Diabetic Retinopathy Clinical Research Network

Treatment for Central-Involved Diabetic Macular Edema in Eyes with Very Good Visual Acuity

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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] 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 increase in rates of associated vascular complications from this chronic disease, which includes diabetic retinopathy. Despite advances in diagnosis and management of ocular disease in diabetic patients, 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] Furthermore, 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

Diabetic macular edema 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 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] The Diabetic Retinopathy Clinical Research Network (DRCR.net) adopted a modified ETDRS focal/grid photocoagulation protocol from the original ETDRS approach as the standard laser technique for DME used in all 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 photocoagulation technique was comparable to results in similar eyes in the ETDRS, and that intravitreal

triamcinolone as monotherapy was not superior to use with the focal/grid photocoagulation technique for central-involved DME in eyes with some visual acuity loss.[10,11]

Results from a 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 ($\geq$24 weeks) or prompt focal/grid photocoagulation provides visual acuity outcomes at one year and two years that are superior to prompt focal/grid photocoagulation alone or intravitreal triamcinolone with prompt focal/grid photocoagulation.[12] DRCR.net Protocol I provided definitive confirmation of the important role of VEGF in DME and the role of anti-VEGF drugs in the treatment of DME. The study enrolled 854 eyes of 691 study participants with DME involving the fovea and with visual acuity (approximate Snellen equivalent) of 20/32 to 20/320. Eyes were randomly assigned to sham injection + prompt focal/grid photocoagulation (N = 293), 0.5-mg ranibizumab + prompt laser (within 3 to10 days, N = 187), and 0.5-mg ranibizumab + deferred laser (deferred for at least 24 weeks, N = 188). Treatment with ranibizumab was generally continued on a monthly basis unless the participant's vision stabilized or reached 20/20, or the retinal swelling resolved. Treatment could be stopped if failure criteria were met (persistent swelling with poor vision), but this occurred in very few participants (less than 5% in any group). The mean change ($\pm$ standard deviation) in visual acuity letter score at one year from baseline was significantly greater in the ranibizumab+prompt laser group (+9 $\pm$ 11) and the ranibizumab+deferred laser group (+9 $\pm$ 12) as compared with the control laser group (+3 $\pm$ 13, $P < 0.001$ for both comparisons) or triamcinolone+prompt laser group (+4 $\pm$ 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 3 trials, including RISE, RIDE and RESTORE.[15, 16] Participants in RISE and RIDE were randomly assigned to 0.5 or 0.3 mg ranibizumab every 4 weeks 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 $\geq$ 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 (0.5 mg) 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 $\geq$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 to 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, 0.3 mg and 0.5 mg groups, respectively).

1.1.4 Eyes with Central-Involved DME and Good Vision

Although the studies described above have clearly demonstrated that ranibizumab therapy is more effective than laser alone for vision gain and avoiding vision loss in patients with central-involved DME, only eyes with a visual acuity letter score of 78 or worse (approximate Snellen equivalent of 20/32 or worse) were eligible for DRCR.net Protocol I; similarly designed studies of anti-VEGF treatment for DME had the same or lower visual acuity eligibility criteria.[15, 16] Eyes that have central-involved DME with "good" visual acuity (20/25 or better) have not been addressed systematically by recent studies for treatment of DME.

Baseline cohort characteristics from the ETDRS suggest that a substantial percentage of eyes with central-involved DME may retain good vision. At baseline in the ETDRS, of all eyes in the focal laser and observation group, center involved macular edema on fundus photographs was present in approximately 42% of eyes. Of these eyes, 64% had baseline visual acuity ≥ 79 letters (approximately 20/25 or better). In the subsequent era of OCT-guided determination of central-involved DME, the DRCR.net randomized trial comparing focal/grid photocoagulation to mild macular grid photocoagulation for DME also revealed only a modest correlation between OCT central subfield (CSF) thickness and concurrent visual acuity (r=0.52).[18]

Several questions remain regarding treatment of the cohort of eyes with central-involved DME and good visual acuity. Since recent trials for DME treatment have focused enrollment on eyes with visual impairment, we do not know definitively whether eyes with central-involved DME and good vision do better with anti-VEGF therapy initially, or focal/grid laser treatment or observation initially followed by anti-VEGF only if vision worsens. Results from DRCR.net Protocol I suggests that anti-VEGF therapy will be effective at reducing retinal thickening, but it is unclear whether this will translate into a benefit in visual acuity outcomes that outweighs the risks attendant upon multiple intravitreal injections, including endophthalmitis or the inconvenience and cost of treatments given as frequently as once a month. It is also unknown how long eyes with central-involved DME and good vision maintain vision of ≥ 20/25 without intervention.

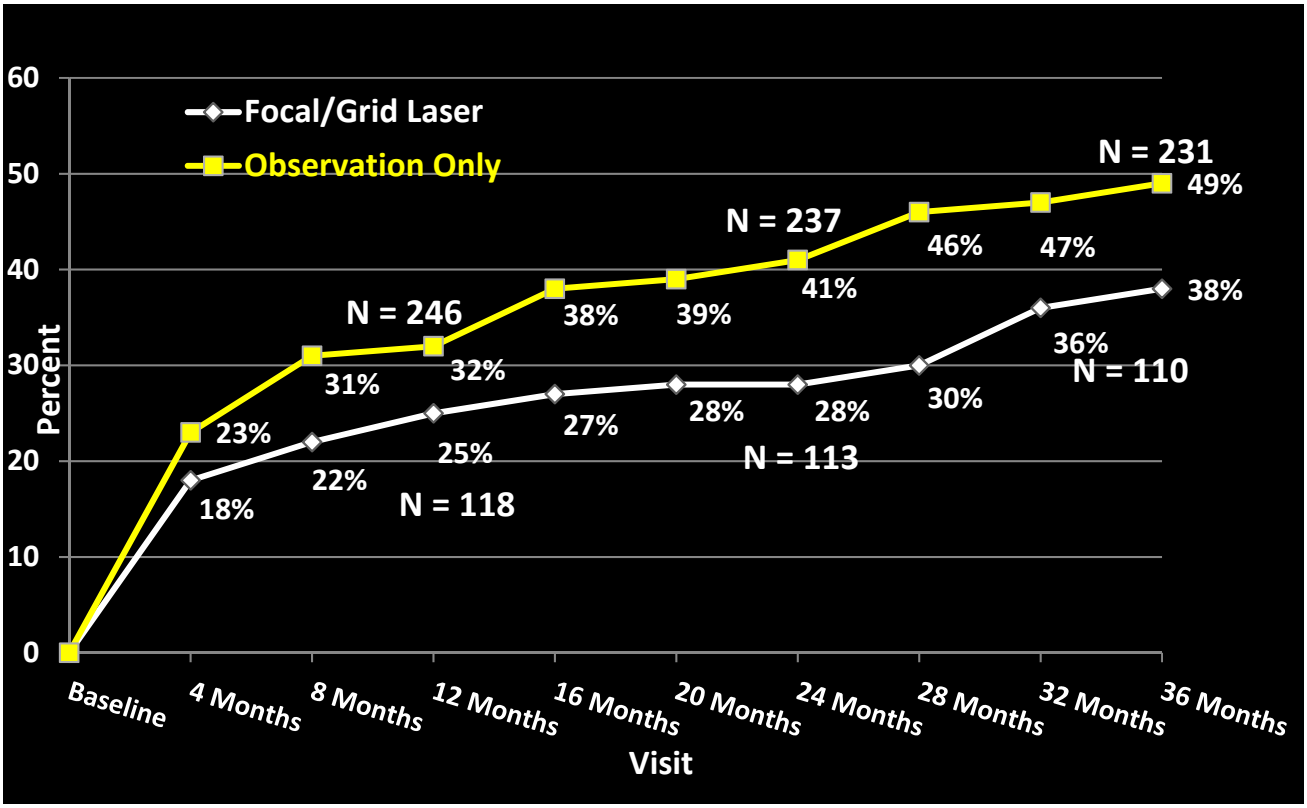
Some information regarding the natural history of eyes with center-involved DME (as assessed by grading of fundus photographs) and good vision could be obtained from the control group of the ETDRS. However, there was no OCT data collected for this study. The advent of OCT now allows us to determine the presence of and monitor changes in central-involved DME with increased sensitivity over the fundus photographic grading method used in the ETDRS. The optimal timing for initiating treatment in this group is uncertain. The American Academy of Ophthalmology's Preferred Practice Pattern for diabetic retinopathy recommends considering focal/grid photocoagulation treatment as soon as DME meets clinically significant criteria.[19] However, many patients may be reluctant to initiate invasive anti-VEGF therapy or laser treatment with potential associated side effects when they are visually asymptomatic or have good vision. Given the potentially large numbers of patients with central-involved DME and good vision, and the current lack of guidance regarding best treatment practice for this group of eyes, an answer to the questions of 1) whether eyes with central-involved DME and good visual acuity that receive prompt treatment have better outcomes than eyes in which treatment is deferred and 2) whether prompt treatment with focal/grid photocoagulation or intravitreal anti-VEGF is superior, might substantially impact clinical practice and management of DME for many patients with diabetes.

1.1.5 Rationale for Comparing Prompt Focal/Grid Photocoagulation + Deferred Anti-VEGF, Observation + Deferred Anti-VEGF, and Prompt Anti-VEGF for DME

Overview of Rationale:

From a subset of eyes in the ETDRS (unpublished data) that had center-involved DME (as assessed on fundus photographs) and visual acuity 20/25 or better, data are available on the course of vision loss in this cohort in the setting of laser or observation alone. The figure below (Figure 1) shows the percentage of eyes in this cohort that lost 5 or more letters, which investigators consider a clinically relevant vision loss in eyes starting with very good vision. Approximately 28% and 41% of eyes in the laser and observation groups, respectively, would ultimately have a visual acuity decrease by 2 years that would likely necessitate intervention with intravitreal anti-VEGF, the now established treatment for eyes with center-involved DME *and decreased vision*. On the other hand, by 2 years 72% to 59% of eyes in the laser and observation groups, respectively, maintained good vision, indicating that many eyes with DME and good vision likely will do very well for at least 2 years without intravitreal injections. The proposed study will evaluate whether it is better to promptly initiate anti-VEGF in eyes with center-involved DME and good vision or if it is better start with either laser treatment or observation and defer anti-VEGF treatment until vision has worsened.

Figure 1. Percent of Eyes in ETDRS with CI-DME and VA ≥ 20/25 at the Baseline Visit that lost 5 or more letters



This study has three proposed treatment arms: prompt focal/grid photocoagulation + deferred intravitreal anti-VEGF (Group A), observation + deferred intravitreal anti-VEGF (Group B), and prompt intravitreal anti-VEGF (Group C). The rationale for each of these arms is as follows:

Group A (prompt focal/grid photocoagulation + deferred intravitreal anti-VEGF): Even though eyes with central-involved DME and baseline visual impairment do not do as well overall when treated with laser alone as compared with ranibizumab in DRCR.net Protocol I, a substantial proportion of eyes with good baseline vision treated with laser alone demonstrate improved vision and decreased retinal thickening. Of the subset of eyes in the ETDRS with center-involved DME (as assessed on fundus photographs) that started with baseline visual acuity of 20/25 or better and were treated with focal laser (N = 113), 81% still had vision of 20/25 or better and 76% had no center-involved DME on fundus photographs at 2 years of follow-up, compared with 64% with 20/25 or better vision and 49% with no center-involved DME of similar eyes in the observation group (N= 224). At 3 years of 110 eyes in the laser group, 70% still had vision of 20/25 or better and 76% had no center-involved DME. In DRCR.net Protocol I, 27% percent of all eyes and 30% of eyes with baseline vision of 20/32 that received sham + focal/grid laser achieved resolution of macular edema, with Stratus CSF thickness < 250 μm and a 25 μm decrease in thickness from baseline by the 1 year visit.[12] Thus, many eyes with central-involved DME treated with laser may never need anti-VEGF therapy in order to have successful visual or anatomic outcomes. The initial use of focal/grid photocoagulation could offer substantial advantages over starting treatment with anti-VEGF in terms of reducing adverse events associated with intravitreal injections as well as fewer treatments given over time with less frequent follow-up needed and decreased associated costs. As alluded to above, in the ETDRS there was a low rate of vision loss in eyes with baseline visual acuity of 20/25 or better treated with laser; 25% of this group lost 5 or more letters, and only 11% lost 10 or more letters of vision at 1 year, with 28% and 13% of eyes loosing 5 and 10 letters at 2 years, respectively. Even if a small group of eyes with central-involved DME treated with laser do not do as well as those treated promptly with anti-VEGF therapy initially, if visual outcomes become equivalent between these groups after rescue therapy with anti-VEGF treatment, clinicians and patients would likely still elect to begin with laser treatment and defer anti-VEGF treatment until a lack of response to laser treatment is clearly demonstrated.

Group B (observation + deferred intravitreal anti-VEGF): Although it has been demonstrated that ranibizumab + prompt or deferred laser is well-tolerated and effective in increasing vision gain and decreasing vision loss in patients with central-involved DME, the optimal timing for initiating anti-VEGF treatment in eyes with central-involved DME is uncertain. There was no significant difference in treatment effect between eyes that were and were not treatment naïve at baseline in DRCR.net Protocol I, suggesting that eyes that are not initially treated with anti-VEGF can benefit from anti-VEGF treatment if they continue to experience visual impairment from DME. On the other hand, three year data from the RISE and RIDE trials suggest that a 2 year delay in treatment with anti-VEGF in eyes with baseline visual impairment and central-involved DME may result in worse visual acuity outcomes than those obtained with prompt anti-VEGF treatment.[20] It is unclear whether a shorter delay in treatment with rescue anti-VEGF therapy, if vision dropped, would result in visual outcomes more similar to those obtained with prompt anti-VEGF treatment. If this were the case, and visual outcomes were shown to be similar in eyes with prompt anti-VEGF as compared with eyes with initial deferral of therapy and rescue treatment with anti-VEGF, patients who are asymptomatic with good vision might prefer to defer treatment until there is evidence for worsening. Of the subset of eyes in the ETDRS with center-involved DME (as assessed on fundus photographs) that started with baseline visual acuity of 20/25 or better and were observed (N = 237), 32% of this group lost 5 or more letters of vision at 1 year, with 41% loosing 5 or more letters at 2 years. Therefore, based on this ETDRS, many eyes will do quite well for at least 2 years without laser or anti-VEGF

therapy. Thus, deferring all treatment until there are signs of visual acuity worsening is a rational approach to avoid treatment that would not be needed.

Group C (prompt intravitreal anti-VEGF): As reviewed above, there is a preponderance of evidence that demonstrates that ranibizumab treatment is effective in reducing retinal thickening in eyes with central-involved DME and vision of 20/32 or worse. Given a similar underlying pathophysiology it would seem highly likely that ranibizumab will be similarly effective at improving retinal thickening in eyes with central-involved DME and vision that is better than 20/25. Furthermore, prompt anti-VEGF therapy may be considered superior to prompt focal/grid photocoagulation + deferred intravitreal anti-VEGF therapy for some patients if any vision loss associated with focal/grid photocoagulation cannot be recovered once anti-VEGF is initiated. In addition, the initiation of prompt intravitreal anti-VEGF therapy may reduce the total number of injections needed long-term compared with initiation of intravitreal anti-VEGF once vision loss has occurred.

1.1.6 Aflibercept

The anti-VEGF drug to be used in this trial is intravitreal aflibercept injection, also known as VEGF-Trap-Eye or Aflibercept (Eylea®), which is a soluble decoy receptor fusion protein that has a high binding affinity to all isoforms of VEGF as well as to placental growth factor. This drug was first reported as a possible treatment for DME in 2009 in a phase one study that enrolled five study participants with center-involved DME.[21] After a single injection of 4.0 mg VEGF-Trap-Eye, five out of five eyes demonstrated reduction in retinal thickening at four weeks that was maintained in 4/5 eyes up to six weeks. There was a median improvement in visual acuity of nine and three letters at four and six weeks, respectively. No ocular toxicity was seen over the six week observation period. Results from a larger, phase two trial have been subsequently published.[22] In this study, 221 participants with center-involved DME were randomized to one of five groups: macular laser therapy, 0.5 mg aflibercept every four weeks, 2 mg aflibercept every four weeks, 2 mg aflibercept every four weeks times 3 doses followed by every 8-week dosing, or 2 mg aflibercept every four weeks times three doses followed by as needed dosing. Eyes that received aflibercept had greater mean improvement in visual acuity from baseline at week 24 as compared with eyes that received macular laser (8.5 to11.4 letter score increase versus a 2.5 letter score increase). The visual gains in the aflibercept arms as compared with the macular laser arm were sustained through 52 weeks.[23] Over 1 year, rates of ocular adverse events were similar to those reported in other trials involving intravitreal injections. Two cases of endophthalmitis and one case of uveitis occurred (all in aflibercept treatment groups). Seven deaths (4.0%) occurred in the groups randomized to VEGF-Trap-Eye treatment as compared with 1 (2.3%) in the group treated with laser. Myocardial infarction or cerebrovascular accident occurred in 6 (3.4%) participants treated with aflibercept as compared with 1 (2.3%) participant treated with laser alone. Percentages of study participants that experienced events meeting Antiplatelet Trialists' Collaboration (APTC) Criteria were 5.1% (N = 9) in the combined aflibercept groups and 4.5% (2) in the laser group.[24]

Aflibercept received approval in November 2011 by the United States Food and Drug Administration for the treatment of neovascular age-related macular degeneration at a recommended dose of 2 mg every 4 weeks for the first 12 weeks, followed by 2 mg every 8 weeks thereafter or monthly dosing.[25] This approval was based on results from two Phase three clinical trials (VIEW 1 and VIEW 2) that assigned participants with neovascular age-related macular degeneration one of four dosing regimens: ranibizumab 0.5 mg every four weeks, aflibercept 2 mg every four weeks, aflibercept 0.5 mg every four weeks, and aflibercept 2 mg

given every eight weeks following three initial monthly doses.[26] All three regimens of aflibercept were demonstrated as non-inferior to monthly ranibizumab in terms of the proportion of subjects who lost fewer than a 15 letter score from baseline. All aflibercept treatment groups gained vision from baseline to one year, with mean gains ranging from 7.6 to 10.9 letter score across the two studies. Serious ocular adverse events, including endophthalmitis, occurred at rates <0.1% per injection in both studies and there did not appear to be a dose or drug-related increase in APTC events in either study. In 2012, Aflibercept was additionally approved by the United States Food and Drug Administration for treatment for macular edema due to central retinal vein occlusion. The COPERNICUS and GALILEO studies demonstrated that eyes with macular edema secondary to central retinal vein occlusion had better visual outcomes at 6 months and 1 year when treated with at least 6 initial monthly injections of aflibercept as compared with sham.[27-29] Common ocular adverse events in the COPERNICUS trial were conjunctival hemorrhage and eye pain. APTC events through week 52 occurred in 0.9% (1) of the aflibercept-treated eyes and 2.7% (2) of the eyes treated initially with sham and then with aflibercept as needed after 6 months.[24]

1.1.7 Summary of Rationale for the Study

DRCR.net Protocol I and other studies have demonstrated that ranibizumab therapy is well-tolerated and more effective than laser alone in increasing vision gain and decreasing vision loss for the duration of at least 2 years in patients with central-involved DME causing vision loss. However, the optimal treatment has not been established in eyes that maintain good vision despite the presence of central-involved DME. This proposed study will compare prompt intravitreal anti-VEGF therapy, prompt focal/grid photocoagulation with deferred intravitreal anti-VEGF, and observation with deferred intravitreal anti-VEGF treatment in eyes with central-involved DME with good vision to help address this question. Initiating prompt anti-VEGF may result in superior visual acuity outcomes and/or reduce the long term number of injections needed to maintain good vision. On the other hand, if prompt anti-VEGF does not result in better visual acuity outcomes as compared with deferring anti-VEGF, either in the setting of prompt laser or observation, deferring anti-VEGF treatment might decrease rates of adverse events associated with intravitreal injections such as endophthalmitis. Deferral of prompt anti-VEGF treatment might also result in decreased inconvenience and costs associated with potentially monthly anti-VEGF treatments, while possibly preserving visual acuity in eyes with central-involved DME.

1.2 Study Objective

To compare the safety and efficacy of prompt focal/grid photocoagulation + deferred intravitreal anti-VEGF, observation + deferred intravitreal anti-VEGF, and prompt intravitreal anti-VEGF in eyes with central-involved DME and good visual acuity defined as a Snellen equivalent of 20/25 or better (electronic-ETDRS letter score of 79 or better).

1.3 Study Design and Synopsis of Protocol

A. Study Design

- Randomized, controlled, phase III multi-center clinical trial.

B. Major Eligibility Criteria

a. Age >=18 years

b. Type 1 or type 2 diabetes

c. Ophthalmoscopic evidence of center-involved DME in study eye confirmed on OCT at two consecutive visits within 1 to 28 days; defined by OCT CSF thickness on one of the following spectral domain OCT machines:

   - OCT CSF thickness at the screening visit:
     - Zeiss Cirrus: ≥ 290µ in women, and ≥ 305µ in men
     - Heidelberg Spectralis: ≥ 305µ in women, and ≥ 320µ in men
   - OCT CSF thickness at the randomization visit:
     - Zeiss Cirrus: ≥ 275µ in women, and ≥ 290µ in men
     - Heidelberg Spectralis: ≥ 290µ in women, and ≥ 305µ in men

d. Best corrected visual acuity letter score in study eye ≥ 79 (approximate Snellen equivalent 20/25 or better) at two consecutive visits within 1 to 28 days

e. No history of prior laser or other surgical, intravitreal, or peribulbar treatment for DME in the study eye within the prior 12 months.

- *If treatment for DME was given more than 12 months prior:*
  - *no more than 1 prior focal/grid macular photocoagulation session, AND*
  - *no more than 4 prior intraocular injections, AND*
  - *in the investigator's judgment, the eye may possibly benefit from all of the possible study treatments.*
- Enrollment will be limited to a maximum of 50% of the planned sample size with any history of prior treatment for DME. Once this number of eyes has been enrolled, any history of prior treatment for DME will be an exclusion criterion

C. Observational Phase

Potential study participants who are not willing or able to participate in the randomized trial may be enrolled into an observational phase and subsequently reconsidered for randomization. The objective of the observational phase is to collect additional data on the natural history of the cohort.

D. Randomization Phase

1. Treatment Groups

Eligible and willing study participants (one eye per participant) will be assigned randomly (1:1:1) to one of the three following groups:

a. Prompt focal/grid photocoagulation + deferred intravitreal anti-VEGF

b. Observation + deferred intravitreal anti-VEGF

c. Prompt intravitreal anti-VEGF

For eyes in the deferred intravitreal anti-VEGF groups (either observation or focal/grid photocoagulation), intravitreal anti-VEGF will be provided if visual acuity decreases by at least 10 letters from baseline visual acuity (defined as the mean of the screening and randomization

visual acuity) at one study visit or 5 to 9 letters from the baseline visual acuity at two consecutive study visits, with vision loss presumed to be due to DME. Further details on the treatment schedule and criteria for retreatment are described in section 5.3.

The anti-VEGF drug provided will be Eylea® (intravitreal aflibercept injection), which is made by Regeneron Pharmaceuticals, Inc. and is approved by the FDA for the treatment of neovascular age-related macular degeneration and macular edema due to central retinal vein occlusion.

2. Sample Size

- A minimum of 702 eyes (one per study participant)

3. Duration of Follow-up

- Primary endpoint will be at 2 years

4. Follow-up Schedule

➢ **Treatment Visits:**

- Prompt anti-VEGF group: visits every 4 weeks during first 24 weeks, visits every 4 to 16 weeks thereafter depending on treatment administered.
- Deferred anti-VEGF groups (prompt focal/grid photocoagulation and observation groups): visits at week 8 and 16, followed by visits every 16 weeks thereafter.*

*For the deferred groups, the follow-up visit interval will be decreased if macular edema is worsening on OCT or visual acuity drops 5 to 9 letters, to assess for continued vision loss needing anti-VEGF treatment. Once anti-VEGF is initiated, visits will be every 4 weeks during the first 24 weeks of treatment and every 4 to 16 weeks thereafter. Further details on the follow-up visit schedule are described in section 5.1.

➢ **Outcome Visits:**

- All participants will have visits at 1 and 2 years for outcome assessment.

5. Main Efficacy Outcomes

Primary:

- Percent of eyes that have lost at least 5 letters of visual acuity at 2 years compared with baseline visual acuity (mean of the two visual acuity letter scores within 1 to 28 days required for eligibility).

Secondary:

At 1 and 2 years:

- Percent of eyes with at least 5, 10 and 15 letter losses in visual acuity from baseline visual acuity
- Percent of eyes with at least 5 letter gain in visual acuity from baseline visual acuity
- Mean change in visual acuity, adjusted for baseline visual acuity
- Mean change in OCT CSF thickness, adjusted for baseline mean thickness (mean of the two OCT central subfield thickness measurements within 1 to 28 days required for eligibility)

- Percent of eyes with at least a 1 and 2 log step increase or decrease on OCT CSF thickness
- Percent of eyes with OCT CSF thickness less than the gender-specific spectral domain equivalent of 250 µm on Zeiss Stratus and at least a 10% OCT CSF thickness decrease
- Number of injections and/or focal/grid photocoagulation sessions performed
- Number of scheduled and unscheduled visits
- Mean change in low-contrast visual acuity on Electronic Visual Acuity Tester
- Total cost of follow-up and treatment
- For eyes randomly assigned to deferred anti-VEGF, the percentage of eyes needing anti-VEGF treatment.

6. Main Safety Outcomes

Injection-related: endophthalmitis, retinal detachment, retinal tears, cataract, intraocular hemorrhage, increased intraocular pressure.
Ocular drug-related: inflammation, cataract, cataract surgery, increased intraocular pressure, glaucoma medications, glaucoma surgery, new or worsening traction retinal detachment.
Systemic drug-related: hypertension, cardiovascular events, cerebrovascular events.

7. Schedule of Study Visits and Examination Procedures

	Screening*	**0**	**Visits Every 4-16w****	**52w**	**104w**
Visit Window			(± 1-4w)	(± 2w)	(± 4w)
E-ETDRS best corrected visual acuity [a]	X	X	X	X	X
Low-contrast acuity on EVA[b]		X		X	X
OCT [c]	X	X	X	X	X
Eye Exam[d]		X	X	X	X
7-field Fundus Photography [c]		X		X	X
Fluorescein Angiography [g]		X			
Blood pressure		X			
HbA1c [e]		X	X[f]	X	X

*= a screening visit is required within 1 to 28 days of randomization in order to confirm the OCT and visual acuity eligibility criteria at two consecutive visits. If the participant is not willing or able to be randomized, they will have the option to enter the observational phase at this time if certain criteria are met.

**= visits every 4 weeks during the first 24 weeks for eyes assigned to prompt anti-VEGF treatment or eyes in the deferred groups that have had intravitreal anti-VEGF treatment initiated for DME. After 24 weeks from initial anti-VEGF treatment for DME, visits every 4 to16 weeks based on treatment administered. For eyes assigned to deferred anti-VEGF, 2 subsequent 8-week visits after randomization, followed by every 16-week visits until there is worsening or anti-VEGF treatment is initiated.

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

b= at sites with electronic visual acuity (EVA) low-contrast acuity testing capabilities

c= study eye only

d= both eyes at randomization and study eye only at each follow-up visit unless treatment is given in the non-study eye, at which point an ocular exam also will be performed on the non-study eye for safety assessment. Includes slit lamp exam (including assessment of lens), measurement of intraocular pressure, and dilated ophthalmoscopy.

e= must be performed using the same lab (or DCA Vantage Analyzer) at baseline and follow-up

f= at 16 weeks (± 4 weeks) only

g = only obtained by a subset of investigators where the investigator routinely performs FA prior to focal/grid laser treatment or is willing to do so for the study and agrees to use the FA to guide the focal/grid laser treatment. FA will also be obtained prior to focal/grid laser re-treatment in the laser group on eyes where an FA was obtained at baseline.

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 Procedures Manual, Photography Testing Procedures Manual, Fluorescein Angiography Testing Procedure Manual, and Study Procedures Manual) provide details of the examination procedures and intravitreal injection procedure.

Visual acuity testers and OCT technicians will be masked to treatment group at the annual visits. Investigators and study participants are not masked to treatment group.

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

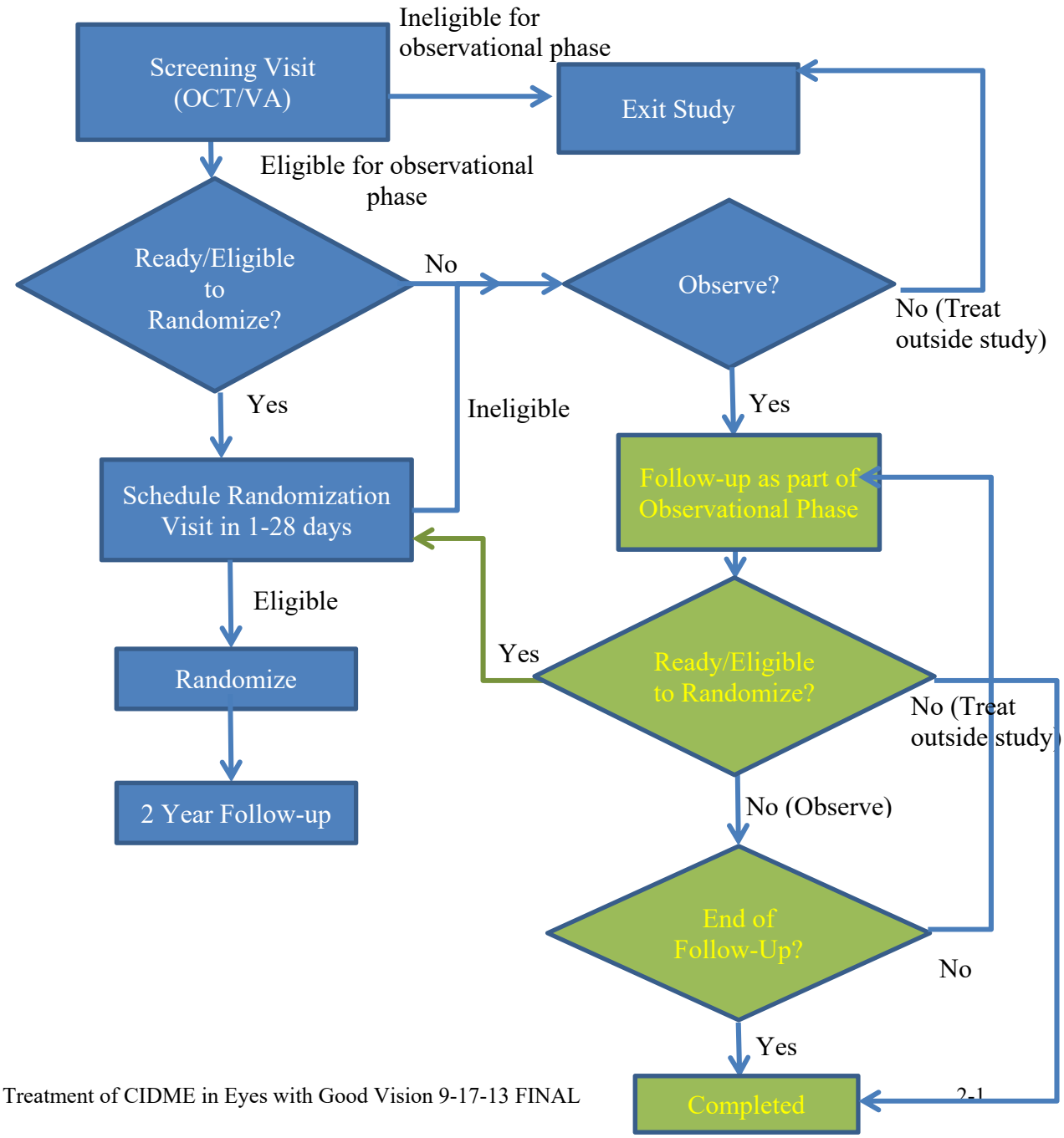
There is no restriction on the number of study participants to be enrolled by a site.

Chapter 2. INITIAL SCREENING AND OBSERVATIONAL PHASE

2.1 Screening for Observational Phase or Randomized Trial

Potentially eligible participants will be screened and if eligible, given the option to complete the randomization visit. Patients who are currently not willing or able to be randomized in the main trial but meet the criteria below in Section 2.2.1 will be followed as part of an observational phase and will be subsequently reconsidered for randomization. Enrollment into the observational phase may continue for the duration of the recruitment period of the main trial. However, if the cost of additional participant enrollment into the observational phase is prohibitive, a decision will be made whether to continue or stop enrollment into the observational phase even if recruitment is ongoing for the trial.

The following flow chart depicts the process for determining whether a participant will enter the randomized trial or the observational phase and the subsequent follow-up.



2.2 Observational Phase Enrollment

2.2.1 Eligibility and Informed Consent

Potential eligibility for the observational phase 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. A separate consent will be used for randomization into the main trial if/when applicable.

Participant-level Criteria

To be eligible, all of the following inclusion criteria and none of the following exclusion criteria must be met:

Inclusions

1. Age ≥18 years.
2. Diagnosis of diabetes mellitus (type 1 or type 2).
3. At least one eye meets the study eye criteria listed below.
4. Able and willing to provide informed consent.
5. Not able or willing to be randomized at this time.

Exclusions

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. Known allergy to any component of the study drug.
9. Pregnant or intending to become pregnant within the next 2 years.
10. 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 2 years.

Study Eye Criteria

The study participant must have at least one eye meeting all of the inclusion criteria and none of the exclusion criteria below. A study participant can have two study eyes only if both are eligible at the time of enrollment. If one eye will be randomized into the main trial and the fellow eye meets criteria below, it may be simultaneously enrolled into the observational phase.

Inclusions

a. Best corrected visual acuity letter score in study eye ≥ 79 (approximate Snellen equivalent 20/25 or better).
b. On clinical exam, definite retinal thickening due to DME involving the center of the macula.
c. DME confirmed on OCT, defined as CSF thickness on one of the following spectral domain OCT machines:
    - Zeiss Cirrus: ≥ 290μ in women, and ≥ 305μ in men

- Heidelberg Spectralis: ≥ 305μ in women, and ≥ 320μ in men

d. Media clarity, pupillary dilation, and individual cooperation sufficient for adequate OCT.

e. The investigator intends to observe at this time (no immediate DME treatment is planned).

Exclusions

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 contributing to the macular edema.*

g. Any history of prior laser or other surgical, intravitreal, or peribulbar treatment for DME (such as focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids, or anti-VEGF) within the prior 12 months.
   - *If treatment for DME was given more than 12 months prior:*
     - *no more than 1 prior focal/grid macular photocoagulation session AND*
     - *no more than 4 prior intraocular injections*

h. History of intravitreal anti-VEGF for an ocular condition other than DME (e.g. choroidal neovascularization, central retinal vein occlusion, PDR) within the prior 6 months or anticipated need in the next 6 months.

i. Any history of vitrectomy.

j. Aphakia.

2.3 Observational Phase Follow-Up and Testing

The study eye(s) will be followed in the observational phase until one of the following occurs:

1. The eye is randomized.
2. The eye receives non-topical DME treatment as part of usual care.
3. The participant reaches two years (104 weeks) from enrollment.

2.3.1 Visit Schedule

The schedule of protocol-specified observational phase visits is as follows:

- 17 weeks (± 4 weeks)
- 34 weeks (± 4 weeks)
- 52 weeks (± 4 weeks)
- 69 weeks (± 4 weeks)
- 86 weeks (± 4 weeks)
- 104 weeks (± 4 weeks)

If the investigator chooses to see the participant more frequently as part of usual care or the participant experiences visual acuity loss requiring earlier follow-up, limited data will be collected at those visits.

2.3.2Testing Procedures

A history will be elicited from the subject and extracted from available medical records at enrollment. Data to be collected may include: age, gender, ethnicity and race, diabetes history and current management, other medical conditions, as well as ocular diseases, surgeries, and treatment.

The following procedures will be performed at each protocol visit unless otherwise specified.

1. E- ETDRS visual acuity testing in each eye (best corrected)
   - A protocol refraction in the study eye(s) is required at all protocol visits.
2. OCT on the study eye(s)
3. Ocular exam in the study eye(s), including slit lamp examination, lens assessment, measurement of intraocular pressure and dilated ophthalmoscopy
4. Measurement of blood pressure (enrollment only)
5. Laboratory Testing- HbA1c (enrollment only)
   - *HbA1c does not need to be repeated if available in the prior 3 months. If not available at the time of enrollment, the subject may be enrolled but the test must be obtained within 3 weeks after enrollment.*

2.4 Discontinuation of Observational Phase

The observational phase may be discontinued by the Executive Committee prior to the preplanned completion of follow-up for all study participants.

2.5 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 if necessary to facilitate the scheduling of the study participant for follow-up visits. A participant-oriented newsletter may be sent twice a year. A study logo item may be sent once a year.

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

2.6 Study Participant Reimbursement

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

2.7 Observational Phase Statistical Methods

The primary objective of the observational phase is to collect data on the natural history of eyes that present with CI-DME and good vision that do not enroll in the randomized trial initially. Therefore, the proportion and 95% confidence interval of eyes that meet the following endpoints will be determined:

- Never need treatment
- Receive non-topical DME treatment
- Are randomized into Protocol V

In addition, data from the observational phase will be used in exploratory analyses to evaluate the following:

- If there are any subgroups for which there appears to be a higher percentage of eyes that do not need DME treatment
- Compare outcome (visual acuity and OCT) data between eyes observed for the duration of the observational phase (i.e. never need treatment) and eyes in the randomized treatment groups
- Compare outcome (visual acuity and OCT) data between eyes that are randomized immediately and eyes that are randomized after being followed in the observational phase initially

Additional details on the statistical approaches will be included in a detailed statistical analysis plan.

Chapter 3.
RANDOMIZED TRIAL ELIGIBILITY AND ENROLLMENT

3.1 Identifying Eligible Study Participants and Obtaining Informed Consent

A minimum of 702 eyes (one per participant) are expected to be enrolled into the randomized trial. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Study participants who have signed an informed consent form 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 patients who are considered potentially eligible for the study based on a routine-care exam, the study protocol will be discussed with the potential study participant by a study investigator and clinic coordinator. The potential study participant will be given the Informed Consent Form to read. Potential 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 randomization and will be for participation in the study. A single consent form will have two signature/date lines for the study participant: one for a study participant to give consent for the completion of the screening procedures and one for the study participant to document consent for the randomized trial. Study participants will be provided with a copy of the signed Informed Consent Form.

Once a study participant is randomized, that participant will be counted regardless of whether the assigned treatment is received. Thus, the investigator must not proceed to randomize an individual until he/she is convinced that the individual is eligible and will accept assignment to any one of the three treatment groups.

3.2 Study Participant Eligibility Criteria

3.2.1 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 3.2.2.
4. Fellow eye meets criteria in section 3.2.3.
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 within 30 days of randomization that involved treatment with any drug that has not received regulatory approval for the indication being studied.
   - *Note: study participants cannot receive another investigational drug while participating in the study.*
10. Known allergy to any component of the study drug.
11. Blood pressure >180/110 (systolic above 180 **OR** diastolic above 110).
    - *If blood pressure is brought below 180/110 by anti-hypertensive treatment, individual can become eligible.*
12. Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization.
    - *These drugs should not be used during the study.*
13. For women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next 24 months.
    - *Women who are potential study participants should be questioned about the potential for pregnancy. Investigator judgment is used to determine when a pregnancy test is needed.*
14. Individual is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the 24 months of the study.

3.2.2 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 can only have one study eye. If both eyes are eligible at the time of randomization, the study eye will be selected by the investigator and subject before randomization. The non-study eye should be considered for enrollment into the observational phase.

The eligibility criteria for a study eye are as follows:

Inclusion

a. Best corrected E-ETDRS visual acuity letter score ≥ 79 (approximate Snellen equivalent 20/25 or better) at two consecutive visits within 1 to 28 days.

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

c. Diabetic macular edema confirmed on OCT at two consecutive visits within 1 to 28 days (screening and randomization); defined by OCT CSF thickness on one of the following spectral domain OCT machines:

Screening Visit:

- Zeiss Cirrus: ≥ 290μ in women, and ≥ 305μ in men
- Heidelberg Spectralis: ≥ 305μ in women, and ≥ 320μ in men

Randomization Visit:

- Zeiss Cirrus: ≥ 275μ in women, and ≥ 290μ in men
- Heidelberg Spectralis: ≥ 290μ in women, and ≥ 305μ in men

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

d. The investigator is comfortable with the eye being randomly assigned to any of the three treatment groups (observation, laser, or anti-VEGF initially).

- *If focal/grid photocoagulation is contraindicated because all leaking microaneurysms are too close to the fovea or the investigator believes the DME that is present will not benefit from focal/grid photocoagulation, the eye should not be enrolled.*

e. Media clarity, pupillary dilation, and individual cooperation sufficient for adequate OCT and fundus photographs.

Exclusions

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

f. Macular edema is considered to be due to a cause other than DME.
   - *An eye should <u>not</u> 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 contributing to the macular edema.*

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

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. Cataract is present that, in the opinion of the investigator, may alter visual acuity during the course of the study.

j. Any history of prior laser or other surgical, intravitreal, or peribulbar treatment for DME (such as focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids, or anti-VEGF) within the prior 12 months.

- *If treatment for DME was given more than 12 months prior:*
  - *no more than 1 prior focal/grid macular photocoagulation session, AND*
  - *no more than 4 prior intraocular injections, AND*
  - *in the investigator's judgment, the eye may possibly benefit from all of the possible study treatments.*
- *Enrollment will be limited to a maximum of 50% of the planned sample size with any history of treatment for DME. Once this number of eyes has been enrolled, any history of treatment for DME will be an exclusion criterion.*

k. History of topical steroid or NSAID treatment within 30 days prior to randomization.

l. History of intravitreal or peribulbar corticosteroid within 4 months prior to randomization for an ocular condition other than DME.

m. History of intravitreal anti-VEGF for an ocular condition other than DME (e.g. choroidal neovascularization, central retinal vein occlusion, PDR) within the prior 6 months or anticipated need in the 6 months following randomization.

n. History of PRP within 4 months prior to randomization or anticipated need for PRP in the 6 months following randomization.

o. Any history of vitrectomy.

p. History of major ocular surgery (cataract extraction, scleral buckle, any intraocular surgery, etc.) within prior 4 months or anticipated within the next 6 months following randomization.

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

r. Aphakia.

s. Exam evidence of external ocular infection, including conjunctivitis, chalazion, or significant blepharitis.

3.2.3 Non-Study Eye Criteria

If anti-VEGF treatment is indicated for any condition in the non-study eye at any time during the study, the investigator must be willing to use the study anti-VEGF drug (2.0 mg aflibercept) for the non-study eye. If the non-study eye is currently being treated with a different anti-VEGF drug for any condition, then the investigator and patient must be willing to switch to aflibercept. If the investigator or patient is unwilling to change anti-VEGF treatment in the non-study eye, the patient should not be enrolled.

3.3 Screening Evaluation and Baseline Testing

3.3.1 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, gender, ethnicity and race, diabetes history and current management, other medical conditions, medications being used, as well as ocular diseases, surgeries, and treatment.

3.3.2 Baseline Testing Procedures

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

- 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, Photography Testing Procedures Manual, Fluorescein Angiography Testing Procedure Manual, and Study Procedures Manual). Visual acuity testing, ocular exam, fundus photography, and OCT will be performed by DRCR.net certified personnel.
- The fundus photographs and fluorescein angiograms will be sent to the Fundus Photograph Reading Center for grading.
- OCTs meeting DRCR.net criteria for manual grading will be sent to a reading center, but study participant eligibility is determined by the site (i.e., individuals deemed eligible by the investigator will be randomized without pre-randomization reading center confirmation).

1. E-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester (including protocol refraction) in each eye *(at screening visit and on day of randomization).*
    - *This testing procedure has been validated against 4-meter ETDRS chart testing.*[30]
    - *A best-corrected E-ETDRS visual acuity (using protocol refraction) must be performed at two consecutive visits (screening and randomization), 1 to 28 days apart, to confirm eligibility.*
2. Low-contrast visual acuity in the study eye using the Electronic Visual Acuity Tester; if site has the capability *(on day of randomization).*
3. OCT on study eye *(at screening and on day of randomization).*
    - *OCT must be performed at two consecutive visits (screening and randomization), 1 to 28 days apart, to confirm eligibility.*
4. Ocular examination on each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy *(on day of randomization).*
5. ETDRS protocol 7 modified-field or 4 wide-field digital stereoscopic fundus photography in the study eye *(within 28 days prior to randomization).*
6. Digital fluorescein angiogram (FA) in the study eye *(within 28 days prior randomization)* at select sites
    a. Only obtained by a subset of investigators where the investigator routinely performs FA prior to focal/grid laser treatment or is willing to do so for the study and agrees to use the FA to guide the focal/grid laser treatment.
7. Measurement of blood pressure.
8. Laboratory Testing- HbA1c.

- *If not available at the time of randomization, the individual may be enrolled but the test must be obtained within 3 weeks after randomization. The same lab (or DCA Vantage Analyzer) must be used at baseline and follow-up.*

3.4 Enrollment/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 treatment (if randomly assigned to prompt focal/grid photocoagulation or prompt intravitreal anti-VEGF) must be given on the day of randomization; therefore, a study participant should not be randomized until this is possible.
3. Randomization is completed on the DRCR.net website.

- Study participants will be randomly assigned (stratified by site and recent or planned DME treatment* in the non-study eye) with equal probability to receive either:
    - Prompt focal/grid photocoagulation + deferred intravitreal anti-VEGF
    - Observation + deferred intravitreal anti-VEGF
    - Prompt intravitreal anti-VEGF

*Randomization will be stratified by recent (within 4 months) or planned DME treatment because of the more frequent visit schedule required as part of usual care for these participants. More frequent visits in the deferred groups than required by protocol could result in earlier initiation of anti-VEGF in such participants.

Chapter 4.
TREATMENT REGIMENS

4.1 Introduction

Each eye is assigned to one of the three treatment groups

The treatment groups are as follows:

a. Prompt focal/grid photocoagulation + deferred intravitreal anti-VEGF

b. Observation + deferred intravitreal anti-VEGF

c. Prompt intravitreal anti-VEGF

Treatment procedures are described below. The timing and criteria for retreatment are detailed in chapter 5.

4.1.1 Prompt Focal/Grid Photocoagulation + Deferred Anti-VEGF Group

Focal/grid photocoagulation is administered on the day of randomization for eyes assigned to prompt focal/grid photocoagulation + deferred intravitreal anti-VEGF. The timing and criteria for retreatment with focal/grid photocoagulation and initiation of anti-VEGF treatment are detailed in chapter 5.

4.1.2 Observation + Deferred Anti-VEGF Group

Treatment is not administered at baseline in eyes assigned to observation + deferred intravitreal anti-VEGF. Timing and criteria for initiation of anti-VEGF treatment are detailed in chapter 4.

4.1.3 Prompt Anti-VEGF Group

Intravitreal 2.0 mg aflibercept is administered on the day of randomization in eyes assigned to the prompt anti-VEGF group. The timing and criteria for retreatment are detailed in chapter 4.

4.2 Focal/Grid Photocoagulation Procedure

For study eyes that receive focal/grid photocoagulation, the laser treatment 'session' should generally be completed in a single 'sitting'. The photocoagulation treatment technique, as described below, is a modification of the ETDRS technique and is the treatment approach that is commonly used in clinical practice. Use of fluorescein angiography to direct the treatment is at the discretion of the investigator.

Burn Characteristic	**Focal/Grid Photocoagulation (non-PASCAL guidelines)* (DRCR.net focal/grid laser technique)**
Direct Treatment	Directly treat all microaneurysms (MA) in areas of retinal thickening between 500 and 3000 μm from the center of the macula (although may treat between 300 and 500 μm of macula if central-involved edema persists after initial focal photocoagulation, but generally not if the visual acuity is better than 20/40). If a fluorescein is obtained, the FA should be used to identify the MAs in the areas defined above.
Change in MA Color with Direct Treatment	Not required, but at least a mild gray-white burn should be evident beneath all microaneurysms
Spot Size for Direct Treatment	50 μm

Burn Duration for Direct Treatment	0.05 to 0.1 sec
Grid Treatment	Applied to all areas with edema not associated with microaneurysms. If fluorescein angiography is obtained, grid is applied to areas of edema with angiographic nonperfusion when judged indicated by the investigator.
Area Considered for Grid Treatment	500 to 3000 µm superiorly, nasally and inferiorly from center of macula 500 to 3500 µm temporally from macular center No burns placed within 500 µm of disc
Burn Size for Grid Treatment	50 µm
Burn Duration for Grid Treatment	0.05 to 0.1 sec
Burn Intensity for Grid Treatment	Barely visible (light gray)
Burn Separation for Grid Treatment	2 visible burn widths apart
Wavelength (Grid and Direct Treatment)	Green to yellow wavelengths

**Additional guidelines for performing laser treatment using the PASCAL are included in the Procedure Manual.*

Note:

- *The investigator may choose any laser wavelength for photocoagulation within the green to yellow spectrum. The wavelength used will be recorded.*
- *Lenses used for the laser treatment cannot increase or reduce the burn size by more than 10%. The Procedure Manual contains a listing of acceptable lenses.*

4.3 Intravitreal Aflibercept Injection (Eylea®)

Eylea® (intravitreal aflibercept injection) is made by Regeneron Pharmaceuticals, Inc. and is approved by the FDA for the treatment of neovascular age-related macular degeneration and macular edema due to central retinal vein occlusion.

Study eyes that receive anti-VEGF will receive a dose of 2.0 mg aflibercept in 0.05 cc. The physical, chemical and pharmaceutical properties and formulation are provided in the Clinical Investigator Brochure. Aflibercept for the study and non-study eye will be distributed by the Network.

4.4 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.

4.5 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.

4.6 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.

4.7 Non-Study Eye Injections

If the non-study eye is going to be treated for any condition which requires treatment with an anti-VEGF agent, study provided aflibercept must be used. However, if intravitreal anti-VEGF treatment is planned on the same day as an intravitreal injection in the study eye, the study eye will be injected first, followed by the non-study eye (see Procedures Manual for additional details). If a different intravitreal anti-VEGF injection than described above is desired in the non-study eye, a discussion with the Protocol Chair is required first.

Chapter 5.
FOLLOW-UP VISITS AND TREATMENT

5.1 Visit Schedule

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

Year 1

Treatment Assessment Visits:

- Prompt anti-VEGF group: visits every 4±1 weeks (with a minimum of 21 days between injections) for the first 24 weeks. After 24 weeks of follow-up, visits every 4 to 16 weeks depending on treatment given:
  - Visits every 4±1 weeks as long as injections are given.
  - The first two times an injection is deferred, the study participant will return in 4 weeks for re-evaluation. If deferral continues, the study participant will return in 8±2 weeks for re-evaluation before beginning the every 16±4 week schedule.
- Deferred anti-VEGF groups (focal/grid photocoagulation and observation groups):
  - Visits at 8 weeks and 16 weeks (±2 weeks) after randomization, followed by visits every 16±4 weeks thereafter as long as the eye is stable.*

*For the deferred groups, the follow-up visit interval will be more frequent if there is worsening on visual acuity or OCT CSF thickness according to the criteria below (unless focal/grid photocoagulation was administered, in which case follow-up should occur no sooner than 8 weeks).

- If visual acuity decreases 5 to 9 letters from baseline (mean visual acuity from the screening and randomization visit), the next visit will be in 4±2 weeks to check for continued vision loss needing anti-VEGF treatment (see section 5.3).
  - If visual acuity is no longer decreased, the next visit will be in 8 weeks to confirm visual acuity is no longer decreased before resuming the every 16-week schedule.
- If the OCT CSF thickness increases by ≥10% from the last visit, the follow-up interval will be cut in half (e.g. 8 weeks if previously 16 or 4 weeks if previously 8) with a minimum of every 4-week visits to check for vision loss needing anti-VEGF treatment (see section 5.3).
  - If OCT subsequently improves or stabilizes at two consecutive visits without vision loss, the next interval will be doubled (e.g. 8 weeks if previously 4 or 16 weeks if previously 8) with a maximum of every 16-week visits.
- If the OCT CSF thickness becomes ≥400 μm (or the spectral domain equivalent), visits will be every 8 weeks.
  - If OCT subsequently improves or stabilizes at two consecutive visits without vision loss, 16-week interval visits may be resumed.
- Once anti-VEGF is initiated, visits will be every 4 weeks for 24 weeks following initiation of anti-VEGF and every 4 to 16 weeks thereafter (see treatment schedule for prompt anti-VEGF group above for visit schedule after 24 weeks).

Outcome Visits:

- Visit at 52 weeks (±2 weeks) for all participants.

Year 2

Treatment Assessment Visits:

- Eyes receiving intravitreal injections:
  - Visits every 4±1 weeks (with a minimum of 21 days between injections) for the first 24 weeks following initiation of anti-VEGF treatment and as long as intravitreal injections are given.
  - After 24 weeks of anti-VEGF treatment, visits every 8 weeks (± 2) to 16 weeks (±4) once injections are deferred.
    Note: The first two times an injection is deferred, the study participant will return in 4 weeks for re-evaluation. If deferral continues, the study participant will return in 8 weeks for re-evaluation before beginning the every 16 week schedule.
- Eyes that have not received anti-VEGF injection during the study:
  - Visits every 16 weeks unless there is worsening (see criteria described in Year 1 above), at which point the next visit will be in 4 to 8 weeks to check for continued vision loss needing anti-VEGF treatment.

Outcome Visit:

- Visit at 104 weeks (±4 weeks) for all participants. This final outcome visit is for data collection only and will not include retreatment evaluation.

Additional visits may occur as required for usual care of the study participant.

5.2 Testing Procedures

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

Visual acuity testers (including refractionist) and OCT technicians will be masked to treatment group at the annual visits.

1. E-ETDRS visual acuity testing in each eye (best corrected).
   - A protocol refraction in the study eye is required at all protocol visits. Refraction in the non-study eye is only required at annual visits. When a refraction is not performed, the most recently performed refraction is used for the testing.
2. Low-contrast visual acuity in the study eye using the EVA at annual visits only; if site has the capability.
3. OCT on the study eye.
4. Ocular exam on the study eye, including slit lamp examination, lens assessment, measurement of intraocular pressure and dilated ophthalmoscopy. Non-study eyes that have received intravitreal anti-VEGF during the study will also receive an ocular exam for safety assessment.
5. Fundus photographs (7 modified or 4 wide-field digital stereoscopic) on the study eye at annual visits only.

6. Digital fluorescein angiogram (FA) in the study eye prior to focal/grid laser re-treatment in the laser group on eyes where an FA was obtained at baseline.
7. HbA1c at 16 weeks (± 4 weeks) and annual visits only.
    - *The same lab (or DCA Vantage Analyzer) must be used at baseline and follow-up.*

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.

5.3 Treatment During Follow Up

The treatment groups are as follows:

a. Prompt focal/grid photocoagulation + deferred intravitreal anti-VEGF
b. Observation + deferred intravitreal anti-VEGF treatment
c. Prompt intravitreal anti-VEGF

5.3.1 Initiation of Intravitreal Anti-VEGF in the Deferred Groups

For eyes in the deferred anti-VEGF groups (either observation or focal/grid), if there is a decrease in visual acuity presumed to be due to DME of at least 10 letters compared with the baseline visual acuity (mean of the screening and randomization visual acuity) at a single visit or 5 to 9 letter decrease compared with baseline visual acuity at two consecutive visits, an injection of anti-VEGF will be given. Once anti-VEGF injections are initiated, retreatment will follow the criteria described in section 5.3.2 below.

The protocol chair or designee must be contacted prior to deviation from the injection protocol.

5.3.2 Intravitreal Injection Retreatment

Once anti-VEGF injections are initiated (either at randomization in the prompt anti-VEGF group or once criteria are met in the deferred groups), the eye will be evaluated at each visit for retreatment. In general, an eye will continue to receive an injection if the eye is improving or worsening on OCT or visual acuity. The first time an eye has not improved or worsened, the eye will receive an injection. If the eye has not improved or worsened for at least 2 consecutive 4-week injections and the OCT CSF thickness is less than the gender specific spectral domain OCT threshold (see below) and visual acuity is 20/20 or better, then injection will be deferred. If the eye has not improved or worsened for at least 2 consecutive 4-week visits and the OCT CSF thickness is ≥ the gender specific spectral domain OCT threshold or visual acuity is worse than 20/20, the following will be done:

- If during the first 24 weeks of anti-VEGF treatment, an injection will be given.
- At and after 24 weeks, the injection will be deferred.

The protocol chair or designee must be contacted prior to deviation from the injection protocol. See the DRCR.net Procedure Manual for additional details.

Spectral domain OCT central subfield gender specific threshold:

- Zeiss Cirrus: 290 microns in women, and 305 microns in men
- Heidelberg Spectralis: 305 microns in women, and 320 microns in men

5.3.3 Initiation of Focal/Grid Photocoagulation While Receiving Anti-VEGF Injections

Once anti-VEGF injections are initiated (either at randomization in the prompt anti-VEGF group or once criteria are met in the deferred groups), focal/grid photocoagulation may be added at investigator discretion if after 24 weeks from the initial injection 1) the OCT CSF thickness is ≥ the spectral domain gender specific OCT CSF threshold (see above) or there is edema that is threatening the fovea AND 2) the eye has not improved on OCT (≥10% decrease) or visual acuity (≥5 letter increase) from the last two consecutive injections. If after 24 weeks from the initial injection, the eye is worsening on OCT (≥10% increase) or visual acuity (≥5 letter decrease) from the last two consecutive injections, focal/grid photocoagulation should be performed provided the investigator believes that macular edema is present for which focal photocoagulation is indicated.

Once focal/grid photocoagulation is added to anti-VEGF, retreatment with focal/grid photocoagulation will follow the criteria described in section 5.3.4 below.

5.3.4 Focal/Grid Photocoagulation Retreatment

Once focal/grid photocoagulation has been initiated (either at randomization in the prompt focal/grid photocoagulation group or once criteria are met to add to anti-VEGF treatment), retreatment with focal/grid photocoagulation will be given unless one of the following is present: 1) focal/grid photocoagulation has been given in the previous 13 weeks, 2) complete focal/grid photocoagulation has already been given in the investigator's judgment, 3) the OCT CSF thickness is < the spectral domain gender specific OCT CSF threshold and there is no edema threatening the fovea, 4) the eye has improved since the last laser treatment, or 5) all treatable microaneurysms are located only within 500 microns of the foveal center. The protocol chair or designee must be contacted prior to deviating from the focal/grid photocoagulation protocol. See the DRCR.net Procedure Manual for details.

Eyes assigned to prompt focal/grid photocoagulation with deferred anti-VEGF will not receive retreatment with focal/grid photocoagulation once anti-VEGF is initiated, until the criteria in section 5.3.3 above are met.

Chapter 6.
MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

6.1 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.

6.2 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.

6.3 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 randomization, 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.

6.4 Use of Intravitreal Anti-VEGF for Conditions Other than DME in the Study Eye

If an ocular condition develops in the study eye for which aflibercept is an FDA approved treatment (e.g. neovascular AMD, macular edema following central retinal vein occlusion), the use of study aflibercept is at the discretion of the investigator. Any off-label use of anti-VEGF in the study eye for an ocular condition other than DME (e.g. PDR, vitreous hemorrhage), will require discussion with and approval by the protocol chair or designee. Study aflibercept must be used for any anti-VEGF treatment in the study eye.

6.5 Treatment of Macular Edema in Non-study Eye

Treatment of DME in the non-study eye is at investigator discretion. However, if anti-VEGF treatment will be given, study aflibercept must be used (see section 4.7).

6.6 Diabetes Management

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

6.7 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 or 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.

6.8 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.

6.9 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 enrollment, and approximately every six months thereafter. 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 may be sent twice a year. A study logo item may be sent once a year.

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

6.10 Study Participant Reimbursement

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

Chapter 7.
ADVERSE EVENTS

7.1 Definition

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

7.2 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.

All adverse events whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported on an adverse event form 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 (including treatment of the non-study eye with study treatment).

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

Yes

There is a plausible temporal relationship between the onset of the adverse event and administration of the study treatment, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study treatment; and/or the adverse event abates or resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the adverse event has an etiology other than the study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study treatment administration (e.g., cancer diagnosed 2 days after first dose of study drug).

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 DRCRnet 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.

7.3 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 persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- Is a congenital anomaly or birth defect.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

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

Serious or unexpected adverse events must be reported to the Coordinating Center immediately via completion of the online serious adverse event form. If the study participant required hospitalization, the hospital discharge summary must also be sent to the Coordinating Center.

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 reporting serious study-related adverse events and abiding by any other reporting requirements specific to their Institutional Review Board.

7.4 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 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.

7.5 Risks

7.5.1 Potential Adverse Effects of Anti-VEGF Drug

Limited data are available for the use of aflibercept in diabetic cohorts, and published results are only available for short duration follow-up of one year. The DA VINCI study, a phase II study evaluating aflibercept for treatment of DME, reported common adverse events that were consistent with those previously seen with intravitreal injections. Over 1 year follow-up, two cases of endophthalmitis and one case of uveitis occurred (all in aflibercept treatment groups).

Seven deaths (4.0%) occurred in the groups randomized to VEGF-Trap-Eye treatment as compared with 1 (2.3%) in the group treated with laser. Myocardial infarction or cerebrovascular accident occurred in 6 (3.4%) participants treated with aflibercept as compared with 1 (2.3%) participant treated with laser alone.[23] Percentages of study participants that experienced events meeting APTC criteria were 5.1% (N = 9) in the combined aflibercept groups and 4.5% (2) in the laser group.[24] In the combined analysis of the VIEW 1 and VIEW 2 phase III studies in age-related macular degeneration, serious ocular adverse events, including endophthalmitis, occurred at rates <0.1% per injection in both studies and there did not appear to be a dose or drug-related increase in APTC events in either study. The rates of APTC arterial thrombolic events were 3.2% and 3.3% in the ranibizumab and the combined aflibercept groups, respectively.[31] Common ocular adverse events in the COPERNICUS trial, which enrolled eyes with macular edema secondary to central retinal vein occlusion and randomized them to either 2 mg intravitreal aflibercept monthly x 6 months followed by prn aflibercept versus sham injection x 6 months followed by prn aflibercept, were conjunctival hemorrhage (16.7% and 18.9%, respectively) and eye pain (15.8% and 9.5%, respectively). APTC events through week 52 occurred in 0.9% (1) of the aflibercept-treated eyes and 2.7% (2) of the eyes treated initially with sham and then with aflibercept as needed after 6 months.[24]

There may be side effects and discomforts that are not yet known.

7.5.2 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 less than 1% of the time.

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 up to a few days is also likely (more than 10% of the time).

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%.

7.5.3 Risks of Laser Photocoagulation Treatment

Serious complications from laser treatment are rare. They occur in less than 1 in 1,000 cases. These include damage to the macula, bleeding inside the eye, immediate or delayed increase in pressure inside the eye, damage to the optic nerve, damage to the iris, damage to the lens or an intraocular lens, retinal hole, blindness, and loss of the eye. If a laser burn occurs too near the center of vision, a scotoma could develop. After several years, the scars caused by the laser may enlarge and cause vision to decrease.

Anesthetic drops and a contact lens may be used as a part of the laser procedure. Risks include allergic reaction, infection, and corneal abrasion (scratch on the clear front surface of the eye) (all less than 1%). If any of these problems occur, they usually clear up rapidly.

In some cases retrobulbar or peribulbar injection may be used to anesthetize the eye and to reduce eye movements. Complications of retrobulbar and peribulbar injections are rare (less than 1 in 5000)[32]. They include, but are not limited to, the following: retrobulbar hemorrhage (bleeding behind your eyeball); perforation of the eye by the needle; damage to the optic nerve; diplopia lasting up to 24 hours or more; ptosis lasting up to 24 hours or more; difficulty speaking or breathing; lightheadedness/syncope/vasovagal response; allergy to any components of the injection; life threatening response due to the spread of anesthesia to the brain stem, resulting in seizures, drowsiness, confusion, loss of ability to talk, convulsions, stoppage of breathing, or stoppage of heartbeat. All of these complications are rare.

7.5.4 Risks of Eye Examination and Tests

There is a very rare risk of an allergic response to the topical medications used to anesthetize the eye or dilate the pupil that occurs in less than 1% of eyes. Dilating drops rarely could cause an acute angle closure glaucoma attack (less than 1 in 1000)[33], 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 or fundus photographs. The bright flashes used to take the photographs may be annoying, but are not painful and cause no damage.

If a fluorescein angiogram is performed, a yellow dye is injected intravenously. Risks include but are not limited to: transient change in skin and urine color; nausea (approximately 5%); allergic reaction to the dye, hives and itching (approximately 0.5%); anaphylaxis and possible death (less than 1 in 100,000 people). The procedure will not be performed if medically contraindicated.

Chapter 8.
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.

The treatment groups are as follows:

a. Prompt focal/grid photocoagulation + deferred intravitreal anti-VEGF
b. Observation + deferred intravitreal anti-VEGF
c. Prompt intravitreal anti-VEGF

The primary analysis consists of three treatment group comparisons of the proportion of eyes with visual loss of at least 5 letters at the 2 year (104 week) visit.

8.1 Sample size

The sample size estimate has been computed for the primary study objective, comparing the efficacy of focal/grid photocoagulation + deferred intravitreal anti-VEGF, observation + deferred intravitreal anti-VEGF, and prompt intravitreal anti-VEGF. The primary analysis consists of three two-group comparisons of the proportion of eyes with a 5 or more letter visual acuity loss at 2 years compared with baseline mean visual acuity (mean of the two screening and randomization visual acuity letter scores obtained within 1 to 28 days required for eligibility).

8.1.1 Prompt Intravitreal Anti-VEGF Group Projection

For the prompt intravitreal anti-VEGF group, the projected proportion of eyes with a 5 or more letter visual acuity loss was estimated using unpublished data from DRCR.net Protocol I. This projection includes 28 eyes in Protocol I that had visual acuity of 20/32 at baseline and were randomized to the prompt anti-VEGF + deferred laser treatment arm, of which 1 eye [(4%) 95%CI (0.01%, 19.6%)] had a visual acuity decrease of 5 or more letters at 2 years of study follow-up. Although the majority of the eligibility criteria between the current study and Protocol I are the same, the proposed study will only include eyes with visual acuity of 20/25 or better at baseline; therefore our projections could either under or overestimate the observed proportion of eyes with 5 or more letter visual acuity loss at 2 years of follow up in this study. We will assume that 5% of the prompt intravitreal anti-VEGF group in the proposed study will have a 5 or more letter visual acuity loss.

8.1.2 Deferred Intravitreal Anti-VEGF Groups Projection

The projected losses in visual acuity at 2 years for the focal/grid photocoagulation + deferred intravitreal anti-VEGF group and the observation + deferred intravitreal anti-VEGF group were estimated using ETDRS data of eyes with center-involved DME evaluated by fundus photography and visual acuity ≥ 20/25 at baseline.

The projection for the focal/grid photocoagulation + deferred intravitreal anti-VEGF group was based on 120 eyes with center-involved DME in the ETDRS that had visual acuity of 20/25 or better at baseline and were randomized to the ETDRS focal/grid photocoagulation treatment arm,

of which 32 eyes [(27%) 95%CI (19%, 36%])] had a visual acuity decrease of 5 or more letters at 2 years of study follow-up.

The projection for the observation + deferred intravitreal anti-VEGF group was based on 251 eyes with center-involved DME in the ETDRS that had visual acuity of 20/25 or better at baseline and were randomized to the ETDRS observation only treatment arm, of which 98 eyes [(40%) 95%CI (34%, 47%])] had a visual acuity decrease of 5 or more letters at 2 years of study follow-up.

Projections based on the above ETDRS data alone could overestimate the proportion of participants expected to have a 5 letter loss at the 2 year visit for each deferred treatment arm in the present study since the ETDRS trial did not provide rescue anti-VEGF. In order to obtain a conservative estimate, the lower limit of the 95% CI will be used as the expected proportion of eyes with a 5 or more letter visual acuity loss in the absence of rescue anti-VEGF for these treatment groups (i.e. 19% for the laser group and 34% for the observation group).

According to protocol I unpublished data, approximately 50% of eyes that were 20/32 at baseline gained 5 or more letters at 2 years of study follow up. Therefore, it can be hypothesized that approximately half of the ETDRS eyes that lost 5 or more letters by 2 years would regain the 5 letters after initiation of anti-VEGF therapy.

Thus, the following deferred group projections will be used:

- Focal/grid laser + deferred intravitreal anti-VEGF: 10% (approximately half of the lower end of the ETDRS confidence interval)
- Observation + deferred intravitreal anti-VEGF: 17% (approximately half of the lower end of the ETDRS confidence interval)

8.1.3 Sample Size and Power Assumptions and Estimates

A multiple comparison adjustment will be used in order to control type I error rate. Sample size calculations were performed using the Hochberg multiple comparisons adjustment procedure. This procedure contrasts ordered *P* values with a set of critical values then rejects all hypotheses with smaller or equal *P* values to that of the pre-determined alpha level.

8.1.4 Power Estimation for Primary Outcome

A sample size of 702 eyes (234 eyes per group) was selected, which includes adjustment for 10% lost to follow-up and a 5% increase for interim data monitoring while maintaining pre-specified type I error and power. Power with 702 eyes for the various pairwise treatment comparisons using the Hochberg procedure is provided in Table 1. The power for the largest pairwise difference is estimated to be 92%. The power to reject any of the three pairwise treatment comparisons is estimated to be 93%. For power estimation, the following assumptions were made:

- Overall Type 1 error rate is = 0.049 (2-sided), after adjusting for total alpha spending of 0.001 for DSMC data review and interim data analysis. The Hochberg adjustment will be used to control the overall type 1 error rate for the multiple treatment comparisons.
- The estimated proportion of eyes with a visual acuity loss of 5 or more letters in the prompt anti-VEGF treatment group = 5%;

- Focal/grid photocoagulation + deferred intravitreal anti-VEGF treatment group = 10%; and
- Observation + deferred intravitreal anti-VEGF treatment group = 17%
- Loss to Follow-up at 2 years: 10%

Table 1. Power for pairwise treatment comparisons using the Hochberg procedure

Assumed outcome proportions (difference in proportions)	Reject Any Pairwise Comparison	Reject the Largest Comparison	Reject the Smallest Comparison
Anti-VEGF = 5%, Focal/grid laser = 10%, Observation = 17% (Focal/grid – Anti-VEGF = 5%) (Observation – Anti-VEGF = 12%)	93%	92%	33%

* Note; given the uncertainty in the projected outcomes a power slightly higher than 90% is being selected. Because the Hochberg procedure is being used, the power to reject the pairwise comparison of treatment X (the treatment with the lowest outcome proportion) vs. Z (the treatment with the highest outcome proportion) depends on the outcome proportion in the intermediate group, Y.

8.2 Statistical Analysis Plan

8.2.1 Primary Outcome

The primary outcome is a 5 or more letter decrease in visual acuity letter score from baseline visual acuity to 2 years. Baseline visual acuity is defined as the mean of the two visual acuity measurements required for eligibility. The primary analysis will be an intent-to-treat analysis that includes all randomized eyes, according to the treatment group assignment at randomization. Similarly, baseline OCT will be the mean of the screening and randomization OCT thickness.

Treatment group comparisons will be conducted using binomial regression adjusting for baseline visual acuity and recent or planned DME treatment in the non-study eye at the time of randomization. If binomial regression is not feasible, then Poisson regression with a robust error variance[24] will be used, adjusting for baseline visual acuity and recent or planned DME treatment in the non-study eye at the time of randomization. If Poisson regression is used, unadjusted risk differences and their unadjusted 95% confidence intervals will be reported to aid in interpretation of the data, but the p-values for the treatment comparisons will be those from the Poisson regression analysis that includes adjustment. Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, presence of confounding will be evaluated in regression models by including baseline covariates related to the patient and study eye. Additional variables that are associated with the outcome will be included if there is an imbalance in the variables between treatment groups.

Missing visual acuity letter scores will be imputed using the multiple imputation technique suggested by Rubin[22]. This method involves creating multiple "complete" datasets by filling in values for the missing data at the common visit schedule time points. The inferences for the missing values then are computed by averaging across the multiple imputed "complete" datasets. In addition, a sensitivity analysis using the "complete-case" method will be performed. Under this method only participants with an available 104 week visit outcome are included in the analysis. If the results from the two methods are discrepant then exploratory analysis will be carried out in order to determine factors that contribute to this difference.

Pre-planned subgroup exploratory analysis will be described in the detailed Statistical Analysis Plan and include subgroups defined by (central subfield thickness, age, duration of diabetes, site-reported duration of DME, lens status, level of diabetic retinopathy, and leakage patterns identified on FA).

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

The number of study participants per center is small for many centers, therefore center effects will not be included in the statistical model; however for centers with a large number of study participants, the treatment effect will be assessed. If a positive overall effect of treatment is found, heterogeneity of treatment effect across centers will be explored using random center effects.

8.2.2 Secondary Outcomes

The treatment groups will be compared on the following key secondary outcomes of interest at 104 weeks:

- Percent of eyes with at least 10 and 15 letter losses in visual acuity from baseline visual acuity
- Percent of eyes with at least 5 letter gain in visual acuity from baseline visual acuity
- Mean change in visual acuity, adjusted for baseline visual acuity
- Mean change in OCT CSF thickness, adjusted for baseline thickness
- Percent of eyes with at least a 1 and 2 log step increase or decrease on OCT CSF thickness
- Percent of eyes with OCT CSF thickness less than the gender-specific spectral domain equivalent of 250 μm on Zeiss Stratus and at least a 10% OCT CSF thickness decrease
- Number of injections and/or focal/grid photocoagulation sessions performed
- Number of scheduled and unscheduled visits
- Mean change in low-contrast visual acuity on Electronic Visual Acuity Tester
- Total cost of follow-up and treatment
- For eyes randomized to deferred anti-VEGF, the percentage of eyes needing anti-VEGF treatment.

In addition, the following will be considered exploratory outcomes:

- Visual acuity area under the curve between baseline and annual visits
- Among eyes with non-proliferative diabetic retinopathy or PDR at randomization, percent with improvement in diabetic retinopathy severity
- Among eyes with PDR at randomization, proportion of eyes avoiding vitreous hemorrhage or PRP or vitrectomy for PDR
- Percent of eyes with worsening diabetic retinopathy graded on color fundus photographs
- Time to worsening of diabetic retinopathy on color fundus photographs

Percent of eyes with highly focal leakage patterns (to be defined further) on FA randomized to laser treatment that do not require subsequent anti-VEGF treatment

Analyses will be adjusted for randomization stratification variables and baseline measures where appropriate. Binary outcomes will be analyzed using Fisher's exact test; or for analyses controlling for baseline or stratification factors, binomial regression or a Poisson regression with a robust error variance[24] will be used as described for the primary outcome. Analysis of continuous outcomes will be performed using analysis of covariance. All linear model assumptions will be verified including linearity and homoscedasticity. If model assumptions are not met a nonparametric analysis will be considered.

Additional secondary analyses mimicking the primary and secondary outcomes at 104 weeks will be conducted at 52 weeks.

8.2.3 Cost Analysis

The purpose of the cost analysis is to compare the treatment groups with respect to treatment and follow-up costs. The viewpoint adopted is that of a third party payer. The analysis will be carried out under the complete-case method.

Data from the clinical trial on number of clinic visits completed, number of procedures performed including diabetic retinopathy treatment (e.g. OCT, fundus photographs, PRP), number of focal/laser treatments, and number of anti-VEGF treatments over 2 years of study follow-up will be used to estimate an average cost per patient for each treatment arm, using the Medicare Fee Schedule to estimate medical costs. For this analysis, the estimated average treatment group difference in costs is computed, with variation being characterized by variation in the quantity of services, which will be reported as a 95% confidence interval.

8.2.4 Safety Analysis Plan

Adverse events will be categorized as study eye, nonstudy eye, and systemic. Adverse events of interest will include:

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

Ocular drug-related: inflammation, cataract, cataract surgery, increased intraocular pressure, glaucoma medications, glaucoma surgery, new or worsening traction retinal detachment

Systemic drug-related: hypertension, cardiovascular events, cerebrovascular events

Due to the different visit schedules among the treatment groups, the ratio of adverse events and number of visits will be provided in addition to the number of eyes with an adverse events and the total number of adverse events for each treatment group. This will account for a potential disproportion of reported adverse events observed in the prompt anti-VEGF treatment group as a result of having a more frequent visit schedule. Further definitions of the events for analysis and the analytic approach will be provided in the detailed statistical analysis plan.

8.2.5 Additional Tabulations and Analyses

The following will be tabulated according to treatment group:

1) Baseline demographic and clinical characteristics
2) Visit completion rate

3) Treatment completion

8.2.6 Per-protocol Analysis

A per-protocol analysis of the primary outcome will be conducted in which any eye receiving a treatment for DME other than laser or an anti-VEGF injection will be excluded. If the results differ from the primary intent-to-treat analysis, exploratory analyses will be performed to evaluate the factors that have contributed to the differences.

8.2.7 Interim Monitoring Plan

A formal plan for interim data monitoring will be established in consultation with the Data and Safety Monitoring Committee and the details will be provided in the Statistical Analysis Plan.

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