Clinical Study Protocol

Prevention **O**f **M**acular Edema **I**n Patients With Diabetic Retinopathy Undergoing Cataract **S**urg**e**ry

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Prevention **O**f **M**acular Edema **I**n Patients With Diabetic Retinopathy Undergoing Cataract **S**urg**e**ry

Drug:	**Intravitreal Aflibercept Injection**
Study Name:	**Pr**evention **O**f **M**acular Edema **I**n Patients With Diabetic Retinopathy Undergoing Cataract **S**urg**e**ry ***(The PROMISE Trial)***
Clinical Phase:	Phase I/II
Date of Issue:	April 29th, 2013; October 10, 2014; October 27,2014; May 7, 2015; May 13, 2015; June 24, 2015; December 6, 2016, October 31, 2017, July 25, 2018
Primary Investigator:	Richard Gans, M.D.

CLINICAL STUDY PROTOCOL SYNOPSIS

TITLE	**Pr**evention **O**f **M**acular Edema **I**n Patients With Diabetic Retinopathy Undergoing Cataract **S**urg**e**ry
TITLE IN LAY TERMS	**Pr**evention **o**f **m**acular edema **i**n patients with diabetic retinopathy undergoing cataract **s**urg**e**ry with Intravitreal Aflibercept Injection
SITE LOCATION(S) **Principal Investigator**	Cleveland, Ohio Richard Gans, M.D.
OBJECTIVE(S)	To determine the safety and efficacy of intravitreal Aflibercept injection in patients with diabetic retinopathy in the prevention of macular edema following cataract surgery.
STUDY DESIGN	This is a prospective randomized trial in patients with a history of diabetic retinopathy who are undergoing cataract surgery. Patients will be sequentially randomized to either intravitreal Aflibercept injection or Sham
STUDY DURATION	Duration of treatment: 90 Days Duration of Assessment: 90 days following surgery
ESTIMATED STUDY COMPLETION DATE	December 2018
POPULATION	
Sample Size:	30 patients
Target Population:	Diabetic retinopathy patients who are at risk of developing macular edema (defined as ≥ 30 % increase from pre-operative baseline in central subfield macular thickness) within 90 days following cataract surgery. Diabetic patients are defined as those who have either Type 1 or Type 2 diabetes. The patients must have either mild, moderate, or severe non proliferative retinopathy or treated

	proliferative retinopathy. Patients must be 18 years of age and older, of any race and either sex, requiring cataract extraction with planned implantation of a posterior chamber intraocular lens into the lens capsule.
TREATMENT(S)	
Study Drug	Intravitreal Aflibercept Injection
Concurrent Control	Sham injection (defined as pressing the needle less syringe against the eye).
Masking	Patient masked only
ENDPOINT(S)	
Primary:	Incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs between treatment arms.
Secondary:	• Percentage of patients who develop macular edema within 90 days following cataract surgery. This is defined as any of the following: o ≥30% increase from pre-operative baseline in central subfield macular thickness as measured by SD-OCT o 2 consecutive measurements (up to 7 days apart) with one of the following: ▪ BCVA decrease of >5 E-ETDRS letters from the Day 7 postoperative visit, AND ▪ visual acuity loss due to retinal thickening based on the medical judgment of the investigator o Presence of cystoid abnormalities as detected by SD-OCT at any visit • Mean change from baseline in best-corrected visual acuity (BCVA) score at Day 90 • Changes in macular volume and central retinal thickness from preoperative assessment to Day 90 • Percentage of patients with a best corrected visual acuity (BCVA) decrease of › 5 E-ETDRS letters from Day 7 postoperative visit • Percentage of patients with greater than 15 letters of visual gain at Day 90

	• Percentage of subjects with a loss of 15 letters or more of vision at Day 90 • Step changes in diabetic retinopathy scale using the ETDRS definitions • Percentage of patients that are 20/40 or better at Day 90 Percentage of patients that are 20/200 or worse at Day 90

PROCEDURES AND ASSESSMENTS	Ongoing safety assessments will include ophthalmic examinations and recording and evaluation of clinical adverse events. Ongoing efficacy assessments will include SD-OCT measurements and E-ETDRS visual acuity measurements.
STATISTICAL PLAN	Demographic and baseline characteristics will be summarized descriptively by treatment group. Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

TABLE OF CONTENTS

LIST OF TABLES

1. INTRODUCTION AND RATIONALE

1.1 Introduction

Macular edema (ME) is a common cause of poor visual outcome following uneventful cataract surgery (Tranos PG et al 2004) that has been reported to occur in up to 2% of patients (Gallemore RP et al 2006, Powe NR et al 1994, Ursell PG et al 1999); the incidence may be as high as 20% when cataract extraction is complicated by posterior capsule rupture with vitreous loss or severe iris trauma (Tranos PG et al 2004). Further, it is well documented that- macular changes are more likely to occur following cataract surgery in diabetic patients, especially those with pre-existing retinopathies, compared with nondiabetic patients (Hayashi K et al 2009, Degenring RF et al 2007, Rossetti L et al 2000, Johnson MW et al 2009). Estimates of the rate of ME development in diabetic populations (with or without diabetic retinopathy) vary across studies, and previously ranging from 31% to 81% at various time points following cataract extraction (Dowler JG et al 1999, Pollack A et al, Krepler K et al 2002, Miyake et al 2002).

Factors involved in the pathogenesis of diabetic ME include chronic hyperglycemia, blood-retinal barrier dysfunction, and chronic subclinical inflammation.[8] Postsurgical inflammation, in particular, is believed to be a major factor in ME that develops subsequent to cataract extraction. Prostaglandins contribute substantially to the inflammatory processes that result in fluid leakage from perifoveal capillaries into the extracellular space of the macular region (Flach AJ 1998). Postsurgical inflammation, in particular, is believed to be a major factor in ME that develops subsequent to cataract extraction. Therefore the use of a pan-VEGF-A inhibitor may prevent the formation of macular edema following cataract surgery.

Aflibercept is a recombinantly produced fusion protein consisting of portions of the human VEGF receptor extracellular domains fused to the Fc domain of human IgG1 (Figure 1). Aflibercept is comprised of portions of the extracellular domains of 2 different VEGF receptors. It contains sequences encoding Ig domain 2 from VEGFR1 fused to Ig domain 3 from VEGFR2, which in turn is fused to the hinge region of the

human IgG1 Fc domain. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kDa, and contains ~15% glycosylation to give a total molecular weight of 115 kDa.

Afibercept is approved for the treatment of exudative macular degeneration and macular edema secondary to central retinal vein occlusion.

Figure 1. The Aflibercept Molecule

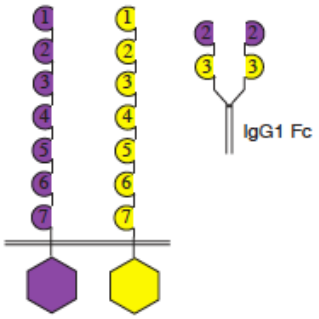

Figure 1. VEGFR1 and VEGFR2 are related receptors that have 7 Ig domains in the extracellular portion and a tyrosine kinase domain intracellularly. Aflibercept contains the VEGFR1 Ig2 domain fused to the VEGFR2 Ig3 domain, which is in turn fused to the IgG1 Fc.

1.2 Rationale

1.2.1 Rationale for Study Design

This is a prospective randomized trial of the use of intravitreal aflibercept injection for the prevention of diabetic macular edema following cataract surgery in patients with preexisting diabetic retinopathy. This particular population is chosen since macular changes are more likely to occur following cataract surgery in diabetic patients, especially those with pre-existing retinopathies, compared with non-diabetic patients. A previous study in patients with diabetic macular edema (DA VINCI Study Clinical Trials.gov# NCT00789477) found that the use of IAI was safe and effective for the treatment of diabetic macular edema. Treatment with a single intravitreal aflibercept injection will be given at the end of the surgery in half of the patients enrolled, and

outcomes will be compared to patients who do not receive the drug, and are followed only with standard of care.

1.2.2 Rationale for Dose Selection

FDA approved dose of 2mg intravitreal aflibercept injection is selected. Specifically, patients will be given 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection at the completion of the surgery. All patients regardless of treatment assignment will receive standard of care (SOC) treatment with topical Moxifloxacin 1 drop four times a day for 1 week and topical Prednisolone acetate 1 drop four times a day for two weeks following cataract surgery.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is the incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs.

2.2 Secondary Objective(s)

The secondary objectives of the study are –

- The percentage of patients who develop macular edema within 90 days following cataract surgery. This is defined as any of the following:
    1. ≥30% increase from pre-operative baseline in central subfield macular thickness
    2. 2 consecutive measurements (up to 7 days apart) with
        a. BCVA decrease of >5 E-ETDRS letters from the Day 7 postoperative visit, AND
        b. visual acuity loss due to retinal thickening based on the medical judgment of the investigator
    3. Presence of cystoid abnormalities as detected by OCT at any visit
- Mean change from baseline in best-corrected visual acuity (BCVA) score at Day 90

- Changes in macular volume and central retinal thickness from preoperative assessment to Day 90
- Percentage of patients with a best corrected visual acuity (BCVA) decrease of › 5 E-ETDRS letters from Day 7 postoperative visit
- Percentage of patients with greater than 15 letters of visual gain at Day 90
- Percentage of subjects with a loss of 15 letters or more of vision at Day 90
- Step changes in diabetic retinopathy scale using the E-ETDRS definitions
- Percentage of patients that are 20/40 or better at Day 90
- Percentage of patients that are 20/200 or worse at Day 90

3. STUDY DESIGN

3.1 Study Description and Duration

This is a prospective randomized trial in patients with a history of non-proliferative or inactive proliferative diabetic retinopathy, without clinically significant macular edema who are undergoing cataract surgery. Patients will be randomized 1:1 to either intravitreal aflibercept injection or sham injection at the time of surgery in a consecutive fashion.

All patients regardless of treatment assignment will receive standard of care (SOC) treatment with topical Moxifloxacin 1 drop four times a day for 1 week and topical Prednisolone acetate 1 drop four times a day for two weeks following cataract surgery.

One site will enroll 30 patients. Study recruitment is planned to take up to six months post IRB approval. Patients will be enrolled in the study for 3 months post screening and enrollment visits.

3.2 Planned Interim Analysis

There are no interim analyses planned.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1 Number of Patients Planned

The target enrollment for this study is 30 patients. Only one eye will be enrolled in the study at a time. If both eyes meet eligibility criteria, the patient may enter the study a second time after completing **ALL** visits for the first eye. The patient may enroll the second eye 90 days after receiving the first study injection provided they meet ALL inclusion and NO exclusion criteria.

4.2 Study Population

The study population will consist of approximately 30 patients (15 per treatment group) who receive one injection of intravitreal aflibercept injection or Sham injection. Patients must meet all inclusion and exclusion criteria outlined in Section 4.2.1_and Section 4.2.2 respectively. All patients will undergo a process of informed consent, and sign and date an informed consent document before any study-specific procedures are performed.

The study population will consist of diabetic patients (Type 1 or Type 2) with non-proliferative or inactive proliferative diabetic retinopathy without clinically significant macular edema, 18 years of age and older, of any race and either sex, requiring cataract extraction with planned implantation of a posterior chamber intraocular lens into the lens capsule.

Patients will be recruited through clinics at the Cole Eye Institute, Cleveland OH. The study will seek approval from the Cleveland Clinic Investigational Review Board (IRB) and all study related procedures will be performed in accordance with the Declaration of Helsinki and US Code 21 of Federal Regulations.

4.2.1 Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Must be 18 years of age and older, of any race and either sex, who have a cataract, and are planning to undergo cataract extraction by phacoemulsification with the implantation of a posterior chamber intraocular lens into the lens capsule
2. History of Type I or Type II diabetes
3. NPDR (mild, moderate, or severe) or inactive proliferative disease in the study eye as defined by the International Clinical Diabetic Retinopathy Disease Severity Scale
4. Willing and able to comply with clinic visits and study-related procedures
5. Patients must be able to understand and sign an informed consent that has been approved by an Institutional Review Board (IRB)
6. Central subfield macular thickness $\leq$ 320 μm in the study eye prior to cataract surgery as determined by SD-OCT and confirmed by the Principal Investigator
7. Absence of clinically significant macular edema (CSME) in the study eye as detected by clinical exam
8. Patients must have visual acuity of 20/20-20/200 (E-ETDRS equivalence is between 85-30 letters) at the Screening Visit

4.2.2 Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Signs of clinically significant vitreomacular traction or clinically significant epiretinal membrane in the study eye as detected by the Principal Investigator
2. Current or previous ocular disease in the study eye that in the opinion of the investigator may confound assessment of the macula, the retina, or central vision other that diabetic retinopathy
3. Active proliferative diabetic retinopathy in the study eye
4. Planned multiple procedures for the study eye during the cataract/IOL implantation surgery (e.g., trabeculectomy, corneal transplant)
5. Patients who have received corneal transplants in the study eye
6. Patients with current or history of clinically significant chronic or recurrent ocular infections or inflammation in the study eye

7. Patients with a visually nonfunctional fellow eye based upon the assessment by the Principal Investigator
8. Patients who are immunocompromised (e.g., patients receiving chemotherapy irradiation therapy, patients with AIDS, leukemia, or cachexia) or patients receiving dialysis
9. Use of medications known to affect the macula, including hydroxychloroquinine (Plaquenil) and phenothiozines (e.g., thioridazine [Mellaril], chloropromazine [Thorazine]) or supplemental niacin ≥3 grams/day
10. Use of systemic steroids, NSAIDS, anti-VEGF agents within 7 days prior to surgery (through study exit). Daily doses of aspirin, up to 325 mg, will be permitted.
11. Use of topical ocular NSAIDS and steroids, in the study eye, within 7 days prior to surgery
12. Treatment with intraocular or periocular steroids in the study eye within 3 months prior to surgery
13. Focal photocoagulation for the treatment of diabetic macular edema in the study eye within 6 months of the pre-operative Screening Visit (Note: peripheral retina treatment for retinal tear or lattice degeneration is permitted)
14. Intravitreal anti-VEGF treatment in the study eye within 6 months of the pre-operative baseline visit
15. Patients with a known hypersensitivity to NSAIDs or steroids or any component of the study medication.
16. Use of a topical ophthalmic prostaglandin (e.g., TRAVATAN, XALATAN) within 4 days of surgery through study exit
17. Any concurrent intraocular condition in the study eye that, in the opinion of the investigator, could require either medical or surgical intervention during the 90 day study period.
18. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the patient beyond what is to be expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety.
19. Pregnant or breast-feeding women

20. Sexually active men or women of childbearing potential who are unwilling to practice adequate contraception* during the study (adequate contraceptive measures include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly.

    **Contraception is not required for men with documented vasectomy.*

    *Postmenopausal women must be amenorrheic for at least 12 months in order **not** to be considered of child bearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation*.
21. Participation in any other clinical study within 30 days of the Baseline examination with the exception of patients who are entering their other eye into the study. Those patients may enter sooner than 30 days after the Post-Op Day 90 visit as it will be > 30 days since the administration of study medicine.

4.3 Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator has the right to withdraw a patient from the study in the event of an intercurrent illness, adverse event ("AE"), treatment failure, protocol violation, and for administrative or other reasons. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients will be avoided.
Should a patient's (or a patient's legally authorized guardian or representative) decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. Early termination procedures will be followed as delineated in section 6.2.5.

4.4 Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

Patients will be assigned to treatment with 2 mg intravitreal Aflibercept injection (0.05 mL or 50 microliters) administered at the time of surgery (post cataract excision) or sham injection. All patients will receive standard of care (SOC) medications in the study eye during the 90-day follow up period. The SOC regimen for all arms will be Ciprofloxacin Hydrochloride QID for 1 week following cataract surgery and prednisolone acetate QID in the study eye for two weeks following cataract surgery.

5.1 Dose Modification and Stopping Rules

5.1.1 Dose Modification

Dose modification for an individual patient is not allowed.

5.1.2 Study Drug Stopping Rules

If the patient discontinues the study after study drug administration, they will be exited from the study and an exit visit will be conducted as outlined in section 6.2. Any patient who discontinues prior to study drug administration will not need to return for an exit visit.

5.2 Method of Treatment Assignment

Patients will be assigned in a prospective alternating fashion to intravitreal aflibercept injection and sham injections.If a patient will be entering *both* eyes in the study (first eye must complete all visits through Post-Op Day 90 before the second eye can be enrolled), they will be assigned the next prospective treatment based on the alternating Randomization Plan until the entire cohort of 30 patients, with either one or both eyes, is achieved.

5.2.1 Masking

This is a single masked treatment study and the patients will not be aware of their treatment assignment.

Emergency Unmasking

Emergency unmasking of treatment assignment for a patient may be necessary due to a medical emergency, a serious adverse event (SAE) that is unexpected and for which a causal relationship to study drug cannot be ruled out, or any other significant medical event (e.g. pregnancy).

If emergency unmasking is required for a medical emergency:

- Only the investigator will make the decision to unmask the treatment assignment.
- Only the patient with the medical emergency will be unmasked.
- The designated study coordinator at the study site will provide the treatment assignment to the investigator.
- The investigator will notify Regeneron and/or designee that the patient has been unmasked.

5.3 Treatment Logistics and Accountability

5.3.1 Packaging, Labeling, and Storage

2.0mg intravitreal aflibercept injection is formulated as a sterile liquid to a final concentration of 40 mg/mL aflibercept in 5% sucrose, 10 mM sodium phosphate pH 6.3, 0.03% polysorbate 20, and 40 mM NaCl. Aflibercept 2.0mg study drug will be supplied by Regeneron Pharmaceuticals Inc. in sealed, sterile vials. Vials must be used only once (defined as entered with a needle). The volume of injection will be 0.05 mL for the 2 mg dose. For study drug in vials, the study drug will be withdrawn using aseptic technique.

Study drug will be shipped to the site via overnight shipping using cold packs to maintain a temperature of 2° to 8° C. The Investigator, or an approved representative (e.g. pharmacist), will ensure that all study drugs are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. The shipping box is to be opened and stored immediately at the site in a refrigerator intended for investigational products at a temperature of 2° to 8°C.

When vials are removed from the refrigerator, the solution should be visually inspected and it should have no evidence of turbidity. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Exposure of the material to temperatures outside these limits, except for warming prior to administration, is not recommended and may result in loss of activity. Records of actual storage conditions (i.e. temperature log) at the study site must be maintained; and must include a record of the dates, when the refrigerator was checked, the initials of person checking, and the temperature.

5.3.2 Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2 to 8ºC to the investigator or designee at regular intervals or as needed during the study. During site close-out, and following drug reconciliation and documentation, all opened and unopened vials of study drug will be destroyed or returned to Regeneron Pharmaceuticals, Inc. or designee.

5.3.3 Treatment Accountability

All drug accountability records will be kept current.

The investigator will account for all opened and unopened vials of study drug. These records will contain the dates, quantity, and study medication

- Date of administration to each patient
- Disposed of at the site or returned to Regeneron Pharmaceuticals, Inc.

All accountability records will be made available for inspection by regulatory agency inspectors.

5.3.4 Treatment Compliance

All drug compliance records will be kept current and will be made available for inspection by regulatory agency inspectors.

5.4 Concomitant Medications and Procedures

Patients may not receive any medications (approved or investigational) in the study eye other than the assigned study treatment (intravitreal Aflibercept injection as specified in this protocol, until they have completed the end of study (90 Days) or early treatment visit assessments. This includes medications administered locally (eg, IVT, topical, juxtascleral or periorbital routes), as well as those administered systemically, with the intent of treating the study and/or fellow eye.

If a patient's fellow (non-study) eye requires treatment with an anti-VEGF agent at study entry, or during the patient's participation in the study, the fellow eye can receive any FDA approved anti-VEGF. If the patient's fellow eye will be entered into the study following completion of all study visits with the first eye, the fellow eye can receive any FDA approved anti-VEGF; however, the timeframes listed in the Inclusion and Exclusion Criteria must be met prior to re-entering the study with the treated fellow eye.

5.4.1 Permitted Medications and Procedures

Any other medications that are considered necessary for the patient's welfare, and that are not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

5.4.2 Prohibited Medications and Procedures

Systemic anti-angiogenic agents will not be permitted during the study.

5.5 Post-Study Treatment

Patient must refrain from the use of oral or topical steroids other than the steroid prescribed by the physician for 90 days during the course of the study. Patients must also refrain from the use of topical nonsteriodal agents, system nonsteroidal agents, intraocular anti-VEGF agents, and systemic anti-VEGF agents for 90 days during the course of the study for treatment of the study eye. All patients regardless of study assignment will receive standard of care (SOC) medications in the study eye during the 90 day follow up period. The SOC regimen for all arms will be Ciprofloxacin

Hydrochloride QID for 1 week following cataract surgery and prednisolone acetate QID in the study eye for two weeks following cataract surgery.

6. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

6.1 Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1.

Table 1 Schedule of Events

Study Procedure	Screening (-4 weeks to -2 days)	Day 0 **Surgery**	Day 1 (± 1 day)	Day 7 (± 2 days)	Day 14 (-1/+4 days)	Day 30 (±7 days)	Day 60 (±7 days)	Day 90/ Early Exit (± 7 days)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**9**
Inclusion/Exclusion	X							
Informed Consent	X							
Demographics/Medical History	X							
Randomization		X						
Concomitant Meds	X	X	X	X	X	X	X	X
Vital Signs	X							X
E-ETDRS BCVA with protocol refraction in Study Eye	X Both Eyes		X	X	X	X	X	X
Intraocular Pressure in Study Eye	X		X	X	X	X	X	X
SD-OCT for Study Eye	X		X	X	X	X	X	X
Dilated Fundus Exam in Study Eye	X							X
Wide-field fundus photography for Study Eye	X							X
Slit Lamp in Study Eye	X		X	X	X	X	X	X
Pregnancy test if applies	X							
Hemoglobin A1C value	X							
Administer Study Drug/Sham		X						
Adverse Events		X	X	X	X	X	X	X

6.2 Study Visit Descriptions

6.2.1 Screening (Day –4 weeks to Day -2) with the retina specialist

After the patient has provided informed consent, the following information will be collected:

- Inclusion/exclusion
- Demographics
- Medical history and concurrent illnesses
- Concomitant medications

The following procedures and assessments will be conducted:

- Assign a screening number to the patient and record it on the enrollment log.
- Record the patient's demographics (birth date, sex, race, and study eye).
- E-ETDRS visual acuity with protocol refraction. The patient should be manually refracted to their best distance acuity by a certified visual acuity examiner using trial lenses in both eyes.
- Measure IOP using Goldmann applanation tonometry **(Study eye only)**.
- Slit lamp examination: Perform slit-lamp examination to assess corneal edema, bulbar conjunctival injection, inflammatory cells and flare **(Study eye only)**.
- Perform dilated fundus evaluation to assess retina/macula/choroid and optic nerve **(Study eye only)**.
- Retinal exam: **NOTE: This step must be performed by a retinal specialist**
  a. Assess severity of diabetic retinopathy for eligibility. The confirmation of retinopathy will be determined by the retina specialist.
  b. Review exclusion criteria pertinent to posterior segment eligibility.
- Perform standard wide field fundus photography in the study eye. In cases where the physician can see evidence of retinopathy but the fundus photographs are not of sufficient quality to accurately determine the severity of retinopathy, the patient may be randomized using the physician's estimate of severity.
- Spectral Domain OCT evaluation: Measure macular thickness and volume in the study eye using SD-OCT performed by a technician.

- Urine pregnancy test. Perform a urine pregnancy test on all females of childbearing potential and record the results. If a pregnancy test is not required, indicate as not applicable.
- Perform HbA1c test.
- Patients must meet all inclusion and exclusion criteria as outlined in Section 4.2.1 and Section 4.2.2 of this protocol to be eligible for randomization into the study.

6.2.1.1 Day 0 (Surgery Visit)

The following information will be collected:

- Concomitant medication changes
- Adverse Events

The following procedures and assessments will be conducted by the cataract surgeon:

- Cataract excision

The following procedures will be conducted by the Principal Investigator or Designee:

- Study Drug Administration post cataract excision: record date and time

Record the following surgical information:

- Surgery start time
- Surgeon's name
- Incision information
- Type of anesthesia
- Problems during surgery, if applicable
- Other surgical procedures, if applicable
- Intraocular lens information
- Degree of difficulty of cataract extraction, IOL insertion, and overall surgery
- Record surgery-related preoperative intraoperative and immediately postoperative medications.
- Record adverse events.

POSTOPERATIVE EXAMINATIONS

6.2.2. Day 1 (± 1 day)

All ocular study evaluations refer to the **STUDY EYE**.

The following will be performed at the Day 1 Visit by any Investigator:

- A protocol refraction with E-ETDRS visual acuity assessment. The patient should be manually refracted to their best distance acuity by a certified visual acuity examiner using trial lenses.
- Slit-lamp examination
- Measure IOP using Goldmann applanation tonometry
- Measure macular thickness and volume using SD-OCT and performed by a technician.
- Record any change in surgery related medications
- Record any changes in concurrent ocular or non-ocular medications (non-surgery-related medications) since the first use of the study medication.
- Record any changes in ocular or non-ocular diseases/conditions since the first use of the study medication.
- Record surgery-related ocular conditions.
- Record adverse events
- All patients regardless of treatment assessment will be given 1 bottle of Ciprofloxacin Hydrochloride 0.3% (Sandoz) to be instilled into the operative eye four times daily for one week. Patients will also receive 1 bottle of 1% Prednisolone acetate (Falcon) to be instilled into the operative eye four times daily for two weeks.
- Schedule patient to return for their next study visit.

6.2.3 Day 7 (± 2 Days), Day 14 (-1 TO +4 Days), Day 30 (± 7 Days), AND Day 60 (± 7 Days) **by any Investigator:**

All ocular study evaluations refer to the **STUDY EYE**.

- Assess E-ETDRS best-corrected visual acuity. The patient should be manually refracted to their best distance acuity by a certified visual acuity examiner using trial lenses.
- Perform slit-lamp examination and posterior capsular opacification (PCO) assessment
- Measure IOP using Goldmann applanation tonometry.
- Measure macular thickness and volume using SD-OCT and performed by a certified technician.
- Record any change in surgery related medications.
- Record any change in concurrent ocular or non-ocular medications (non-surgery-related medications) since the first use of the study medication.
- Record any changes in ocular or non-ocular diseases/conditions since the first use of the study medication.
- Record surgery-related ocular conditions
- Record adverse events.
- Assess patient for treatment failure.
    - Treatment failure is defined as:
        - .≥ 30% increase from pre-operative baseline in central subfield macular thickness

        OR

        - 2 consecutive measurements (up to 7 days apart) with BCVA decrease of >5 E-ETDRS letters from the Day 7 postoperative visit, AND visual acuity loss due to retinal thickening based on the medical judgment of the investigator.
        - presence of cystoid abnormalities as detected by OCT at any visit
    - Once treatment failure is determined, the patient will be prescribed treatment per the Investigator's discretion. The patient will remain in the study and complete all future follow-up visits .

- For patients who have not had their severity of retinopathy confirmed by the Reading Center, fundus photographs will be taken on Day 7 and submitted for confirmation
- Schedule patient to return for the next study visit.

6.2.4 End of Study Visit/Early Termination/ Day 90 (± 7 days) by any Investigator

The following procedures and assessments will be conducted:

All ocular study evaluations refer to the **STUDY EYE**.

- Record any change in concurrent ocular or non-ocular medications (non-surgery-related medications) since the first use of the study medication
- Record any changes in ocular or non-ocular diseases/conditions since the first use of the study medication.
- Assess E-ETDRS best-corrected visual acuity. The patient should be manually refracted to their best distance acuity by a certified visual acuity examiner using trial lenses
- Perform slit-lamp examination and PCO assessment (PCO)
- Measure IOP using Goldmann applanation tonometry
- Measure macular thickness and volume using SD-OCT performed by a technician.
- Perform dilated fundus evaluation
- Record any change in surgery related medications.
- Record surgery-related ocular conditions.
- Record adverse events.
- Exit the patient

6.2.5 Early Termination Visit

Patients who are withdrawn from the study should be instructed to return to the clinic for end of study assessments, as described in section 6.2.4.

6.2.6 Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary, for follow-up of AEs, or for any other reason, as warranted.

6.3 Study Procedures

6.3.1 Efficacy Procedures

Vision: Visual Acuity Visual function of the study eye and the fellow eye will be assessed using the E-ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985) at 4 meters during the Screening Visit. Only the Study Eye will be assessed during all Post-Op Visits. Visual Acuity examiners must be certified to ensure consistent measurement of BCVA.

Spectral Domain Optical Coherence Tomography (OCT): Retinal and lesion characteristics will be evaluated using SDOCT on the study eye. At the Screen Visit images will be captured and archived. The scanning protocol will consist of fast macular thickness maps as well as high definition 6.0 mm linear scans centered on the fovea. OCT scans will be recorded by scoring their morphological patterns, and by recording the foveal minimum and volumetric analysis for each patient (Cirrus OCT, Humphrey Zeiss Inc., San Leandro, CA, software version 5.0). OCT images will read by the investigator.

Fundus Evaluation and Fundus Photography: The anatomical state of the retinal vasculature of the study eye will be evaluated by funduscopic examination. Wide-field fundus images will be taken on the designated intervals with the Optos Wide-field imaging device.

Intraocular Pressure: Intraocular pressure (IOP) of the study eye will be measured using Goldmann Applanation tonometry.

6.3.2 Safety Procedures

6.3.2.1 Adverse Event Information Collection

The investigator (or designee) will record all AEs that occur during the study. AEs will be recorded on the AE pages of the CRF (Case report Form) from Screen Visit to Day 90 or Early Termination Visit. Information on follow-up for AEs is provided in section 7. The definition of an AE and SAE, and information on the determination of severity and relationship to treatment are provided in section 7.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1 Definitions

7.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (i.e. any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

7.1.2 Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (e.g. a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or prolongation of existing hospitalization. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is

prolonged due to the development of a new AE as determined by the investigator or treating physician.

- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse). Any malignancy (other than basal cell skin cancers) would be considered a medically important event.

7.2 Recording and Reporting Adverse Events

All AEs will be recorded on the electronic CRF ("eCRF") and in the patient's source documents. In addition, all AE's will be documented on the AE Summary Log and reported to the IRB with the Continuing Review Report.

All SAEs, regardless of assessment of causal relationship to study drug will be reported to Richard Gans, M.D., Andrew Schachat, M.D., and Regeneron Pharmaceuticals, Inc.

The investigator will promptly report to the IRB and FDA all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to the use of the study drug.

7.2.1 Deaths

Any AE that results in death is considered an SAE. Deaths that occur from the time the patient signs the informed consent form ("ICF") until 90 days after dosing will be reported to the appropriate IRB, FDA, Richard Gans, M.D., Sponsor, Regeneron Pharmaceuticals, Inc., and Andrew Schachat, MD.

Any available autopsy reports and relevant medical reports will be sent to Richard Gans, M.D. and Regeneron Pharmaceuticals, Inc. as soon as possible. A MedWatch report will be submitted to the FDA in the occurrence of a subject death.

To report an SAE, to Richard Gans, M.D. will be contacted at the following:

gansr@ccf.org

Fax: 216-445-2264

SAE hotline: 216 444 2020

To report an SAE, Regeneron will be contacted at the following:

Medical.safety@regeneron.com

Fax: 914-345-7476

SAE hotline: 914-593-1504

7.2.2 Pregnancy and Other Events that Require Accelerated Reporting

The following events will be reported to Richard Gans, M.D. within 24 hours of learning of the event:

Overdose: Accidental or intentional overdose of the study drug or concomitant medication, whether or not it is considered an AE.

Pregnancy: Although it is not considered an AE, the investigator will report to Richard Gans, M.D., any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 30 days following the last dose of study drug. The investigator will follow the pregnancy until delivery, or longer. If the pregnancy continues to term (delivery), the health of the infant will also be reported to Richard Gans M.D. and Regeneron Pharmaceuticals, Inc.

To report an SAE, to Richard Gans, M.D. will be contacted at the following:

gansr@ccf.org

Fax: 216-445-2264

SAE hotline: 216 444 2020

To report an SAE, Regeneron will be contacted at the following:

Medical.safety@regeneron.com

Fax: 914-345-7476

SAE hotline: 914-593-1504

7.2.3 Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study will be reported to Richard Gans, M.D., Andrew Schachat, M.D.,and Regeneron Pharmaceuticals, Inc. within 30 days.

To report an SAE, Richard Gans, M.D. will be contacted at the following:

gansr@ccf.org

Fax: 216-445-2264

SAE hotline: 216 444 2020

To report an SAE, Regeneron will be contacted at the following:

Medical.safety@regeneron.com

Fax: 914-345-7476

SAE hotline: 914-593-1504

7.2.4 Abnormal Vital Signs Results

The criteria for determining whether an abnormal objective test finding will be reported as an AE are as follows:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

7.2.5 Follow-up

Adverse event information will be collected until the end of study visit, or the early termination visit, if the patient withdraws consent.

The investigator must make every effort to obtain follow-up information on the outcome of any SAE until the event is considered chronic and/or stable.

7.3 Evaluation of Severity and Causality

7.3.1 Evaluation of Severity

The severity of an AE will be graded by the investigator using a 3–point scale (mild, moderate, or severe) and reported in detail as indicated on the eCRF and/or SAE form, as appropriate.

- **Mild:** Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

  Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

The severity of an AE will be graded by the investigator using a 3–point scale (mild, moderate, or severe) and reported in detail as indicated on the CRF and/or SAE form, as appropriate.

Mild: Mild AE (minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance).

Moderate: Moderate AE (minimal intervention; local intervention; noninvasive intervention [packing, cautery]).

Severe: Severe and undesirable AE (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Life–threatening: Life-threatening or disabling AE (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

Death: Death associated with an AE.

7.3.2 Evaluation of Causality

The relationship to treatment will be determined by the investigator and reported on the eCRF and/or SAE form, as appropriate. The following terms will be used:

Not Related: likely or clearly due to causes other than the study drug.

Related: possibly, probably, or definitely related to the study drug.

8. STUDY VARIABLES

8.1 Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (e.g. age, race, sex, etc.), disease characteristics including medical history, and medication history for each patient.

8.2 Primary and Secondary Endpoints

Primary Endpoint

- The incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs.

Secondary Endpoints -

- The primary endpoint of the study is the percentage of patients who develop macular edema within 90 days following cataract surgery. This is defined as any of the following:
    - ≥30% increase from pre-operative baseline in central subfield macular thickness
    - 2 consecutive measurements (up to 7 days apart) with
        - BCVA decrease of >5 E-ETDRS letters from the Day 7 postoperative visit, AND
        - Visual acuity loss due to retinal thickening based on the medical judgment of the investigator
    - Presence of cystoid abnormalities as detected by OCT at any visit
    - Mean change from baseline in best-corrected visual acuity (BCVA) score at Day 90
    - Changes in macular volume and central retinal thickness from preoperative assessment to Day 90
    - Percentage of patients with a best corrected visual acuity (BCVA) decrease of › 5 E-ETDRS letters from Day 7 postoperative visit
    - Percentage of patients with greater than 15 letters of visual gain at Day 90
    - Percentage of subjects with a loss of 15 letters or more of vision at Day 90
    - Step changes in diabetic retinopathy scale using the E-ETDRS definitions
    - Percentage of patients that are 20/40 or better at Day 90
    - Percentage of patients that are 20/200 or worse at Day 90

9. STATISTICAL PLAN

9.1 Determination of Sample Size

Based on previous studies performed within the same patient cohort, assuming the study would have at least 80% power, there would be the ability to detect a difference of approximately 45%-50% (i.e. 50% vs. 5%) between groups. With 40 total patients you would be able to detect a difference of at least 40%-45% (45% vs. 5%).

9.2 Analysis Sets

9.2.1 Efficacy Analysis Sets

Demographic and baseline characteristics will be summarized descriptively by treatment group for all patients. Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage

9.2.2 Safety Analysis Set

Adverse events from all enrolled patients will be utilized to summarize safety data.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at the study site.

The CRF data for this study will be collected with an Electronic Data Capture ("EDC") tool [ImageIQ].

Electronic Systems

Electronic systems used to process and/or collect data in this study will include the following:

- [Epic and ImageIQ] – EDC system.

- Statistical Analysis Software ("SAS") – statistical review and analysis.

11. STUDY MONITORING

11.1 Source Document Requirements

Investigator will prepare and maintain adequate and accurate patient records (source documents).

The investigator will keep all source documents on file with the CRF. Case report forms and source documents will be available at all times for inspection by authorized representatives of the regulatory authorities.

11.2 Case Report Form Requirements

An eCRF for each patient enrolled in the study will be completed and signed by the study investigator or authorized designee. Study data obtained in the course of the clinical study will be recorded on eCRFs by trained site personnel. ImageIQ will serve as the eCRF systems. An eCRF will be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator will provide an electronic signature. A copy of each eCRF page will be retained by the investigator as part of the study record and will be available at all times for inspection by authorized representatives of the regulatory authorities.

Corrections to the eCRF will be entered in the eCRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration will be provided.

12. AUDITS AND INSPECTIONS

This study may be patient to a quality assurance audit or inspection by the regulatory authorities. Should this occur, the investigator will be responsible for:

- Informing Regeneron of a planned inspection by the authorities as soon as notification is received

- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the Regeneron immediately
- Taking all appropriate measures requested by the regulatory authorities to resolve the problems found during the audit or inspection

Documents patient to audit or inspection include but are not limited to all source documents, eCRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also patient to inspection.

In all instances, the confidentiality of the data will be respected.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Good Clinical Practice Statement

It is the responsibility of the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

13.2 Informed Consent

The principles of informed consent are described in ICH Guidelines for GCP. Regeneron will have the right to review and comment on the informed consent form.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF will be

signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.

Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF will be retained by the investigator as part of the patient's study record, and a copy of the signed ICF will be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF will be reviewed and updated appropriately. All study patients will be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF will be maintained in the patient's study record and a copy will be given to the patient.

13.3 Patient Confidentiality and Data Protection

The investigator will take all appropriate measures to ensure that the anonymity of each study patient will be maintained.

The patient's and investigator's personal data will be treated in compliance with all applicable laws and regulations.

13.4 Institutional Review Board

An appropriately constituted IRB/IEC, as described in ICH Guidelines for GCP, will review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (e.g. advertising) before any patient may be enrolled in the study

- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB will be informed as soon as possible

Ongoing studies will be reviewed by the IRB/EC on an annual basis or at intervals appropriate to the degree of risk.

In addition, the IRB will be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB approval letter will be sent to Regeneron prior to shipment of drug supplies to the investigator. The approval letter will include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB review and approval of all study documents (including approval of ongoing studies) will be kept on file by the investigator.

14. PROTOCOL AMENDMENTS

The investigator will not implement a change in the design or operation of the protocol or ICF without an IRB-approved amendment.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1 Premature Termination of the Study

The investigator will notify Regeneron of a desire to close-out a site in writing, providing approximately 30 days' notice. The final decision will be made through mutual agreement with Regeneron. Both parties will arrange the close-out procedures after review and consultation.

In all cases, the appropriate IRB and Health Authorities will be informed according to applicable regulatory requirements, and adequate consideration will be given to the protection of the patients' interests.

16. STUDY DOCUMENTATION

16.1 Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs will be signed by the investigator. This certification form accompanies each set of CRFs.

16.2 Retention of Records

The investigator will retain all essential study documents, including ICFs, source documents, CRFs, and drug accountability records for at least 5 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. Records will be destroyed in a manner that ensures confidentiality.

17. REFERENCES

1. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema. Diabetes Care. 2003;26:2653-2664.

2. Cetin EN, Yıldırım C. Adjuvant treatment modalities to control macular edema in diabetic patients undergoing cataract surgery. Int Opthalmol. 2012.

3. Kleinbek R, Moss SE. Prevalence of cataracts in a population-based study of persons with diabetes mellitus. Ophthalmology 1985; 92:1191-1196.

4. Nielsen NV, Vinding T. The prevalence of cataract in insulin-dependent and non-insulindependent-diabetes mellitus. Acta Ophthalmol Scand 1984; 62:595-602.

5. Bensen WE. Cataract surgery and diabetic retinopathy. Curr Opin Ophthalmol 1992;3:396-400.

6. Mentes J, Erakgun T, Afrashu F, Kerci G. Incidence of cystoid macular edema after uncomplicated phacoemulsification. Ophthalmologica. 2003;217:408-412.
7. Tranos PG, Wickremasinghe SS, Stangos NT, Topouzis F, Tsinopoulis I, Pavesio CE. Major review: Macular edema. Survey of Ophthalmology. 2004;49(5):470-487.

8. Schmier JK, Halpern MT, Covert DW, Matthews GP. Evaluation of costs for cystoid macular edema among patients after cataract surgery. Retina 2007; 27:621-628.

9. Hee MR, Puliafito CA, Wong C. et al. Quantitative assessment of macular edema with optical coherence tomography. Arch Ophthalmol 1995; 113:1019-1029.

10. Hee MR, Puliafito CA, Duker JS, Reichel E, Coker JG, Wilkins JR, Schuman JS, Swanson EA, Fujimoto JG. Topography of diabetic macular edema with optical coherence tomography. Ophthalmology 1998; 105:360-370.

11. Goebel W, Kretzchmar-Gross T. Retinal thickness in diabetic retinopathy: A study using optical coherence tomography (OCT). Retina 2002; 22:759-767.

12. Goebel W, Franke R. Retinal thickness in diabetic retinopathy: Comparison of optical coherence tomography, the retinal thickness analyzer, and fundus photography. Retina 2006; 26:49-57.

13. Campbell RJ, Coupland SG, Buhrmann RR, Kertes PJ. Optimal optical coherence tomography-based measures in the diagnosis of clinically significant macular edema: retinal volume vs foveal thickness. Arch Ophthalmol 2007; 125:619-623.

14. Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. Ophthalmology 2007;

114:881-889.

15. Wikberg-Matsson A, Granstam E, Eriksson U. A prospective comparative case-controlled study of type-2 diabetes patients and a healthy control group after cataract surgery. XXV Congress of the ESCRS, Stockholm, Sweden, September 2007.

16. Cho H, Madu A. Etiology and treatment of the inflammatory causes of cystoid macular edema. Journal of Inflammation Research. 2009;2:37-43.

17. Gaynes BI, Onyekwuluje A. Topical ophthalmic NSAIDs: A discussion with focus on nepafenac ophthalmic suspension. Clinical Ophthalmology. 2008;2(2):355-368.

18. Ke T, Graff G, Spellman JM, Yanni JM. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation: II. in vitro bioactivation and permeation of external ocular barriers. Inflammation. 2000;24(4):371-384.

19. Singh R, Alpern L, Jaffe GJ, et al. Evaluation of nepafenac in prevention of macular edema following cataract surgery in patients with diabetic retinopathy.
Clinical Ophthalmology. 2012;6:1259-1269.