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**TRIAL STUDY PROTOCOL (ENGLISH VERSION)**

# **Bevacizumab Versus Triamcinolone for Persistent Diabetic Macular Edema: A Randomized Clinical Trial**

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## 1. BACKGROUND

### 1.1 PATHOPHYSIOLOGY

In 2050, the prevalence of Diabetes mellitus (DM) will triplicate in the worldwide and imply certainly in an important concern of universal healthcare [1]. Diabetic retinopathy (DR) is prevalent in approximately 35% of diabetic patients and diabetic macular edema (DME) is the major cause of visual loss in patients with diabetes [2,3]. There is fewer epidemiologic data about DR in Brazil but general DR prevalence in Ribeirão Preto city, is about 29% for patients with type II DM and 29.9% for patients with type I DM [4-6]

DME occurs due to a breakdown of the blood-retinal barrier with subsequent leakage of plasma and lipids in the macula. Hyperglycemia is thought to be the strongest risk factor contributing to the pathogenesis of DME due to its activation of pathways that lead to increased oxidative stress, inflammation, and vascular dysfunction.[7] The resulting oxidative stress and inflammation also lead to the up-regulation of multiple cytokines and various growth factors, including VEGF, which then contribute to further breakdown of the blood-retinal barrier and the accumulation of fluid in the macula.[8] DME can occur in any stage of DR, including non-proliferative and proliferative DR.

### 1.2 TREATMENT OF DIABETIC MACULAR EDEMA

The Early Treatment of Diabetic Retinopathy Study (ETDRS) established the use of focal/grid photocoagulation for patients with clinically significant DME, resulting in a 50% reduction in severe vision loss for these patients.[9] With FDA approval of two anti-VEGF agents, focal/grid laser is now reserved for those with non-centrally-involved DME, while anti-VEGF therapy is indicated for those with centrally-involved DME. Ranibizumab is an antibody fragment and bevacizumab is a full length antibody are that block VEGF-A and intraocular injections of these agents substantial improve vision in patients with DME.[10,11] Aflibercept (Eylea, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) is a 115-kDa fusion protein containing the binding domains of human VEGF receptors 1 and 2 and the Fc domain of human immunoglobulin G1.

Two phase 3 parallel, double-masked, multicenter trials (VISTA and VIVID) compared aflibercept to focal/grid laser for DME.[12] Patients (872) were randomized to intravitreal aflibercept 2 mg every 4 weeks, 2 mg every 8 weeks after 5 initial monthly doses, or focal/grid laser and at 1 year, mean improvement from baseline BCVA was 42%, 31%, and 8%, respectively. Mean reduction in retinal thickness was 186, 183, and 73  $\mu\text{m}$ , respectively. In the aflibercept groups, less than 10% required rescue laser treatment thereby limiting laser as a confounding influence on the visual gains. The visual acuity gains demonstrated in the aflibercept groups were sustained through week 100.[13] In DRCR.net protocol I, approximately 40% of eyes receiving ranibizumab injections with prompt or deferred focal/grid laser had a CSFT $\geq$ 250  $\mu\text{m}$  on time domain (TD) optical coherence tomography (OCT) at 2 years. [14] These data suggest that there may be VEGF-independent molecular mechanisms that are involved in the development and sustenance of macular edema. Thus, there is a need for alternative or additional treatments that will improve vision by reducing retinal edema in eyes with persistent DME following previous anti-VEGF therapy. Because corticosteroids have been demonstrated to inhibit the expression of both VEGF and the VEGF gene [15-17] and utilized in DME due to their ability to inhibit inflammatory cytokine production a strong rationale exists for their use in the treatment of DME. In pseudophakic eyes, visual improvement at 1-year in patients receiving intravitreal triamcinolone plus prompt laser was comparable to that in groups receiving ranibizumab plus laser; however, by 2 years, the effects of corticosteroids plus laser were not superior to laser alone with regards to visual acuity or macular edema.[18] In a randomized multicenter trial, fluocinolone acetonide intravitreal inserts provided substantial visual improvement in patients with DME at 2 years.[19] Ozurdex, a dexamethasone intravitreal implant, has been shown to improve visual outcomes in patients in numerous studies.[20-22]

### **1.3 Triamcinolone and Clinical Applications**

Triamcinolone acetonide (TA) is a synthetic corticosteroid formulated as an injectable suspension and has a 7.5-fold higher anti-inflammatory potency than cortisone.[23] Because TA is water insoluble, it can remain in the vitreous for much longer than other corticosteroids, which are usually eliminated within a few days. Because TA is water insoluble, it can remain in the vitreous for much longer than other corticosteroids, which are usually eliminated within a few days. In the protocol B (DRCR.net study) 3 groups of DME therapy was performed: 1-laser, 2-TA (1mg) and 3-TA (4mg). After 3 years; 44%, 25% and 38% of patients had 10 or more letters improvement in BCVA respectively.[24] Related to basal center subfield foveal thickness (CSFT): 67%, 43% and 51% of eyes had macular thickened to less than 250 $\mu\text{m}$  after 3 years of treatment respectively.

## **2. OBJECTIVES**

### **2.1 Primary**

Patients who have residual edema after 6 months of pro re nata intravitreal 1.25mg (0.05cc) bevacizumab (prn-IVB) will be randomized to prn-IVB or 1.20mg (0.03cc) quarterly intravitreal TA (qIVT) and mean change from baseline and from randomization CSFT will be compared at 24 weeks after randomization.

## **2.2 Secondary**

- To compare the mean change from baseline and randomization BCVA in the prn-IVB versus qIVT groups.
- To compare the mean number of intravitreal injections between the prn-IVB versus qIVT groups.
- To compare effects on intraocular pressure (IOP) and need for IOP-lowering drops and/or surgery to reduce IOP between prn-IVB versus qIVT groups.

## **3. STUDY DESIGN**

### **3.1 DESCRIPTION OF THE STUDY**

This trial study will enroll a total of 83 DME patients (115 eyes). Each patient will receive an injection of prn-IVB at baseline and as need monthly based on macular thickness through 6 months. At week 24, patients who have recurrent or persistent edema will be randomized 1:1 to Group 1 (prn-IVB) or Group 2 (qIVT). Patients with no recurrent or persistent edema at week 24 will comprise Group 3 and continue to receive prn-IVB every 4 weeks. Prn treatment will be administered when central subfield foveal thickness (CSFT) >300  $\mu$ m. There will be a minimum interval of 12 weeks between qIVT injections.

Study visits will occur every 4 weeks with the primary endpoint at week 48. At each visit, patients will have an eye exam and CSFT, BCVA, and IOP will be assessed. Fundus photography and fluorescein angiography will also be performed at baseline, week 36, and week 48.

Rescue therapy: If, after 3 consecutive injections, there was not a reduction in CSFT of at least 10% and/or an increase in BCVA of at least 5 letters compared with baseline, the patient could continue to receive the same intravitreal medication for an additional 3 consecutive visits or discontinue treatment. All patients will resume standard care after exiting.

### **3.2 RATIONALE FOR STUDY DESIGN**

Despite the use of anti-VEGF therapy as first-line treatment for centrally involved DME, there are many patients whose response to therapy is poor or transient at best.[25] In the RISE/RIDE trials, approximately 50% of patients failed to achieve  $\geq$  15-letter gain in BCVA despite 2 years of monthly Ranibizumab (0.5

mg) injections.[26] In addition to the need to find effective alternative treatment strategies for patients with refractory DME, monthly injections can become burdensome for many patients. Given the key role of inflammation in the pathogenesis of DME, corticosteroids are frequently used as a treatment option due to their suppression of inflammatory cytokines.[27] In addition, corticosteroids suppress the expression of VEGF and may also function as neuroprotectants in the retina.[28] The FAME study group found that fluocinolone acetonide inserts in patients who previously had  $\geq 1$  macular laser treatment for DME provided substantial visual benefits for up to 3 years, with 28.7% of patients receiving the low-dose insert gaining  $\geq 15$  letters at month 36.[29]

Our real life study seeks to assess the effects of Triamcinolone as one such alternative treatment option for patients with DME despite prior anti-VEGF therapy. We hope that our study will expand our knowledge on alternative treatment strategies for patients suffering from persistent DME.

### **3.3 SAFETY PLAN**

*The safety assessments to be conducted for this study are listed in Section 5 and Appendix B.*

Potential safety issues are associated with the route of administration of triamcinolone/bevacizumab, the pharmacology of triamcinolone, the pharmacology of bevacizumab, and fluorescein angiography. Subjects will be instructed to contact their physician at any time should they have health-related concerns. All adverse events (serious and non-serious) will be recorded for the duration of the study.

#### *Fluorescein Angiography*

Risk associated with fluorescein angiography (FA) may include bleeding and/or bruising at the site of the needle insertion, itching, rash, or vomiting. A rare and severe allergic reaction can also occur during fluorescein angiography. Patients allergic to shellfish may be at risk for an allergic reaction to fluorescein or other dye. However, individuals with allergies to shellfish can receive a medication before the dye test to minimize allergic responses. Serious allergic reactions such as severe swelling and difficulty breathing can happen in 1 out of 10,000 patients and about 1 out of 222,000 patients can have a heart attack, stroke, or even die from the fluorescein dye administration. If the patient has ever had a severe allergic reaction to fluorescein dye, he or she will not be included in the study. To minimize allergic reaction to fluorescein angiography, any patient who has had mild reactions to previous FA (e.g. itching) will be given medication prior to undergoing FA.

#### *Risk of Intravitreal Injections*

Intravitreal injection has a 0.1 to 0.2% risk of complications such as vitreous hemorrhage, retinal detachment, endophthalmitis (intraocular infection), intraocular hypertension, and cataract formation (in patients who have not had their cataract



removed). Repeated injections may increase this risk. However, the vast majority of patients tolerate repeated injections well.

To minimize the risks of intravitreal injections, all injections will be performed employing standard surgical sterile techniques as described in Appendix B. All investigators in this trial have been instructed in this technique and are experienced in performing intravitreal injections. Following each injection, subjects will have a retinal examination to ensure that there is good perfusion of retinal vessels.

#### Plans to Decrease Potential Risks and Increase Safety

We will use strict sterile technique for injection of triamcinolone/bevacizumab. Detailed ocular examinations (e.g., BCVA, IOP, slit lamp examination and dilated fundus examination) will be performed every month. Any subject who develops significantly raised intraocular pressure ( $\geq 30$  mmHg) at any time during the study will be monitored according to the physician's clinical judgment and may undergo additional measurements of intraocular pressure beyond those specified in the protocol. Pressure-lowering eye drops including Alphagan P (brimonidine tartrate ophthalmic solution) or Cosopt (dorzolamide hydrochloride-timolol maleate) may also be used. The Principal Investigator will review all adverse events. The appropriate IRB will be notified immediately of any serious adverse events and will be notified in yearly renewals of all other adverse events. The IRB and FDA will be notified of any interruption in enrollment or change in the conduct of the study.

If subjects experience ocular inflammation that delays or causes discontinuation of intravitreal injections, appropriate IRBs and other relevant governing bodies will be notified. Study drug administration will be held for subjects who experience certain ocular events or infection events. In the event any subject develops an adverse event in the study eye that is considered by the designated evaluating physician to be severe in intensity, serious consideration should be given to withdrawing the subject from the study. Subjects withdrawn from the study prior to completion will be asked to return for an early termination evaluation 30 days ( $\pm 7$  days) following their last injection/study visit for monitoring of all adverse events (serious and non-serious; ocular and non-ocular).

### **3.4 COMPLIANCE WITH LAWS AND REGULATIONS**

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs) as well as local ethical and legal requirements in Brazil.

## **4. MATERIALS AND METHODS**

### **4.1 SUBJECTS**

#### **4.1.1 Subject Selection**

83 eligible patients (115 eyes) with DME will be enrolled over a period of 12 months. Subjects will be identified and recruited through the clinic population of the study in Brazil.

#### **4.1.2 Inclusion Criteria**

All subjects must meet the following criteria to be eligible for study entry:

- Signed informed consent and authorization of use and disclosure of protected health information.
- Age  $\geq 18$  years.
- Type 1 or type 2 diabetes.
- Patients diagnosed with fovea-involved DME in the study eye, with CST  $>300$   $\mu\text{m}$ .
- BCVA 20/32 to 20/400.
- No history of treatment for DME in study eye for 4 months prior to enrollment, including anti-VEGF, focal/grid photocoagulation, intravitreal or peribulbar corticosteroids.

#### **4.1.3. Exclusion Criteria**

Subjects who meet any of the following criteria will be ineligible for study entry:

- Evidence of permanent reduction in vision in study eye indicated by pigmentary abnormalities or some other structural abnormality (such as macular hole or significant epiretinal membrane) involving the fovea.
- Macular edema due to a cause other than diabetes, such as from surgery or vitreoretinal interface abnormalities (e.g., epiretinal membrane).
- Myocardial infarction, other acute cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 3 months of study entry.
- For women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next 24 months. Women who are potential study participants should be questioned about the potential for pregnancy. Potential child-bearing subjects will be instructed to use contraceptive methods. Investigator judgment is used to determine when a pregnancy test is needed.

- History of major ocular surgery (cataract extraction, scleral buckle, surgery for DME or any macular condition such as macular hole, any intraocular surgery, etc.) within the prior 4 months or anticipated within the next 6 months following randomization.
- Confluent hard exudates involving the center of the fovea.
- History of macula-off retinal detachment, irrespective of whether patient underwent successful surgery.
- Aphakia.

## **4.2 METHOD OF TREATMENT ASSIGNMENT**

This study will enroll 115 eyes, with pseudophakic and phakic subjects. All study subjects will receive prn bevacizumab at baseline and through initials 24 weeks. At week 24, each eye will be evaluated for macular edema, and those patients who have no recurrent or persistent edema will continue to receive prn bevacizumab (1.25 mg) every 4 weeks as part of Group 3. Those patients who have persistent edema at week 24 will undergo 1:1 randomization within each subgroup to either prn bevacizumab (1.25 mg) every 4 weeks or quarterly triamcinolone (1.20 mg) every 12 weeks (Group 1 and Group 2, respectively). Prn treatment will be administered when central subfield foveal thickness (CSFT) > 300  $\mu$ m and/or there are intraretinal cystoid spaces in the fovea. There will be no placebo or sham treatment. There will be no masking; patients and physicians will know the assignments to each group.

## **4.3 METHOD OF TREATMENT ASSIGNMENT**

Intravitreal injections of bevacizumab or triamcinolone will be carried out under controlled aseptic conditions, which include the use of gloves and a sterile eyelid speculum. Topical or subconjunctival anesthesia will be used based upon patient and physician preference. The site of injection will be sterilized with 5% povidone iodine. The needle will be through the pars plana 3.5–4.0 mm posterior to the limbus and the triamcinolone or bevacizumab will be injected into the vitreous cavity. Following the injection, patients will be examined by indirect ophthalmoscopy to make sure there is good perfusion of retinal vessels. Patients will be instructed to report any symptoms suggestive of endophthalmitis without delay.

## **4.4 CONCOMITANT AND EXCLUDED THERAPIES**

Any patient being treated for a serious systemic infection or an ocular infection in the study eye will be excluded. Subjects may continue to receive all medications and standard treatments administered for their conditions at the discretion of their treating physician.

## 4.5 STUDY ASSESSMENTS

### 4.5.1 Assessments during the Treatment Period

*For a complete overview of the study assessments, see Flow Chart in Appendix A.*

Subjects will be followed monthly for a total of 48 weeks.

#### Screening Visit (Day 0)

- Obtain informed consent.
- Record demographics, medical and ocular history, concomitant medications.
- ETDRS BCVA (logMAR).
- IOP (mmHg) measurement.
- Slit lamp examination.
- Indirect ophthalmoscopy.
- Fundus photography.
- Fluorescein angiography.
- Measurement of foveal thickness by Spectralis OCT.

If eligible, the patient may proceed to treatment

Intraocular injection of bevacizumab.

#### Weeks 4-20

- ETDRS BCVA.
- IOP measurement.
- Slit lamp examination.
- Indirect ophthalmoscopy.
- Measurement of foveal thickness by Spectralis OCT.
- Record concomitant medications.
- Record adverse events.
- Intraocular injection of bevacizumab

#### Week 24

- ETDRS BCVA.
- IOP measurement.
- Slit lamp examination.

- Indirect ophthalmoscopy.
- Measurement of foveal thickness by Spectralis OCT.
- Record concomitant medications.
- Record adverse events.
- Fundus photography.
- Fluorescein angiography.
- Randomization of patients with residual macular edema to bevacizumab (Group 1) or triamcinolone (Group 2).
- Patients with no residual edema will not be randomized and will be evaluated every 4 weeks and receive prn bevacizumab (Group 3) through week 48.

## **GROUP 1**

### Week 28-48

- ETDRS BCVA.
- IOP measurement.
- Slit lamp examination.
- Indirect ophthalmoscopy.
- Measurement of foveal thickness by Spectralis OCT.
- Record concomitant medications.
- Record adverse events.
- Intraocular injection of prn bevacizumab as per protocol.

Within week-visit 36 and last week-visit 48: Include:

- Fundus photography.
- Fluorescein angiography.

## **GROUP 2**

### Week 28-48

- ETDRS BCVA.
- IOP measurement.
- Slit lamp examination.
- Indirect ophthalmoscopy.
- Measurement of foveal thickness by Spectralis OCT.
- Record concomitant medications.
- Record adverse events.
- Intraocular injection of quarterly triamcinolone as per protocol.

Within week-visit 36 and last week-visit 48: Include:

- Fundus photography.
- Fluorescein angiography.

### **GROUP 3**

#### Week 28-48

- ETDRS BCVA.
- IOP measurement.
- Slit lamp examination.
- Indirect ophthalmoscopy.
- Measurement of foveal thickness by Spectralis OCT.
- Record concomitant medications.
- Record adverse events.
- Intraocular injection of prn bevacizumab as per protocol.

Within week-visit 36 and last week-visit 48: Include:

- Fundus photography.
- Fluorescein angiography.

#### **4.5.2 Early Termination Assessments**

Subjects who withdraw from the study prior to completion should return for an early termination evaluation 30 days ( $\pm 14$  days) following the last injection/study visit for monitoring of all adverse events (serious and non-serious). The schedule of assessments for early termination is the same as that for the final visit.

#### **4.6 SUBJECT DISCONTINUATION**

Subjects have a right to withdraw from the study at any time.

The subject may be withdrawn from the study for any reason: if it is in the best interest of the subject, concurrent illness, adverse events, or a worsening condition. Participating centers in the trial may request the withdrawal of a subject because of protocol violations, administrative reasons, or any other valid and ethical reasons.

If a subject discontinues from the study, he or she will not be allowed to re-enter the study.

Reasons for subject discontinuation may include, but are not limited to, the following:

- Rhegmatogenous retinal detachment or Stage 3 or 4 macular hole.
- Investigator determination that it is not in the best interest of the subject to continue participation.
- Pregnancy.
- Serious adverse event (SAE).
- Any other safety concerns.

## **4.7 STATISTICAL METHODS**

### **4.7.1 Analysis of the Conduct of the Study**

This study will provide data on the effects of prn bevacizumab and quarterly triamcinolone on CSFT, BCVA, and IOP in patients with persistent DME despite receiving prior anti-VEGF therapy.

### **4.7.2 Efficacy Analyses**

#### **Primary Outcome Measure**

- Mean change from baseline and from randomization CSFT at week 48.

#### **Secondary Outcome Measures**

- Mean change from baseline and from randomization BCVA at week 48.
- Mean change from baseline and from randomization IOP at week 48.

### **4.7.3 Safety Analyses**

Adverse events and results of ocular examinations from all 83 patients will be utilized to summarize safety data. The following outcomes will be assessed: 1) Percentage of eyes with IOP  $\geq$  25 or 30 mm Hg at any visit, 2) Percentage of eyes requiring IOP-lowering drops or surgery to reduce IOP at any visit, 3) Percentage of patients with significant worsening of cataract in the study eye during the study.

### **4.7.4 Missing Data**

Analyses of efficacy and safety will be based on available cases without imputation for missing values.

### **4.7.5 Interim Analyses**

No formal schedule of interim analyses is planned. Reports of adverse events from this study may be reviewed and summarized periodically while the study is ongoing to ensure the safety of subjects.

## 5. ASSESSMENT OF SAFETY

### 5.1 ADVERSE EVENTS

AEs that start on Day 0 through the last study visit will be recorded on the appropriate AE pages of the CRF. Subjects discontinuing early from the study should return for an early termination evaluation and will be contacted 30 days after their last injection or study visit to assess for adverse events (serious and non-serious).

For this protocol, an AE is any “on study” untoward medical occurrence (e.g., sign, symptom, disease, syndrome, concurrent illness) that occurs in a study subject, regardless of the suspected cause. “On study” refers to Day 0 through the last study visit.

Unchanged, chronic conditions are NOT AEs and should not be recorded on the AE pages of the CRF. An exacerbation or worsening of a chronic condition should be recorded as an AE.

Both serious and non-serious AEs should be graded on a three-point scale (mild, moderate, severe) and reported in detail on the appropriate AE page of the CRF.

The suggested definitions are as follows:

Mild: Discomfort without disruption of normal daily activity.

Moderate: Discomfort sufficient to reduce or affect normal daily activity.

Severe: Incapacitating discomfort with inability to work or perform normal daily activity.

Using the following criteria, investigators also need to assess whether there is a reasonable possibility that study drug caused or contributed to the AE.

- Yes (possibly or probably):

There is a clinically plausible time sequence between onset of the AE and study drug administration; and/or

There is a biologically plausible mechanism for study drug causing or contributing to the AE; and

The AE may or may not be attributed to concurrent/underlying illness, other drugs, or procedures.

- No

A clinically plausible temporal sequence is inconsistent with the onset of the AE and study drug administration; and/or



A causal relationship is considered biologically implausible.

## 5.2 BASELINE MEDICAL CONDITIONS

It is not necessary to complete an AE CRF page for chronic medical conditions present at enrollment that do not worsen in intensity or frequency during the trial. These medical conditions should be adequately documented on the appropriate page of the CRF (medical history and/or physical examination). However, medical conditions present at enrollment that worsen in intensity or frequency during the treatment or post-treatment periods and ongoing AEs that started during the previous study should be reported and recorded as AEs.

### 5.2.1 Serious Adverse Events

An AE occurring **at any dose** (including overdose) should be classified as **SERIOUS** if:

- It resulted in death (i.e., the AE caused or led to death).
- It was life threatening (i.e., the AE placed the subject at immediate risk of death; it does not apply to an AE that hypothetically might have caused death if it were more severe).
- It required or prolonged inpatient hospitalization (i.e., the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion).
- It was disabling (i.e., the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions).
- It resulted in a congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the molecule or study drug prior to conception or during pregnancy).
- It does not meet any of the above serious criteria but may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

#### *Sight-threatening adverse events*

An adverse event is considered to be sight-threatening if it meets one or more of the following criteria and will be reported as a serious adverse event (SAE):

- The event causes a decrease in visual acuity of greater >30 letters (compared with the last assessment of visual acuity prior to the most recent treatment) lasting >1 hour.
- The event causes a decrease in visual acuity to the level of light perception or worse lasting >1 hour.
- The event requires surgical intervention (e.g, conventional surgery, vitreous tap or biopsy with intravitreal injection of antibiotics, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
- The event is associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis).
- In the opinion of the investigator, the event may require medical intervention to prevent permanent loss of sight.

### **SAE Reporting**

Sub-Investigators should report all SAEs to the Principal Investigator (PI) within 48 hours of observing or learning of the event. For initial SAE reports, investigators should record all case details that can be gathered within 48 hours on the SAE page of the CRF.

It is requested that the PI report the following events to Reading Center within 7 days: unexpected, drug-related fatal or life threatening SAEs.

It is requested that the PI report the following events to Reading Center within 15 days: events of special interest (e.g. endophthalmitis, catastrophic outcomes such as enucleation, stroke).

The completed SAE page and SAE Fax Cover Sheet should be faxed immediately upon completion to Reading Center

Relevant follow-up information should be submitted to Reading Center as soon as it becomes available.

#### **5.2.2 Special Reporting Situations**

##### **a. Death**

Death is an outcome of an event. The **event** that resulted in death should be recorded and reported on the SAE pages of the CRF.

##### **b. Hospitalizations for Surgical or Diagnostic Procedures**

The **illness** leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the case narrative as part of the action taken in response to the illness.

### **c. Pregnancy**

Any pregnancy occurring during study treatment should be reported, and the subject may be removed according to the discretion of the Principal Investigator.

#### **5.2.3 Type And Duration Of Follow-Up After Adverse Events**

All reported AEs should be followed until resolution or until the subject's participation in the study ends. Subjects who have an ongoing study drug-related SAE at study completion or at discontinuation from the study will be followed by the investigator or his or her designee until the event is resolved or determined to be irreversible, chronic, or stable by the investigator.

## **6.0 INVESTIGATOR REQUIREMENTS**

### **6.1 STUDY INITIATION**

Before the start of this study, the following documents must be on file:

- Current curricula vitae of the Principal Investigators.
- Written documentation of IRB approval of protocol and informed consent document.
- A copy of the IRB-approved informed consent document.
- Written documentation of IRB review and approval of any advertising materials to be used for study recruitment, if applicable.
- Certified translations of IRB approval letters, pertinent correspondence, and approved informed consent document (when applicable).
- Current laboratory certification of the laboratory performing the analysis as well as current normal laboratory ranges for all laboratory tests.

### **6.2 INFORMED CONSENT**

Informed consent documents will be provided to each subject.

The informed consent document must be signed and dated by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed

consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The following basic elements must be included:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures or drug used for purposes which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the patients.
- A description of any benefits to the patient or to others that may reasonably be expected from the research. A description that there may be no benefit from this research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient.
- A statement describing the extent, if any, to which confidentiality records identifying the patient will be maintained and that notes the possibility that the national and local health authorities and drug manufacturer may inspect the records.
- For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available should injury occur and, if so, what they consist of or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and patients' rights, and whom to contact in the event of a research-related injury to the patient.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.

### **6.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL**

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB/EC for review and must be approved before the study is initiated. The study will be conducted in accordance with applicable national and local health authorities, and IRB/EC requirements.

The Principal Investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB/EC must be updated at least once a year. The Principal Investigator must also keep the IRB/EC informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB/EC of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the study drug by the investigator. Some IRBs or ECs may have other specific adverse event requirements that investigators are expected to adhere to. Investigators must immediately forward to their IRB/EC any written safety report or update. (e.g., Investigator Brochure, safety amendments and updates, etc.).

### **6.4 CASE REPORT FORMS**

All CRFs should be filled out completely by appropriate personnel. The CRF should be reviewed, signed, and dated by the investigator.

All CRFs should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced CRF copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID ON THE ORIGINAL.

### **6.5 STUDY DRUG ACCOUNTABILITY**

The Investigator is responsible for the control and distribution of the study drug.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure.

## **6.6 DISCLOSURE OF DATA**

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the national and local health authorities, the drug manufacturer and the IRB/EC for each study site, if appropriate.

## **6.7 RETENTION OF RECORDS**

The Principal Investigators will retain records for 2 years after the investigation is discontinued.

## **7. PAYMENTS, REMUNERATIONS AND COSTS TO PARTICIPANTS**

### **7.1 PAYMENTS AND REMUNERATION**

There is no compensation for participants in this study.

### **7.2 COSTS**

There are no costs for study procedures or study drugs to participants.

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## APPENDIX A: STUDY FLOW CHART

	Baseline	W4	W8	W12	W16	W20	W24 (Random)
Informed Consent	X						
Eligibility Criteria	X						
Demographics	X						
Medical History/Medications	X	X	X	X	X	X	X
ETDRS BCVA	X	X	X	X	X	X	X
IOP	X	X	X	X	X	X	X
Slit Lamp Exam	X	X	X	X	X	X	X
Fundoscopy Exam	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X
Fluorescein Angiography	X						X
Fundus Photography	X						X
<b>Prn-IVB (all)</b>	X	X (prn)	X (prn)	X (prn)	X (prn)	X (prn)	X (prn)
<b>Prn-IVB: Group 1</b>	-	-	-	-	-	-	-
<b>Group 3</b>	-	-	-	-	-	-	-
<b>IVT: Group 2</b> (quarterly as need)	-	-	-	-	-	-	-
Adverse Events	X	X	X	X	X	X	X

	W28	W32	W36	W40	W44	W48
Informed Consent						
Eligibility Criteria						
Demographics						
Medical History/Medications	X	X	X	X	X	X
ETDRS BCVA	X	X	X	X	X	X
IOP	X	X	X	X	X	X
Slit Lamp Exam	X	X	X	X	X	X
Fundoscopy Exam	X	X	X	X	X	X
OCT	X	X	X	X	X	X
Fluorescein Angiography			X			X
Fundus Photography			X			X
<b>Prn-IVB (all)</b>	-	-	-	-	-	-
<b>Prn-IVB: Group 1 (transient)</b>	X	X(prn)	X(prn)	X(prn)	X(prn)	-
<b>Group 3 (responder)</b>	-	X(prn)	X(prn)	X(prn)	X(prn)	-
<b>qIVT: Group 2</b> (quarterly as need)	X	-	-	X(prn)	X(prn)	-
Adverse Events	X	X	X	X	X	X

## **APPENDIX B**

### **Pre-Injection Procedures for All Subjects**

The following procedures will be used to minimize the risk of potential adverse events associated with intravitreal injections (e.g., endophthalmitis). Aseptic technique will be observed by clinic staff involved in the injection tray assembly, anesthetic preparation, and study drugs' preparation and administration. In addition to the procedures outlined below, any additional safety measures in adherence to specific institutional policies associated with intravitreal injections will be observed.

The following procedures (except where noted) will be conducted by the physician performing the intravitreal injection of the study drugs.

At the discretion of the investigator, the site may use either ophthalmic drops or lidocaine injection for study eye anesthesia.

If using propacaine- tetracaine-or lidocaine -based ophthalmic drops for anesthesia, the injecting physician or technician (if applicable) assembles the supplies and prepares a sterile field. Supplies include 10% povidone iodine swabs, sterile surgical gloves, a pack of sterile cotton-tipped applicators, eyelid speculum, 5% povidone iodine ophthalmic solution, and injection supplies. Note: The use of generic formulations or next-generation formulations of the antimicrobials listed above is permitted.

#### **Procedure for Anesthesia:**

- Instill two drops proparacaine or tetracaine-based ophthalmic drops into the study eye
- Wait 90 seconds.
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye, ensuring that the drops cover the planned injection site on the conjunctiva.
- Wait 90 seconds.
- Instill two more drops of proparacaine- or tetracaine-based ophthalmic drops into the study eye.
- The physician will glove and place the speculum underneath the eyelid of the study eye.
- Use 10% povidone iodine swabs to thoroughly clean the area of the conjunctiva that will be penetrated.
- Saturate a sterile, cotton-tipped applicator with proparacaine- or tetracaine-or lidocaine -based drops and hold the swab against the planned intravitreal injection site for 60 seconds.
- Instruct patient to direct gaze away from syringe prior to IVB or IVT injection.