CLINICAL STUDY PROTOCOL SYNOPSIS

TITLE	**Prospective Randomized Comparative Trial for Combination Dexamethasone Implant with PRN Anti-VEGF therapy to Anti-VEGF Therapy Alone in Treatment Resistant Diabetic Macular Edema: Informing the Role for Imaging Biomarkers and Combination Therapy (PRECISION Study)**
TITLE IN LAY TERMS	Evaluation of Imaging Biomarkers in DME
SPONSOR:	Cleveland Clinic
FINANCIAL SUPPORT/GRANT:	Allergan
STUDY COORDINATING CENTER AND READING CENTER	
Study Chair	Justis P. Ehlers MD Cole Eye Institute Cleveland Clinic Cleveland, Ohio
CLINICAL SITE LOCATION(S)	
Co-Investigators	Charles Wykoff, MD PhD Retina Consultants of Houston Houston, Texas Jeremy Wolfe, MD Associated Retina Consultants Royal Oak, MI Arshad Khanani, MD, MA Sierra Eye Associates Reno, Nevada

OBJECTIVE(S)	1. To compare the anatomic and functional response of dexamethasone therapy to anti-VEGF therapy alone in eyes with treatment resistant diabetic macular edema (DME). 2. To evaluate imaging features that correlate with specific therapeutic response (e.g., dexamethasone vs anti-VEGF). 3. To correlate automated angiographic analysis patterns with aqueous cytokine expression profile in DME. 4. To correlate anatomic response to dexamethasone implant with cytokine expression profile and angiographic analysis patterns. 5. To compare treatment frequency in combination therapy group to anti-VEGF alone.
STUDY DESIGN	This study is an interventional, prospective randomized study comparing the dexamethasone implant to intravitreal aflibercept. Subjects will have an initial single injection of aflibercept and will be randomized if diabetic macular edema persists. Each subject will be evaluated for 6 months following randomization. Thus, the study duration will be 12 months plus the recruitment period. Subjects will be evaluated every month for safety, efficacy as measured by SDOCT and best corrected visual acuity (BCVA) using the Electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) protocol. In addition, ultra-widefield angiography will be performed at run-in visit, baseline, month 3, and month 6.
STUDY DURATION	6 Months (after randomization)
ESTIMATED STUDY COMPLETION DATE	December 1, 2023
POPULATION	
Sample Size:	50 randomized subjects; 25 subjects in each arm. 60 anticipated to participate in the run-in phase.

Target Population:	Patients presenting with foveal-involving macular edema secondary to DME with central subfield thickness greater than or equal to 325 microns on Spectralis (Heidelberg) or 300 microns on Cirrus (Zeiss).

TREATMENT(S)	Subjects will be given 2 mg intravitreal aflibercept (0.05 mL or 50 microliters) at run-in visit (i.e., screening visit). If the DME resolves as determined by the investigator (e.g., complete resolution of foveal cystic changes), subjects will be exited from the study after completing the Month 0/Visit 1 encounter. Those subjects will have all imaging completed, but no treatment will be performed at month 0.
	
	If DME persists (e.g., foveal-involving DME based on central significant cystic changes on OCT as determined by the investigator greater), the subject will be randomized between groups.
	o Group A: Intravitreal dexamethasone implant given at month 0. PRN intravitreal dexamethasone implant given if 10 weeks or more since last dexamethasone implant. If < 10 weeks, PRN aflibercept given if edema persists.
	o Group B: Intravitreal aflibercept given at month 0. PRN intravitreal Aflibercept given at months 1-6 for persistent DME.
	o PRN therapy given for parameters as outlined in protocol, specifically:
	  o Loss of 5 or more ETDRS letters from best previous measurement associated with foveal-involving macular edema
	  o Foveal-involving macular edema (i.e., foveal cystic changes) with central subfield thickness greater than 325 microns on Spectralis or 300 microns on Cirrus.
	  o At investigator's discretion for other causes where therapy may be beneficial (e.g., vitreous hemorrhage, visually significant foveal-involving edema with central subfield thickness less than or equal to 325 microns)

ENDPOINT(S)

Primary:

The primary study endpoint is the mean change in central subfield thickness at 6 months.

Secondary:

Secondary endpoints would include

- Number of Injections at 6 months
- Change in BCVA at 6 months
- Change in leakage index at 6 months
- Change in ischemic index at 6 months
- Change in microaneurysm counts at 6 months
- Change in ellipsoid zone integrity at 6 months
- Change in intraretinal fluid metrics at 6 months.
- Change in DRSS at 6 months
- The incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs at 6 months.

Exploratory:

Exploratory analyses would include:

- Radiomics and machine learning assessments of angiographic, SD-OCT, and OCT angiographic features.
- Correlation of cytokine expression profiles and treatment response.
- Correlation of cytokine expression profiles with imaging features.

PROCEDURES AND ASSESSMENTS	Ongoing assessments will include BCVA measurement, ophthalmic examinations and recording and evaluation of clinical adverse events. Subjects will undergo SDOCT at each visit. Ultra-widefield angiography will be performed at run-in visit, baseline, month 3, and month 6. OCT angiography will be performed at run-in visit, baseline, month 3, and month 6. Aqueous samples will be obtained at the run-in visit, baseline, and month 1 (if injection performed)
	
	Subjects will be given intravitreal aflibercept 2 mg (0.05 mL or 50 microliters) at run-in visit. If the DME resolves as determined by the investigator (e.g., complete resolution of foveal cystic changes), subjects will be exited from the study after completing the Month 0/Visit 1 encounter. Those subjects will have all imaging completed, but no treatment will be performed at month 0.
	
	If DME persists, the subject will be randomized between groups.
	o Group A: Intravitreal dexamethasone implant given at month 0. PRN intravitreal dexamethasone implant given for persistent foveal-involving DME if 10 weeks or more since last dexamethasone implant. If < 10 weeks, PRN aflibercept given for persistent foveal-involving DME.
	o Group B: Intravitreal aflibercept given at month 0. PRN intravitreal Aflibercept given at months 1-6 if foveal-involving DME persists.
	o In both groups PRN therapy will be indicated for the following clinical reasons:
	  o Loss of 5 or more ETDRS letters from best previous measurement associated with foveal-involving macular edema
	  o Central subfield thickness greater than 325 microns with foveal-involving macular edema on SD-OCT.
	  o At investigator's discretion for other causes where therapy may be beneficial (e.g., vitreous hemorrhage, visually significant foveal-involving edema with central subfield thickness less than or equal to 325 microns)

STATISTICAL PLAN	The patients will be compared to their baseline measurement for the primary and secondary outcome. Trends and statistical significant difference will be reported.

1. INTRODUCTION AND RATIONALE

The underlying pathophysiology of diabetic macular edema (DME) is multifactorial and complex. Optimizing therapeutic choice is important for facilitating efficient anatomic improvement and enabling improved functional outcomes. Numerous cytokines and mediators have been described to play a role in the formation and progression of DME. The relative expression of these mediators may play a critical role in therapeutic response, prognosis, and risk of disease progression. Currently, there are no noninvasive biomarkers available to clinicians that provide information related to cytokine expression or the overall cytokine profile in a given patient that is driving these disease states.

Although anti-VEGF therapy is currently considered first-line therapy for DME, limited data is available on the optimal timing for introducing steroid pharmacotherapy, either alone or in combination. Being able to identify features early in diagnosis/treatment could facilitate enhanced precision and individualized decision-making.

The analysis of vascular parameters on angiography as well as automated segmentation of volumetric OCT parameters have the potential to provide high order quantitative assessment of disease characteristics. Utilizing this rich data set, integrative pattern analysis and learning algorithms can be utilized to characterize the overall disease features at a new level.

Using a novel objective computerized assessment tool, in-depth analysis of the amount and type of leakage in the form of pixels per area of the retina or choroid is possible. Assessment is performed at various time points during the angiogram to allow for normalization to assess not only baseline abnormalities in fluorescence, but to also enable assessment of change over time to facilitate identification and quantification of leakage. Longitudinal assessment is able to be performed over time to assess treatment response, change in disease activity, and overall disease burden (See Figures). Software allows quantification of vascular leakage which would allow a more precise evaluation of retinal or choroidal vascular flow. The ability to quantify amount of leakage would allow assessment on level of disease burden, areas of ischemia, and quantitative assessment of vascular permeability and would provide a durable outcome measure for clinicians to follow and to titrate therapy, provide a reproducible outcome measure for clinical trials and drug development.

These patterns provide the opportunity to utilize this automated assessment as an imaging biomarker for disease burden, treatment response, and prognosis. Correlating cytokine expression patterns with specific imaging patterns has the potential to create a novel approach for imaging biomarkers that may help clinicians to customize and tailor therapeutic decision-making by optimizing therapeutic selection.

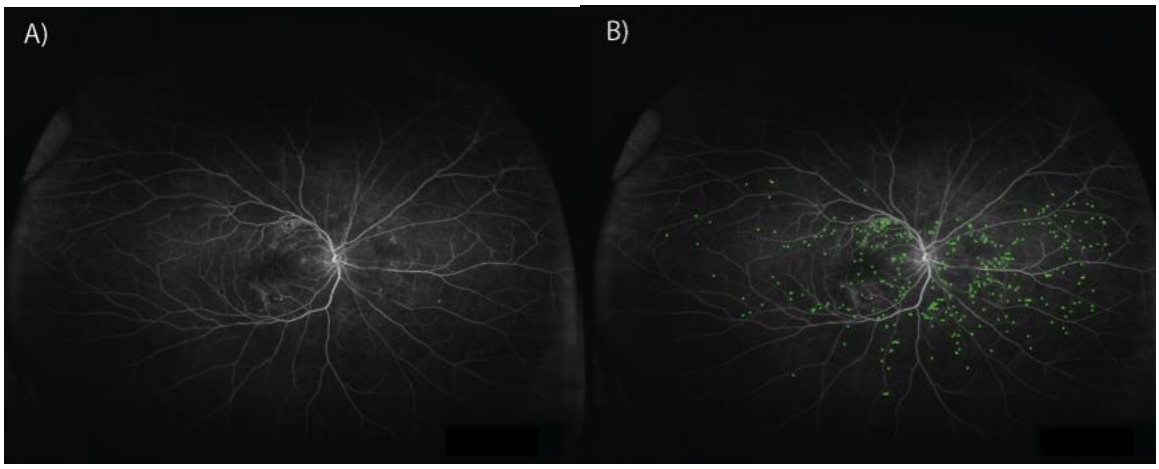
In this study, aqueous samples would be obtained from subjects prior to undergoing therapy for diabetic macular edema. Additionally, subjects would undergo ultra-widefield fluorescein angiography, OCT-angiography, and spectral domain OCT. Comparative analysis of these imaging results will be performed using an automated quantitative segmentation algorithm to correlate with cytokine profiles. Integrative

pattern analysis will be utilized to identify specific imaging patterns that maybe particularly linked to a cytokine expression profile and evaluated to assess for predictive features of targeted therapeutic approaches (e.g., steroid responsive DME vs anti-VEGF responsive DME).

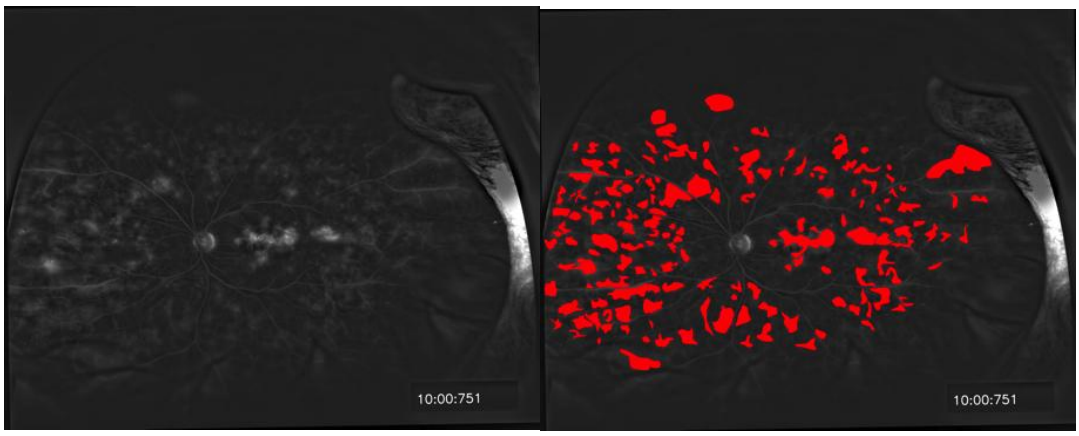
Overall, this clinical trial would provide critical information related to the role of the dexamethasone implant with possible combination therapy in treatment resistant DME. In addition, this study would provide a unique opportunity to evaluate the opportunity of imaging biomarkers for characterizing treatment response and to evaluate combination therapy approaches.

Automated Algorithm Segmentation Samples

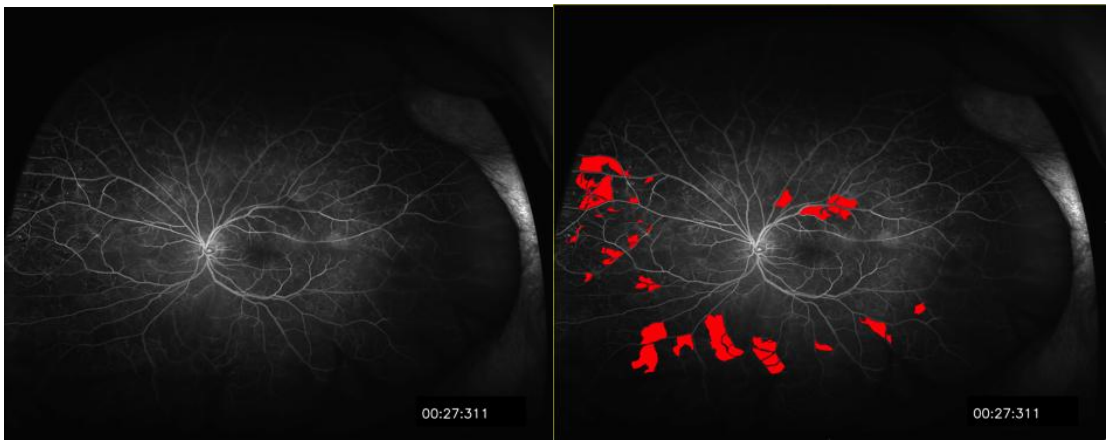
Microaneurysm Segmentation:



Leakage Analysis Samples:



Ischemia Analysis:



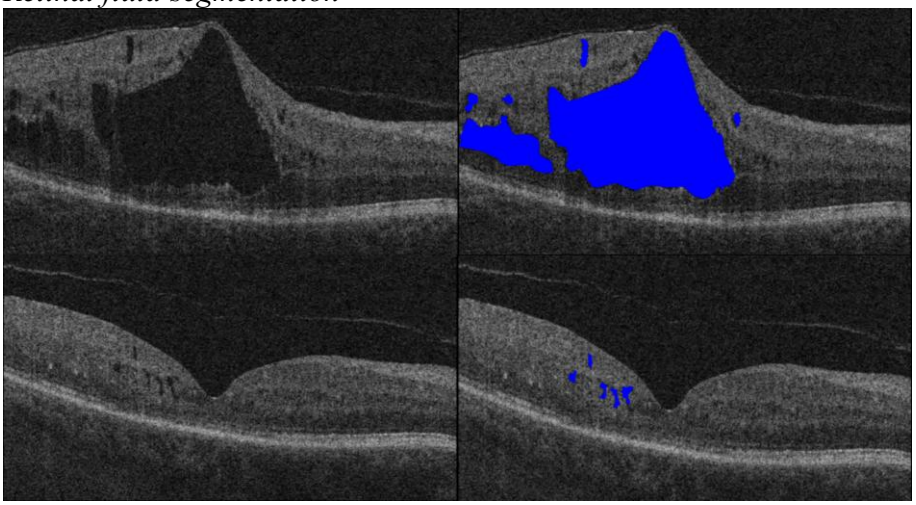
Fluid Dynamics, Outer Retinal Integrity, and Effect of Dosing on Outcomes:

This study would provide higher-order assessment of SD-OCT features in eyes from this clinical trial. The 2 major SD-OCT analyses will be retinal fluid dynamics and outer retinal integrity.

Fluid Dynamics:

The goal of the fluid dynamics assessment portion of this study would be to provide a higher-order assessment of overall retinal tissue dynamics in DME during treatment and to assess differential features and to assess the impact of various features on treatment response to explore potential features that may be associated with more optimal response. In addition, these features will be analyzed as outcome variables for the 2 groups.

Retinal fluid segmentation



Top row is prior to intravitreal pharmaco therapy with intraretinal fluid segmented (blue, top right). Bottom row is same patient following anti-VEGF therapy with segmented intraretinal fluid (blue, bottom right)

Each eligible scan will be analyzed for the following:

- Macular intraretinal fluid volume
- Actual retinal volume (fluid volume subtracted)
- Macular subretinal fluid volume

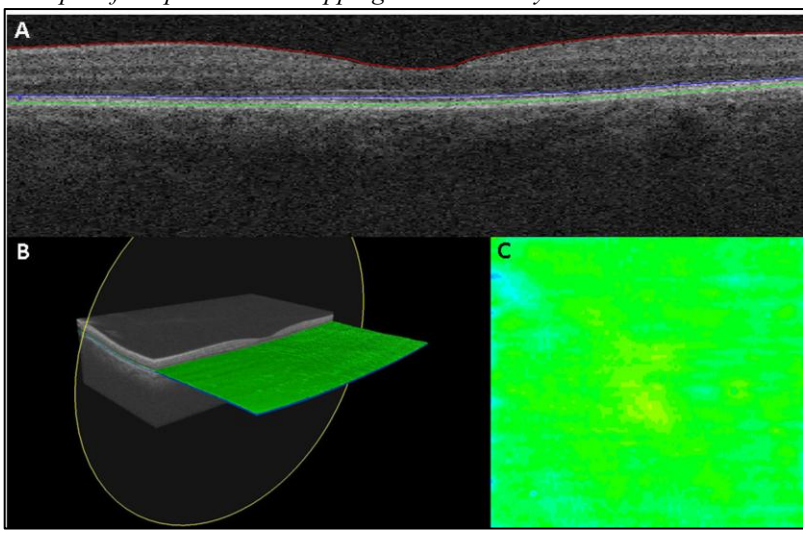
Outer Retinal Integrity

In addition to fluid dynamics, additional retinal features may play a critical role in the functional response to intravitreal pharmacotherapy. In particular, total retinal atrophy and ellipsoid zone attenuation may be linked to visual acuity potential and contribute to the overall response to therapy.

Ellipsoid zone integrity is critical to evaluating prognosis and overall visual performance in numerous diseases, including macular degeneration and diabetic retinopathy. The evaluation of the ellipsoid zone in a quantitative and objective fashion remains elusive for many reading centers due to the challenges around ellipsoid zone measurements. Our lab has developed a novel ellipsoid zone mapping assessment tool. The mapping tool allows

for volumetric and panmacular assessment of the ellipsoid zone status, including *en face* thickness analysis.

Example of Ellipsoid Zone Mapping in a normal eye.



Ellipsoid zone mapping in a normal eye. (A) B-scan segmentation of the ellipsoid zone. (B) Three-dimensional reconstruction of the ellipsoid zone revealing the overall integrity (green). (C) En face mapping of relative ellipsoid zone to retinal pigment epithelium thickness.

Utilizing this tool, OCT scans from studies could be evaluated for ellipsoid zone features and analyzed at various time points for correlation with outcomes, therapeutic response, and prognostication.

In addition, overall retinal tissue integrity is also likely critical for functional outcomes. Current assessment algorithms utilize total retinal thickness, which includes not only actual retinal tissue but also any fluid burden present within the retinal tissue. The ability to assess actual retinal tissue volume/area (e.g. total retinal thickness minus intraretinal fluid) may be a critical factor in understanding overall prognosis.

The following measurements would be performed:

- EZ-RPE central subfield thickness
- EZ-RPE macular volume
- Percent of macular scan with EZ atrophy (0 micron thickness)
- Percent of macular scan with EZ attenuation (20 micron thickness or less)
- Actual retinal foveal area (total foveal area minus intraretinal fluid)
- Actual retinal volume (total macular volume minus intraretinal fluid)

Radiomics, Subvisual Features and Machine Learning Analysis:
In addition to the higher order image analysis described above, additional exploratory assessments will be potentially pursued including machine learning and subvisual feature assessment. Potential areas of analysis include textural entropy, vascular lesion tortuosity, and fractal feature assessment.

Cytokine Analysis:

Aqueous samples will be evaluated by a commercial laboratory. Tentatively, Ray Biotech is the lab that is being considered as the lead candidate to assess the cytokines. Based on preliminary quality control assessment and volume assessment, the following arrays will likely be utilized:

i. 40 Cytokine Array: Activin A, AgRP, Angiopoietin-1, Angiopoietin-2, Angiogenin, Angiostatin, ANGPTL4, bFGF, CXCL16, EGF, ENA-78 (CXCL5), FGF-4, Follistatin, GCSF, GM-CSF, GRO alpha/beta/gamma, HB-EGF, HGF, I-309 (TCA-3/CCL1), IFN-gamma, IGF-1, IL-10, IL-12 p40, IL-12 p70, IL-17A, IL-1 alpha (IL-1 F1), IL-1 beta (IL-1 F2), IL-2, IL-4, IL-6, IL-8 (CXCL8), IP-10 (CXCL10), I-TAC (CXCL11), Leptin, LIF, MCP-1 (CCL2), MCP-2 (CCL8), MCP-3 (MARC/CCL7), MCP-4 (CCL13), MMP-1, MMP-9, PDGF-BB, PECAM-1 (CD31), PLGF, RANTES (CCL5), TGF alpha, TGF beta 1, TGF beta 3, Tie-1, Tie-2, TIMP-1, TIMP-2, TNF alpha, TNF beta (TNFSF1B), Thrombopoietin (TPO), uPAR, VEGF-A, VEGFR2, VEGFR3, VEGF-D

1.1.1 Rationale for Dose Selection

The dose and treatment regimen was selected based on the phase III studies, the drug package inserts for the dexamethasone implant and for intravitreal aflibercept, and standard-of-care clinical practice approaches. The dexamethasone dose utilized will be the FDA-approved 700 mcg implant. The intravitreal aflibercept dose utilized will be the FDA-approved 2 mg (0.05 mL or 50 microliters) dose administered by intravitreal injection.

2. STUDY OBJECTIVES

2.1 Primary Objective

A. To compare the anatomic and functional response of dexamethasone therapy to anti-VEGF therapy alone in eyes with treatment resistant DME.

2.2 Secondary Objective(s)

A. To evaluate imaging features that correlate with specific therapeutic response (e.g., dexamethasone vs anti-VEGF).

B. To correlate automated angiographic analysis patterns with aqueous cytokine expression profile in diabetic macular edema

C. To correlate anatomic response to dexamethasone implant with cytokine expression profile and angiographic analysis patterns.

D. To compare treatment frequency in combination therapy group to anti-VEGF alone.

STUDY DESIGN

2.3 Study Description and Duration

- Subjects will be treated at a single run-in visit (i.e. Month -1, screening) with 2 mg intravitreal aflibercept.
- If the DME resolves as determined by the investigator (e.g., complete resolution of foveal cystic changes), subjects will be exited from the study after completing the Month 0/Visit 1 encounter. Those subjects will have all imaging completed, but no treatment will be performed at month 0.
- If significant DME (e.g., foveal-involving DME based on central significant cystic changes as determined by the investigator) remains following the single intravitreal aflibercept injection, subjects will be randomized between group A and group B. Following randomization, they will be followed monthly and treated as follows:
    - Group A: Intravitreal dexamethasone implant given at month 0. PRN intravitreal dexamethasone implant given if 10 weeks or more since last dexamethasone implant. If < 10 weeks, PRN aflibercept given.
    - Group B: Intravitreal aflibercept given at month 0. PRN intravitreal Aflibercept given at months 1-6.
- The planned enrollment for the 50 subjects needed for this study is estimated to be 12 months randomized approximately 1:1 between the 2 treatment groups (i.e., approximately 25 subjects in each group). The study duration for each subject is scheduled to be 7 months including the screening visit (6 months from randomization visit). Evaluations will occur every month for the duration of the study. OCT examinations will be conducted at every visit.
- For the purposes of this study, a month is defined as 28 days with a visit window of +/- 7 days.

Only one eye will be designated as the study eye. For subjects who meet eligibility criteria in both eyes, the investigator and/ or patient will select the study eye.

2.4 Study Committees

Appropriate action, if needed, will be taken based upon this review and in consultation with the principal investigator. All events will be managed and reported in compliance with all applicable regulations and included in the final clinical study report.

3. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

3.1 Number of Subjects Planned

The target enrollment for this study is 50 randomized subjects with an approximate 1:1 ratio between the 2 treatment group. It is estimated that approximately 60 subjects will be initially enrolled through the run-in visit.

3.2 Study Sites and Data Management/Reading Centers

Subjects will be recruited through clinics at the Retina Consultants of Houston, Houston, TX, and Associated Retina Consultants, Royal Oak, MI and any additional sites. The local sites will seek approval from local IRB. The Cole Eye Institute at the Cleveland Clinic, Cleveland OH, will serve as the sponsor for the study and the data management and image reading center for the study. All study related procedures will be performed in accordance with the Declaration of Helsinki and US Code 21 of Federal Regulations.

3.2.1

Inclusion Criteria

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

1. Signed Informed Consent.
2. Men and women ≥ 18 years of age.
3. Foveal-involving retinal edema secondary to DME based on investigator review of SD-OCT.
4. Central subfield thickness on SDOCT of greater than or equal to 325 microns on Spectralis or 300 microns on Cirrus.
5. E-ETDRS or ETDRS best-corrected visual acuity of 20/400 or better in the study eye.
6. Willing, committed, and able to return for study-related visits and complete all study related procedures.
7. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member) understand and willing to sign the informed consent form.

Exclusion Criteria

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

1. **Any prior or concomitant therapy with another investigational agent to treat DME in the study eye.**
2. **Prior panretinal photocoagulation in the study eye.**
3. **Prior intravitreal anti-VEGF therapy in the study eye within 12 weeks of the run-in/screening visit.**
4. **Prior focal/grid laser photocoagulation in the study eye.**
5. **Prior history of intravitreal steroid therapy in the study eye.**

6. Any history of severe allergy to fluorescein sodium (e.g., anaphylaxis, difficulty breathing) or other reason that the patient is unable to undergo fluorescein angiography (e.g., inability to get vascular access, unable to tolerate procedure). If allergy is mild and investigator believes can be pretreated with diphenhydramine to avoid allergic response, this is not an exclusion to enrollment.
7. Uncontrolled glaucoma at baseline evaluation (defined as intraocular pressure ≥25 mmHg despite treatment with anti-glaucoma medication) and/or cup-to-disc ratio greater or equal to 0.8 in the study eye.
8. Active intraocular inflammation in either eye.
9. Active ocular or periocular infection in either eye.
10. Torn or ruptured posterior lens capsule in study eye. Laser capsulotomy is not a contraindication.
11. Prior systemic anti-VEGF therapy, investigational or FDA-approved, is only allowed up to 3 months prior to Screening visit (i.e., Month -1), and will not be allowed during the study.
12. Significant vitreous hemorrhage obscuring view to the macula or the retinal periphery as determined by the investigator on clinical exam and ultra-widefield angiography, in study eye.
13. Presence of other causes of macular edema, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, choroidal neovascularization, age-related macular degeneration or multifocal choroiditis in the study eye. Epiretinal membranes are allowed.
14. Presence of macula-threatening traction retinal detachment in the study eye.
15. Prior vitrectomy in the study eye.
16. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
17. Any history of macular hole of stage 2 and above in the study eye.
18. Any intraocular or periocular surgery within 3 months of Screening visit (i.e., Month -1) in the study eye, except lid surgery, which may not have taken place within 1 month of Screening visit (i.e., Month -1), as long as it's unlikely to interfere with the injection.
19. Prior trabeculectomy or other filtration surgery in the study eye.
20. Any ocular or periocular infection within the last 2 weeks prior to Screening in either eye.
21. Any history of uveitis in either eye.
22. Active scleritis or episcleritis in either eye.
23. Presence or history of scleromalacia in either eye.

24. Aphakia in the study eye.
25. Previous therapeutic radiation in the region of the study eye.
26. History of corneal transplant or corneal dystrophy in the study eye.
27. Significant media opacities, including cataract, in the study eye which might interfere with visual acuity, assessment of safety, or fundus photography.
28. Any concurrent intraocular condition in the study eye (e.g. cataract) that, in the opinion of the investigator, could require either medical or surgical intervention during the study period.
29. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the subject 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.
30. Participation as a subject in any clinical study within the 12 weeks prior to Screening visit (i.e., Month -1).
31. Any systemic therapy with an investigational agent in the past 3 months prior to Screening visit (i.e., Month -1).
32. Any history of allergy to povidone iodine.
33. Pregnant or breast-feeding women
34. 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 visit (i.e., Month -1); intrauterine device [IUD]; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly)

*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 who are amenorrheic for at least 12 months, have a documented hysterectomy, have a documented tubal ligation.

3.3 Premature Withdrawal from the Study

A subject 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 subject from the study in the event of an intercurrent illness, AE, treatment failure, protocol violation, cure, and for administrative or other reasons. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of subject should be avoided.

Should a subject (or a subject's legally authorized guardian or representative) decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible.

3.4 Replacement of Subjects

Subjects prematurely discontinued from the study will be allowed to be replaced if they have not completed at least month 3 (Visit 4) of the study.

4. STUDY TREATMENTS

- Subjects will be treated at a single run-in visit (i.e., Screening visit/Month -1) with 2 mg intravitreal aflibercept.
- If the DME resolves as determined by the investigator (e.g., complete resolution of foveal cystic changes), subjects will be exited from the study after completing the Month 0/Visit 1 encounter. Those subjects will have all imaging completed, but no treatment will be performed at month 0.
- If significant foveal-involving DME remains at randomization visit (Month 0) based on investigator discretion following initial aflibercept therapy at screening visit (Month -1), the subject will be randomized into 1 of 2 groups. "Significant foveal-involving DME" in this case will be determined by the investigator, this may include OCT-based criteria such as central subfield thickness with associated DME or central foveal location of DME that is thought to be visually/clinically significant to merit ongoing treatment. Based on randomization at Month 0 they will be followed monthly and treated as follows:
    - Group A: Intravitreal dexamethasone implant given at month 0. PRN intravitreal dexamethasone implant given if 10 weeks or more since last dex implant. If < 10 weeks, PRN aflibercept given.
    - Group B: Intravitreal aflibercept given at month 0. PRN intravitreal Aflibercept given at months 1-6.
- PRN therapy as outlined above will be administered for the following indications:
    - Loss of 5 or more ETDRS letters from best previous measurement associated with foveal-involving macular edema.
    - Foveal-involving macular edema (i.e., foveal cystic changes) with central subfield thickness greater than 325 microns on Spectralis or 300 microns on Cirrus.
    - At investigator's discretion for other causes where therapy may be beneficial (e.g., vitreous hemorrhage, visually significant foveal-involving edema with central subfield thickness less than or equal to 325 microns).

4.1 Dose Modification and Stopping Rules

4.1.1 Dose Modification

Dose modification for an individual subject is not allowed.

4.2 Method of Treatment Assignment

All subjects who remain eligible after the run-in visit will be randomized to group A or group B based on a randomization table that will be distributed through the coordinating center (Cole Eye Institute, Cleveland clinic). The randomization group assignment will be given the site prior to the randomization visit for each subject.

4.2.1 Blinding/Masking

This is an open-label study and there is no blinding or masking for the study.

4.2.2 Storage

The dexamethasone implant and aflibercept will be stored according to manufacturer's guidelines.

4.2.3 Treatment Accountability

All drug treatments will be logged on the case report form and in the medical record.

4.3 Concomitant Medications and Procedures

Subjects may not receive any medications (approved or investigational) for their DME in the study eye other than the assigned study treatment until they have completed the end of study (6 months) or ET visit assessments. Laser photocoagulation procedures will not be allowed during the first six months of the study in the study eye, unless the investigator believes it is necessary due to severity of disease activity

If a subject's fellow (non-study) eye requires treatment for DME study entry, or during the subject's participation in the study, the fellow eye can receive therapy with any standard-of-care medication, at investigator discretion. The fellow eye may also receive laser photocoagulation, as needed, at investigator discretion. These treatments will not be considered part of this study.

4.3.1 Permitted Medications and Procedures

Any other medication that are considered necessary for the subject'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.

4.3.2 Prohibited Medications

Systemic anti-VEGF therapy is prohibited from use during the subject's study participation. Subjects may be early termed from study to receive systemic anti-VEGF therapy.

5. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

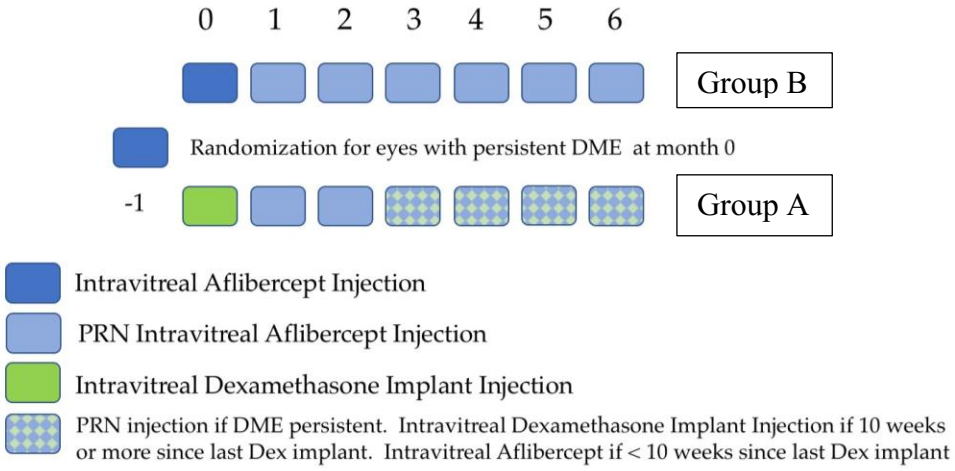
5.1 Schedule of Events

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

Study Design:

Group A (bottom row): Dexamethasone injection at baseline after run-in visit

Group B (top row): Aflibercept injection at baseline after run-in visit



PRN therapy in both groups will be indicated as outlined below:

- Loss of 5 or more ETDRS letters from best previous measurement associated with foveal-involving macular edema
- Foveal-involving macular edema (i.e., foveal cystic changes) with central subfield thickness greater than 325 microns on Spectralis or 300 microns on Cirrus.
- At investigator's discretion for other causes where therapy may be beneficial (e.g., vitreous hemorrhage, visually significant foveal-involving edema with central subfield thickness less than or equal to 325 microns)

Table 1 Schedule of Events

Study Procedure	Run-in		Treatment Period (Visit intervals after baseline are 28 days since last visit +/- 7 days)					Additional	
	Screening /Run-in Visit 0	Randomization Baseline Visit 1	2	3	4	5	6	End of Treatment Visit 7	Unscheduled Follow up Visit
Day/Month	Month -1	Month 0 28 days +/- 7 days	M 1 28 days +/- 7 days	M 2 28 days +/- 7 days	M 3 28 days +/- 7 days	M 4 28 days +/- 7 days	M 5 28 days +/- 7 days	Month 6 28 days +/-7 days	NA
Inclusion/Exclusion	x	x							
Informed Consent	x								
Medical History	x								
Blood Pressure	x							x	
Weight/Height	x								
Urine Pregnancy Test	x								
Demographics	x								
ETDRS with Autorefraction/Slit Lamp/Tonometry/ Fundus Exam study eye	x	x	x	x	x	x	x	x	x
Ultra-widefield Fluorescein angiogram study eye	x	x			x			x	
Optos Fundus Photography study eye	x	x			x			x	
Zeiss 7-Field Fundus Photography study eye	x							x	
SDOCT study eye	x	x	x	x	x	x	x	x	x (optional)
OCT angiography study eye	x	x			x			x	
Administer Study Drug study eye	x	x	*	*	*	*	*	*	
Aqueous Sample study eye	x	x	x**						
Adverse Events	x	x	x	x	x	x	x	x	x

* Additional treatment determined as follows:

- Group A: Intravitreal dexamethasone implant given at month 0. PRN intravitreal dexamethasone implant given if 10 weeks or more since last dex implant. If < 10 weeks, PRN aflibercept given.
- Group B: Intravitreal aflibercept given at month 0. PRN intravitreal Aflibercept given at months 1-6.
- PRN dosing for both groups based on criteria outlined in the study.

** If injection performed

5.2 Study Visit Descriptions

5.2.1 Screening/Run-in Visit, Month -1

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

- Inclusion/exclusion
- Informed consent documentation
- Demographics
- Medical history and concurrent illnesses
- Blood pressure
- Weight/height
- Urine pregnancy test
- Concomitant medications

The following procedures and assessments will be conducted of the study eye:

- ETDRS or E-ETDRS visual acuity with preferred refraction technique (i.e. autorefraction, manifest refraction)
- Tonometry
- Slit lamp examination
- Fundus examination
- Spectral Domain OCT
- OCT angiography
- Ultra-widefield Optos fluorescein angiogram
- Ultra-widefield Optos fundus photographs
- 7-field Zeiss fundus photographs
- Aqueous fluid sampling
- Adverse events review
- Intravitreal aflibercept injection

5.2.2 Randomization/Baseline Visit, Month 0 (28 +/- 7 Days)

- Inclusion/exclusion
- Concomitant medications
- Adverse events review

The following procedures and assessments will be conducted of the study eye:

- ETDRS or E-ETDRS visual acuity with preferred refraction technique (i.e. autorefraction, manifest refraction)
- Tonometry
- Slit lamp examination
- Fundus examination
- Spectral Domain OCT
- OCT angiography
- Ultra-widefield fluorescein angiogram
- Fundus photography with Optos ultra-widefield photos.
- If the DME resolves as determined by the investigator (e.g., complete resolution of foveal cystic changes), subjects will be exited from the study after completing the Month 0/Visit 1 encounter. Those subjects will have all imaging completed, but no treatment will be performed at month 0.
- If significant foveal-involving DME remains at randomization visit (Month 0) based on investigator discretion the subject will be randomized into 1 of 2 groups. "Significant foveal-involving DME" in this case will be determined by the investigator, this may include OCT-based criteria such as central subfield thickness with associated DME or central foveal location of DME that is thought to be visually/clinically significant to merit ongoing treatment.
    - Treatment based on group randomization.
- Aqueous fluid sampling.

5.2.3 Follow-up Period

5.2.3.1 Month 1--Month 5 (28 +/- 7 Days)

The following information will be collected:

- Concomitant medications
- Adverse events review

The following procedures and assessments will be conducted of the study eye:

- ETDRS or E-ETDRS visual acuity with preferred refraction technique (i.e. autorefraction, manifest refraction)
- Tonometry
- Slit lamp examination
- Fundus examination

- Spectral Domain OCT
- OCT angiography (month 3/visit 4 only)
- Ultra-widefield fluorescein angiography (month 3/visit 4 only)
- Fundus photography with Optos ultra-widefield photos (month 3/visit 4 only)
- PRN therapy based on treatment group criteria.
- Aqueous fluid sampling at month 1/visit 2 only, if injection performed.

5.2.3.2 End of Treatment/Month 6 (28 +/- 7 Days))/Early Termination visit

The following information will be collected:

- Concomitant medications
- Blood pressure
- Adverse events review

The following procedures and assessments will be conducted of the study eye:

- ETDRS or E-ETDRS visual acuity with preferred refraction technique (i.e. autorefraction, manifest refraction)
- Tonometry
- Slit lamp examination
- Fundus examination
- Spectral Domain OCT
- OCT angiography
- Ultra-widefield fluorescein angiography
- Ultra-widefield Optos fundus photographs
- 7-field Zeiss fundus photographs
- PRN therapy based on treatment group criteria.

5.2.4 Additional Visits

5.2.4.1 Unscheduled visit

The following information will be collected:

- Concomitant medications
- Adverse events review

The following procedures and assessments will be conducted of the study eye:

- ETDRS or E-ETDRS visual acuity with preferred refraction technique (i.e. autorefraction, manifest refraction)
- Tonometry
- Slit lamp examination
- Fundus examination
- Spectral Domain OCT (at investigator discretion)

5.2.5 Early Termination Visit

Subjects who are withdrawn from the study should be instructed to return to the clinic for end of study assessments.

5.2.6 Unscheduled Visits

All attempts should be made to keep subjects on the study schedule. Unscheduled visits may be necessary to repeat testing following AEs, or for any other reason, as warranted.

5.2.7 Missed/Out-of-window Visits

All attempts should be made to keep subjects on the study schedule. If a subject returns late (i.e., out-of-window), that visit will be designated as the first missed visit and the study calendar will reset. As an example, if a subject returns 45 days after the scheduled visit 2, that visit will be considered visit 2. Visit 3 will then be scheduled 28 days +/- 7 days after the date of the new visit 2 date.

5.3 Study Procedures

5.3.1 Procedures Performed only at the Screening/Baseline Visit

No specific procedures other than above will be performed for the sole purpose of determining study eligibility or characterizing the baseline population.

5.3.2 Efficacy Procedures

Vision: Visual Acuity Visual function of the study will be assessed using either the E-ETDRS chart or the ETDRS chart utilizing autorefraction or manifest refraction procedure based on the sites preference.

Spectral Domain Optical Coherence Tomography (OCT): Retinal characteristics will be evaluated using SDOCT on the study eye. The Cirrus OCT (Zeiss) or Spectralis, (Heidelberg) will be used for the study. The study imaging protocol should be referenced for imaging protocols. The same OCT machine should be used for the same subject at all visits.

Fundus Evaluation, Fundus Photography, and Fluorescein Angiography (FA):

Fundus photography with the Optos system will be performed at all designated photography timepoints. In addition to the Optos images, fundus photography with the standard 7-field images will be performed at the screening/run-in visit (Month -1) and at study exit. Ultra-widefield fluorescein angiography (California, Optos) will be performed at the screening/run-in visit (Month -1), baseline/randomization visit (Month 0), month 3, and month 6. Spectral domain OCT angiography will be performed at screening/run-in visit (Month -1), baseline/randomization visit (Month 0), month 3, and month 6. The study imaging protocol should be referenced for imaging protocols.

Intraocular Pressure:
Intraocular pressure (IOP) of the study eye will be measured using applanation tonometry or Tonopen. The same method of IOP measurement must be used in each subject throughout the study.

Slit Lamp Exam:
Slit lamp exam (SLE) of the study eye will include evaluation of the cornea, anterior chamber, and lens status with cataract grading (if applicable).

Fundus Exam:
Fundus examination of the study eye will be performed to assess the vitreous, optic nerve, macula, retinal vasculature, and retinal periphery.

5.3.3 Safety Procedures

5.3.3.1 Adverse Event Information Collection

The investigator (or designee) will record all AEs that occur during the study following the run-in visit.

The definition of an AE and SAE, and information on the determination of severity and relationship to treatment are provided in section 6.

6. SAFETY DEFINITIONS, REPORTING, AND MONITORING

6.1 Definitions

6.1.1 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.

6.1.2 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.

6.2 Recording and Reporting Adverse Events

All AEs and SAEs will be recorded in the patient's source documents. Laboratory values or vital signs will be recorded as AEs only if they are medically relevant.

The investigator will promptly report to the IRB all unanticipated problems involving risks to subjects. This includes death from any cause and all SAEs related to the use of the study drugs. All SAEs will be reported to the IRB, regardless of assessed causality.

These should be reported to the local IRBs and to the sponsor (Cleveland Clinic).

6.2.1 Recording and Reporting Serious Adverse Events.

Sites shall disclose to the pertinent IRB any SAEs that occur during the course of the Study as outlined in 6.1.2 within 24 hours of first knowledge of the SAE.

In addition to reporting to the IRB, the site shall disclose the SAE to the sponsor (Cleveland Clinic) within 24 hours of first knowledge of the SAE. And will provide relevant details regarding the SAE as needed to the sponsor.

In addition, sites will provide notice to the sponsor within twenty-four (24) hours of any occurrence of either pregnancy or lactation during study enrollment.

6.2.2 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.

6.3 Evaluation of Severity and Causality

6.3.1 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 CRF 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.

6.3.2 Evaluation of Causality

The relationship to treatment will be determined by the investigator and reported on the CRF 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.

7. STUDY VARIABLES

7.1 Demographic and Baseline Characteristics

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

7.2 Primary and Secondary Endpoints

Primary Endpoint:

- The primary study endpoint is the mean change in central subfield thickness at 6 months.

Secondary Endpoints:

- Number of Injections at 6 months
- Change in BCVA at 6 months
- Change in leakage index at 6 months
- Change in ischemic index at 6 months
- Change in microaneurysm counts at 6 months
- Change in ellipsoid zone integrity at 6 months
- Change in intraretinal fluid metrics at 6 months.
- Change in DRSS at 6 months
- The incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs at 6 months.

Exploratory Endpoints:

- Radiomics and machine learning assessments of angiographic, SD-OCT, and OCT angiographic features.
- Correlation of cytokine expression profiles and treatment response.
- Correlation of cytokine expression profiles with imaging features.

7.3 Statistical Methods

7.3.1 Demography and Baseline Characteristics

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.

7.3.2 Efficacy Analyses

7.3.2.1 Primary Efficacy Analysis

- The primary efficacy variable is the mean change in central subfield thickness at 6 months.

7.3.2.2 Secondary Efficacy Analysis

Secondary efficacy variables include the following:

- Number of Injections at 6 months
- Change in BCVA at 6 months
- Change in leakage index at 6 months

- Change in ischemic index at 6 months
- Change in microaneurysm counts at 6 months
- Change in ellipsoid zone integrity at 6 months
- Change in intraretinal fluid metrics at 6 months.
- Change in DRSS at 6 months
- The incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs at 6 months.

7.3.3 Safety Analysis

7.3.3.1 Adverse Events

Analysis

- Incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs

8. 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 Cleveland Clinic.

The CRF data for this study will be collected with a paper Data Capture tool. These CRF paper capture tools will be scanned and e-mailed to Cleveland Clinic. A lead coordinator e-mail address will be provided to the Sites for sending the CRFs. A digital cloud-based database may also be utilized.

No patient-identifier information should be provided to the Cleveland Clinic from the sites.

8.1 Electronic Systems

Electronic systems used to process and/or collect data in this study will include, but not be limited to the following:

- EMR system or medical record system
- Statistical analysis software – statistical review and analysis
- An electronic database system for logging study-related data for central data storage.
- Image transfer will be accomplished through electronic transfer process agreed upon by the site and the Cleveland Clinic. All image files will be de-identified by the site prior to transfer to Cleveland Clinic

9. STUDY MONITORING

9.1 Monitoring of Study Sites

The site will designate an internal monitor from the site for review of the study documents every 3 months following study initiation and until final subject completion. In accordance with International Conference on Harmonization (ICH) guidelines, the coordinator will compare the CRF entries with the appropriate source documents. The local monitor will provide a scanned/electronic monitoring report to the central data coordinating center (Cleveland Clinic) by e-mail following completion of each monitoring review. Study monitoring may include, but is not limited to, subject ICFs, documentation of subject recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability, as relevant. In addition, the central coordinating site/sponsor reserves the right to perform additional monitoring of any peripheral sites, if deemed necessary based on previous monitoring reports. The coordinating center will work with the local sites to coordinate monitoring visits and the local site will provide access to needed study documents and source materials. In addition, the Cleveland Clinic will review each CRF for data completion

9.2 Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate subject records (source documents).

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

The central coordinating center may request any source documents as part of a monitoring process and validation of the case report form. The central coordinating center will not store identifiable subject information, as possible.

9.3 Case Report Form Requirements

A CRF for each subject enrolled in the study must be completed and signed by the study investigator or authorized designee for each visit. The CRF must be typed or filled out using indelible ink. The writing must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or authorized designee. The investigator must ensure the accuracy, completeness, legibility, and timeliness of the data reported to the designee in the CRFs. Case report forms must be available at all times for inspection by authorized representatives of the designee and regulatory authorities.

Tentatively, CRF from remote sites will be scanned and e-mailed to the central coordinating site for entry into an electronic database.

All Serious Adverse Events must be reported to the Cleveland Clinic within 24 hours of the site investigator becoming aware of the event

9.4 Study imaging transfer requirements

Imaging data, including SD-OCT, UWFA, Fundus photos and OCTA data will be acquired using a separately provided imaging protocol guideline. This will be provided by the sponsor to the sites. Imaging data will be exported and transferred to the reading center/sponsor in the methods outlined in the imaging protocol and as agreed upon by the site and Cleveland Clinic.

9.5 Aqueous sample storage and transfer

Aqueous samples will be stored in a PHI de-identified method using the visit number and study ID number as sample identifiers. These will be stored based on standard site procedures in a deep ultra-low temperature freezer (i.e., -80 degree Celsius, -20 degree Celsius) until transfer for analysis as directed by the sponsor (i.e., Cleveland Clinic).

10. AUDITS AND INSPECTIONS

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

- Informing the designee of a planned inspection by the authorities as soon as notification is received, and authorizing the designee's participation in the inspection
- 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 designee immediately
- Taking all appropriate measures requested by the designee to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, 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 subject to inspection. In addition, representatives of the designee may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

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

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Good Clinical Practice Statement

It is the responsibility of both the designee and 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.

11.2 Informed Consent

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each subject 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 subject in language that he/she can understand. The ICF should be signed and dated by the subject and by the investigator or authorized designee who reviewed the ICF with the subject.

- Subjects who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Subjects 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 must be retained by the investigator as part of the subject's study record, and a copy of the signed ICF must be given to the subject.

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

11.3 Subject Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study subject will be maintained. Subjects should be identified by their initials and a subject identification number, only, on CRFs or other documents submitted to the designee. Documents that will not be submitted to the designee (e.g., signed ICF) must be kept in strict confidence.

The subject's and investigator's personal data, which may be included in the investigator's study database, will be treated in compliance with all applicable laws and regulations. The investigator shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

11.4 Institutional Review Board

For each clinical site, an appropriately constituted IRB, as described in ICH Guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the subjects (e.g., advertising) before any subject 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 subjects, in which case the IRB should be informed as soon as possible

- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the local IRB and the sponsor should be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical study.

Records of the IRB review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator. IRB communications should also be provided to the Cleveland Clinic with any protected health information eliminated.

12. PROTOCOL AMENDMENTS

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

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

13.1 Premature Termination of the Study

Cleveland Clinic has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others.

14. STUDY DOCUMENTATION

14.1 Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the designee with the final set of CRFs for each subject.

14.2 Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs 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. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

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