Diabetic Retinopathy Clinical Research Network

Short-term Evaluation of Combination Corticosteroid+Anti-VEGF Treatment for Persistent Central-Involved Diabetic Macular Edema Following Anti-VEGF Therapy

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BACKGROUND INFORMATION AND STUDY SYNOPSIS

1.1 Rationale

1.1.1 Public Health Impact of DME

The age-adjusted incidence of diabetes mellitus in the United States has reportedly doubled in recent history,[1] and estimates suggest that by the year 2030, approximately 439 million individuals worldwide will be affected by this chronic disease.[2] The increasing global epidemic of diabetes implies an associated increase in rates of vascular complications from this chronic disease, including diabetic retinopathy. Despite advances in diagnosis and management of ocular disease in patients with diabetes, eye complications from diabetes mellitus continue to be the leading cause of vision loss and new onset blindness in working-age individuals throughout the United States.[3]

Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision. In a review of three early studies concerning the natural history of DME, Ferris and Patz found that 53% of 135 eyes with DME, presumably all involving the center of the macula, lost two or more lines of visual acuity over a two-year period.[4] Without intervention, 33% of 221 eyes included in the Early Treatment Diabetic Retinopathy Study (ETDRS) with center-involved DME experienced "moderate visual loss" (defined as a 15 or more letter score decrease in visual acuity) over a three-year period.[5]

1.1.2 Rationale for Anti-VEGF Treatment for DME

DME results from abnormal leakage of fluid and macromolecules, such as lipoproteins, from retinal capillaries into the extravascular space. This is followed by an influx of water into the extravascular space due to increased oncotic pressure.[6] The retinal pigment epithelium normally acts as a barrier to fluid flow from the choriocapillaris to the retina and also actively pumps fluid out of the retina. Thus, abnormalities in the retinal pigment epithelium may contribute to DME by allowing increased fluid access from the choriocapillaries or decreasing the normal efflux of fluid from the retina.[6] The mechanism of breakdown of the blood retina barrier at the level of the retinal capillaries and the retinal pigment epithelium may be mediated by changes in tight junction proteins such as occludin.[7]

Vascular endothelial growth factor (VEGF), a 45 kD homodimeric glycoprotein, potently increases retinal capillary permeability and subsequent retinal edema in part by inducing breakdown of the blood retina barrier.[8] Thus, agents that inhibit VEGF may reduce vascular permeability due to diabetes and thereby decrease retinal thickening.

1.1.3 Evolution of Standard Therapy for DME

For 25 years, focal/grid laser photocoagulation was the mainstay of treatment for DME. In the ETDRS, focal/grid photocoagulation of eyes with DME reduced the risk of moderate visual loss by approximately 50% (from 24% to 12%) three years after initiation of treatment.[9] A modified ETDRS focal/grid photocoagulation protocol adapted from the original ETDRS approach has been adopted as the standard laser technique for DME used in all Diabetic Retinopathy Clinical

Research Network (DRCR.net) studies. The DRCR.net trial, "A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Focal/grid Photocoagulation for DME", showed that efficacy over 2 years of use with the DRCR.net focal/grid laser technique was comparable to results in similar eyes in the ETDRS, and that intravitreal triamcinolone as monotherapy was not superior to use with the DRCR.net focal/grid laser technique for central-involved DME in eyes with some visual acuity loss.[10,11]

Results from a more recent DRCR.net study, "Intravitreal Ranibizumab or Triamcinolone Acetonide in Combination with Laser Photocoagulation for Diabetic Macular Edema"(DRCR.net Protocol I), indicated that treatment for DME with intravitreal anti-VEGF therapy (0.5 mg ranibizumab) plus deferred (≥24 weeks) or prompt focal/grid laser provides visual acuity outcomes at one year and two years that are superior to prompt focal/grid laser alone or intravitreal triamcinolone with prompt focal/grid laser.[12] DRCR.net Protocol I provided definitive confirmation of the important role of VEGF in DME and the role of anti-VEGF drugs in the treatment of DME. The study enrolled 854 eyes of 691 study participants with DME involving the fovea and with visual acuity (approximate Snellen equivalent) of 20/32 to 20/320. Eyes were randomized to sham injection+prompt focal/grid laser (N = 293), 0.5-mg ranibizumab+prompt laser (within 3 to 10 days, N = 187), and 0.5-mg ranibizumab+deferred laser (deferred for at least 24 weeks, N = 188). Treatment with ranibizumab was generally continued on a monthly basis unless the participant's vision stabilized or reached 20/20, or the retinal swelling resolved or no longer improved. Treatment could be stopped if failure criteria were met (persistent swelling with poor vision), but this occurred in very few participants (less than 5% in any group). The mean change (± standard deviation) in visual acuity letter score at one year from baseline was significantly greater in the ranibizumab+prompt laser group (+9 ± 11) and the ranibizumab+deferred laser group (+9 ± 12) as compared with the control laser group (+3 ± 13, $P < 0.001$ for both comparisons) or triamcinolone+prompt laser group (+4 ± 13, $P < 0.001$ for both comparisons). The one-year optical coherence tomography (OCT) results paralleled the visual acuity results in the ranibizumab and control laser groups. No apparent increases in treatment-related systemic events were observed.

DRCR.net Protocol I results provided confirmation of the promising role of ranibizumab therapy suggested by phase 2 trials[13, 14] and have been further supported by findings from additional phase III trials, including RISE, RIDE and RESTORE.[15, 16] Participants in RISE and RIDE were randomized to every 4 week 0.5 or 0.3 mg ranibizumab for at least 2 years versus sham injections as treatment for center-involved DME causing vision impairment, with macular laser available to all treatment arms starting 3 months after randomization. The percentage of individuals gaining ≥ 15 letters from baseline at 24 months was significantly higher in the ranibizumab groups in both studies (RISE: sham- 18.1%, 0.3mg ranibizumab- 44.8%, 0.5mg ranibizumab 39.2%; RIDE sham- 12.3%, 0.3mg ranibizumab- 33.6%, 0.5mg ranibizumab 45.7%).[15] In RESTORE, both ranibizumab (0.5mg) monotherapy and combination ranibizumab+laser treatment resulted in better visual acuity outcomes than laser alone at one year in patients with center-involved DME causing vision impairment.[16] The percentage of participants who gained ≥ 15 letters from baseline at month 12 were 22.6%, 22.9% and 8.2% in the ranibizumab alone, ranibizumab+laser and laser alone groups, respectively. In general, ranibizumab therapy was well-tolerated in these studies, although the overall rate of Antiplatelet Trialists' Collaboration events was slightly higher in the 0.3 mg (5.6%) and 0.5 mg (7.2%)

groups as compared with the sham group (5.2%) in the pooled data from the RISE and RIDE studies.[17] Deaths were also more frequent in the ranibizumab groups (0.8% and 1.6% of sham and 2.4-4.8% of ranibizumab treated patients) in these trials.[15] The rate of non-fatal cerebrovascular events in this pooled analysis was higher in the 0.5mg group (2%) than in the sham (1.2%) or 0.3mg group (0.8%) but the rate of non-fatal myocardial infarctions was similar across treatment groups (2.8%, 2.8% and 2.4% in the sham, 0.3mg and 0.5mg groups, respectively).

1.1.4 Eyes with Persistent DME following Therapy with Anti-VEGF Drugs

Although the studies described above have clearly demonstrated that anti-VEGF therapy is efficacious for improving vision and decreasing retinal thickness in eyes with center-involved DME, there is clearly a subgroup of eyes that do not respond completely to anti-VEGF therapy for DME. Indeed, in DRCR.net Protocol I over 50% of ranibizumab-treated eyes did not achieve a 2 or more line improvement in visual acuity from baseline at 2 years and more than 40% did not achieve complete resolution of retinal thickening (time domain [TD] OCT central subfield [CSF] thickness <250 microns) by 2 years.[18] Of eyes that were edematous (CSF thickness on TD OCT ≥ 250 microns) with visual acuity of 20/32 or worse at the 6-month study visit (N = 145), 83% - 90% were also thickened at 1 month and subsequent follow-ups. Seventy-three percent of these eyes had CSF thickness ≥ 250 microns at all study visits prior to 6 months. Of eyes that were edematous with visual acuity worse than 20/32 at 1 year, 72%-82% of eyes were thickened at 6 months and subsequent follow-ups. Forty-eight percent of these eyes had ≥ 250 microns at all study visits prior to 1 year. These results suggest that eyes that remain edematous at 6 months and 1 year following anti-VEGF treatment have for the most part been consistently thickened throughout the treatment period. More recently in a prospective randomized trial of 63 eyes with DME assigned to monthly intravitreal injections of 1.5 mg bevacizumab or 0.5 mg ranibizumab if CSF thickness on spectral-domain OCT was >275µm, 59% and 37% of bevacizumab and ranibizumab eyes respectively had CSF thickness of >275 µm at 48 weeks.[19] In summary, there is a need to explore alternative or additional therapies for DME for eyes with persistent thickening after anti-VEGF treatment.

1.1.5 Rationale for Corticosteroid Treatment for DME

Corticosteroids ("steroids"), a class of substances with anti-inflammatory properties, have been demonstrated to inhibit the expression of the VEGF gene.[20] In a study by Nauck et al, the platelet-derived growth-factor (PDGF) induced expression of the VEGF gene in cultures of human aortic vascular smooth muscle cells, which was abolished by corticosteroids in a dose-dependent manner.[20] A separate study by Nauck et al demonstrated that corticosteroids abolished the induction of VEGF by the pro-inflammatory mediators PDGF and platelet-activating factor (PAF) in a time and dose-dependent manner.[21] The study was performed using primary cultures of human pulmonary fibroblasts and pulmonary vascular smooth muscle cells.

As discussed above, corticosteroids have been experimentally shown to down regulate VEGF production and possibly reduce breakdown of the blood-retinal barrier. Similarly, steroids have anti-angiogenic properties, possibly due to attenuation of the effects of VEGF.[22, 23] Both of these steroid effects have been utilized. For example, triamcinolone acetonide is often used clinically as a periocular injection for the treatment of cystoid macular edema (CME) secondary to uveitis or as a result of intraocular surgery.[24, 25] In animal studies, intravitreal triamcinolone acetonide

has been used in the prevention of proliferative vitreoretinopathy[26] and retinal neovascularization.[27, 28] In addition, intravitreal triamcinolone acetonide has been used clinically in the treatment of proliferative vitreoretinopathy[29] and choroidal neovascularization.[30-32]

Although steroid-associated reduction of vascular permeability in eyes with DME is thought to be mediated at least partially through the regulation of VEGF, steroids have a wide-range of anti-inflammatory actions that include direct effects on leukostasis, ICAM-1 expression, and production of tight junction proteins, some of which may be upstream or independent of VEGF pathways.[33-35] Therefore, rationale exists to assess whether intravitreal steroid treatment combined with anti-VEGF therapy is more efficacious in reducing center-involved DME than anti-VEGF therapy alone.

Multiple studies, including two phase III randomized controlled trials conducted by the DRCR.net have demonstrated that there is a short-term early increase in visual acuity with intravitreal steroid treatment for DME. Although the DRCR.net Protocol B study ("A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Laser Photocoagulation for Diabetic Macular Edema") found that monotherapy with intravitreal steroid is not as efficacious as monotherapy with laser treatment alone,[10] there are data to suggest that adjunctive therapy with intravitreal steroid may have a role in selected eyes with DME. In Protocol I, eyes that were pseudophakic at baseline that were treated with intravitreal triamcinolone and laser appeared to have similar visual acuity and OCT results as the anti-VEGF-treated eyes.[12] Since this study is a phase II trial, it will assess a proof of concept for beneficial effect of the combination corticosteroid+anti-VEGF agents. Although this study will include both phakic and pseudophakic eyes, the short-term primary outcome at 6 months is not expected to be affected by the potential cataract development that is associated with corticosteroid use. Should this study show beneficial effect of the combination corticosteroid+anti-VEGF agents in eyes with persistent DME short-term, a future longer term phase III trial may be designed to further assess the efficacy and safety of this regimen long-term.

Since eligible eyes for this study can be pseudophakic, there is a potential for their macular edema to have an inflammatory component from prior cataract surgery in addition to the DME. Therefore, eligibility criteria will require that if cataract surgery has been performed, it must have been performed at least 9 months before randomization (6 months before enrollment), to reduce the chance of a post-cataract surgery macular edema (Irvine-Gass Syndrome) being present at baseline.

1.1.6 Combination Steroid and Anti-VEGF treatment for DME

Several studies have been reported on combined steroid and anti-VEGF treatment for DME.[36-40] Some studies have suggested that there may be benefits with the combined bevacizumab/triamcinolone as compared with bevacizumab treatment alone that include earlier visual improvement and longer maintenance of treatment effect.[38, 39] However, other studies do not suggest substantive additional benefit in visual outcome or thickening with combination steroid/anti-VEGF treatment over anti-VEGF treatment alone. One such study randomized 150 eyes to treatment with intravitreal bevacizumab alone, combined intravitreal bevacizumab and triamcinolone, or macular focal or modified grid laser.[36] Although intravitreal bevacizumab treatment yielded better visual outcomes as compared with macular laser treatment, no additional benefit in visual acuity or degree of retinal thickening was apparent when adjunctive

triamcinolone was also given. However, the triamcinolone dose utilized (2 mg) was half the dose that is commonly used in clinical practice for treatment of DME and a substantial proportion of the combined anti-VEGF/steroid group (26%) was lost to follow-up before the 36-week primary endpoint was achieved.

1.1.7 Available Steroids

There are several commercially available steroid preparations that have been used intravitreally. Currently available steroids include dexamethasone sodium phosphate, the dexamethasone intravitreal implant (Ozurdex), triamcinolone acetonide, and preservative-free triamcinolone (Triesence). Dexamethasone sodium phosphate is highly potent, but its use is limited by a very short half-life (~3.5 hours). Triamcinolone acetonide is readily available, but preservatives in the suspension may result in higher rates of pseudoendophthalmitis secondary to ocular inflammation. Preservative-free triamcinolone is less immunogenic and can be administered through a 27 or 30-gauge needle. Although cases have been reported of "blooming" of this steroid after injection, with rapid spread throughout the vitreous and consequent decreased vision and inability to evaluate the fundus, the steroid usually settles inferiorly after a period of time.

The steroid that will be used in this study will be the dexamethasone intravitreal implant (Ozurdex). This preparation provides sustained delivery of 700 µg of preservative-free dexamethasone, and has been approved by the United States Food and Drug Administration (FDA) for treatment of noninfectious posterior uveitis as well as macular edema due to retinal vein occlusion, and diabetic macular edema.[41-43] It is administered through a single-use 22 gauge injection system. In patients with diabetes, the implant has been evaluated in an open-label study of 55 eyes with persistent DME and a history of vitrectomy at least 3 months prior to the study enrollment visit.[44] Study eyes received a single intravitreal injection of the dexamethasone implant and were then followed over 26 weeks. Both central retinal thickness and mean visual acuity were significantly improved as compared with baseline beginning at week 1 with peak efficacy seen at week 8 (OCT CSF thickness mean change [95% confidence interval (CI)]: −156 µm [−190 to −122 µm], $P<0.001$; VA mean change [95% CI]: 6 letters [3.9 to 8.1 letters], $P<0.001$). At week 26 both retinal thickness and visual acuity were significantly better than baseline. The most common adverse events found in 10% or more of eyes were conjunctival hemorrhage (52.7%), conjunctival hyperemia (20.0%), eye pain (16.4%), increased IOP (16.4%), conjunctival edema (12.7%), and vitreous hemorrhage (10.9%). Of the 48 study participants who were not on IOP-lowering medication at baseline, 8 (17%) began on IOP-lowering medication during the study.

1.1.8 Summary of Rationale for the Study

Although anti-VEGF therapy is generally effective as treatment for center-involved DME, some anti-VEGF-treated eyes with DME do not achieve visual acuity of 20/20 or complete resolution of retinal thickening. Thus, there is a need for alternative or additional treatments that might improve visual acuity by reducing retinal edema in eyes with persistent DME despite previous anti-VEGF therapy. Intravitreal steroid is not as efficacious as ranibizumab in eyes with DME overall, but it has been shown to have a positive effect on DME in some eyes and might add benefit in eyes that are already receiving anti-VEGF. This proposed study will assess whether the addition of steroid to an anti-VEGF treatment regimen in eyes that have persistent DME despite

anti-VEGF treatment increases visual acuity and decreases DME in the short term, compared with continued anti-VEGF treatment alone.

1.2 Study Objectives

To assess the short-term effects of combination steroid+anti-VEGF therapy on visual acuity and retinal thickness on OCT in comparison with that of continued anti-VEGF therapy alone in eyes with persistent central-involved DME and visual acuity impairment despite previous anti-VEGF treatment.

Furthermore, this phase II study is being conducted (1) to determine whether the conduct of a phase III trial has merit based on functional and anatomic outcomes, (2) to estimate recruitment potential of a phase III investigation, (3) to provide information needed to design a phase III trial, and (4) to assess the safety of administering combination steroid+anti-VEGF therapy in eyes with persistent DME. The study is not designed to definitively establish the efficacy of corticosteroid+anti-VEGF therapy in the treatment of persistent central-involved DME.

1.3 Study Design and Synopsis of Protocol

A. Study Design

- Randomized, controlled phase II multi-center clinical trial

B. Major Eligibility Criteria

- Age ≥18 years
- Type 1 or type 2 diabetes
- The study eye must meet the following criteria:
  - Visual acuity letter score in study eye ≤ 78 and ≥24 (approximate Snellen equivalent 20/32 to 20/320)
  - Ophthalmoscopic evidence of center-involved DME
  - OCT CSF thickness value (microns):
    - Zeiss Cirrus: ≥290 in women; ≥305 in men
    - Heidelberg Spectralis: ≥305 in women; ≥320 in men
  - At least three intravitreal anti-VEGF injections given within the prior 20 weeks
  - No previous history of glaucoma or steroid intraocular pressure response in either eye

C. Run-In Phase

All potential study participants will be required to participate in a 12-week run-in phase. In order to enter the run-in phase, all eligibility criteria must be assessed and met. During the run-in phase, study eyes will receive 3 study ranibizumab 0.3mg injections approximately 4 weeks apart.

At the end of the run-in phase (12-week visit), eyes with persistent DME despite prior intravitreal anti-VEGF therapy that still meet eligibility criteria (see section 4.2) will be randomized. "Persistent DME" at end of the run-in phase is defined as meeting all of the following:

- CSF thickness (microns) on OCT meeting either one of the following two gender and OCT machine-specific criteria:
  - Zeiss Cirrus: ≥290 in women; ≥305 in men
  - Heidelberg Spectralis: ≥305 in women; ≥320 in men
- Visual acuity letter score ≤ 78 and ≥24 (approximate Snellen equivalent 20/32 to 20/320)
- DME is the cause of OCT thickening and vision loss by the investigator's judgment

D. Treatment Groups

Eligible study eyes at the end of the run-in phase will be assigned randomly (1:1) to one of the following groups:

- Group A: Sham + intravitreal ranibizumab
- Group B: Intravitreal dexamethasone +intravitreal ranibizumab

Study participants may have one or two study eyes. Study participants with two study eyes will be randomized to receive continued anti-VEGF therapy (ranibizumab) in one eye and dexamethasone +ranibizumab in the other eye.

For both treatment groups, the initial ranibizumab injections must be given on the day of randomization. The sham or dexamethasone injection will be given within 0-8 days of the ranibizumab injection. Study eyes will be evaluated for retreatment every 4 weeks based on OCT and visual acuity. Further details on the treatment schedule and criteria for retreatment are included in section 4.8.

E. Sample Size

A minimum of 150 study eyes (from approximately 125 participants assuming 20% have two study eyes)

F. Duration of Follow-up

- 12-week run-in phase prior to randomization
- Primary outcome at 24 weeks after randomization

G. Follow-up Schedule

- Follow-up visits occur every 4±1 weeks

H. Main Efficacy Outcomes

At 24 weeks after randomization:

<u>Primary</u>:

- Mean change in visual acuity letter score, adjusted for visual acuity at time of randomization

<u>Secondary</u>:

- Percent of eyes with at least 10 and at least 15 letter gain (increase) or loss (decrease) in E-ETDRS letter score visual acuity
- Visual acuity area under the curve (AUC) between randomization and 24 weeks
- Mean change in OCT CSF thickness, adjusted for thickness at time of randomization
- Percent of eyes with ≥1 and ≥2 logOCT step gain or loss in CSF thickness
- Percent of eyes with OCT CSF thickness (in micros) < the following gender and OCT machine-specific values: <290 in women and <305 in men in Zeiss Cirrus; <305 in women and <320 in men in Heidelberg Spectralis
- OCT CSF thickness AUC between randomization and 24 weeks
- Percent of eyes with worsening or improvement of diabetic retinopathy on clinical exam

I. Main Safety Outcomes

Injected-related: endophthalmitis, retinal detachment, retinal tears, intraocular hemorrhage, increased intraocular pressure

Ocular drug-related: inflammation, increased intraocular pressure, need for ocular anti-hypertensive, glaucoma surgery, or other IOP-lowering procedures, development or worsening of cataract and cataract extraction, intraocular hemorrhage, migration of dexamethasone to the anterior chamber and subsequent corneal complications

Systemic drug-related: Deaths, participants with at least one hospitialization, participants with at least one SAE, and cardiovascular events, and cerebrovascular events as defined by Antiplatelet Trialists' Collaboration

J. Schedule of Study Visits and Examination Procedures

Visit	Enroll in Run-In	Run-In Visits*	Randomization 0	4w-24w**
Visit Window		(+/− 1w)		(+/− 1w)
E-ETDRS best corrected visual acuity [a]	X	X	X	X
OCT [b]	X	X	X	X
Eye exam [c]	X	X	X	X
Blood pressure	X		X	
HbA1c[d]			X	

* Visits at 4 and 8 (±1) weeks during the run-in phase. Randomization visit (0) occurs at 12 (± 1) weeks from enrollment.

**Visits every 4 (±1) weeks post-randomization.

a= both eyes at each visit; includes protocol refraction in study eye at each visit and the non-study eye at the randomization visit and 24 week visit. E-ETDRS refers to electronic ETDRS testing using the Electronic Visual Acuity Tester that has been validated against 4-meter chart ETDRS testing.

b=study eye

c=both eyes at enrollment and randomization and study eye only at each follow-up visit. Includes slit lamp exam (including assessment of lens), measurement of intraocular pressure, and dilated ophthalmoscopy.

d=does not need to be repeated if HbA1c is available from within the prior 3 months. If not available, can be performed within 3 weeks after randomization.

1.4 General Considerations

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

The DRCR.net Procedures Manuals (Visual Acuity-Refraction Testing Procedures Manual, OCT Manuals, and Study Procedures Manual) provide details of the examination procedures and intravitreal injection procedure.

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

The participant will be masked to the treatment group assignment. Visual acuity testers (including refractionists) and OCT technicians will be masked to treatment group at the primary outcome visit (24 weeks). Investigators will not be masked to treatment group assignment.

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

A risk-based monitoring approach will be followed, consistent with the FDA “Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring” (August 2013).

The risk level is considered to be research involving greater than minimal risk.

Chapter 2.
STUDY PARTICIPANT ELIGIBILITY AND ENROLLMENT

2.1 Identifying Eligible Study Participants and Obtaining Informed Consent

A minimum of 150 eyes are expected to be enrolled into the randomization phase. Assuming that 20% of the study participants have two study eyes, this equates with an enrollment of about 125 study participants, with a goal to enroll an appropriate representation of minorities. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Study participants who have signed an informed consent form or are in the run-in phase can be randomized up until the end date, which means the recruitment goal might be exceeded.

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

Consent may be given in two stages (if approved by the IRB). The initial stage will provide consent to complete any of the screening procedures needed to assess eligibility that have not already been performed as part of a usual-care exam. The second stage will be obtained prior to enrollment into the run-in phase and will be for participation in the study, including the post-randomization phase. A single consent form will have two signature and date lines for the study participant: one for the study participant to give consent for the completion of the screening procedures and one for the study participant to give consent for the randomized trial. Study participants will be provided with a copy of the signed Informed Consent Form. After the run-in phase, participants will have the opportunity to decline continuation into the randomized trial.

2.2 Study Participant Eligibility Criteria

Eligibility for the run-in phase will be assessed using the criteria below. See section 4.2 for eligibility criteria for randomization.

2.2.1 Participant-level Criteria

Inclusion

To be eligible, the following inclusion criteria must be met:

1. Age ≥ 18 years
    - *Individuals <18 years old are not being included because DME is so rare in this age group that the diagnosis of DME may be questionable.*
2. Diagnosis of diabetes mellitus (type 1 or type 2)
    - Any one of the following will be considered to be sufficient evidence that diabetes is present:
        - *Current regular use of insulin for the treatment of diabetes*
        - *Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes*

- *Documented diabetes by ADA and/or WHO criteria (see Procedures Manual for definitions)*

3. At least one eye meets the study eye criteria listed in section 2.2.2.
4. Fellow eye (if not a study eye) meets criteria in section 2.2.3.
5. Able and willing to provide informed consent.

Exclusion

An individual is not eligible if any of the following exclusion criteria are present:

6. History of chronic renal failure requiring dialysis or kidney transplant.
7. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure, cardiovascular disease, and glycemic control).
8. Initiation of intensive insulin treatment (a pump or multiple daily injections) within 4 months prior to randomization or plans to do so in the next 4 months.
9. Participation in an investigational trial that involved treatment with any drug that has not received regulatory approval for the indication being studied within 30 days of enrollment.
    - *Note: study participants cannot receive another investigational drug while participating in the study.*
10. Known allergy to any component of the study drugs (including povidone iodine prep).
11. Blood pressure > 180/110 (systolic above 180 **OR** diastolic above 110).
    - *If blood pressure is brought below 180/110 by anti-hypertensive treatment, the individual can become eligible.*
12. Myocardial infarction, other acute cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 1 month prior to enrollment.
13. Systemic steroid, anti-VEGF or pro-VEGF treatment within 4 months prior to enrollment or anticipated use during the study.
    - *These drugs cannot be used during the study.*
14. For women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next 9 months.
    - *Women who are potential study participants should be questioned about the potential for pregnancy. Investigator judgment is used to determine when a pregnancy test is needed.*
15. Individual is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the next 9 months.

2.2.2 Study Eye Criteria

The study participant must have one eye meeting all of the inclusion criteria and none of the exclusion criteria listed below.

A study participant may have two study eyes only if both are eligible at the time of enrollment into the run-in phase.

The eligibility criteria for a study eye to enter the run-in phase are as follows:

Inclusion

a. At least 3 injections of anti-VEGF drug (ranibizumab, bevacizumab, or aflibercept) within the prior 20 weeks.

b. Visual acuity letter score in study eye ≤ 78 and ≥24 (approximate Snellen equivalent 20/32 to 20/320).

c. On clinical exam, definite retinal thickening due to DME involving the center of the macula.

d. OCT CSF thickness (microns), within 8 days of enrollment:

    - Zeiss Cirrus: ≥290 in women; ≥305 in men
    - Heidelberg Spectralis: ≥305 in women; ≥320 in men

    - *Investigator must verify accuracy of OCT scan by ensuring it is centered and of adequate quality*

e. Media clarity, pupillary dilation, and individual cooperation sufficient for adequate OCTs.

Exclusions

The following exclusions apply to the study eye only (i.e., they may be present for the non-study eye unless otherwise specified):

f. Macular edema is considered to be due to a cause other than DME.

    - *An eye should not be considered eligible if: (1) the macular edema is considered to be related to ocular surgery such as cataract extraction or (2) clinical exam and/or OCT suggest that vitreoretinal interface abnormalities (e.g., a taut posterior hyaloid or epiretinal membrane) are the primary cause of the macular edema.*

g. An ocular condition is present such that, in the opinion of the investigator, visual acuity loss would not improve from resolution of macular edema (e.g., foveal atrophy, pigment abnormalities, dense subfoveal hard exudates, non-retinal condition, etc.).

h. An ocular condition is present (other than DME) that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc.).

i. Substantial lens or posterior capsule opacity that, in the opinion of the investigator, is likely to be decreasing visual acuity by 3 lines or more (i.e., opacity would be reducing acuity to 20/40 or worse if eye was otherwise normal).

j. History of intravitreal anti-VEGF drug within 21 days prior to enrollment.

k. History of intravitreal or peribulbar corticosteroids within 3 months prior to enrollment.

l. History of macular laser photocoagulation within 4 months prior to enrollment.

m. History of panretinal (scatter) photocoagulation (PRP) within 4 months prior to enrollment or anticipated need for PRP in the 6 months following enrollment into run-in phase.

n. Any history of vitrectomy.

o. History of major ocular surgery (including scleral buckle, any intraocular surgery, etc.) within prior 4 months or anticipated within the next 6 months following enrollment.

p. History of cataract extraction within 6 months prior to enrollment or anticipated need for cataract extraction within the study follow-up period.

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

r. Exam evidence of external ocular infection, including conjunctivitis, chalazion, or substantial blepharitis.

s. Intraocular pressure ≥ 25 mmHg.

t. History of open-angle glaucoma (either primary open-angle glaucoma or other cause of open-angle glaucoma; note: history of angle-closure glaucoma is not an exclusion criterion).

- *history of ocular hypertension is not an exclusion as long as (1) intraocular pressure is <25 mmHg, (2) the subject is using no more than one topical glaucoma medication, (3) the most recent visual field, performed within the last 12 months, is normal (if abnormalities are present on the visual field they must be attributable to the subject's diabetic retinopathy – if a recent visual field within 12 months is not available, a new one should be obtained if IOP is 22 to <25 mmHg), and (4) the optic disc does not appear glaucomatous.*

- *Note: if the intraocular pressure is 22 to <25 mmHg, then the above criteria for ocular hypertension eligibility must be met.*

u. History of steroid-induced intraocular pressure elevation that required IOP-lowering treatment.

v. History of prior herpetic ocular infection.

w. Exam evidence of ocular toxoplasmosis.

x. Exam evidence of pseudoexfoliation or any other condition associated with zonular dehiscence or lens instability.

y. Aphakia.

z. Anterior-chamber intraocular lens present.

aa. Sutured posterior-chamber intraocular lens with a ruptured posterior capsule present.

2.2.3 Non-study Eye Criteria

In subjects with only one eye meeting criteria to be a study eye at the time of enrollment into the run-in phase, the fellow eye must meet the following criteria:

a. Intraocular pressure < 25 mmHg.

b. No history of open-angle glaucoma (either primary open-angle glaucoma or other cause of open-angle glaucoma; note: angle-closure glaucoma is not an exclusion criterion).

- *A history of ocular hypertension is not an exclusion as long as (1) intraocular pressure is <25 mmHg, (2) the subject is using no more than one topical glaucoma medication, (3) the most recent visual field, performed within the last 12 months, is normal (if abnormalities are present on the visual field they must be attributable to the subject's diabetic retinopathy), and (4) the optic disc does not appear glaucomatous.*

- *Note: if the intraocular pressure is 22 to <25 mmHg, then the above criteria for ocular hypertension eligibility must be met, including obtaining a normal visual field if one is not available within the last 12 months.*

c. No history of steroid-induced intraocular pressure elevation that required IOP-lowering treatment.

d. No exam evidence of pseudoexfoliation.

2.3 Screening Evaluation

2.3.1 Historical Information

A history will be elicited from the potential study participant and extracted from available medical records. Data to be collected will include: age, sex, ethnicity and race, diabetes history and current management, other medical conditions, medications being used, as well as ocular diseases, surgeries, and treatment.

2.3.2 Screening Procedures

The following procedures are needed to assess eligibility for the run-in phase.

- If a procedure has been performed (using the study technique and by study certified personnel) as part of usual care, it does not need to be repeated specifically for the study if it was performed within the defined time windows specified below.
- The testing procedures are detailed in the DRCR.net Procedures Manuals (Visual Acuity-Refraction Testing Procedures Manual, OCT Procedures Manual, and Study Procedures Manual). Visual acuity testing, ocular exam, and OCT will be performed by DRCR.net certified personnel.
- OCTs obtained for enrollment into the run-in phase of the study eye may be sent to a centralized reading center for grading, although participant eligibility is determined by the site (i.e., individuals deemed eligible by the investigator will be enrolled into run-in phase without pre-enrollment reading center confirmation). Subsequently, if the reading center determines that the automated CSF reading by the OCT machine is inaccurate, and manual adjustment of the CSF thickness on OCT is less than the OCT eligibility criteria, the eye will be dropped from the run-in phase.

1. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester (including protocol refraction) in each eye. *(within 8 days prior to enrollment)*
    - *This testing procedure has been validated against 4-meter ETDRS chart testing.*[45]
2. OCT on study eye *(within 8 days prior to enrollment and at least 21 days after any prior intravitreal anti-VEGF treatment)*
3. Ocular examination on each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy *(within 8 days prior to enrollment)*
4. Measurement of blood pressure

2.4 Enrollment of Eligible Study Participants into Run-In Phase

1. Prior to enrollment, the study participant's understanding of the trial, willingness to accept the assigned treatment group at the end of the run-in phase, and commitment to the follow-up schedule should be reconfirmed.

2. The initial run-in injection(s) must be given on the day of enrollment; therefore, a study participant should not be enrolled until this is possible. For study participants with two study eyes, both eyes must be treated on the day of enrollment. If the investigator is not willing to perform bilateral injections on the same day, only one eye should be enrolled.

Chapter 3.
RUN-IN PHASE

3.1 Overview

Each study eye is required to complete a 12-week run-in phase. The run-in phase will identify study eyes that truly have persistent DME despite anti-VEGF therapy by requiring an additional 3 injections while also collecting standardized visual acuity and OCT measurements. This chapter describes visit schedules, procedures and treatment during the run-in phase of the study.

3.2 Visit Schedule

The schedule of protocol-specified follow-up visits during the run-in phase is as follows:

- 4 weeks (±1 week)
- 8 weeks (±1 week)
- 12 weeks (±1 week) – *randomization visit*

A minimum of 21 days is required between visits.

3.3 Testing Procedures During the Run-In Phase

The following will be performed at the 4-week and 8-week run-in phase visits:

1. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester in each eye, including protocol refraction in the study eye
2. OCT on study eye
3. Ocular examination on study eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy

All of the testing procedures do not need to be performed on the same day, provided that they are completed within the time window of a visit and prior to initiating any retreatment.

Testing procedures at the 12-week visit to assess eligibility for the randomization phase are detailed in section 4.3.

3.4 Treatment During the Run-in Phase

All study eyes will receive an injection of ranibizumab 0.3 mg at enrollment, 4 weeks, and 8 weeks. The injections must be at least 21 days apart. If an eye experienced adverse effects from a prior intravitreal injection during the run-in phase precluding future injections or additional injections are otherwise contraindicated according to the investigator (e.g. DME is no longer present), the eye will not continue in the study.

3.4.1 Anti-VEGF Drug

Ranibizumab 0.3 mg (Lucentis®) will be the anti-VEGF drug that will be used in the study, both during the run-in phase and post-randomization. The physical, chemical and pharmaceutical properties and formulation will be provided in the Ranibizumab Clinical Investigator Brochure.

3.4.2 Intravitreal Injection Technique

The injection is preceded by a povidone iodine prep of the conjunctiva. Antibiotics in the pre-, peri-, or post-injection period are not necessary but can be used at investigator discretion if such use is part of his/her usual routine.

The injection will be performed using sterile technique. The full injection procedure is described in the DRCR.net Study Procedures Manual.

3.4.3 Deferral of Injections Due to Pregnancy

Female study participants must be questioned regarding the possibility of pregnancy prior to each injection. In the event of pregnancy, study injections must be discontinued.

Chapter 4.
RANDOMIZATION PHASE

4.1 Overview

After completing the run-in phase of the study, eligibility criteria for the randomization phase will be assessed for enrolled eyes at the 12-week run-in visit ("randomization visit"). This chapter describes randomization, testing procedures, and follow-up visit and treatment schedules during the randomization phase.

4.2 Eligibility Criteria for Randomization

Once the run-in phase has been completed, the study participant must have at least one eye meeting all of the inclusion criteria and none of the exclusion criteria listed below, confirmed at the 12-week run-in visit ("randomization visit") to be eligible for randomization. A study participant may have two study eyes only if both are eligible at the time of randomization.

Inclusions

a. All 3 run-in phase visits and ranibizumab injections were completed within ±10 days of the target visit date.
b. Randomization visit no more than 5 weeks (35 days) from 8-week visit.
c. At least 21 days since prior study injection.
d. Visual acuity letter score in study eye ≤ 78 and ≥24 (approximate Snellen equivalent 20/32 to 20/320)
e. On clinical exam, definite retinal thickening due to DME involving the center of the macula.
f. CSF thickness (microns) on OCT meeting either one of the following two gender- and OCT machine-specific criteria:
    i. Zeiss Cirrus: ≥290 in women; ≥305 in men
    ii. Heidelberg Spectralis: ≥305 in women; ≥320 in men

Exclusions

g. All participant-level exclusion criteria in section 2.2.1 must not have developed or occurred during the run-in phase.
h. All study eye-level exclusion criteria in section 2.2.2 (except the criterion for prior anti-VEGF treatment) must not have developed or occurred during the run-in phase.

4.3 Randomization Visit Testing Procedures

The following procedures are needed to assess eligibility for randomization and/or to serve as baseline measures for the study analyses.

- The testing procedures are detailed in the DRCR.net Procedures Manuals (Visual Acuity-Refraction Testing Procedures Manual, and Study Procedures Manual). Visual acuity testing, ocular exam, and OCT will be performed by DRCR.net certified personnel.
- OCTs meeting DRCR.net criteria for manual grading may be sent to a reading center but study participants' eligibility is determined by the site (i.e., individuals deemed eligible by the investigator will be randomized without pre-randomization reading center confirmation).

1. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester (including protocol refraction) in each eye. *(on day of randomization)*
    - *This testing procedure has been validated against 4-meter ETDRS chart testing.*[45]
2. OCT on study eye *(on day of randomization)*
3. Ocular examination on each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy *(on day of randomization)*
4. Laboratory Testing- HbA1c
    - *HbA1c does not need to be repeated if available in the prior 3 months. If not available at the time of randomization, the individual may be enrolled but the test must be obtained within 3 weeks after randomization.*
5. Measurement of blood pressure

4.4 Randomization of Eligible Study Participants

1. Prior to randomization, the study participant's understanding of the trial, willingness to accept the assigned treatment group, and commitment to the follow-up schedule should be reconfirmed.
2. The baseline injections must be given on the day of randomization; therefore, a study participant should not be randomized until this is possible. For study participants with two study eyes, both eyes must be treated on the day of randomization. If the investigator is not willing to perform bilateral injections on the same day, only one eye should be randomized.
3. Randomization is completed on the DRCR.net website.
    - <u>Study participants with one study eye</u> will be randomly assigned, with equal probability, to receive either:
        - Group A: Sham + intravitreal ranibizumab 0.3 mg
        - Group B: Intravitreal dexamethasone +intravitreal ranibizumab 0.3 mg

    Randomization will be stratified by two factors:
        1. Presence or absence of improvement in retinal thickness during the run-in phase, defined as reduction in CSF thickness by 10% at any run-in visit, compared with the prior visit.
        2. Presence or absence of improvement in visual acuity during the run-in phase, defined as 5 or more letter gain in visual acuity at any run-in visit, compared with the prior visit.

    - <u>For study participants with two study eyes</u> (both eyes eligible at the time of randomization):
        - The study participant will be randomized with equal probability to receive either:
            - Group A in the eye with greater OCT improvement and Group B in the eye with lower OCT improvement
            - Group B in the eye with greater OCT improvement and Group A in the eye with lower OCT improvement

Note: if both eyes have the same OCT improvement, the right eye will be consider the eye with the greater improvement.

4.5 Randomization Treatment

The treatment groups are as follows:

- Group A: Sham + intravitreal ranibizumab 0.3 mg
- Group B: Intravitreal dexamethasone +intravitreal ranibizumab 0.3 mg

For both treatment groups, the initial ranibizumab injection must be given on the day of randomization. The sham or dexamethasone injection will be given within 0-8 days of the ranibizumab injection. If the injections are given consecutively on the same day, the sham injection must be given first in Group A and the ranibizumab injection must be given first in Group B.

Focal/grid laser is not permitted in the study eye.

4.6 Follow-Up Study Visits During the Randomization Phase

The schedule of protocol-specified follow-up visits post-randomization is as follows:

- 4 weeks (±1 week)
- 8 weeks (±1 week)
- 12 weeks (±1 week)
- 16 weeks (±1 week)
- 20 weeks (±1 week)
- 24 weeks (±1 week)– *primary outcome visit*

A minimum of 21 days is required between injections. An additional visit may be required for completion of the second (steroid/sham) injection at randomization and 12 weeks.

4.7 Follow-Up Testing Procedures During the Randomization Phase

The following procedures will be performed at each protocol visit unless otherwise specified. A grid in section 1.3 (J) summarizes the testing performed at each visit.

Visual acuity testers (including refractionist) and OCT technicians will be masked to treatment group at the primary outcome visit (24 weeks).

1. Best-corrected E- ETDRS visual acuity testing in each eye
   - A protocol refraction in the study eye is required at all protocol visits. Protocol refraction in the non-study eye at the 24 week-visit only. When a refraction is not performed, the most-recently performed refraction is used for the testing.
2. OCT on the study eye
3. Ocular exam on the study eye, including slit lamp examination, lens assessment, measurement of intraocular pressure and dilated ophthalmoscopy

All of the testing procedures do not need to be performed on the same day, provided that they are completed within the time window of a visit and prior to initiating any retreatment.

Testing procedures at unscheduled visits are at investigator discretion. However, it is recommended that procedures that are performed should follow the standard DRCR.net protocol for each procedure. If the study participant returns following a protocol visit specifically to receive a study injection, testing prior to the injection is at investigator discretion.

4.8 Post-Randomization Treatment

From the 4-week visit to the 20-week visit, the study eye is evaluated for retreatment based on visual acuity and OCT. If an eye experienced adverse effects from a prior intravitreal injection, retreatment with study injections is at the discretion of the investigator; however, non-protocol treatment for DME should not be given. Otherwise:

- If the visual acuity letter score is ≥84 (20/20 or better) and the OCT CSF thickness is < the gender-specific spectral domain OCT cutoffs below injection(s) will be deferred:
  - Zeiss Cirrus: 290 in women and 305 in men
  - Heidelberg Spectralis: 305 in women and 320 in men

- If the visual acuity letter score is <84 (worse than 20/20) or OCT CSF thickness ≥ the gender-specific spectral domain OCT cutoffs below, injection(s) will be given.
  - Zeiss Cirrus: 290 in women and 305 in men
  - Heidelberg Spectralis: 305 in women and 320 in men

If at any time the investigator wishes to treat the study eye(s) with a treatment for DME that is different than the protocol treatment due to perceived failure or futility, the protocol chair or designee must be contacted for approval prior to administering such treatment.

The type of injection(s) given depends on the time since baseline treatment and treatment assignment:

4 and 8-Week Visits: Ranibizumab Only

If indicated based on retreatment criteria above, eyes in both treatment groups will receive a ranibizumab injection only.

12-Week Visit: Combination Treatment

If indicated based on retreatment criteria above, combination treatment will be given at the 12-week visit. The sham or dexamethasone injection will be given within 0-8 days of the ranibizumab injection. If the injections are given consecutively on the same day, the sham injection must be given first in Group A, and the ranibizumab injection must be given first in Group B. If injections are given on different days, then the ranibizumab injection is given first and the sham or dexamethasone injections is given within 8 days. If visual acuity and/or OCT are re-measured prior to the second injection (at the discretion of the investigator), the sham or dexamethasone injection should still be given based on the pre-ranibizumab injection values.

A minimum of 70 days is required between the first (baseline) and second (12-week) sham or dexamethasone injections.

16 and 20-Week Visits:

If combination injections were not given at the 12-week visit for any reason (for example due to missed visit or deferring injection based on retreatment criteria above), combination injections should be given at the first visit at which retreatment criteria for injections are met (16- or 20-week visits).

If combination injections were given at the 12-week visit, eyes in both treatment groups will receive only a ranibizumab injection at the 16 and 20-week visits if indicated based on the retreatment criteria above.

Treatment at the 24 week visit is at investigator discretion; however, study drug cannot be used.

4.8.1 Anti-VEGF Drug

Ranibizumab 0.3 mg intravitreal injections (Lucentis®) is the anti-VEGF drug that will be used in this study. Ranibizumab (Lucentis®) is manufactured by Genentech, Inc. and is approved for the treatment of DME in a dose of 0.3 mg. A 0.5 mg dose of ranibizumab is also FDA-approved for age-related macular degeneration and macular edema secondary to retinal vein occlusion. Ranibizumab 0.3 mg intravitreal injections will be given in 0.05 cc volume. The physical, chemical and pharmaceutical properties and formulation will be provided in the Ranibizumab Clinical Investigator Brochure. Ranibizumab will be provided by Genentech Inc.

4.8.2 Steroid

Study eyes assigned to dexamethasone + ranibizumab will receive will receive sustained dexamethasone drug delivery system (Ozurdex®). Ozurdex is a pellet consisting of a 0.45 mm in diameter and 6.5 mm in length biodegradable polymer matrix of dexamethasone that provides sustained delivery of 700µg of preservative-free dexamethasone into the vitreous cavity and retina through injection using a single-use special prepackaged applicator. The physical, chemical and pharmaceutical properties and formulation are provided in the Clinical Investigator Brochure. Ozurdex® will be provided by Allergan Inc.

4.8.3 Intravitreal Injection Technique

Each injection is preceded by a povidone iodine prep of the conjunctiva. Antibiotics in the pre-, peri-, or post-injection period are not necessary but can be used at investigator discretion if such use is part of his/her usual routine.

The injection will be performed using sterile technique. The full injection procedure is described in the DRCR.net Study Procedures Manual.

4.8.4 Sham Injection Technique

The prep will be performed as for an intravitreal injection. Either a syringe without the needle attached or the dexamethasone applicator will be used. The hub of the syringe or the applicator will be pressed against the conjunctival surface to simulate the force of an actual injection.

4.8.5 Delay in Giving Injections

If a scheduled injection is not given by the end of the visit window, it can still be given up to 1 week prior to the next visit window opening. If it is not given by that time, it will be considered missed.

If an injection is given late, the next scheduled injection should occur no sooner than 3 weeks after the previous injection.

4.8.6 Deferral of Injections Due to Pregnancy

Female study participants must be questioned regarding the possibility of pregnancy prior to each injection. In the event of pregnancy, study injections must be discontinued.

Chapter 5.
MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

5.1 Endophthalmitis

Diagnosis of endophthalmitis is based on investigator's judgment. Obtaining cultures of vitreous and/or aqueous fluid is strongly recommended prior to initiating antibiotic treatment for presumed endophthalmitis.

5.2 Surgery for Vitreous Hemorrhage and Other Complications of Diabetic Retinopathy

A study eye could develop a vitreous hemorrhage and/or other complications of diabetic retinopathy that may cause visual impairment. The timing of vitrectomy for the complications of proliferative diabetic retinopathy such as vitreous hemorrhage is left to investigator discretion.

5.3 Panretinal (Scatter) Photocoagulation (PRP)

PRP can be given if it is indicated in the judgment of the investigator. Individuals are not eligible for this study if, at the time of enrollment, it is expected that they will need PRP within 6 months. In general, PRP should not be given if the study participant has less than severe non-proliferative diabetic retinopathy. In general, PRP should be given promptly for previously untreated eyes exhibiting PDR with high-risk characteristics and can be considered for persons with non-high-risk PDR or severe non-proliferative diabetic retinopathy. Guidelines for PRP can be found in the Protocol Procedure Manuals on the DRCR.net website.

5.4 Treatment of Macular Edema in Non-study Eye

Treatment of DME in the non-study eye is at investigator discretion.

5.5 Diabetes Management

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

5.6 Management of Ocular Hypertension or Glaucoma

Treatment of rise in intraocular pressure is at investigator discretion.

5.7 Study Participant Withdrawal and Losses to Follow-up

A study participant has the right to withdraw from the study at any time. If a study participant is considering withdrawal from the study, the principal investigator should personally speak to the individual about the reasons, and every effort should be made to accommodate him/her.

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

Study participants who withdraw will be asked to have a final closeout visit at which the testing described for the protocol visits will be performed. Study participants who have an adverse effect attributable to a study treatment or procedure will be asked to continue in follow-up until the adverse event has resolved or stabilized.

Study participants who withdraw or are determined to have been ineligible post-randomization will not be replaced.

5.8 Discontinuation of Study

The study may be discontinued by the Executive Committee (with approval of the Data and Safety Monitoring Committee) prior to the preplanned completion of follow-up for all study participants.

5.9 Contact Information Provided to the Coordinating Center

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

Phone contact from the Coordinating Center will be made with each study participant in the first month after randomization and prior to the 24-week visit. Additional phone contacts from the Coordinating Center will be made if necessary to facilitate the scheduling of the study participant for follow-up visits. A participant-oriented newsletter and/or study logo item may be sent during the study.

Study participants will be provided with a summary of the study results in a newsletter format after completion of the study by all participants.

5.10 Study Participant Reimbursement

The study will be providing the study participant with a $25 gift card per completed protocol visit. Additional travel expenses will be paid in select cases for participants with higher expenses.

Chapter 6.
ADVERSE EVENTS

6.1 Definition

An adverse event is any untoward medical occurrence in a study participant, irrespective of whether or not the event is considered treatment-related.

6.2 Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the study participant, and appropriate medical intervention will be made.

The investigator will elicit reports of adverse events from the study participant at each visit and complete all adverse event forms online. Each adverse event form is reviewed by the Coordinating Center to verify the coding and the reporting that is required.

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the treatment.

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events will be coded using the MedDRA dictionary.

Definitions of relationship and intensity are listed on the DRCR.net website data entry form.

Adverse events that continue after the study participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

6.3 Reporting Serious or Unexpected Adverse Events

A serious adverse event is any untoward occurrence that:

- Results in death
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in significant disability/incapacity (sight threatening)
- Is a congenital anomaly/birth defect

Unexpected adverse events are those that are not identified in nature, severity, or frequency in the current Clinical Investigator's Brochure or the current package insert.

Serious or unexpected adverse events must be reported to the Coordinating Center immediately via completion of the online serious adverse event form.

The Coordinating Center will notify all participating investigators of any adverse event that is both serious and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for informing his/her IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB.

6.4 Data and Safety Monitoring Committee Review of Adverse Events

A Data and Safety Monitoring Committee (DSMC) will approve the protocol, template informed consent form, and substantive amendments and provide independent monitoring of adverse events. Cumulative adverse event data are tabulated semi-annually for review by the Data and Safety Monitoring Committee (DSMC). Following each DSMC data review, a summary will be provided to IRBs. A list of specific adverse events to be reported expeditiously to the DSMC will be compiled and included as part of the DSMC Standard Operating Procedures document.

6.5 Risks

6.5.1 Potential Adverse Effects of Study Drug

6.5.1.1 Anti-VEGF

Ranibizumab is well tolerated in people. More than 5000 individuals have been treated with injections of ranibizumab in clinical studies to date, however the full safety profile with long-term injections is not yet known. Some participants in ongoing clinical studies have developed inflammation in the eye (uveitis) which can be treated with anti-inflammatory drops. Increased eye pressure leading to glaucoma or cataract has also resulted from injections of ranibizumab. Other ocular adverse events that have occurred in ongoing clinical studies are believed to be due to the intravitreal injection itself and not the study drug (Section 6.5.2 Potential Adverse Effects of Intravitreal Injection).

Some study participants have experienced systemic adverse events that may possibly be related to ranibizumab. There is evidence that intravitreally administered ranibizumab is associated with a decrease in serum VEGF concentrations, but it has not been established whether this decrease results in clinically significant adverse events.[46] Until cumulative safety data are analyzed, precise incidence figures are unknown and a causal relationship cannot be ruled out. These include arterial thromboembolic events and other events potentially related to systemic VEGF inhibition. In a phase IIIb study to evaluate the long-term safety and efficacy of ranibizumab (The Safety Assessment of Intravitreous Lucentis for AMD (SAILOR trial), which randomized patients with wet age-related macular degeneration to 0.5 mg ranibizumab or 0.3 mg ranibizumab, there was a higher rate of cerebrovascular stroke in the group that received the higher drug dose (1.2 vs. 0.7%), although this trend did not achieve statistical significance.[47] It appeared that patients who had a prior history of stroke may be at greater risk for having a stroke after receiving ranibizumab, although there was a low incidence of stroke overall in this group.

Additional data regarding systemic safety of ranibizumab in a diabetic population is also available from the DRCR.net Protocol I primary results.[12] This study enrolled a combined total of 375 patients in the two ranibizumab arms, who received an average of eight to nine intravitreal injections of 0.5 mg ranibizumab over the first year of treatment. There was no indication of an increased risk of cardiovascular or cerebrovascular events in the ranibizumab-treated study participants as compared with the triamcinolone-treated study participants or study participants who received no intravitreal drug. Indeed, lower rates of cardiovascular events, as

defined by the Antiplatelet Trialists' Collaboration, were seen in the ranibizumab groups as compared with the sham group at both one (3% versus 8%) and two (5% versus 12%) years. In the RISE and RIDE studies, ranibizumab therapy was also well-tolerated overall, although the rate of Antiplatelet Trialists' Collaboration events was slightly higher in the 0.3 mg (5.6%) and 0.5 mg (7.2%) groups as compared with the sham group (5.2%) in the pooled RISE and RIDE results. Deaths were also more frequent in the ranibizumab groups (0.8% and 1.6% of sham and 2.4-4.8% of ranibizumab treated patients) in these trials.[15] The rate of non-fatal cerebrovascular events in this pooled analysis was higher in the 0.5 mg group (2%) than in the sham (1.2%) or 0.3 mg group (0.8%) but the rate of non-fatal myocardial infarctions was similar across treatment groups (2.8%, 2.8% and 2.4% in the sham, 0.3mg and 0.5mg groups, respectively). On the other hand, mortality was reported to be below expected in subjects who received ranibizumab for AMD with the standardized mortality rate of 0.75 (95% confidence interval, 0.62-0.89).[48] In hospital and death records review, Kemp et al. reported higher 12-month myocardial infarction rate in patient who received vascular endothelial growth factor inhibitor (1,267 patients) than those who received photodynamic therapy (399 patients) for AMD or those in nontreated community sample (1,763 patients) (1.9/100 vs. 0.8 and 0.7, respectively) with no differences observed between patients treated with bevacizumab and ranibizumab.[49]

There may be side effects and discomforts that are not yet known. Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ranibizumab or its effect on fertility.

6.5.1.2 Steroid

The 0.7 mg dexamethasone implant (Ozurdex) generally appeared to be safe and well-tolerated in phase III studies in which it was evaluated as treatment for macular edema secondary to retinal vein occlusion.[42] No cases of endophthalmitis occurred in these studies which included 1,256 study participants followed for 12 months after enrollment. The 12-month incidence of subconjunctival hemorrhage ranged from 22.3%- 24.9% in study eyes, some of which received 1 and some of which received 2 implants at either the 0.7 mg or 0.35 mg dose. Cataract progression occurred in 29.8% of phakic eyes that received two 0.7 mg implants versus only 5.7% of sham-treated phakic eyes. An increase in IOP of 10 mmHg or more was observed in eyes that received two 0.7 mg implants at rates of 12.6% after the first implant and 15.4% after the second treatment. A total of 32.8% of study eyes receiving two 0.7 mg implants had at least a 10 mmHg increase in IOP from baseline during the 12 months of follow-up. Of eyes that received a 0.7 mg implant at baseline, 25.5% were started on an IOP-lowering medication during the first 180 days of the study. When a single 0.7 mg dexamethasone implant was administered in 55 vitrectomized eyes with DME,[44] the most common adverse events were conjunctival hemorrhage (52.7%), conjunctival hyperemia (20.0%), eye pain (16.4%), increased IOP (16.4%), conjunctival edema (12.7%), and vitreous hemorrhage (10.9%). Of the 48 study participants who were not on IOP-lowering medication at baseline, 8 (17%) began on IOP-lowering medication during the study. Additional adverse events that occurred in more than 5% but less than 10% of eyes were maculopathy (either epiretinal membrane or macular thickening), anterior chamber cells, foreign body sensation, iritis, and floaters. Migration of Ozurdex to the anterior chamber with subsequent corneal edema is a rare complication of Ozurdex injections. This risk is associated with with aphakic eyes,[50-52] and pseudophakic eyes with anterior chamber intraocular lens and iridectomy or disruption of the posterior capsule.[53-55] In one study of 342 eyes with macular edema due to retinal vein occlusion treated with Ozurdex, two eyes (~0.5%) had Ozurdex dislocated to the anterior chamber requiring surgical repositioning in the vitreous

cavitity.[55]

6.5.2 Potential Adverse Effects of Intravitreal Injection

Rarely, the drugs used to anesthetize the eye before the injections (proparacaine, tetracaine, or xylocaine) can cause an allergic reaction, seizures, and an irregular heartbeat.

Subconjunctival hemorrhage or floaters will commonly occur as a result of the intravitreal injection. Mild discomfort, ocular hyperemia, increased lacrimation, discharge or itching lasting for a few days is also likely.

Immediately following the injection, there may be elevation of intraocular pressure. It usually returns to normal spontaneously, but may need to be treated with topical drugs or a paracentesis to lower the pressure. The likelihood of permanent loss of vision from elevated intraocular pressure is less than 1%.

As a result of the injection, endophthalmitis (infection in the eye) could develop. If this occurs, it is treated by intravitreal injection of antibiotics, but there is a risk of permanent loss of vision including blindness. The risk of endophthalmitis is less than 1%.

As a result of the injection, a retinal detachment could occur. If this occurs, surgery may be needed to repair the retina. The surgery is usually successful at reattaching the retina. However, a retinal detachment can produce permanent loss of vision and even blindness. The risk of retinal detachment is less than 1%.

The injection could cause a vitreous hemorrhage. Usually the blood will resolve spontaneously, but if not, surgery may be needed to remove the blood. Although the surgery usually successfully removes the blood, there is a small risk of permanent loss of vision and even blindness. The risk of having a vitreous hemorrhage due to the injection is less than 1%.

6.5.3 Risks of Eye Examination and Tests

There is a rare risk of an allergic response to the topical medications used to anesthetize the eye or dilate the pupil. Dilating drops rarely could cause an acute angle closure glaucoma attack, but this is highly unlikely since the participants in the study will have had their pupils dilated many times previously.

There are no known risks associated with OCT.

Chapter 7.
STATISTICAL METHODS

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

This phase II clinical trial is conducted to assess the short term effect of combination steroid + anti-VEGF therapy on visual acuity and OCT retinal thickness, in comparison with that of continued anti-VEGF therapy alone, in eyes with persistent central-involved DME and visual acuity impairment despite previous anti-VEGF treatment. The primary outcome of the study will be the mean change in visual acuity at the 24-week post-randomization visit, adjusted for the baseline (randomization) visual acuity.

The treatment groups include the following:

- Group A: Sham + intravitreal ranibizumab 0.3 mg
- Group B: Intravitreal dexamethasone +intravitreal ranibizumab 0.3 mg

7.1 Sample Size

This phase II study will include 75 study eyes (from approximately 62 participants) in each treatment group.

The primary analysis consists of a statistical estimation of the difference in mean change in visual acuity letter score at the 24-week post-randomization visit, adjusted for the baseline visual acuity and correlation between eyes, between the sham + ranibizumab group and the combination of corticosteroid+ ranibizumab group.

7.2 Sample Size Assumptions and Precision Estimates

To estimate the standard deviation (SD) of change in visual acuity from baseline (randomization) to the 24-week visit (primary outcome visit), data from the DRCR.net Protocol I were reviewed. Of eyes that completed the 1-year visit, 61 eyes were identified at the 32-week visit to have 1) OCT CSF≥250 μm, 2) VA between 20/320 to 20/32; and 3) received at least 3 ranibizumab injections from the 16-week visit to prior to the 32 week-visit. All these eyes had received at least 3 ranibizumab injections prior to the 16-week visit and met the OCT and VA thresholds above, mimicking the minimum number of injections required for enrollment into the run-in phase of this protocol. The mean change in visual acuity letter score from the 32-week visit (to mimic randomization visit of this protocol) to the 52-week visit (to mimic the 24-week visit of this protocol) for these 61 eyes, adjusted for baseline visual acuity, was +1.9 (95%CI: +0.1 to +3.7). The standard deviation for the mean change in visual acuity letter score adjusted for correlation with baseline visual acuity value was 6.9 letter score (95% CI: 5.9 to 8.4).

The following table shows half-widths of 95%CI on the difference in mean visual acuity change between treatment groups for a range of SDs and sample sizes. For the sample size in each group of 70 (increased to 75 for approximately 5% lost to follow-up) that will be used, a two-sided 95% CI for the difference of the two means in visual acuity change from randomization to 24-week visit will extend 2.3 visual acuity letter score in either direction from the observed difference in means, assuming that the common standard deviation is a letter score of 7 (~the midpoint for the estimated standard deviation), not adjusting for correlation between eyes in participants with two study eyes.

Similarly, half-width of the 95% CI using a standard deviation of 9 (~ the upper confidence limit for the estimated standard deviation) will be a letter score of 3.0. Adjustment in the primary analysis for between-eye correlation is expected to slightly reduce the expected width of the confidence interval over the tabled values.

Based on the above information, with an alpha of 0.05, if the true visual acuity mean difference is 5 letters and the standard deviation is 9 then there is 90% power to detect a difference in visual acuity change between treatment groups.

Half-Width of a 95% Confidence Interval for the Difference in Mean visual acuity Change

Standard Deviation	Sample Size Per Group				
	25	**50**	**70**	**100**	**125**
6	3.3	2.4	2.0	1.7	1.5
7	3.9	2.7	2.3	1.9	1.7
8	4.4	3.1	2.7	2.2	2.0
9	5.0	3.5	3.0	2.5	2.2
10	5.5	3.9	3.3	2.8	2.5
11	6.1	4.3	3.6	3.0	2.7
12	6.7	4.7	4.0	3.3	3.0

7.3 Efficacy Analysis Plan

7.3.1 Primary Outcome Analysis

The primary analysis consists of the estimation of the difference in mean change between the treatment groups in visual acuity letter score from randomization to the 24-week post-randomization visit, adjusted for randomization visual acuity and correlation between eyes of participants with two study eyes.

The estimation of treatment group difference in mean change in visual acuity from randomization to the 24-week visit will be performed using an analysis of covariance (ANCOVA) model, with the change in visual acuity measurements at 24 weeks fitted as the dependent variable, and the treatment group as the independent variable, adjusting for the randomization stratification factor, and for the baseline measurement (visual acuity value at randomization visit) by including each as a covariate in the model. The treatment effect will be reported as the mean difference (and standard deviation) between treatment groups in change of visual acuity letter score from randomization to 24-week visit with 95%CI from ANCOVA model. The significance level used for the final primary analysis will be 0.05. The study is not powered to establish treatment efficacy; however, treatment comparison will be conducted for visual acuity and OCT retinal thickness outcomes to assess treatment effect.

There will be two analyses: an “intent-to-treat” analysis (ITT) and a “per-protocol” analysis:

- The intent-to-treat analysis will include all randomized eyes. Rubin’s multiple imputation method will be used to impute missing data at the 24-week visit.

- The per-protocol analysis will be performed including only participants who complete all required injections without receiving any non-protocol treatments and have data at the 24-week visit.
- The intent-to-treat analysis is considered the primary analysis. If the intent-to-treat and per-protocol analyses yield the same results, the per-protocol analysis will be used to provide supportive evidence of the magnitude of treatment effect among patients who received the treatment. If the results of the two methods differ, exploratory analyses will be performed to evaluate the factors that have contributed to the differences. A sensitivity analysis will be conducted to compare the results from multiple imputation with those using a per-protocol analysis only including study participants who completed the 24-week visit and with results from last-observation-carried-forward.

Generalized estimating equations (GEE) will be used to adjust for the correlation between eyes of patients who have two study eyes.

Although expected to be under-powered, pre-planned subgroup analyses will be conducted in the same way as the primary analysis and include stratification by improvement in OCT CSF thickness during run-in phase visits by ≥10% at any visit, and improvement in VA during run-in phase by 5 or more letters at any visit. Other subgroup analyses will be described in the detailed Statistical Analysis Plan. These subgroup analyses will be used to guide choice of pre-planned subgroup analyses in the phase III trial.

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding; however, a second analysis that adjusts for imbalanced baseline covariates will be performed. If results are similar to the primary analysis, the primary analysis will be accepted as the definitive analysis; otherwise, the reasons for the difference will be explored.

There are no data to suggest that the treatment effect will vary by sex or race and ethnicity. However, both of these factors will be evaluated in exploratory analyses.

7.4 Secondary Outcomes

In addition to the primary outcome, the following secondary outcomes will be estimated, and their 95% CI will be obtained in each treatment group and compared between treatment groups:

- Percent of eyes with at least 10 and at least 15 letter gain (increase) or loss (decrease) in E-ETDRS letter score visual acuity at 24 weeks
- Visual acuity AUC between randomization and 24 weeks
- Mean change in OCT CSF thickness, adjusted for thickness at time or randomization, using ITT, and per-protocol analyses
- Percent of eyes with ≥1 and ≥2 logOCT step gain or loss in CSF thickness at 24-week visit
- Percent of eyes with OCT CSF thickness (in micros) < the following gender and OCT machine-specific values at 24-week visit: <290 in women and <305 in men in Zeiss Cirrus; <305 in women and <320 in men in Heidelberg Spectralis
- OCT CSF thickness area under the curve (AUC) between randomization and 24 weeks
- Percent of eyes with worsening or improvement of diabetic retinopathy on clinical exam

7.4.1 Secondary Outcomes Analysis

Analyses of secondary outcomes will be conducted as follows:
Binary outcomes will be analyzed using logistic regression to control for baseline level of the outcome. Continuous outcome comparisons will be performed using ANCOVA with adjustment for baseline values. All linear model assumptions will be verified including linearity, normality of residuals, and homoscedasticity. If model assumptions are not met, a nonparametric analogue for ANCOVA will be considered. Multple imputation method will be implemented for missing data. GEE will be used to adjust for correlation between eyes of participants with two study eyes.

7.5 Safety Analysis Plan

Adverse events will be categorized as study eye, non-study eye, and systemic. The events will be tabulated and compared between treatment groups. Separate analyses will compare related adverse events between groups.

Specific adverse events of interest will include:

- Injected-related: increased intraocular pressure, endophthalmitis, retinal detachment, retinal tears, intraocular hemorrhage
- Ocular drug-related: increased intraocular pressure, need for ocular anti-hypertensives, glaucoma surgery or other IOP-lowering procedures, development or worsening of cataract and cataract extraction, intraocular hemorrhage, inflammation, migration of Ozurdex to the anterior chamber and subsequent corneal complications
- Systemic drug-related: Deaths, participants with at least one hospitialization, participants with at least one SAE, and cardiovascular events and cerebrovascular events as defined by Antiplatelet Trialists' Collaboration
    - *Systemic adverse events for participants with two study eyes will be evaluated separately from participants with one study eye.*

Further definitions of the events for analysis and the analytic approach will be provided in the detailed statistical analysis plan.

7.6 Additional Analysis Objectives Related to Design of Phase III Trial

If the results of this study support proceeding with a phase III trial, information from this study will 1) be used to estimate recruitment potential; and 2) contribute to designing the phase III trial. The standard deviation of the difference in mean change in visual acuity will be used in the sample size calculation of the phase III trial. The recruitment potential for a phase III trial will be assessed based on the average monthly enrollment of participants into this study. The sample size estimate that would be calculated for a phase III trial weighed against recruitment projection from this phase II trial will aid in the assessment of feasibility of a phase III trial in terms of recruitment.

Additional outcomes that will be assessed to aid in the design of a phase III trial include: 1) success of the run-in phase in identifying eyes with "persistent DME" following anti-VEGF therapy (for example, depending on proportion of enrolled eyes that are randomized, the run-in phase duration

or criteria for randomization may be adjusted), 2) success of masking via sham injections and 3) duration of steroid effect.

7.7 Additional Tabulations and Analyses

The following will be tabulated according to treatment group:

1) Baseline demographic and clinical characteristics (subject and ocular-level data)
2) Visit completion rate for each visit
3) Protocol deviations

7.8 Interim Monitoring Plan

Formal interim efficacy analyses are not planned. However, at approximately 6-month intervals the DSMC will review a compiled ocular and systemic adverse event data report as well as visual acuity by treatment group.

A minimal amount of alpha spending (0.0001) will be allocated for each DSMC review of the data and depending on the actual number of reviews, the final overall type 1 error at the end of the trial will be adjusted accordingly.

Chapter 8. REFERENCES

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