can occur only if IRB approval is granted prior to the patient completing the Month 48 visit of the original extension and if informed consent and inclusion/exclusion criteria are met.</p>			

## **APPENDIX 3: CLINICAL LABORATORY TESTS**

### **Haematology**

Automated CBC to include:

- hemoglobin
- hematocrit
- RBCs
- WBCs with differential
- platelets

### **Serum Chemistry**

- Creatinine
- Sodium
- Potassium
- Chloride
- Albumin
- SGOT (AST)
- SGPT (ALT)
- Alkaline Phosphatase
- Total and Direct Bilirubin

## APPENDIX 4: INFUSION INSTRUCTIONS

### PDT TREATMENT

#### Drug Dosage and Administration

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

#### Reconstitution

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 7.5 mL per 15 mg vial. In order to achieve the desired drug doses of 6 mg/m<sup>2</sup> 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

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

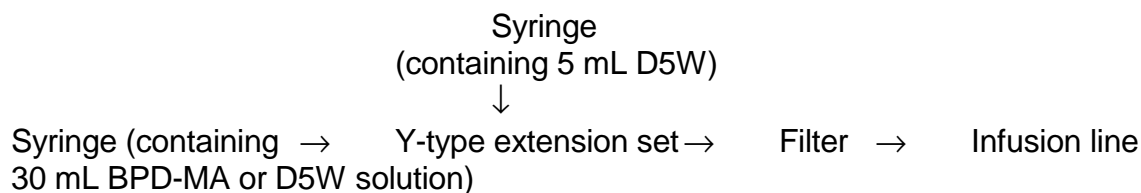
Mix the reconstituted BPD-MA (2.0 mg/mL) together with the required volume of D5W and infusion line in the syringe. The final volume of BPD-MA solution will be 30 mL. Cover the syringe and infusion line with aluminum foil. The color of the infusate must not be seen by either patient or investigator.

## 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 vein walls of some elderly patients, it is strongly recommended that the largest arm vein possible, preferably antecubital, be used for injection. Small veins in the back of the hand should be avoided if 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.

### **Recommended 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

### **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 or designate notices any extravasation at any time during the infusion the infusion must be stopped immediately.

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

The unmasked nurse/study coordinator or designate 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 or designate 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.

## **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  $49 \pm 2$  (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 only by a certified visual acuity examiner 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.* Refraction and vision testing must be performed by a certified visual acuity examiner prior to visual acuity and contrast sensitivity testing and pupillary dilation. 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. For spherical corrections of plus or minus 6 diopters or greater, care must be taken to insure that the spherical lens remains at the proper vertex distance from the cornea.
  - 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)	+ .50 - .37 + .50	+ .50 - .25 + .50	.50 JCC	.25 JCC	+.25 -.25	+.37 -.37 + .37	+.25 -.25 + .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	+.50 -.50 +.50	+.50 -.50 + .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 (1 meter)	+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 as "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 and spherical equivalent obtained by subjective refraction for the right eye on the *Record of Subjective Refraction*. To calculate spherical equivalent, add one-half of the cylinder power algebraically to the sphere. 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 read correctly is scored as one point. 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 (e.g., "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 are marked with an "X" 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 (i.e., 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 (i.e., 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 (40,41). 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 diopter 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 color 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 color photographs and fluorescein angiograms. The Zeiss 30° fundus camera is recommended, however, other fundus cameras are acceptable. (A 45° fundus camera is acceptable. Fields of 25° or 60° are not acceptable for the study.)
- Tri-X or Tmax film should be used for fluorescein angiograms. Color photographs may be taken with either Kodachrome, Ektachrome, or FUJI 50 color slide film. Since there may be a slight difference in the color 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 70° 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 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 Color Fundus Stereoscopic Photography**

#### **1.4.1 Required Fields**

The stereoscopic color photographs of the disc and stereoscopic color 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, color 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 color 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 color photographs of the disc and stereoscopic color 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 color 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 color and on the fluorescein angiogram.

## 1.7 Clinical Center Preparation and Labeling of All Photographs

Although only baseline, 12 and 24 month photographs are routinely sent to the Photograph Reading Center, all photographs should be prepared and labeled similarly. Using the labels supplied by the Sponsor, color photographs and fluorescein angiograms should be labeled 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 color 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 color 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 from baseline, 12-month and 24-month follow-ups 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. All other visits (3-, 6-, 9-, 15-, 18- and 21-month follow-up visits) should be retained with the clinical center. For patients lost to follow-up, the last available follow-up visit photographs will be sent to the Photograph Reading Center.

## **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 form 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 and macular features for subgroup analysis (Exhibit H - 1).
- Follow-up visit study eye photographs will be evaluated for leakage from CNV, size of lesion, 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 status of the lesion. (Exhibit H - 3).

- ICG angiograms will be evaluated for size of lesion (Exhibit H - 4).
- The completed grading forms (Exhibits H - 1, H - 2, H - 3 and H - 4) 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.
- At the 12- and 24-month follow-up, 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 a 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, etiology, and its location in relationship to the foveal center.
- Review the procedures for measuring the CNV lesions on fluorescein angiograms and, if used, ICG angiograms, and determining the spot size to be used for treatment at baseline and follow-up.
- With the use of example cases, apply the eligibility and exclusion criteria as well as follow-up treatments.
- 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 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 Section 5.2) except for review of the enrollment criteria. The Principle 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 003 AMENDMENT 3

### 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 VIP study procedures

**By Whom:** Principal investigator

**Instructions:** Sent to Novartis Ophthalmics (Attention: Al Reaves) once training of co-investigator has been completed as outlined below. Novartis Ophthalmics 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 VIP study Amendment 3. 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 Novartis Ophthalmics Use:

Completeness of Documentation verified: \_\_\_\_\_

Copy to VIP 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 labeling 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 color 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 labeled 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.

## 6.0 LIST OF EXHIBITS

Exhibit	Name	Description
<b>A</b>	Photography Equipment Form	Provide information to Photograph Reading Center regarding photographic equipment that will be available at clinical center.
<b>B</b>	Required Photographs Fields of the Fundus	Description of photographic fields centered on the disc and centered on the macula.
<b>C - 1 &amp; C - 2</b>	Photographic Sequence for Fluorescein Angiography	Schematic of required frames on fluorescein angiogram.
<b>D</b>	Instructions for Labeling Photographs	Schematic of placement of labels on photographs/angiograms
<b>E</b>	Preparation of All Photographs for Shipping	Placement of slides in slide pages and placement of negative strips in negative sleeves.
<b>F - 1</b>	Photograph Inventory Form	Form to accompany each set of photographs shipped to Photograph Reading Center.
<b>F - 2</b>	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.
<b>F - 3</b>	Checklist for Submitting Photographic Materials	Summary of important aspects of preparing and shipping photographic materials
<b>G</b>	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.
<b>H - 1</b>	Baseline Consensus Grading Form - Study Eye - <b>Color Photos and Fluorescein Angiograms</b>	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.
<b>H - 2</b>	Follow-up Visit Grading Form - Study Eye - <b>Color Photos and Fluorescein Angiograms</b>	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.
<b>H - 3</b>	Baseline, Visit 12, Visit 24 Grading Form - Fellow Eye - <b>Color Photos and Fluorescein Angiograms</b>	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.
<b>H - 4</b>	Baseline, Visit 12, Visit 24 Grading Form - ICG Angiogram - Study Eye and 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.
<b>I</b>	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.

<b>Exhibit</b>	<b>Name</b>	<b>Description</b>
<b>J - 1</b>	Recommendation for Photographer to Initiate Standardization Procedures	Informs Photograph Reading Center of person who will be submitting photographs for review for standardization.
<b>J - 2</b>	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.
<b>K</b>	Photographer Standardization Checklist	Form to accompany photographs submitted for standardization.
<b>L</b>	MPS disc area 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 maximum lesion size allowed at initial treatment is 5,400  $\mu\text{m}$  in greatest linear diameter. Thus the largest light treatment spot (lesion plus the 500  $\mu\text{m}$  margins) will extend no more than 6,400  $\mu\text{m}$  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  $\mu\text{m}$  to the edge of the optic nerve. Thus CNV closer to the optic nerve than 200  $\mu\text{m}$  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  $689 \pm 3 \text{ nm}$ , delivered via a slit lamp, and utilizing 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 Photoactivation 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 ( $\text{J}/\text{cm}^2$ )	Treatment Time (seconds)
50	83

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

#### 4. Spot Size and Laser Treatment Power

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

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

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

To set the slit-lamp adapter (i.e., Coherent LaserLink<sup>®</sup> or Zeiss VisuLink or VISULINK adapters) to the correct treatment spot diameter, 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.

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  $m = x 1.05$** 

<b>Lens Type: Ocular Inst. Mainster Lens</b>		<b>Magnification: x 1.05</b>	
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**

<b>Lens Type: Goldmann 3 Mirror or Fundus lens Magnification: x 1.08</b>			
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**

<b>Lens Type: Ocular Inst. Mainster Wide Field Lens Magnification: x 1.5</b>			
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**

<b>Lens Type: Volk QuadrAspheric Lens</b>		<b>Magnification: x 2.01</b>	
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  $\mu\text{m}$

Margin:	+	1000 $\mu\text{m}$
		<hr/>
		3200 $\mu\text{m}$
		=====

**Step 2**

Select lens to be used, e.g. Volk QuadrAspheric Lens.

### **Step 3**

Table 4 shows the diameter of the area to receive laser treatment for the nearest setting as 3216  $\mu\text{m}$ . The corresponding laser link setting can be chosen: 1600  $\mu\text{m}$ . The power to be used is 48.7 mW with energy setting of 4.06.

## APPENDIX 10: INVESTIGATORS

Twenty-eight 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.

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

<b>Institution</b>	<b>Principal Investigator</b>	<b>Center #</b>
Eye Outpatients Aberdeen Royal Infirmary Forester Hill AB25 3XS Aberdeen Scotland	Dr. J. Olson	7
St. Paul's Eye Unit Royal Liverpool University Hospital Prescot Street L 78 XP Liverpool England	Dr. Simon P. Harding	8
Hôpital Bellevue Service Ophtalmologie 42055 Saint Etienne Cedex 2 France	Dr. Francoise Koenig	9
Harvard Medical School Massachusetts Eye & Ear Infirmary Department of Ophthalmology 243 Charles Street Boston, Massachusetts 02114, USA	Dr. Joan W. Miller	10
The Wilmer Ophthalmological Institute Maumenee 713 600 N. Wolfe Street Baltimore, MD 21287-9275, USA	Dr. Andrew Schachat	11
Cole Eye Institute Cleveland Clinic Foundation 9500 Euclid Avenue, i-22 Cleveland, Ohio 44195, USA	Dr. Hilel Lewis	12
Zweng Memorial Retinal Research Foundation 1225 Crane Street Menlo Park, California 94025, USA	Dr. Mark Blumenkranz	13
UBC/VH Eye Care Center 2550 Willow Street Vancouver, BC V5Z 3N9 Canada	Dr. Michael Potter	14
Texas Retina Associates Suite 400 7150 Greenville Avenue Dallas, Texas 75231, USA	Dr. Gary Fish	15

<b>Institution</b>	<b>Principal Investigator</b>	<b>Center #</b>
Vitreous, Retina, Macula Consultants of New York 519 East 72nd Suite 203 New York, NY 10021, USA	Dr. Jason Slakter	16
Retina Associates of Cleveland 26900 Cedar Road, Suite 303 Cleveland, Ohio 44122, USA	Dr. Lawrence Singerman	17
Associated Retinal Consultants 632 William Beaumont Medical Building 3535 West 13 Miles Royal Oak Medical Center Michigan 48073, USA	Dr. Raymond Margherio	18
Toronto Western Medical Bldg. 25 Leonard Avenue, Suite 101 Toronto, Ontario M5T 2R2 Canada	Dr. Patricia Harvey	19
Bascom Palmer Eye Institute 900 N.W. 17th Street Miami, Florida 33136. USA	Dr. Robert Rosa Dr. Phillip Rosenfeld	20
Retina Northwest Lovejoy Medical Building, Suite 300, 2525 N.W. Lovejoy Portland, Oregon 97210. USA	Dr. Colin Ma	21
Retina Vitreous Consultants Suite 500 3501 Forbes Ave. Pittsburgh, Pennsylvania 15213. USA	Dr. Louis Lobes	22
Barnes Retina Institute Suite 17413 East Pavilion, One Barnes Hospital Plaza St. Louis, MO 63110 USA	Dr. Travis Meredith	23
Emory Eye Clinic 1365-B Clifton Rd., Atlanta, GA 30322 USA	Dr. Thomas M. Aaberg, Sr.	24
University of Southern California Doheny Eye Institute 1450 San Pablo Street Los Angeles, CA 90033 USA	Dr. Jennifer I. Lim	25

<b>Institution</b>	<b>Principal Investigator</b>	<b>Center #</b>
Policlinico Cit'de Udine, Viale Venezia 410, I-33100, Udine Italy	Dr. U. Menchini	26
Örebro Regionsjukhuset, Ögonkliniken, S-70185 Örebro Sweden	Dr. I. Johansson	27
University of Essen Department of Ophthalmology Hufsländstrasse 55 D-45147 Essen Germany	Dr. B. Jurkles	28
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 FOR LASER INELIGIBLE PATIENTS**

### **Title:**

### **Verteporfin In Photodynamic Therapy (VIP)**

### **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) or Pathologic Myopia (PM). Your ophthalmologist considers you a candidate for this study because your condition is not considered treatable with standard laser surgery. A total of approximately 400 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 600 humans to date. More than 500 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 or worse outcome than patients who do not (and who heal their condition naturally with natural scar formation). Whether you have PDT or placebo will be decided by a process called randomization, which is like "flipping a coin". 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 about 10 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 and blood tests, including a blood pregnancy test when required. 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 be asked to score your perception of the vision in your study eye. 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<sup>2</sup> 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 24 HOURS AFTER THE 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 1 day after the infusion. **USE OF SUNSCREENS WILL NOT BLOCK ANY PHOTSENSITIVITY REACTION.**

Within two to four days after any treatment, we will call you and ask whether you have experienced any changes in vision in the treated eye or have 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 and ICG angiography, and color photography of your eye. If the vision test shows that your study eye has a significant

decrease in vision, we will ask you to return for repeat testing about 2 and 4 weeks after your last treatment, and continue to follow you every 3 months but without further treatment.

Four weeks after treatment you will be telephoned and asked to score your perception of the vision in your study eye. This request will be repeated at the in-clinic visit every 3 months. 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, contrast threshold, and a urine pregnancy test when required. Depending on the condition of your CNV, you may be retreated with PDT after the angiography test.

### Risks and Discomforts

A few AMD patients in this study have noticed in their study eye a significant decrease in vision or increase in cloudiness or haziness of their vision soon after treatment which may be associated with photodynamic therapy with BPD-MA or placebo. Of more than 120 AMD patients treated with BPD-MA or placebo to date, decreased vision in the study eye shortly after treatment has been noted in 6 patients. Of about 40 treated patients with pathologic myopia, decreased vision in the study eye shortly after treatment has not been noted. In another on-going study of approximately 400 BPD-MA-treated patients and 200 placebo-treated patients who have a more advanced stage of AMD disease, this significant vision decrease was noted in only 2 patients who had received the same treatment being used in this study. At this time, we do not know if the affected patients in those studies were treated with BPD-MA or placebo. In most cases, this significant decrease in vision has partially resolved. A significant decrease in vision in your study eye shortly after treatment is a possible complication which may or may not be permanent.

PDT was initially 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 these 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.

Approximately, 400 additional patients are receiving PDT in an ongoing study that started in December 1996. There have been no safety concerns raised by a committee of ophthalmologists and statisticians who are monitoring safety issues.

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.

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 24 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, surgically, to 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 Inc., and Novartis 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. If you withdraw, we hope that you will still return for check-ups even if no further treatments are given. 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 Inc. and Novartis 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 or designate. You will be informed of any new significant findings which may affect your willingness to participate in the study.

Investigator:

Phone:

Study coordinator or designate:

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, 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 - SAMPLE INFORMED CONSENT FOR LASER-ELIGIBLE PATIENTS

### 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:**

**Verteporfin In Photodynamic Therapy (VIP)**

**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). A total of approximately 400 patients will be enrolled into the study worldwide. 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 600 humans to date. More than 500 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 or worse outcome than patients who do not (and who heal their condition naturally with natural scar formation). Whether you have PDT or placebo will be decided by a process called randomization, which is like "flipping a coin". 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 about 10 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 and blood tests, including a blood pregnancy test when required. 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 be asked to score your perception of the vision in your study eye. 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<sup>2</sup> 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 24 HOURS AFTER THE 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 1 day after the infusion. **USE OF SUNSCREENS WILL NOT BLOCK ANY PHOTSENSITIVITY REACTION.**

Within 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 have 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 and ICG angiography, and color photography of your eye. If the vision test shows that your study eye has a significant decrease in vision, we will ask you to return for repeat testing about 2 and 4 weeks after your last treatment, and continue to follow you every 3 months but without further treatment.

Four weeks after treatment you will be telephoned and asked to score your perception of the vision in your study eye. This request will be repeated at the in-clinic visit every three months. 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, contrast threshold, and a urine pregnancy test when required. Depending on the condition of your CNV, you may be retreated with PDT after the angiography test.

### Risks and Discomforts

A few AMD patients in this study have noticed in their study eye a significant decrease in vision or increase in cloudiness or haziness of their vision soon after treatment which may be associated with photodynamic therapy with BPD-MA or placebo. Of more than 120 AMD patients treated with BPD-MA or placebo to date, decreased vision in the study eye shortly after treatment has been noted in 6 patients. Of about 40 treated patients with pathologic myopia, decreased vision in the study eye shortly after treatment has not been noted. In another on-going study of approximately 400 BPD-MA-treated patients and 200 placebo-treated patients who have a more advanced stage of AMD disease, this significant vision decrease was noted in only 2 patients who had received the same treatment being used in this study. At this time, we do not know if the affected patients in those studies were treated with BPD-MA or placebo. In most cases, this significant decrease in vision has partially resolved. A significant decrease in vision in your study eye shortly after treatment is a possible complication which may or may not be permanent.

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 was initially 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 these 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.

Approximately, 400 additional patients are receiving PDT in an ongoing study that started in December 1996. There have been no safety concerns raised by a committee of ophthalmologists and statisticians who are monitoring safety issues.

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.

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 24 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, surgically, to 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 Inc., and Novartis 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. If you withdraw, we hope that you will still return for check-ups even if no further treatments are given. 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 Inc. and Novartis 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 or

designate. You will be informed of any new significant findings which may affect your willingness to participate in the study.

Investigator: \_\_\_\_\_ Phone: \_\_\_\_\_

Study coordinator or designate: \_\_\_\_\_ 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, 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 13 - ICG ANGIOGRAPHIC ASSESSMENTS**

### **1. INTRODUCTION/RATIONALE**

At the request of many of the investigators participating in this study, and with the approval of the Study Advisory Group and the sponsors, ICG angiographic examination of patients enrolled in the VIP trial may be conducted as an exploratory ancillary test. Indocyanine green (ICG) angiography may provide enhanced imaging of the choroidal circulation versus conventional angiography using sodium fluorescein dye. In addition, better delineation of occult choroidal neovascularization may be 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 VIP trial 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**

ICG angiography is an optional ancillary assessment. Informed Consent can be incorporated into the main Informed Consent form or provided separately. A sample Informed Consent which can be used and amended as needed at different institutions is attached (Exhibit 13.1). Any center wishing to participate in this ancillary study must supply the IRB letter of approval together with the IRB-approved Informed Consent describing the ICG angiography assessment to the sponsor.

ICG angiography may be performed at any visit at which fluorescein angiography is conducted. 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, scanning laser ophthalmoscope are described in Exhibits 13.2 and 13.3 respectively.

#### **4. STUDY POPULATION**

Patients enrolled in any of the North American or European centers of the BPD OCR 003 clinical study (VIP trial) 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 VIP investigators 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 have ICG angiographic assessments conducted.

#### **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 13.4). Hard copy of unenhanced images will be forwarded to the Photograph Reading Center for the baseline, 12 and 24 month visits. The data will be archived centrally on completion of the study at a location to be determined.

## **EXHIBIT 13.1**

### 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 Verteporfin In Photodynamic Therapy (VIP) Trial, 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 VIP trial 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. The ICG may be injected simultaneously with the fluorescein or sequentially following the fluorescein angiographic examination and should not add significantly to the time needed in the office for participation in the VIP trial.

#### 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 VIP trial. 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 VIP trial. 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.

### Costs

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

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



## **EXHIBIT 13.2**

### **ICG Ancillary Study** **Photographic Protocol for the Topcon System**

#### **13.2.1 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 13.4).

#### **13.2.2 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.

### 13.2.3 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.

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

**ICG Ancillary Study**  
**Photographic Protocol for the Topcon System**

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

**ICG Ancillary Study**  
**Photographic Protocol for the Topcon System**

17  3 min. Fellow Eye <div style="text-align: right;">Stereo 35°</div>	18   Pair 35°	19  3 min. Fellow Eye <div style="text-align: right;">Stereo 50°</div>	20   Pair
21  5-7 min. Study Eye	22  5-7 min. Fellow Eye	23  10-13 min. Study Eye <div style="text-align: right;">Stereo</div>	24   Pair
25  10-13 min. Study Eye 35°	26  10-13 min. Fellow Eye 35°	27  10-13 min. Fellow Eye <div style="text-align: right;">Stereo</div>	28   Pair
29  25-40 min. Study Eye (Late phase) <div style="text-align: right;">Stereo</div>	30   Pair	31  25-40 min. Fellow Eye (Late phase) <div style="text-align: right;">Stereo</div>	32   Pair

## **EXHIBIT 13.3**

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

#### **Additional information compared to the Topcon system:**

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

#### **13.3.1 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

#### **13.3.2 Ophthalmoscopy without ICG:**

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

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

#### **13.3.3 ICG angiography:**

- all single frames should be taken at 30° (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 13.4**

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 14 - QUALITY OF LIFE ASSESSMENT

### 1. INTRODUCTION

AMD and PM are progressive diseases that result 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.<sup>1</sup> The impact of vision loss on overall HQL, however, has not been documented for either AMD or PM. 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.

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 and PM. Baseline HQL assessments will provide estimates of the cross-sectional HQL profile of AMD and PM. Relationships between visual acuity and HQL will enhance our understanding of the impact of visual function on patients' everyday functioning, activities, and feelings.

### 2. STUDY OBJECTIVES (These objectives are secondary to those of the main BPD OCR 003 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 and PM 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.\*

### 3. STUDY PLAN

English-, French- or German-speaking patients will be asked to participate in a 10- to 15-minute telephone interview at the time of enrollment in the BPD OCR 003 clinical study and again at months 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 6-, 12 and 18 month clinical visits, and, within 28 days before the 24-month visit.. During the interview, patients will be asked to respond to 30

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\* ©RAND 1996

structured questions about multiple areas of HQL (see below: Health-Related Quality-of-Life Assessments).

#### **4. PROCEDURES AND RESPONSIBILITIES**

At the initial enrollment visit the study coordinator or designate of the treating center must provide patients with an institutional review board (IRB)-approved informed consent form applicable to the HQL study (Exhibit 14.1 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 or designate at the treating center will immediately fax an Initial HQL Interview Alert form (Exhibit 14.2) 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.

At subsequent visits, it is the responsibility of the study coordinator or designate at participating treating centers to fax Covance a Follow-up HQL Interview Alert form (Exhibit 14.3) to ensure that an interview is conducted by Covance at relevant follow-up visits as 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 or designate 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.

#### **5. STUDY POPULATION**

English-speaking patients enrolled in the North American and UK centers and French- or German-speaking patients enrolled in Europe.

#### **6. HEALTH-RELATED QUALITY-OF-LIFE ASSESSMENTS**



The HQL interview (Exhibit 14.4) 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 and PM 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. 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.<sup>3</sup> 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.

## **7. 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 003. 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 for each disease stratum (AMD and PM). 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 and PM using the VFQ-25.*

To compare the HQL burden of AMD and PM 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.<sup>2</sup> 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.

## **8. REFERENCES**

1. 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.
2. Mangione CM. "NEI VFQ-25 Scoring Algorithm (2/21/97)," Draft preprint version available from Carol Mangione, MD, UCLA Division of General Internal Medicine.
3. Nunnally JC. *Psychometric Theory*. New York: McGraw-Hill Book Company, 1978.

## **Exhibit 14.1**

### **Sample Informed Consent**

**TITLE: Verteporfin In Photodynamic Therapy (VIP):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 choroidal neovascularization due to age-related macular degeneration or pathologic myopia. 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 VIP clinical study and again at months 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 6, 12, and 18 month follow-up visits, and, within 28 days before the 24-month visit. The total number of telephone contacts will be 5.

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 behavior, 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 or PM as well as the impact of AMD or PM 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 14.2**  
**VIP**  
**INITIAL HQL INTERVIEW ALERT**

Fax to: <i>Paola Murphy</i>	Fax from:
Location: <i>Covance Clinical &amp; 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 14.3

VIP - North America  
MONTH 24 HQL INTERVIEW ALERT

Fax to: <b>Ellen Adler</b> <b>COVANCE HEALTH ECONOMICS and</b> <b>OUTCOMES SERVICES</b>	Fax from:
Location: 1100 New York Ave. N.W., Suite 200 East, Washington D.C. 20005	
Fax No.: (202) 637-6690	Telephone No.:
Telephone No.: (202) 508-1357	

Clinical Center: \_\_\_\_\_ Principal Investigator: \_\_\_\_\_

Patient No.: \_\_\_\_\_

Patient Initials: \_\_\_\_\_ Patient Name: \_\_\_\_\_

Planned Date of M24 Visit: \_\_\_\_\_  
(Use alpha characters, eg. 3 Mar 99)

Contact Telephone No.: \_\_\_\_\_

Best contact dates/times:	Date	Time(s)
<i>Please note that the M24 interview will be conducted within 4 weeks <b>before</b> the M24 visit. General times and days of the week that the patient is available are preferable.</i>		

**VIP - Europe**  
**MONTH 24 HQL INTERVIEW ALERT**

Fax to: <b>Ellen Adler</b> <b>COVANCE HEALTH ECONOMICS and</b> <b>OUTCOMES SERVICES</b>	Fax from:
Location: 1100 New York Ave. N.W., Suite 200 East, Washington D.C. 20005	
Fax No.: (202) 661-2826	Telephone No.:
Telephone No.: (202) 508-1357	

Clinical Center: \_\_\_\_\_ Principal Investigator: \_\_\_\_\_

Patient No.: \_\_\_\_\_

Patient Initials: \_\_\_\_\_ Patient Name: \_\_\_\_\_

Planned Date of M24 Visit: \_\_\_\_\_  
(Use alpha characters for month, eg. 3 MAR 99)

Contact Telephone No.: \_\_\_\_\_

<b>Best contact dates/times:</b>	<b>Date</b>	<b>Time(s)</b>
<i>Please note that the M24 interview will be conducted within 4 weeks <b>before</b> the M24 visit. General times and days of the week that the patient is available are preferable.</i>		

## **Exhibit 14.4**

### **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	Most of the time	Some of the time	A little of the time	None of the time
-----------------	------------------	------------------	----------------------	------------------

Do you accomplish less than you would like because of your vision?

1	2	3	4	5
---	---	---	---	---

Are you limited 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 in or around your eyes, 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 15 - PUBLICITY AND PUBLICATION POLICY

### POLICY ON PUBLIC DISCLOSURE OF STUDY RESULTS GENERATED BY THE VIP TRIAL GROUP

#### 1. INTRODUCTION

Public disclosure of findings from any study evaluating a new treatment must be strictly controlled and carefully coordinated. The highest scientific integrity needs to be maintained in the dissemination of any data to avoid misinterpretation concerning the value of the treatment and jeopardizing the public image of the study. Data presented before completion of patient enrollment or patient follow-up may adversely affect patient recruitment or patient cooperation and thereby complicate interpretation of the final study data. The Sponsors must also be given appropriate warning and the ability to alter the content of any public disclosure to ensure that appropriate patent protection is in place and that any disclosure conforms with the Sponsor's legal obligations to securities regulators. Failure to do so could have a material adverse effect on the Sponsors. Moreover, the Sponsors have a legal responsibility to the FDA to ensure that public disclosures are not considered promotional (e.g. making unsupported claims or poorly supported claims for the treatment that the authority subsequently does not approve in the product labeling). Ensuring these issues are appropriately handled is essential to the Sponsors' business.

This policy document sets out procedures that ensure that scientific and corporate requirements are met in public disclosure of the VIP trial results.

#### 1.1 Definitions

The Sponsors: QLT Inc. and Novartis Ophthalmics Inc.

Study coordinator or designate: Sponsors' Director of Clinical Research or other Sponsors designate.

Study Advisory Group (SAG): Predefined members of the investigating centers and the Sponsors (including the Study coordinator or designate) invited by the Sponsors to give advice to the Sponsors on scientific, technical and safety issues associated with the performance of the study.

Data and Safety Monitoring Committee (DSMC): Predefined scientific and medical experts who are not participating investigators in the study invited by the Sponsors to provide advice to the Sponsors on study design and interpretation of study results for protocols and reports under development.

VIP Trial Group: All professional participants of the Verteporfin In PDT (VIP) Trial i.e., certified personnel at the clinical centers and investigators, staff members of resource centers, members of DSMC and consultants to the resource centers and SAG.

## **2. PUBLICITY**

All publicity and press releases must have prior approval of the Sponsors. Drafts of items originating from the Sponsors are distributed by the Study coordinator or designate to the Study Advisory Group (SAG) for their comments. The SAG-chairman may, at the request of the Sponsors, convene a meeting of the SAG for their comments. Investigators who are approached by the press (including ophthalmic news periodicals) for information concerning the clinical trials should ensure that the journalist has first been referred to the Sponsors.

It is recognized that when information is sought from an individual investigator by the press it is desirable for him/her to handle the request. In such an event, the participating investigator should speak as an individual and not as the official representative of the Research Group or the Sponsors. This fact should be made clear to the press; however, the information given out should be accurate and should reflect the general policy and views of the SAG. The Study coordinator or designate should be informed of all anticipated interactions with the press and be sent a copy of the material published which will be distributed to the SAG and Sponsors Corporate Communications.

## **3. EDITORIAL POLICY FOR PUBLICATION OF STUDY DESIGN, METHODS, AND FINDINGS**

### **3.1 Coordination of Manuscript Preparation and Review**

Proposals for publications of any data are initially submitted to the study coordinator or designate. The Sponsors may veto or limit the extent of disclosure for business reasons. The Sponsors will respond within 10 working days of receipt of each proposal. Sponsors-approved proposals are submitted to the SAG, which establishes writing committees for principal papers from among the investigators and coordinates and assigns priority to manuscripts under development.

Investigators may volunteer for writing assignments and suggest additional topics where appropriate.

The Chairman of the SAG assigns each manuscript to a subgroup of the SAG, including outside specialists when necessary, for thorough review. The subgroup reports its recommendations to the full SAG. Papers prepared for publication must be sent to the Study Coordinator for circulation among the SAG, the Sponsors and, whenever appropriate, the Data and Safety Monitoring Committee (DSMC). All manuscripts must be approved in writing by the Sponsors before submission for publication.

For all manuscripts, it is recommended that a letter from the Chairman of the SAG that documents SAG approval be sent with the manuscript when it is submitted for publication. Some journals require that all individuals listed as members of the Study group sign the

copyright transfer form. If so, the writing team may enlist the assistance of the Study Coordinator to obtain these signatures.

Copies of numbered manuscripts will be sent to all center principal investigators, as well as to members of the SAG and DSMC for information before publication.

Reprints of each publication are sent to the Study Coordinator for distribution to the SAG, each center and to outside consultants.

### **3.2 Authorship**

Each publication must acknowledge Sponsors support. Other support from industry, private foundations, or other sources may not be acknowledged unless approved by the SAG, in consultation with the Sponsors.

The SAG reviews all written reports prepared for publication. All reports from the clinical trials list the "VIP Trial Group" as author. Reports are numbered sequentially. All professional participants of the VIP Trial Group, i.e., certified personnel, investigators and co-investigators at the clinical centers and SAG are listed at the end of each paper and are considered as authors or contributors. In addition, in major papers, all Study personnel, past and present, may be listed with the approval of the clinical center's principal investigator with whom they worked.

Comparisons of treatment groups for primary or secondary outcomes are published with the VIP Trial Group as the author. Publishers or editorial staff of journals typically require a corresponding author. This individual will be determined by the SAG and the Sponsors, either by a policy decision or individually for each manuscript. Typically, the corresponding author is either the Chairman of the SAG, or an investigator of one of the resource centers.

Other publications that present data collected exclusively for the Study, including secondary analyses, also list the Research Group as the author, individual members of the writing team may be listed, subject to SAG approval. Individuals who are not members of the VIP Trial Group may not be listed as authors.

Ancillary study publications (see Policy Manual on Ancillary Studies Associated with the VIP Trial) are not designated as numbered reports. They may list individual authors, including the VIP Trial Group, if in the judgment of the SAG, substantial resources were invested in the project.

Methodological publications are judged individually by the SAG to determine appropriate authorship attribution and appropriate recognition of the VIP Trial Group.

### **3.3 Presentations**

Oral presentations of VIP trial data must be approved in advance by the Sponsors and the SAG. Abstracts should be sent to the Study Coordinator to be distributed for review initially by the Sponsors followed by the SAG. At least 45 working days must be allowed for review of the abstract. Abstracts submitted less than 45 working days prior to submission deadlines will be rejected. No unpublished results may be included in oral presentations, local or otherwise, unless a specific exception is granted by the SAG, Sponsors and the DSMC.

Local presentations on the design and methods of the study require approval only from the Sponsors. Such presentations are encouraged to stimulate patient recruitment. It is recommended that each center receives a standard set of slides from the Sponsors summarizing previously presented results of the Phase 1/2 study and the outline of the VIP Trial design and methods.

### **3.4 Publications from Ancillary Studies**

Manuscripts emanating from ancillary studies carried out in conjunction with the Study with prior approval of the SAG and with support from non-study sources must be sent to the SAG and the Sponsors for review before submission for publication; (see Appendix 16, Section 1.6 - Policy on Ancillary Studies). No investigator at any center may publish photographs, videotapes, or data from study patients on file in that center that were obtained as part of the study without explicit written permission from the SAG. Individual authors are listed on publications from ancillary studies along with appropriate acknowledgment of the study and the source of support.

### **3.5 Publications Concerning Methodology**

Investigators publication of methods employed to carry out their study functions are encouraged. Papers concerning methodology developed at the resource centers may be published in conventional or modified conventional authorship format, i.e., with individual authors named. However, study centers and investigators as well as the Sponsors must be recognized. The authors are responsible for distributing copies of methodological publications to the SAG and other study investigators. Review and approval by the SAG and the Sponsors are required before manuscripts concerning methodology are submitted for publication.

## **4. ACCESS TO STUDY INFORMATION**

### **4.1 Study Documents**

The Manual of Procedures can be accessed through the Study Coordinator. These documents may be referenced without prior approval.

The Study Coordinator oversees replacement of documents in the archives with updated copies whenever substantive changes have been made in the study procedures or methods, as determined by either the SAG or the DSMC.

#### **4.2 Study Data**

Access to study data for individual patients is prohibited to unauthorized individuals, whether on file in a clinical center or in the Photograph Reading Center. The identity of individual study patients may not be revealed in any public report or presentation.

The principal investigator of each participating study center is responsible for assuring that the integrity and confidentiality of study records is maintained.

#### **5. FAILURE TO COMPLY WITH POLICIES ON PUBLIC DISCLOSURE**

Failure to comply with the policies defined above can lead to termination of the contract between the Sponsors and the Principal Investigator/Research Institute that is in violation of the policies. Inclusion of the violating center in the authorship of future publications of the VIP Trial Group will be decided by the SAG in consultation with the Sponsors.

## **APPENDIX 16 - POLICY ON ANCILLARY STUDIES ASSOCIATED WITH THE VIP TRIAL**

### **1. INTRODUCTION**

Experience in previous multicenter clinical trials has shown that oversight of ancillary studies may consume a disproportionate share of the study resources. Ancillary studies will be considered before initiation of the main study and before the finalization of the main study protocol. After the study protocol has been finalized no ancillary study will be considered until patient accrual is completed. To assure that ancillary studies do not detract from key study tasks, no research that requires an excessive participation of the study patients or resource center personnel or any way diverts study-funded effort of clinical center personnel may be undertaken. Ancillary studies requiring BPD also require considerable resources for QLT Inc. and/or Novartis Ophthalmics Inc. ("the Sponsors") to meet regulatory requirements and in general will not be approved. Proposals for ancillary studies after patient accrual is completed may be submitted for review and prioritization after an investigator has enrolled 50% of the target number of patients. However, these ancillary studies may not be initiated until the total target sample size is enrolled and the studies of highest priority have been approved and initiated and funding for the ancillary project has been secured.

Ancillary studies may enhance the value of the study and ensure the continued interest of all investigators. However, to protect the integrity of the study, ancillary studies must be reviewed and approved by the Sponsors and SAG before their inception, whether or not they involve the need for supplemental funds. Support for data file extraction and documentation, data analysis, and photograph grading must be provided by the ancillary study investigators. Therefore, proposing investigators should consult with the principal investigator of the appropriate resource center for an estimate of the cost of the effort required. These activities will be undertaken at the study resource centers in order of priority assigned by the SAG.

#### **1.1 Definition of An Ancillary Study**

An ancillary study is any research study that requires any of the following:

- Supplemental observations or procedures to be performed upon all or a subgroup of study patients according to a set protocol.
- Use of data, materials, tissues, specimens, or other items obtained for the Study.
- Additional work to be done by, or information to be obtained from, one or more of the clinical centers, the Sponsors, or the Photograph Reading Center.

#### **1.2 Reason for Requirement of Approval**

Everyone concerned with the study is entitled to prior assurance that no ancillary study will:

- Complicate or delay the interpretation of findings from the primary study;
- Adversely affect patient cooperation with respect to enrollment, treatment, or follow-up;
- Jeopardize the public image of the study;
- Create a serious diversion of study resources locally, at the Sponsors, or at the Photograph Reading Center or at any other committee or group that serves the whole VIP Trial Group.

### **1.3 Procedures for Obtaining Ancillary Study Approval**

The investigator proposing an ancillary study should send a written request (see Section 1.4) to the Study Coordinator who is responsible for distributing copies to all members of the SAG. However, proposals received after finalization of the main study protocol from investigators affiliated with a clinical center that has not yet enrolled half or more of the expected number of patients will not be distributed for review until that goal is met and accrual is on target. Within a reasonable time after distribution, the SAG Chairman summarizes any questions and/or objections raised by members of the SAG and sends this summary to the applicant to permit amplification, clarification, and/or withdrawal of the request. The members of the SAG have another opportunity to review the request and the SAG Chairman then prepares a statement of the SAG consensus, including any remaining reservations or objections and the current priority rank assigned to the ancillary study. This statement is forwarded to the investigator who requested approval for the ancillary study. Once patient accrual has been completed for all clinical trials, the SAG will approve initiation of ancillary studies submitted after finalization of the protocol in order of priority, while taking account of demands on the Sponsors, and the Photograph Reading Center. Each ancillary study investigator will be notified of the priority assigned to the proposed study and the likely date of approval to initiate it.

### **1.4 Preparation of Request for Approval of an Ancillary Study**

The request for approval of an ancillary study should be in narrative form. It should follow the usual outline for research proposals, i.e., it should identify the responsible principal investigator for the ancillary study and provide a brief description of the objectives, methods, and significance of the study. Full details should be given concerning any procedures to be carried out on any study patients, such as laboratory tests, interviews, psychophysical testing, etc. Mention should be made of any substance to be injected or otherwise administered to the patients. Any observations to be made or procedures to be carried out on a patient outside of the clinic should be described. Mention should be made of the extent to which the ancillary study is expected to require extra clinic visits by the patient or to prolong the patient's usual study examinations. Information should be given concerning the extent to which the ancillary study will require blood or other specimens. If specimens are to be obtained from the patients, mention should be made of all procedures to be carried out on these specimens. A sample consent form should be provided with the proposal. Before approval is given to initiate an ancillary study, the



consent form for the research that has been approved by the local IRB must be submitted to the SAG.

### **1.5 Funding of Ancillary Studies**

If no additional funds and no assistance from resource centers are required, the investigator may proceed with the ancillary study as soon as it has been approved for initiation by the SAG and the Sponsors. If additional funds are needed, the investigator may prepare and submit a new research grant application to the potential sponsor for review in the same manner as any other new research grant application. It is understood that the investigator is not to accept the grant or activate the ancillary study until approval of initiation has been received from the SAG and the Sponsors.

### **1.6 Publication of Ancillary Study Results**

All manuscripts or presentations for scientific meetings based on ancillary study data must be reviewed and approved by the SAG and Sponsors before publication or presentation. See Policy Manual on Public Disclosure of Study Results generated by the VIP Trial Group: Section 3.2, for study policy governing authorship and Section 3.3 for study policy concerning presentations. Such review pertains only to impact on study objectives and not to scientific merit, although scientific issues may be addressed by reviewers.

No investigator may publish data on vision or anatomic changes, treatment complications, or quality of life measurements among patients enrolled in the study at his or her clinical center during the course of the study.

After publication, 30 reprints or photocopies of the ancillary study report should be sent to the Study Coordinator for distribution to the SAG, DSMC and for the study library.

### **1.7 Progress Report**

The principal investigator of each ancillary study is required to report to the SAG at six-month intervals on the progress or termination of the ancillary study. This report may be prepared as a letter copied to the Sponsors. The status of all ancillary studies is reported at each SAG meeting. The SAG may withdraw approval of ancillary studies for which no report is received for one year or for which no progress is reported for two years.

## **APPENDIX 17**

### **VIP Trial: Fellow Eye Open-Label Treatment**

#### **General Description**

To qualify for fellow eye open-label treatment, a patient must be enrolled in VIP and present with a predominantly classic CNV lesion (the area of classic CNV is  $\geq 50\%$  of the area of the entire lesion) in the fellow eye secondary to AMD or PM. Neither the investigator nor the patient will be unmasked as to the identity of treatment assignment of the study eye that remains double-masked in the randomized study until all patients have completed their 24-month visit and statistical analyses are completed.

Open-label treatment with verteporfin will be provided to qualifying fellow eyes at the 18-month and/or the 21-month visit(s) only of the masked VIP trial. No treatment will be administered to either eye at the 24-month visit. Under this protocol, fellow eyes not meeting the eligibility criteria by the 21-month visit of the masked trial will not be treated. Once a fellow eye is enrolled for open-label treatment, ocular assessments will be performed for both eyes as specified in the masked treatment study. If the patient has discontinued study eye treatment during the masked study for any reason other than a study eye adverse event, the fellow eye is not eligible for treatment.

#### **Informed Consent**

The informed consent addendum must be signed prior to their fellow eye open-label treatment to provide patients with the latest safety information (sample informed consent addendum is attached).

#### **Study Procedures**

Routine study procedures should be done during the remaining follow-up visits at 3-month intervals through the 24-month visit according to the detailed descriptions of the protocol dated December 19, 1997. The required procedures include the following: best-corrected visual acuity, peak contrast threshold, color fundus photography, fluorescein angiography, dilated ophthalmoscopy, telephone contact 2 to 4 days after treatment, and assessment of concomitant medication and adverse events. The HQL assessment, subjective visual performance rating and ICG angiography do not apply to the fellow eye treatment. Verteporfin PDT treatment of qualifying fellow eyes will be performed at the 18-month and/or 21-month visit(s) only of the masked VIP trial if all criteria are met. At visits when both eyes require treatment, the study eye (masked medication) must be treated at that visit using its assigned masked medication while the fellow eye (verteporfin open-label) cannot be treated until at least four days later but not more than 14 days later. For fellow eye open-label treatment, the document flow for reporting and evaluating ocular adverse events in the treated eye(s) remains as described in the masked study. Serious Adverse Event procedures should be followed as outlined in section 12 of the VIP protocol.

### **Inclusion Criteria of a Fellow Eye for Open-Label Treatment**

To be eligible to enter the open-label treatment program, the fellow eye must fulfill the following criteria at the 18-month or 21-month visit:

1. Has clinical signs of subfoveal CNV secondary to AMD or PM.
2. Has a CNV lesion with the following characteristics determined by fluorescein angiography:
  - a) the CNV lesion involves the geometric center of the foveal avascular zone,
  - b) the CNV lesion is predominantly classic (the area of classic CNV is  $\geq 50\%$  of the area of the entire lesion); for definitions, see Section 9.1.1),
  - c) the greatest linear dimension of the entire CNV lesion does not exceed 5400  $\mu$  diameter (approximately equivalent to the diameter of the 9 MPS disc area circle).

### **Exclusion Criteria of a Fellow Eye for Open-Label Treatment**

The fellow eye is not eligible for enrollment into the open-label treatment program if any of the following criteria are met:

1. Has any of the following in the fellow eye: a tear (rip) of the RPE; any vitelliform-like lesion of the outer retina (e.g. as in pattern dystrophies or basal laminar drusen), any idiopathic parafoveal telangiectasis, any central serous retinopathy, or any serous pigment epithelial detachment without CNV.
2. Has one of the following conditions in the fellow eye: uncontrolled glaucoma, anterior ischemic optic neuropathy, clinically significant diabetic macular edema, severe non-proliferative or proliferative diabetic retinopathy.
3. Has subfoveal CNV in the fellow eye secondary only to any of the following conditions: ocular histoplasmosis syndrome (OHS), pseudo OHS, multifocal choroiditis (including punctate inner choroidopathy), angioid streaks or idiopathic CNV.
4. Patient has discontinued study eye treatment for any reason other than a study eye adverse event.

### **Treatment and Retreatment Criteria For Fellow Eye Open-Label Treatment**

To determine the initial enrollment eligibility for open-label treatment and for retreatment of the fellow eye, fluorescein angiography (early and late frames) must be performed to

determine if fluorescein leakage is present and the size (GLD) of the CNV lesion. It is the responsibility of the investigator in cooperation with their photographers to determine whether the appropriate views can be achieved in the same fluorescein angiography setting required for the study eye or whether a separate setting is required to capture the required angiograms of the fellow eye. This may require a separate visit and should be discussed with the patient.

The initial fellow eye treatment and any retreatment may 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. As all patients have completed their 15-month visit, there is opportunity for fellow eye treatment at the 18- and 21-month visits during the VIP trial. Each fellow eye treatment or retreatment must be conducted within 7 days of their most recent fluorescein angiogram. Fellow eye treatments or retreatments must be performed between 4 and 14 days, inclusively, after masked treatment of the study eye. If fluorescein angiography of the fellow eye must be repeated after treatment of the study eye, the study eye should not be re-evaluated or re-photographed to ensure that the masked treatment assignment of the study eye is maintained.

To be eligible for fellow eye treatment or retreatment, patients must also fulfill the following criteria:

1. Have no additional ocular disease that has developed and may compromise the safety of the fellow eye. Cataract, that 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 fellow eye lesion.
3. Have no retinal arteriolar or retinal venular non-perfusion caused by previous treatment to the fellow eye in this study.
4. Women of childbearing potential must have a negative pregnancy test (urine) within 3 days of any retreatment and must use an effective method of contraception during the study.
5. Have no confirmed decrease in vision in the fellow eye relative to pre-treatment, on Day 1 to Day 4 after treatment, of 20 letters or more in best-corrected visual acuity.

Every attempt must be made to retreat the fellow eye if it meets the retreatment eligibility criteria at months 18 and 21. If the fellow eye qualifies for treatment but the treatment cannot be carried out, the fellow eye must still undergo routine study procedures according to protocol.

## **Handling of Fellow Eye Photographs**

Each center will individually evaluate their fellow eye fluorescein angiograms to determine if the fellow eye qualifies for this open-label treatment program and, subsequently, for retreatment (leakage, GLD, etc.). Confirmation of leakage and area of the lesion to be treated by the Photograph Reading Center is not required prior to enrolling the fellow eye. Once a fellow eye qualifies for open-label treatment and is treated, the qualifying fellow eye fluorescein angiograms and color fundus photographs must be forwarded to the Photograph Reading Center for quality control review. Instructions for completing the transmittal form will be provided to each clinical site. The Investigator should retain a copy of each photograph for their study file.

## **Recording Fellow Eye Treatment Information**

Additional pages to the VIP CRF are not required for treatment of the fellow eye. Information pertaining to each fellow eye treatment should be recorded on a fellow-eye worksheet and retained in the study file at each investigative site. The following pages of the VIP CRF modules should be used to capture treatment and adverse event information:

***Concomitant Medications:*** When the fellow eye is treated, use this page to document treatment and complete each column as follows:

generic name:	verteporfin - fellow eye PDT
unit dose:	6 mg/m <sup>2</sup>
dosage regimen and route:	IV - once
reason for medication:	2 specify: CNV
start date/stop date:	date of actual treatment (do not check the ongoing box)

***Adverse Events (Other Than The Study Eye):*** Use this page to record all adverse events, except in the study eye, that the investigator determines to have resulted from verteporfin treatment of the fellow eye (e.g., relationship = possible, probable or definite). In the event description column, list the adverse event followed by a hyphen and the words “fellow eye PDT” (e.g., headache – fellow eye PDT). Use of the fellow eye PDT terminology will distinguish these events from those that resulted from study eye treatment or from other factors. Complete the remaining columns according to the VIP protocol.

## **Order of Treatments and Retreatments**

The fellow eye will be treated in open-label fashion using the same treatment parameters for verteporfin infusion and light application as described in the VIP protocol (6 mg/m<sup>2</sup>, 50 J/cm<sup>2</sup> beginning 15 minutes after starting the infusion). At visits when both eyes require treatment, the study eye (masked medication) must be treated at that visit using its assigned masked medication while the fellow eye (verteporfin open-label) cannot be treated until at least four days later but not more than 14 days later.

### **Statistical Design and Analysis**

Data obtained from fellow eye treatments will be summarized descriptively without formal statistical testing. Safety data will be pooled together with data from the masked VIP trial.

## **SAMPLE INFORMED CONSENT FORM ADDENDUM FOR FELLOW EYE OPEN-LABEL TREATMENT**

### **Introduction:**

This addendum is to provide you with information about possible treatment of your other eye, to inform you of minor changes to the VIP study procedures and to provide you with updated safety information on verteporfin. Your eye that is currently being treated in the VIP study is your 'study eye' while your other eye will be referred to as your 'fellow eye'.

### **Changes to Study Procedures:**

1. If your fellow eye has predominantly classic CNV at the 18- or 21-month visit, you may choose to have your fellow eye treated with verteporfin at those visits. If you choose to participate and your study eye also requires treatment at those visits, you must return to the clinic for a second visit about 4 to 14 days later to examine and treat your fellow eye. If it has been more than 7 days since your last fluorescein angiogram, another must be done to properly assess your lesion.
2. If you are participating in the health-related quality of life interview, your 24-month telephone interview will be done during the 4 weeks before your 24-month visit.

All other study procedures remain as previously described to you.

### **New Safety Information on Verteporfin**

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 in 4% of patients or less.

In the 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. The TAP study is very similar to VIP but has patients who had poorer vision and a different type of lesion (classic-containing CNV lesion) due only to AMD. The most frequently reported adverse events to verteporfin were headache, extravasation (verteporfin leaking into the skin at the injection site), rash near the injection site, blurred vision, decreased vision, and spots in vision. Those events occurred in approximately 10 – 20 % of patients. The following events, were reported more frequently with verteporfin than with placebo and occurred in 1 – 10% of patients: In the Eye (inflammation, redness, tearing, itching, severe vision loss, bleeding inside the eye, and double vision); Rest of Body (weakness, back pain usually during drug infusion, fever, flu, sunburn, eczema, irregular heart beat, high blood pressure, blood circulation problems, varicose veins, constipation, nausea, anemia, too many or too few white blood cells, abnormal liver blood tests, protein in urine, elevated creatinine, joint degeneration or pain,

muscle weakness, dizziness, problems sleeping, inflamed or sore throat, pneumonia, decreased hearing, abnormal sensations in the arm or leg, and prostate gland problems. Severe vision loss (decrease in reading ability of 4 lines or more on the VIP eye chart) within 7 days of being treated has been reported in 1 – 4% of patients. Partial recovery of vision was observed in many patients.

**Consent:**

I am aware that the protocol and this Informed Consent Addendum 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 verteporfin (BPD-MA) treatment of choroidal neovascularization in the VIP study. 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 understand that confidentiality and other information contained in the original consent form signed at the start of the VIP study remain in effect. I have been given a copy of the following:

1. The information and consent form I signed at the start of the VIP study.
2. This consent form addendum.

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



## **APPENDIX 18**

### **VIP Trial: Open-Label Extension Study**

#### **General Description**

To participate in the extension study, a patient must have at least one eye that has potential for treatment benefit as determined by their investigator at the initial evaluation for the extension study. The patient must have been diagnosed with PM by the investigator during the VIP screening visit, must have completed their 24-month visit including the last visit module in the masked VIP study, and must meet the inclusion/exclusion criteria for the extension study. Exceptions to the 24-month visit requirement are patients who missed this visit due to hospitalization and those patients whose study-eye required emergency treatment with verteporfin-PDT at the 21-month visit and were discontinued from VIP. Open-label treatment with verteporfin will be provided every 3 months for up to the 45-month visit to qualified eyes with CNV leakage as assessed by fluorescein angiography. No treatment will be administered at the 48-month visit. Patients whose study eye does not require retreatment at the 24-month visit due to absence of CNV leakage can qualify for the extension study as long as there is potential for treatment benefit in either eye. Neither the investigator nor the patient will be unmasked as to the identity of treatment assignment to the study eye during the double-masked randomized study until all patients have completed their 24-month visit and statistical analyses are completed.

Fellow eyes with a subfoveal CNV lesion secondary to PM that meet the inclusion/exclusion criteria may be enrolled into the extension study. A fellow eye may qualify for the extension study regardless of whether the study eye qualifies.

Some PM patients may complete the 24-month visit and exit the VIP study prior to approval of this amendment. Those patients will be allowed to enter the extension study if they can satisfy the inclusion/exclusion criteria.

#### **Informed Consent**

The informed consent addendum must be signed prior to their treatment in the open-label extension to provide patients with the latest safety information (sample informed consent addendum is attached).

#### **Study Procedures**

Routine study procedures should be performed during follow-up visits at 3-month intervals through the 48-month visit as described in the amended VIP protocol. The required procedures include the following: best-corrected visual acuity, peak contrast threshold, color fundus photography, fluorescein angiography, dilated ophthalmoscopy, pregnancy test (if required), telephone contact 2 to 4 days after treatment, and assessment of concomitant medication and adverse events. Vital signs, HQL assessments, subjective

visual performance ratings and ICG angiography will not be done in the extension study. Verteporfin PDT treatment of qualified eyes should be performed at intervals of 3-months through the 45-month visit if all criteria are met. At the first visit (24-month visit or later) for a patient with two qualified eyes that require treatment and neither eye has received prior open-label verteporfin treatment, only one eye (jointly decided between the investigator and the patient) can be treated at that visit. If no significant safety issues are identified, the second eye can be treated 4 to 14 days later following another infusion. At all subsequent visits when both eyes require treatment, one infusion of verteporfin should be administered and laser light should be applied first to the study eye and then to the fellow eye. For bilateral treatment, laser light should be applied to the second eye no later than 20 minutes from the start of the infusion. The document flow for reporting and evaluating ocular adverse events in either eye remains as described in the masked study. Serious Adverse Event procedures should be followed as outlined in section 12 of the VIP protocol. Examinations as described above will be done at the last scheduled visit (month 48) but no treatment will be provided.

### **Inclusion Criteria for the Extension Study**

To participate in the extension study, a patient must have at least one eye that has potential for treatment benefit as determined by their investigator at the initial evaluation for the extension study.

#### **A. Study Eye**

To qualify the study eye for the extension study, the patient must fulfill the following criteria at the 24-month visit:

1. Was diagnosed with PM by the investigator at the VIP screening visit.
2. Has potential for treatment benefit in their study eye according to their treating ophthalmologist even if there is an absence of CNV leakage.
3. Has completed the 24-month visit and the last visit module in the masked VIP study. Patients who do not need to complete the 24-month visit are: 1) Patients who discontinue from VIP at the 21-month visit due to emergency treatment of their study-eye with verteporfin-PDT; 2) Patients who miss the 24-month visit due to hospitalization. These two groups of patients must have a completed Last Visit Module from VIP and return for consideration into the extension study within four weeks of when their 24-month visit would have occurred in VIP.

#### **B. Fellow Eye**

To qualify the fellow eye for the extension study, the study eye must have been diagnosed with PM at the VIP screening visit and the fellow eye must fulfill the following criteria at or after the 24-month visit:

1. Has a CNV lesion secondary to PM that involves the geometric center of the foveal avascular zone as determined by the investigator using fluorescein angiography.
2. Has potential for treatment benefit in their fellow eye according to their treating ophthalmologist even if there is an absence of CNV leakage.
3. Has completed the 24-month visit and the last visit module in the masked VIP study. Patients who do not need to complete the 24-month visit are: 1) Patients who discontinue from VIP at the 21-month visit due to emergency treatment of their study-eye with verteporfin-PDT; 2) Patients who miss the 24-month visit due to hospitalization. These two groups of patients must have a completed Last Visit Module from VIP and return for consideration into the extension study within four weeks of when their 24-month visit would have occurred in VIP.

### **Exclusion Criteria for the Extension Study**

#### **A. Study Eye**

The study eye does not qualify if any of the following criteria are met prior to enrolling into the extension study:

1. Patient discontinued VIP study eye treatment for any reason other than emergency treatment of the study eye with verteporfin-PDT at the 21-month visit.
2. Patient received any surgical (submacular surgery, retinal translocation, etc.), radiation or subfoveal laser (photocoagulation) treatment of their study eye CNV lesion since completing the VIP 24-month visit.
3. Patient received any medicinal treatment of their study eye CNV lesion since completing the VIP 24-month visit. [Note: Open-label treatment with Visudyne PDT is allowed for emergency treatment of the study eye after discontinuing from VIP at the 21-month visit and after the 24-month visit prior to enrolling into the extension study.]
4. Patient has participated in a clinical study other than VIP since discontinuing the masked VIP study. [Note: Patient treatment under a Physician IND or as part of standard medical practice is not considered a clinical study.]

#### **B. Fellow Eye**

The fellow eye does not qualify for the extension study if any of the following criteria are met prior to enrolling into the extension study:

1. Patient discontinued VIP study eye treatment for any reason other than emergency treatment of the study eye with verteporfin-PDT at the 21-month visit.

2. Patient received any surgical (submacular surgery, retinal translocation, etc.), radiation or subfoveal laser (photocoagulation) treatment of their fellow eye CNV lesion since completing the VIP 24-month visit.
3. Patient received any medicinal treatment of their fellow eye CNV lesion since completing the VIP 24-month visit. [Note: Open-label treatment with Visudyne PDT is allowed after the 24-month visit prior to enrolling into the extension study.]
4. Patient has participated in a clinical study other than VIP since discontinuing the masked VIP study. [Note: Patient treatment under a Physician IND or as part of standard medical practice is not considered a clinical study.]
5. Has any of the following in the fellow eye: a tear (rip) of the RPE; any vitelliform-like lesion of the outer retina (e.g. as in pattern dystrophies or basal laminar drusen), any idiopathic parafoveal telangiectasis, any central serous retinopathy, or any serous pigment epithelial detachment without CNV. [Note: This exclusion is not applicable to a fellow eye that qualified and received treatment in VIP prior to the 24-month visit.]
6. Has any of the following conditions in the fellow eye: uncontrolled glaucoma, anterior ischemic optic neuropathy, clinically significant diabetic macular edema, severe non-proliferative or proliferative diabetic retinopathy. [Note: This exclusion is not applicable to a fellow eye that qualified and received treatment in VIP prior to the 24-month visit.]
7. Has subfoveal CNV in the fellow eye secondary only to any of the following conditions: ocular histoplasmosis syndrome (OHS), pseudo OHS, multifocal choroiditis (including punctate inner choroidopathy), angioid streaks or idiopathic CNV. [Note: This exclusion is not applicable to a fellow eye that qualified and received treatment in VIP prior to the 24-month visit.]
8. Fellow eye experienced severe vision loss from VIP study fellow eye treatment prior to the 24-month visit.

### **Treatment and Retreatment Criteria**

Once an eye is qualified for the extension study, treatment and retreatment eligibility must be established by fluorescein angiography (early and late frames) to determine if CNV leakage is present and the size (GLD) of the CNV lesion. When both eyes are treatment candidates, it is the responsibility of the investigator in cooperation with their photographers to determine whether the appropriate fluorescein angiographic views can be achieved for both eyes during one visit or whether a separate visit will be required to capture the required angiographic information.

The initial extension treatment and any retreatment should be performed if evidence of CNV leakage is detected by fluorescein angiography. Retreatments should only be conducted at

intervals of 3 months  $\pm$  2 weeks. As described in the VIP protocol, each treatment or retreatment should be conducted within 7 days of the most recent fluorescein angiogram.

To be eligible for extension treatment or retreatment, patients must also fulfill the following criteria:

1. The investigator must consider that a qualified eye(s) has potential for treatment benefit. Each qualified eye must be considered independently.
2. Have no additional ocular disease that has developed and may compromise the safety of the eye(s). Cataract, that 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 protocol Section 7.4).
3. It must be possible for the Investigator to visualize the lesion in the eye(s) considered for treatment.
4. Have no retinal arteriolar or retinal venular non-perfusion caused by previous treatment to the eye(s) considered for treatment.
5. Women of childbearing potential must have a negative pregnancy test (urine) within 3 days of any retreatment and must use an effective method of contraception during the extension study.
6. Following the previous treatment, have no confirmed decrease in vision relative to pretreatment in either eye considered for treatment on Day 1 to Day 4 after treatment, of 20 letters or more in best-corrected visual acuity.

Every attempt should be made to re-treat a qualified eye(s) if it meets the retreatment eligibility criteria at 3-month intervals. If an eye qualifies for treatment but the treatment cannot be carried out, that eye must still undergo routine study procedures according to protocol.

### **Review and Retention of Photographs**

Each center will individually evaluate their photographs (fluorescein angiograms and color fundus photographs) to determine if either eye qualifies (leakage, GLD, etc.) for treatment or retreatment in the extension study. Confirmation of the investigator's angiographic findings by the Photograph Reading Center is not required prior to enrolling a patient into the extension study. All photographs should be labeled as described in the VIP protocol and retained at the site.

### **Recording Extension Study Information**

New worksheets and CRF pages specific to the extension study will be provided to record relevant information pertaining to the study.

Some patients may exit VIP prior to the approval of the extension study by their investigator's ethics committee. If any of those patients later qualify and enter the extension study, their open-label treatment(s) with Visudyne PDT that occurred after exiting VIP should be recorded in the extension CRF as a concomitant medication. Additions or changes in significant medical history, underlying medical conditions and concomitant medications since exiting VIP should also be recorded. Adverse events that were ongoing when the patient exited VIP should be recorded and/or updated in the extension CRF.

The visit month recorded on the initial extension CRF should reflect the 3-month cycle of visits as continued from when the patient first entered the original VIP study. For example, a patient who completed the 24 month visit but who had to wait for 3 months until the extension study amendment was approved before entering the extension would have the first extension visit recorded as month 27 rather than as month 24. For patients who have the first extension visit in mid-cycle, the visit month recorded on the CRF should reflect the follow-up 3-month visit that is closer to the actual visit date. For example, a patient who completed the 24 month visit but who had to wait for 4 months until the extension study amendment was approved before entering the extension would have the first extension visit recorded as month 27 rather than as month 24.

### **Order of Treatments and Retreatments**

All qualified eyes will be treated with verteporfin-PDT in open-label fashion using the same treatment parameters for verteporfin infusion and light application as described in the VIP protocol (6 mg/m<sup>2</sup>, 50 J/cm<sup>2</sup> beginning 15 minutes after starting the infusion). At the first visit where both eyes require treatment and neither eye has previously received open-label verteporfin treatment, the investigator and the patient should jointly decide which eye to treat first as described in the "Study Procedures" section of this amendment. At all other visits where both eyes require treatment at the same visit, one infusion will be administered and laser light should be applied first to the study eye and then to the fellow eye. For bilateral treatment, laser light should be applied to the second eye beginning no later than 20 minutes from the start of the infusion.

### **Continuation or Termination From the Extension Study**

To continue in the extension study, the investigator must consider that a patient has at least one qualified eye that has potential for treatment benefit. If, at any visit, neither eye demonstrates potential for treatment benefit as determined by the investigator, the patient must be discontinued from the extension study. The 48-month visit will be considered as the last possible visit in the extension study. Any patient who experiences a decrease in vision within 4 days of treatment in either treated eye of 20 letters or more in best-corrected visual acuity relative to pre-treatment must be discontinued from further treatment to either eye. These patients but should be scheduled for follow-up evaluation at least until vision in that eye(s) returns to the pre-treatment level or until the investigator establishes that additional improvement in vision is unlikely.

## **Data Handling**

Data obtained from the extension study will be summarized descriptively without formal statistical analyses. For the study eye, visual acuity scores will be summarized separately for patients who switch from placebo to active treatment during the extension, and for patients who continue on active treatment during the extension. Visual acuity scores for any fellow eyes that receive active treatment will be summarized beginning at the visit they were first treated.

All non-ocular adverse events that occur during the extension while patients are on open-label verteporfin treatment will be pooled and summarized with all adverse events from the verteporfin treatment group of the 2-year masked study. The ocular events will be summarized separately by study eye and by fellow eye, and, separately by masked treatment and by open-label treatment.

## **Sample Addendum to Informed Consent**

### **SAMPLE INFORMED CONSENT FORM ADDENDUM FOR THE VIP EXTENSION STUDY**

#### **Introduction:**

This addendum is to provide you with information about a 2-year extension to the VIP study and to provide you with updated safety information on the study drug (verteporfin). If you agree to participate in the extension study, one or both of your eyes may be treated with active drug (verteporfin) after you complete the masked VIP study. During the extension study, your eye that was treated with masked medication in VIP will continue to be referred to as your 'study eye' while your other eye will be referred to as your 'fellow eye'.

#### **The VIP Extension Study:**

If you were diagnosed with PM during the VIP study and your doctor believes that your study eye might respond to treatment, you will be examined to determine if you qualify for the extension study. Your fellow eye may also qualify if your doctor determines that it has CNV due to PM that might respond to treatment in the extension study. If you choose to participate and your study eye and/or fellow eye qualify for treatment, you will be examined every 3 months and treated with active drug (verteporfin) when necessary. All VIP procedures except for vital signs, quality of life interviews, visual performance ratings and the ICG angiography will be done in the extension study. At the 48-month visit, you will be examined and you will not receive any treatment and the study will end.

## **Updated Safety Information on Verteporfin:**

### **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 adverse events are from 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 (in 19% of placebo patients). Except for the visual disturbance adverse events, the safety profile for VIP patients was very similar to that described above for the TAP study 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 VIP 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 19**

### **VIP Trial Open-Label Continuation of Extension Study**

#### General Description

To participate in the extension study for an additional 12 months, the patients must have not been discontinued prematurely from the initial extension study and must meet the inclusion/exclusion criteria for the continuation of the extension study. With IRB approval, open-label treatment with verteporfin will be provided at Month 48 and at Month 54 to qualified eyes with CNV leakage as assessed by fluorescein angiography. No treatment will be administered at the 60-month visit.

Some PM patients may complete the 48-month visit and exit the VIP PM extension prior to approval of this amendment. Those patients will be allowed to enter the extension study at the Month 54 visit if they can satisfy the inclusion/exclusion criteria.

#### Informed Consent

The informed consent addendum must be signed prior to continuing in the extension to provide patients with the latest safety information (sample informed consent addendum is included).

#### Study Procedures

Routine study procedures should be performed during follow-up visits at 6-month intervals through the 60-month visit as described in the revised Appendix 2. The required procedures include the following: medical history update (if the patient exited the study at Month 48 and re-entered the continuation), best-corrected visual acuity, color fundus photography, fluorescein angiography, dilated ophthalmoscopy, pregnancy test (if required), telephone contact 2 to 4 days after treatment, and assessment of concomitant medication and adverse events. Vital signs, HQL assessments, subjective visual performance ratings, peak contrast threshold, and ICG angiography will not be done in the extension study. Verteporfin PDT treatment of qualified eyes should be performed at Month 48 and Month 54 if all criteria are met. At the first visit (48-month visit or later) for a patient with two qualified eyes that require treatment and neither eye has received prior open-label verteporfin treatment, only one eye (jointly decided between the investigator and the patient) can be treated at that visit. If no significant safety issues are identified, the second eye can be treated 4 to 14 days later following another infusion. At all subsequent visits when both eyes require treatment, one infusion of verteporfin should be administered and laser light should be applied first to the study eye and then to the fellow eye. For bilateral treatment, laser light should be applied to the second eye no later than 20 minutes from the start of the infusion. The document flow for reporting and evaluating ocular adverse events in either eye remains as described in the masked study. Serious Adverse Event procedures should be followed as outlined in section 12 of the VIP protocol. These procedures will be done at the last scheduled visit (month 60), but no treatment will be provided.

### Inclusion Criteria for the Continuation of the Extension Study

To participate in the continuation of the extension study, a patient must have been enrolled in the extension study.

#### A. Study Eye

To qualify the study eye for continuing in the extension study, the patient must fulfill the following criteria at the first continuation visit:

1. Study eye was previously enrolled in the extension.

#### B. Fellow Eye

To qualify the fellow eye for the continuation of the extension study, the patient must have been previously enrolled in the extension and the fellow eye must fulfill the following criteria at or after the 48-month visit:

Previously enrolled fellow eye:

1. Fellow eye was enrolled in the extension study.

Never enrolled fellow eye:

1. Has a CNV lesion secondary to PM that involves the geometric center of the foveal avascular zone as determined by the investigator using fluorescein angiography.
2. Has potential for treatment benefit in their fellow eye according to their treating ophthalmologist even if there is an absence of CNV leakage.

### Exclusion Criteria for the Extension Study

#### A. Study Eye

The study eye does not qualify if any of the following criteria are met prior to continuing into the extension study:

5. Patient discontinued study eye treatment for any reason.
6. Patient received any surgical (submacular surgery, retinal translocation, etc.), radiation or subfoveal laser (photocoagulation) treatment of the study eye CNV lesion since completing the VIP 48-month visit.
7. Patient received any medicinal treatment of the study eye CNV lesion since completing the VIP 48-month visit. [Note: Open-label treatment with Visudyne PDT is allowed.]

8. Patient has participated in a clinical study other than VIP since completing the VIP 48 month visit.

B. Fellow Eye

The fellow eye does not qualify for continuing in the extension if any of the following criteria are met prior to enrolling into the continuation of the extension study:

9. Patient discontinued previously enrolled fellow eye treatment for any reason.
10. Patient received any surgical (submacular surgery, retinal translocation, etc.), radiation or subfoveal laser (photocoagulation) treatment of the previously enrolled fellow eye CNV lesion since completing the VIP 48-month visit.
- ~~11.~~ Patient received any medicinal treatment of the previously enrolled fellow eye CNV lesion since completing the VIP 48-month visit.
- ~~12.~~ Patient has participated in a clinical study other than VIP since discontinuing the Month 48 visit.
13. Has any of the following in the fellow eye: a tear (rip) of the RPE; any vitelliform-like lesion of the outer retina (e.g. as in pattern dystrophies or basal laminar drusen), any idiopathic parafoveal telangiectasis, any central serous retinopathy, or any serous pigment epithelial detachment without CNV. [Note: This exclusion is not applicable to a fellow eye that qualified and received treatment in VIP prior to the 48-month visit.]
14. Has any of the following conditions in the fellow eye: uncontrolled glaucoma, anterior ischemic optic neuropathy, clinically significant diabetic macular edema, severe non-proliferative or proliferative diabetic retinopathy. [Note: This exclusion is not applicable to a fellow eye that qualified and received treatment in VIP prior to the 48-month visit.]
15. Has subfoveal CNV in the fellow eye secondary only to any of the following conditions: ocular histoplasmosis syndrome (OHS), pseudo OHS, multifocal choroiditis (including punctate inner choroidopathy), angioid streaks or idiopathic CNV. [Note: This exclusion is not applicable to a fellow eye that qualified and received treatment in VIP prior to the 48-month visit.]
16. Fellow eye experienced severe vision loss from Visudyne fellow eye treatment prior to the 48-month visit.

Treatment and Retreatment Criteria

Once an eye is qualified for the continuation of the extension study, treatment and retreatment eligibility must be established by fluorescein angiography (early and late frames) to determine if CNV leakage is present and the size (GLD) of the CNV lesion. When both eyes are treatment candidates, it is the responsibility of the investigators in cooperation with their photographers to determine whether the appropriate fluorescein angiographic views can be achieved for both eyes during one visit or whether a separate visit will be required to capture the required angiographic information.

The initial extension treatment and any retreatment should be performed if evidence of CNV leakage is detected by fluorescein angiography. As described in the VIP protocol, each treatment or retreatment should be conducted within 7 days of the most recent fluorescein angiogram.

To be eligible for extension treatment or retreatment, patients must also fulfill the following criteria:

7. The investigator must consider that a qualified eye(s) has potential for treatment benefit. Each qualified eye must be considered independently.
8. Have no additional ocular disease that has developed and may compromise the safety of the eye(s). Cataract, that does not obscure visualization and treatment of the CNV, is allowed. Cataract that is considered to have significantly compromised the visual acuity should undergo corrective operation (see protocol Section 7.4).
9. It must be possible for the Investigator to visualize the lesion in the eye(s) considered for treatment.
10. Have no retinal arteriolar or retinal venular non-perfusion caused by previous treatment to the eye(s) considered for treatment.
11. Women of childbearing potential must have a negative pregnancy test (urine) within 3 days of any retreatment and must use an effective method of contraception during the extension study.
12. Following the previous treatment, have no confirmed decrease in vision relative to pretreatment in either eye considered for treatment on Day 1 to Day 4 after treatment, of 20 letters or more in best-corrected visual acuity.

Every attempt should be made to re-treat a qualified eye(s) if it meets the retreatment eligibility criteria. If an eye qualifies for treatment but the treatment cannot be carried out, that eye must still undergo routine study procedures according to protocol.

#### Review and Retention of Photographs

Each center will individually evaluate their photographs (fluorescein angiograms and color fundus photographs) to determine if either eye qualifies (leakage, GLD, etc.) for treatment or

retreatment. Confirmation of the investigator's angiographic findings by the Photograph Reading Center is not required prior to continuing a patient in the extension study. All photographs should be labeled as described in the VIP protocol and retained at the site. No photographs taken during the continuation of the extension study will be required for submission to the Photograph Reading Center unless needed to substantiate a serious ocular adverse event (Exhibit I) or unless specifically requested by the Photograph Reading Center or Sponsor.

### Recording Extension Study Information

New worksheets and CRF pages specific to the extension study will be provided to record relevant information pertaining to the study.

Some patients may exit the VIP PM extension prior to the approval of the continuation of the extension study by their investigator's ethics committee. If any of those patients later qualify and continue in the extension study, their open-label treatment(s) with Visudyne PDT that occurred after exiting VIP PM extension should be recorded in the extension CRF as a concomitant medication. Additions or changes in significant medical history, underlying medical conditions and concomitant medications since exiting VIP PM extension should also be recorded. Adverse events that were ongoing when the patient exited VIP PM extension should be recorded and/or updated in the extension CRF.

The visit month recorded on the initial extension continuation CRF should reflect the 6-month cycle of visits as continued from when the patient first entered the original VIP study.

### Order of Treatments and Retreatments

All qualified eyes will be treated with verteporfin-PDT in open-label fashion using the same treatment parameters for verteporfin infusion and light application as described in the VIP protocol (6 mg/m<sup>2</sup>, 50 J/cm<sup>2</sup> beginning 15 minutes after starting the infusion). At the first visit where both eyes require treatment and neither eye has previously received open-label verteporfin treatment, the investigator and the patient should jointly decide which eye to treat first as described in the "Study Procedures" section of this amendment. At all other visits where both eyes require treatment at the same visit, one infusion will be administered and laser light should be applied first to the study eye and then to the fellow eye. For bilateral treatment, laser light should be applied to the second eye beginning no later than 20 minutes from the start of the infusion.

### Termination From the Extension Study

The 60-month visit will be considered as the last possible visit in the extension study. Any patient who experiences a decrease in vision within 4 days of treatment in either treated eye of 20 letters or more in best-corrected visual acuity relative to pre-treatment must be discontinued from further treatment to either eye. These patients should be scheduled for

follow-up evaluation at least until vision in that eye(s) returns to the pre-treatment level or until the investigator establishes that additional improvement in vision is unlikely.

### Data Handling

Data obtained from the extension study will be summarized descriptively without formal statistical analyses. For the study eye, visual acuity scores will be summarized separately for patients who switch from placebo to active treatment during the extension, and for patients who continue on active treatment during the extension. Visual acuity scores for any fellow eyes that receive active treatment will be summarized beginning at the visit they were first treated.

All non-ocular adverse events that occur during the extension while patients are on open-label verteporfin treatment will be pooled and summarized with all adverse events from the verteporfin treatment group of the 2-year masked study. The ocular events will be summarized separately by study eye and by fellow eye, and, separately by masked treatment and by open-label treatment.

### Sample Addendum to Informed Consent

#### **SAMPLE INFORMED CONSENT FORM ADDENDUM FOR THE VIP EXTENSION CONTINUATION STUDY**

#### Introduction:

This addendum is to provide you with information about a 12-month continuation of the 2-year extension to the VIP study and to provide you with updated safety information on the study drug (verteporfin). If you agree to continue to participate in the extension study, one or both of your eyes may be treated with active drug (verteporfin). During the extension study, your eye that was treated with masked medication in VIP will continue to be referred to as your 'study eye' while your other eye will be referred to as your 'fellow eye.'

If you require a visit or treatment at a time other than at your Month 48, 54, or 60 follow-up visits, another visit can be scheduled at the discretion of your investigator. At that visit, you and your doctor may choose to have your eye(s) retreated with study drug, if necessary. However, because Month 60 is your last visit, you will not receive treatment at this visit.

#### The VIP Extension Study:

If you participated in the VIP PM extension study, you will be examined to determine if you qualify for continuing in the extension study. Your fellow eye may also qualify if your doctor determines that it has CNV due to PM that might respond to treatment in the extension study. If you choose to participate and your study eye and/or fellow eye qualify for treatment, you will be examined every 6 months and treated with active drug (verteporfin) when necessary. All VIP procedures except for vital signs, quality of life interviews, visual

performance ratings, peak contrast threshold and the ICG angiography will be done in the extension study. At the 60-month visit, you will be examined and you will not receive any treatment and the study will end.

#### Updated Safety Information on Verteporfin:

##### Risks and Discomforts

The following adverse events are from the US package insert for verteporfin.

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 10-30% 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).

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 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 VIP 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
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_____ Date	_____ Name of Investigator	_____ Signature of Investigator
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