Diabetic Retinopathy Clinical Research Network

An Observational Study of the Development of Diabetic Macular Edema Following Scatter Laser Photocoagulation

Version 1.3

June 1, 2005

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CHAPTER 1.
BACKGROUND AND SYNOPSIS

1.1 Background

The development or worsening of macular edema following full scatter photocoagulation is a well recognized occurrence. However, there is limited literature in this regard. Most of the literature consists of case reports and case series.[2-5] Shimura et al[6] conducted a randomized trial of 36 patients with type 2 diabetes who had bilateral symmetric severe nonproliferative or early proliferative retinopathy but did not have clinically significant macular edema. Visual acuity was 20/20 or better in each eye. Patients were randomized to receive scatter photocoagulation weekly in one eye and biweekly in the other eye. Macular thickness was measured with OCT weekly for 8 weeks and then after 12 weeks and 16 weeks. Seven eyes of four patients were excluded because the eyes developed macular edema with a more rapid and progressive course than did the remaining eyes. Ninety percent of eyes maintained their visual acuity level and did not develop clinically significant macular edema, although many eyes had a transient increase in retinal thickness. Among the eyes maintaining their level of visual acuity, central retinal thickness increased by 42% and among eyes that had a reduction in visual acuity, central retinal thickness increased by 150%. There was a greater increase in central retinal thickening in the eyes treated weekly than in the eyes treated biweekly and the resolution of the edema was slower in the eyes treated weekly. This study, although it provides meaningful data, does not provide sufficient data for a precise estimate of the incidence of macular edema after scatter photocoagulation and the sample size is too small to explore factors that may be associated with an increased risk of macular edema. The Early Treatment Diabetic Retinopathy Study (ETDRS), which was performed prior to OCT availability, found that among eyes with no central retinal thickening at baseline in graded fundus photographs, retinal thickening was present at 4 months in 16% of eyes that underwent full scatter photocoagulation compared with 12% in eyes for which scatter photocoagulation was not performed.

The full scatter photocoagulation can be given in a single sitting or can be spread out over several sittings. A survey of the DRCRnet investigators found that for early proliferative or severe nonproliferative retinopathy, 10 (27%) would administer the photocoagulation in a single sitting, 11 (31%) in 2 sittings, and 15 (42%) in 4 sittings.

1.2 Study Objectives

1. To determine the incidence and extent of macular edema following scatter laser photocoagulation surgery using optical coherence tomography (OCT) in eyes without macular edema prior to scatter laser photocoagulation.
2. To explore whether the incidence and extent of macular edema varies according to the number of sittings included in the treatment regimen.

1.3 Study Design and Synopsis of Protocol

A. Study Design

- Prospective, multi-center nonrandomized clinical trial.

B. Major Eligibility Criteria

- Age >=18 years

- Study eye with (1) OCT center point thickness <=200 microns and (2) early proliferative or severe nonproliferative diabetic retinopathy for which investigator intends to perform full scatter photocoagulation in either 1 sitting or 4 sittings.
  - Eyes requiring treatment for DME and eyes with high-risk retinopathy are not eligible for the study.
  - Patients may have only one study eye.

C. Intervention

Study eyes will receive scatter photocoagulation given by one of the following two regimens to be selected by the investigator at his/her discretion:

- 1 sitting with a minimum of 1200 to a maximum of 1600 burns, with one burn width separation of burns and scatter extending from the peripheral arcades to beyond the equator.
- 4 sittings, each separated by four weeks ($\pm$4 days), with approximately 300 burns in each of the first two sittings and investigator judgment for number of burns for the third and fourth sittings as long as the total for the four sittings is between 1200 and 1600 burns.

Both of these regimens conform with usual clinical practice. To reduce selection bias, investigators will be required, prior to study initiation, to indicate which treatment (1 PRP sitting or 4 PRP sittings) they will administer. Only the selected treatment will be performed by a given investigator on study eyes.

D. Sample Size

The study aims to enroll 150 eyes. At least 40 eyes will be enrolled with prior focal laser photocoagulation and at least 40 eyes without prior focal laser treatment. After enrollment of 80 eyes (40 with prior treatment and 40 without prior treatment), an interim analysis will be conducted so that focused enrollment strategies can be implemented if the analysis suggests that more subjects in a subgroup should be entered. Approximately half of the eyes will receive each scatter treatment regimen.

E. Follow-up Schedule

Time from first sitting	1 Sitting Group	4 Sitting Group
Baseline	X*	X*
2-4 days after 1st sitting	X	X
4 weeks (window 24 to 32 days)	X	X*
8 weeks (window 52 to 60 days)		X*
12 weeks (window 80 to 88 days)		X*
17 weeks (window 16 to 18 weeks)	X	X
34 weeks (window 33 to 35 weeks)	X	X

* Scatter treatment given at this visit (exam data not collected at 8 and 12 weeks from first sitting)

F. Examination Procedures

The following procedures will be done on the study eye at baseline and at each scheduled visit (except 8 and 12 weeks at which exam data are not collected) unless otherwise specified:

- OCT

- E-ETDRS visual acuity in both eyes (refraction in the study eye at baseline, 17 weeks, and 34 weeks)
- Fundus photographs (7-fields at baseline and 3-fields at 34 weeks only)
- Photographs to document the scatter photocoagulation (day of the first PRP sitting only)

G. Main Efficacy Outcomes

Primary

- Retinal thickening (measured with OCT)

Secondary

- Visual Acuity (measured with E-ETDRS)

CHAPTER 2.
SUBJECT ELIGIBILITY AND ENROLLMENT

2.1 Identifying Eligible Subjects and Obtaining Informed Consent

Enrollment will include approximately 150 patients. At least 40 eyes will be enrolled with prior focal laser photocoagulation and at least 40 eyes without prior laser treatment. After enrollment of approximately 80 eyes (40 with prior treatment and 40 without prior treatment), an interim analysis will be conducted so that focused enrollment strategies can be implemented if the analysis suggests that more subjects in a subgroup should be entered. Subgroups of interest include prior macular treatment, age, retinal thickness, and retinopathy severity. Half of the eyes will receive each scatter treatment regimen.

It is expected that recruitment will include an appropriate representation of minorities.

Potential eligibility will be assessed as part of a routine-care examination. Patients are only eligible if based on the routine-care examination the investigator has determined that scatter photocoagulation is indicated and the investigator intends to provide treatment in either one sitting or four sittings. Patients for whom the investigator intends to provide scatter treatment in two or three sittings are not eligible.

Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. For subjects who are considered potentially eligible for the study based on a routine-care exam, the study protocol will be discussed with the patient by a study investigator and clinic coordinator. The patient will be given the Informed Consent Form to read. Patients will be encouraged to discuss the study with family members and their personal physician(s) before deciding whether to participate in the study. Patients will be provided with a copy of the signed Informed Consent Form.

2.2 Patient Eligibility Criteria

2.2.1 Subject-level Criteria

Inclusion

To be eligible, the following inclusion (1-4) and exclusion criteria (5-8) must be met:

1. Age >= 18 years
   - *Patients <18 years old are not being included because there would be an insufficient number of patients <18 years old who would meet eligibility criteria for the study in order to be able to generalize the results to patients <18 years old or to provide informative data as to the effects of treatment in this age group.*
2. Diagnosis of diabetes mellitus (type 1 or type 2)
   - Any one of the following will be considered to be sufficient evidence that diabetes is present:
     - Current regular use of insulin for the treatment of diabetes
     - Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes
     - Documented diabetes by ADA and/or WHO criteria
3. At least one eye meets the study eye criteria listed in section 2.2.2.
4. Able and willing to provide informed consent.

Exclusion

A patient is not eligible if any of the following exclusion criteria (5-8) are present:

5. History of chronic renal failure requiring dialysis or kidney transplant.
6. History of pancreatic transplant.
7. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure and glycemic control).
   - Patients in poor glycemic control who, within the last 4 months, initiated intensive insulin treatment (a pump or multiple daily injections) or plan to do so in the next 4 months should not be enrolled.
8. Patient is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the next 8 months.

2.2.2 Study Eye Criteria

The patient must have at least one eye meeting all of the inclusion criteria (a-d) and none of the exclusion criteria (e-k) listed below.

A patient can have only one study eye. If both eyes are eligible, the investigator at his/her discretion will select one to be the study eye.

The eligibility criteria for a study eye are as follows:

Inclusion

a. Presence of early proliferative or severe nonproliferative diabetic retinopathy for which investigator intends to perform full scatter photocoagulation in either one sitting or four sittings.
b. Center point retinal thickness measured on OCT <= 200 microns.
   - *Note: Clinically significant macular edema is not an exclusion provided the center point is <=200 microns.*
c. Visual acuity 73 letters or greater (20/32 or better).
d. Media clarity, pupillary dilation, and patient cooperation sufficient to administer full scatter photocoagulation and obtain adequate fundus photographs and OCT.

Exclusion

e. Prior scatter photocoagulation.
f. High risk (severe proliferative) retinopathy.
g. Presence of an ocular condition (other than diabetes) that, in the opinion of the investigator, might produce macular edema or alter visual acuity during the course of the study (e.g., vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass Syndrome, significant vitreomacular interface disease, etc.).
h. Treatment for diabetic macular edema is planned.
i. History of any treatment for DME within prior 6 months, including focal/grid macular photocoagulation and corticosteroids by any route.

j. History of major ocular surgery (including cataract extraction, vitrectomy, scleral buckle, any intraocular surgery, etc.) within prior 6 months or anticipated within the next 8 months following enrollment.

k. History of YAG capsulotomy performed within 2 months prior to enrollment.

2.3 Screening Evaluation and Baseline Testing

2.3.1 Historical Information

A history will be elicited from the patient and extracted from available medical records. Data to be collected will include: age, gender, self-reported ethnicity and race, diabetes history and current management, other medical conditions, medications being used, and ocular diseases, surgeries, and treatment.

2.3.2 Testing Procedures

The following procedures are needed to assess eligibility and/or to serve as a baseline measure for the study. The testing procedures are detailed in the DRCRnet Procedures Manuals (Visual Acuity-Refraction Testing Procedures Manual, Photography and OCT Testing Procedures Manual, and Site Procedures Manual). Visual acuity testing, fundus photography, and OCT will be performed by certified personnel.

If a procedure was performed as part of usual care prior to the patient signing informed consent by study certified personnel using the study technique and within the specified time window, it does not need to be repeated.

Testing results will be recorded in the database on the study eye only unless otherwise specified. Performing the testing on the fellow eye as part of usual care is at the discretion of the investigator. Testing must be done within 8 days prior to enrollment.

1. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester in both eyes (including protocol refraction in the study eye)
   - *This testing procedure has been validated against 4-meter ETDRS chart testing.*[1[
2. Dilated fundus examination
3. OCT
4. ETDRS protocol 7-standard field stereoscopic fundus photography (1M, 2, 3M, 4, 5, 6, 7, reflex)
5. Measurement of blood pressure
6. HbA1c
   - *Does not need to be repeated if available in the prior 3 months. If not available at the time of enrollment, the patient may be enrolled but the test must be obtained within 3 weeks after enrollment.*

2.4 Enrollment of Eligible Patients

The fundus photographs and OCT will be sent to the Fundus Photograph Reading Center for grading, but patient eligibility is determined by the site (i.e., patients deemed eligible by the investigator will be enrolled without need for Reading Center confirmation).

Prior to enrollment in the trial, the patient's understanding of the study, willingness to accept the assigned treatment group, and commitment to the follow-up schedule should be reconfirmed.

CHAPTER 3.
SCATTER LASER PHOTOCOAGULATION

3.1 Photocoagulation Regimen

All study eyes will receive scatter photocoagulation by one of the following two regimens:

- 1 sitting with a minimum of 1200 to a maximum of 1600 burns.
- 4 sittings, each separated by four weeks (±4 days), with approximately 300 burns in each of the first two sittings and investigator judgment for the number of burns for the third and fourth sittings as long as the total for the four sittings is at least 1200 to 1600 burns.

The burn characteristics will be as follows:

Size (on retina)	Argon laser using 200 micron spot size with Rodenstock lens (or equivalent) or 500 micron spot size with three mirror contact lens
Exposure	0.1 seconds recommended, 0.05 to 0.2 allowed
Intensity	Standard mild white retinal burns, i.e., 2+ to 3+ burns, no 4+ burns permitted (as defined by DRS and ETDRS)
Distribution	edges at least 1 burn width apart No closer than two rows within the arcades No closer than two disk diameters temporal to the fovea
Extent	Arcades (~3000 microns from the macular center) to at least the equator
# of Final Burns:	1200 to 1600
Wavelength	Green or yellow (red can be used if vitreous hemorrhage is present precluding use of green or yellow)

A retrobulbar injection, peribulbar or sub-Tenon's injection can be used at investigator discretion. An indirect laser approach cannot be used.

3.2 Post-treatment Photographs

Post-treatment photos will be taken on the day of the first PRP sitting. Required fields will be the posterior pole (ETDRS field 2) and one peripheral field. For persons in the one-sitting group, ETDRS fields 6 (superior nasal) is taken. For persons in the four-sitting group, field selection will correspond to the quadrant of the retina treated that day.

3.3 Deferral of Additional Treatment for Decreased Visual Acuity in the Four-sitting Group

If at any visit, visual acuity is decreased from baseline by 10 or more letters, a study protocol refraction should be repeated. An OCT is to be performed if the visual acuity is decreased by 10 or more letters. Dilated funduscopic examination should be carried out to determine that the decreasing vision is not secondary to vitreous hemorrhage. If vitreous hemorrhage is the cause of decreased vision, appropriate scatter therapy for proliferative diabetic retinopathy should be carried out per the investigator's discretion. If proliferative diabetic retinopathy and vitreous hemorrhage are not responsible for the decreased vision, the protocol continues to be followed. At the investigator's discretion, laser treatment should be carried out whenever possible, but can be deferred for two weeks.

If treatment is deferred because of DME, a two-week follow up visit should be scheduled. Visual acuity (with study protocol refraction if 10 or more letters worse than baseline) and OCT are repeated. Continuation of the scatter photocoagulation should be considered and in general is appropriate even if there is a decrease in visual acuity. However, if the visual acuity remains decreased by 10 or more letters and this decrease is secondary to macular edema, the investigator may defer completion of scatter treatment and initiate treatment for macular edema. If treatment for macular edema is performed, the patient needs to return in two weeks for follow up. Continuation of the four-sitting scatter treatment should be considered at that time.

CHAPTER 4.
FOLLOW-UP VISITS

4.1 Visit Schedule and Exam Procedures

For both the 1-sitting and 4-sitting group, follow-up exams will occur at the following times after the initial scatter photocoagulation sitting:

- 2 to 4 days
- 4 weeks (24 to 32 days)
- 17 weeks (16 to 18 weeks)
- 34 weeks (33 to 35 weeks)

The following procedures will be performed for both treatment groups on the study eye at each visit listed above (exam data not collected at the 8 and 12-week visits):

- E-ETDRS visual acuity (both eyes)
  - A refraction will be performed on the study eye at the 17-week and 34-week visits and at any other visit in which there has been a 10 or more letter decrease in acuity from baseline (when there is a change in refraction, visual acuity testing will be repeated with the new refraction).
- OCT
- 3-Field fundus photographs (34-weeks only)

4.2 Additional Visits for Laser Treatment in 4-sitting Group

For patients in the 4-sitting group, the additional laser treatment sittings will occur at the following times after the initial scatter photocoagulation:

- 2^{nd} sitting: 4 weeks (24 to 32 days)
  - *This coincides with the 4 week follow-up visit.*
- 3^{rd} sitting: 8 weeks (52 to 60 days)
- 4^{th} sitting: 12 weeks (80 to 88 days)

4.3 Development of Macular Edema

If vision decreases by more than 10 letters in either treatment group, a protocol refraction and OCT are to be performed. If the decrease in visual acuity is determined to be secondary to macular edema, the patient should be seen again in two weeks with protocol refraction and OCT. If at this visit the DME persists, focal treatment can be performed at the discretion of the investigator.

For the 4-sitting group, deferral of additional scatter photocoagulation is discussed in section 3.3.

CHAPTER 5.
MISCELLANEOUS CONSIDERATIONS

5.1 Diabetes Management

Diabetes management is left to the patient's medical care provider.

5.2 Patient Withdrawal and Losses to Follow-up

A patient has the right to withdraw from the study at any time. If a patient is considering withdrawing from the study, the Principal Investigator should personally speak to the patient about the reasons and every effort should be made to accommodate the patient. The Coordinating Center should be contacted prior to formally withdrawing the patient from the study. Ownership of the data collected up until the time of withdrawal is retained by the DRCR Network.

The goal for the study is to have as few losses to follow-up as possible. The Coordinating Center will assist in the tracking of patients who cannot be contacted by the site. The Coordinating Center will be responsible for classifying a patient as lost to follow-up.

Patients who withdraw will be asked to have a final close-out visit at which the testing described for the outcome examination visits will be performed. Patients who have an adverse effect attributable to a study procedure will be asked to continue in follow-up until the adverse event has resolved or stabilized, if not resolved or stabilized at the time of the final study visit.

Subjects who are determined to be ineligible or for whom there are substantial deviations from the protocol may be discontinued from the study.

Subjects who withdraw will not be replaced.

5.3 Discontinuation of Study

The study may be discontinued by the Steering Committee (with approval of the Data and Safety Monitoring Committee) prior to the preplanned completion of thirty-four week follow-up for all patients.

5.4 Contact Information Provided to the Coordinating Center

The Coordinating Center will be provided with contact information for each subject. Permission to obtain such information will be included in the Informed Consent Form. The contact information will be maintained in a secure database and will be maintained separately from the study data.

Phone contact from the Coordinating Center will be made with each patient in the first month after enrollment. Additional phone contacts from the Coordinating Center will be made, if necessary, to facilitate the scheduling of the patient for follow-up visits. A patient newsletter will be sent at least twice a year. A study logo item valued under $10 may be sent once a year.

Patients will be provided with a summary of the study results in a newsletter format after completion of the study by all patients. Patients may also be briefed about the results by the local center at a study visit or by telephone.

5.5 Patient Reimbursement

The study will be paying $25 per completed visit for baseline, 2 day, 4 week, 17 week, and 34 week visits. Payment will not be made for missed visits. Payment will be made from the Coordinating Center following each visit. If there are extenuating circumstances, additional funds may be provided for travel if expenses exceed $25 and the patient will be unable to complete the visit without the reimbursement of the travel expenses.

5.6 General Considerations

The study is being conducted in compliance with the policies described in the DRCRnet Policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

The DRCRnet Procedures Manuals (Visual Acuity-Refraction Testing Procedures Manual, Photography and OCT Testing Procedures Manual, and Site Procedures Manual) provide details of the examination procedures.

Data will be directly collected in electronic case report forms, which will be considered the source data.

There is no restriction on the number of patients to be enrolled by a site.

CHAPTER 6.
ADVERSE EVENTS

6.1 Events to Be Reported

Since the study does not involve an investigational drug or device, adverse event reporting will be limited to those events that are possibly related to study procedures **and** are unanticipated. In addition, all serious adverse events will be reported.

An *Unanticipated Adverse Event* is defined as an adverse event caused by or associated with a procedure, if that effect or problem was not previously identified in nature or severity. The following occurrences will require reporting:

- Macular hemorrhage, foveal burn, choroidal neovascularization, chorioretinal anastomosis and Bruch's membrane break within 4 weeks of laser photocoagulation and thought to be possibly related to the photocoagulation treatment.
- A laser malfunction that produces harm to the patient.
- A deviation from the photocoagulation technique that produces visual loss (will be considered an unanticipated event).
- Complication from a retrobulbar injection.

A *Serious Adverse Event* is any adverse event that meets one or more of the following criteria:

- Results in death.
- Is life threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

6.2 Reporting Requirements for Adverse Events

Any reportable adverse event must be reported to the Coordinating Center within one working day of occurrence. A written report on such an event will be sent to the Coordinating Center within five days of occurrence, stating a description of the reaction, any required intervention, and the outcome. Each principal investigator is responsible for informing his/her IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB. Contact information for the Coordinating Center is located in the Study Directory.

6.3 Risks and Discomforts

6.3.1 Scatter Photocoagulation

Serious, but rare complications associated with scatter photocoagulation and which may reduce vision include, but are not limited to: worsening of macular edema, loss of some peripheral (side) vision, foveal burn, choroidal neovascularization, chorioretinal anastomosis, Bruch's Membrane break, creation of a scotoma, immediate or delayed increase in pressure inside the eye, damage to the optic nerve, damage to the iris, damage to the patient's lens or an intraocular lens, retinal hole, blindness, or loss of the eye. Numbing drops and a contact lens may be used during the procedure, and rarely a corneal abrasion may result.

6.3.2 Retrobulbar Injection

Retrobulbar injection of anesthetic may be used in some cases. Risks associated with this procedure are rare and may include: retrobulbar hemorrhage; perforation of the eye by the needle; damage to the optic nerve; double vision lasting up to 24 hours or more; drooping of the eye lid lasting up to 24 hours or more; difficulty speaking or breathing; lightheadedness/syncope/vasovagal response; allergy to any components of the injection; life threatening response due to the spread of anesthesia to the brain stem, resulting in epileptic fits, drowsiness, confusion, loss of verbalization, convulsions, respiratory arrest, or cardiac arrest.

6.3.3 Examination Procedures

The procedures in this study are part of daily ophthalmologic practice in the United States and pose no additional known risks. Dilating eye drops will be used as part of each exam. In rare instances the dilating drops may cause an increase in pressure or attack of narrow angle glaucoma.

6.3.4 Fundus Photography

Fundus photography carries no risk. The camera flash may cause temporary discomfort for the patient.

6.3.5 Optical Coherence Tomography

OCT carries no known risk. Dilating eye drops will be used as part of each exam.

CHAPTER 7.
SAMPLE SIZE AND ANALYSIS PLAN

7.1 Sample Size

A convenience sample will be enrolled of at least 40 eyes with prior focal laser photocoagulation and at least 40 eyes without prior focal laser treatment. Approximately half of the eyes in each of these groups will be treated in four sittings and half will be treated in one sitting. After enrollment of these 80 eyes, up to an additional 70 eyes will be enrolled after an interim analysis is conducted so that focused enrollment may be implemented if the analysis suggests that more subjects in a subgroup should be entered.

As an observational study this protocol aims to determine if any trends exist and if the trends are strong enough to warrant a phase III trial. Statistical power to detect a significant difference between groups in the retinal thickening outcome will be low.

For dichotomous outcomes (e.g., development of macular edema), the table below shows the width of a 2-sided 95% confidence interval for various proportions of a sample size of 20 eyes.

	Half-width of 2-sided 95% CI		
Expected Proportion	**N=20**	**N = 40**	**N = 60**
.5	0.219	0.155	0.127
.4	0.215	0.152	0.124
.3	0.201	0.142	0.116
.2	0.175	0.124	0.101
.1	0.131	0.093	0.076

For dichotomous outcomes (e.g., development of edema, resolution of edema), the table below displays the magnitude of relative risk that can be detected with 80% power for various edema rates in the 4-sitting group versus the edema rates in the 1-sitting group.

Magnitude of Relative Risk

Proportion of Dichotomous Outcome 4-Sitting Group	Detectable Relative Risk with 80% Power		
	N =20	**N = 40**	**N = 60**
.1	5.3	3.8	3.2
.2	3.4	2.6	2.3
.3	2.6	2.1	1.9
.4	2.2	1.8	1.7

7.2 Statistical Analyses

The analysis plan is summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study. The analysis plan below contains the framework of the anticipated final analysis plan, which will supersede this summary when it is finalized.

This protocol is aimed at hypothesis generating. As an observational study the analysis will consist of estimation of the event rate for several outcomes.

Thirty-four weeks of follow up has been selected as the time point for the primary analysis. Secondary analysis will be conducted at 2 days, 4 weeks, and 17 weeks.

7.2.1 Outcome Estimates

The goals of this study are to obtain estimates of important efficacy outcomes for each of the treatment regimens. Promising results could provide a basis for sample size estimation and hypothesis generation in a phase III trial. Estimates for the following outcomes will be calculated for each treatment regimen. Analyses will be stratified by severity of retinopathy (severe nonproliferative and early proliferative). The retinal thickening outcomes below will be used to report the incidence of macular edema after full scatter photocoagulation and to describe the time course of its occurrence and resolution. In addition, eyes with macular edema will be analyzed as a subgroup if the number of eyes is sufficient for a meaningful analysis.

7.2.1.1 OCT

- Development of macular edema defined on OCT as at least 250 microns at the center point AND 25% increase in thickening from baseline.
- Time point of development of edema (as defined above) for eyes developing macular edema.
- Time point of resolution of edema should resolution occur (only for eyes developing edema).

Analyses of OCT data will focus on the center point. Additional analyses will replicate the center point analyses on the inner zone (central subfield and 4 inner subfields) and within the grid (all 9 subfields). Results will be explored based on whether the eye had received prior focal laser treatment for macular edema.

7.2.1.2 Visual Acuity

- Distribution of change in visual acuity
- Proportion of eyes with 10 letter decrease in visual acuity

7.2.2 Subgroup Analysis

Subgroup analysis will mirror the primary analysis described above. Subgroups of interest are prior treatment for DME, age, retinal thickness, and severity of retinopathy.

7.2.3 Correlation

The correlation of changes in visual acuity with changes in central retinal thickening also will be assessed. Scatter plots for the changes will be displayed and the Spearman correlation calculated.

7.3 Safety Analysis Plan

All adverse events that are possibly related to study procedures and are unanticipated adverse events will be reported.

References

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