

Diabetic Retinopathy Clinical Research Network

Intravitreal Anti-VEGF Treatment for Prevention of Vision Threatening Diabetic Retinopathy in Eyes at High Risk

Version 6.0

December 9, 2019

Table of Contents

1
2
3 **Chapter 1. Background Information and Study Synopsis 1-1**
4 1.1 Background Information 1-1
5 1.1.1 Diabetic Retinopathy Complications and Public Health Impact 1-1
6 1.1.2 PDR and Its Treatment..... 1-1
7 1.1.3 DME and Its Treatment 1-2
8 1.1.4 Rationale for Prevention of PDR and DME in Eyes at High Risk 1-2
9 1.1.5 Aflibercept 1-3
10 1.1.6 Summary of Study Rationale 1-4
11 1.2 Study Objective 1-5
12 1.3 Study Design and Synopsis of Protocol 1-5
13 1.4 General Considerations 1-9
14 **Chapter 2. Study Participant Eligibility and Enrollment 2-1**
15 2.1 Identifying Eligible Subjects and Obtaining Informed Consent 2-1
16 2.2 Subject Eligibility Criteria 2-1
17 2.2.1 Individual-level Criteria..... 2-1
18 2.2.2 Study Eye Criteria..... 2-2
19 2.2.3 Non-Study Eye Criteria..... 2-4
20 2.3 Screening Evaluation and Baseline Testing 2-5
21 2.3.1 Historical Information..... 2-5
22 2.3.2 Baseline Testing Procedures 2-5
23 2.3.2.1 Screening Visit..... 2-5
24 2.3.2.2 Randomization Visit 2-5
25 2.4 Randomization of Eligible Study Participants 2-6
26 **Chapter 3. Follow-up Visits and Testing 3-1**
27 3.1 Visit Schedule 3-1
28 3.1.1 Assessment Visits 3-1
29 3.1.2 Additional Study Visits..... 3-1
30 3.2 Testing Procedures 3-2
31 **Chapter 4. Treatment Regimen 4-1**
32 4.1 Treatment Groups..... 4-1
33 4.2 Injection Procedure 4-1
34 4.2.1 Intravitreal Aflibercept Injection (Eylea®)..... 4-1
35 4.2.2 Intravitreal Injection Technique 4-1
36 4.2.3 Sham Injection Technique 4-1
37 4.2.4 Deferral of Injections Due to Pregnancy 4-1
38 4.2.5 Non-Study Eye Injections 4-1
39 4.3 Follow-Up Treatment Protocol for Prevention of PDR/DME 4-2
40 4.3.1 Injections at 4 and 8 Weeks and Each 4-Month Interval Visit until 2 Years..... 4-2
41 4.3.2 Injections at and After the 2-Year Visit..... 4-2
42 4.4 Treatment for CI-DME..... 4-2

| | | | |
|----|---|--|------------|
| 43 | 4.4.1 | Initiation of Focal/Grid Photocoagulation While Receiving Anti-VEGF Injections | |
| 44 | | 4-3 | |
| 45 | 4.4.2 | Continuation of Prevention Treatment Protocol | 4-3 |
| 46 | 4.5 | Treatment for PDR | 4-3 |
| 47 | 4.5.1 | Primary Outcome for PDR | 4-3 |
| 48 | 4.5.2 | Initiating Treatment for PDR | 4-4 |
| 49 | 4.5.3 | Intravitreal Injection for PDR at 4 weeks, 8 weeks and 12 weeks | 4-4 |
| 50 | 4.5.4 | Intravitreal Injection for PDR at and after 16 weeks | 4-4 |
| 51 | 4.5.5 | Continuation of Prevention Treatment Protocol | 4-6 |
| 52 | 4.6 | Panretinal Photocoagulation Technique | 4-6 |
| 53 | 4.7 | Surgery for Vitreous Hemorrhage, Traction Detachment, and Other Complications of | |
| 54 | DR | 4-7 | |
| 55 | Chapter 5. Miscellaneous Considerations in Follow-up | | 5-1 |
| 56 | 5.1 | Endophthalmitis | 5-1 |
| 57 | 5.2 | Treatment in Non-study Eye | 5-1 |
| 58 | 5.3 | Diabetes Management | 5-1 |
| 59 | 5.4 | Study Participant Withdrawal and Losses to Follow-up | 5-1 |
| 60 | 5.5 | Discontinuation of Study | 5-1 |
| 61 | 5.6 | Contact Information Provided to the Coordinating Center | 5-1 |
| 62 | 5.7 | Study Participant Reimbursement | 5-2 |
| 63 | Chapter 6. Adverse Events | | 6-1 |
| 64 | 6.1 | Definition | 6-1 |
| 65 | 6.2 | Recording of Adverse Events | 6-1 |
| 66 | 6.3 | Reporting Serious or Unexpected Adverse Events | 6-2 |
| 67 | 6.4 | Data and Safety Monitoring Committee Review of Adverse Events | 6-2 |
| 68 | 6.5 | Risks | 6-3 |
| 69 | 6.5.1 | Potential Adverse Effects of Aflibercept | 6-3 |
| 70 | 6.5.2 | Potential Adverse Effects of Intravitreal Injection | 6-3 |
| 71 | 6.5.3 | Risks of Eye Examination and Tests | 6-4 |
| 72 | Chapter 7. Statistical Methods | | 7-1 |
| 73 | 7.1 | Primary Objectives and Key Outcomes | 7-1 |
| 74 | 7.2 | Sample Size | 7-2 |
| 75 | 7.2.1 | Projected Control Group Proportion | 7-2 |
| 76 | 7.2.2 | Projected Treatment Group Rate | 7-3 |
| 77 | 7.2.3 | Sample Size Estimates | 7-4 |
| 78 | 7.2.4 | Power for the Visual Acuity Outcome | 7-4 |
| 79 | 7.3 | Primary Analysis Plan | 7-5 |
| 80 | 7.3.1 | Principles for Analysis | 7-5 |
| 81 | 7.3.2 | Per-protocol Analysis | 7-6 |
| 82 | 7.3.3 | Interim Analysis Plan | 7-6 |
| 83 | 7.4 | Secondary Outcomes for Treatment Group Comparison | 7-6 |
| 84 | 7.5 | Economic Analysis | 7-7 |
| 85 | 7.6 | OCT Angiography Ancillary Study | 7-8 |
| 86 | 7.7 | Safety Analysis Plan | 7-8 |

| | | |
|----|---|------------|
| 87 | 7.8 Additional Tabulations and Analyses | 7-9 |
| 88 | Chapter 8. References..... | 8-1 |
| 89 | | |

CHAPTER 1. BACKGROUND INFORMATION AND STUDY SYNOPSIS

1.1 Background Information

1.1.1 Diabetic Retinopathy Complications and Public Health Impact

The age-adjusted incidence of diabetes mellitus in the United States has reportedly doubled in recent history.¹ Estimates suggest that by the year 2035, approximately 592 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 diabetes. At present at least 5 million people over the age of 40 in the United States are estimated to have diabetic retinopathy (DR) in the absence of diabetic macular edema (DME), and an additional 800,000 have DME, according to data from the Centers for Disease Control.³ Despite advances in diagnosis and management of ocular disease in patients with diabetes, eye complications from diabetes mellitus continue to be a leading cause of vision loss and new onset blindness in working-age individuals throughout the United States.^{4,5}

1.1.2 PDR and Its Treatment

Worsening DR is characterized by the development of increasing areas of retinal vascular non-perfusion causing ischemia or infarction of retina tissue. The anatomic sequel of retinal vascular ischemia is retinal neovascularization (NV) or proliferative diabetic retinopathy (PDR), a major cause of preventable and potentially irreversible vision loss in patients with diabetes. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy published in 1985 suggest that given long enough duration of diabetes, approximately 60% of patients with diabetes mellitus will develop PDR.⁶ Although current rates may be lower, they are still substantial. More recently, the Protein Kinase C β Inhibitor Diabetic Retinopathy Study (PKC-DRS) and Diabetic Retinopathy Study (DRS)-2 study groups reported that eyes with moderate to severe non-proliferative DR enrolled in 2 separate phase 3 trials of the protein kinase C inhibitor, ruboxistaurin, demonstrated approximate rates of 60% and 40%, respectively, of worsening of 3 steps on the Early Treatment for Diabetic Retinopathy Study (ETDRS) person scale across both eyes, 2 steps on the ETDRS individual eye scale, or application of PRP over 3 years.^{7,8}

It is also well-documented that worsening to PDR is associated with worse visual outcomes in many eyes. According to the DRS without intervention, nearly half of eyes with high-risk PDR will experience profound vision loss from associated complications including vitreous hemorrhage or traction retinal detachment, but rates are reduced dramatically with panretinal photocoagulation (PRP).⁹ The ETDRS demonstrated PRP reduces the risk of severe vision loss to 4% for eyes with or approaching high risk PDR.¹⁰ Although remarkably effective at reducing visual loss if applied in a timely and appropriate manner, PRP treatment destroys viable retinal tissue and is associated with well-documented potential side effects that may lead to transient or permanent loss of visual function, including exacerbation of existing macular edema,¹¹ peripheral visual field defects, night vision loss, loss of contrast sensitivity, potential complications from misdirected or excessive burns. In addition, subsequent need for vitrectomy for vitreous hemorrhage or traction retinal detachment has been reported in at least 5% of individuals despite appropriate laser treatment.^{12,13}

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) in eyes with PDR led to decreased risk of DR worsening (need for PRP, vitreous hemorrhage, or vitrectomy for

136 complications of PDR) compared with no anti-VEGF therapy in a secondary outcome reported
137 by the Diabetic Retinopathy Clinical Research Network (DRCR.net) in a trial evaluating
138 ranibizumab for DME.^{14, 15} However, some eyes still worsen despite anti-VEGF therapy and DR
139 severity can worsen when anti-VEGF therapy is discontinued.

140
141 The efficacy and safety of intravitreal anti-VEGF for treatment of PDR have been evaluated
142 over a 2 year period in the ongoing DRCR.net trial, Prompt PRP versus Intravitreal
143 Ranibizumab with Deferred PRP for PDR (Protocol S, NCT01489189). This study randomized
144 eyes with PDR either with or without DME to either standard care PRP delivered at baseline or
145 to treatment with ranibizumab as per a predefined treatment algorithm with deferred PRP given
146 only if these eyes met failure or futility criteria. The study demonstrated that anti-VEGF
147 treatment led to visual acuity at 2 years that was non-inferior to that obtained with PRP. The
148 mean VA letter change was $+2.8 \pm 15.2$, ranibizumab group, versus $+0.2 \pm 13.7$, PRP group
149 (difference $+2.2$, 95% confidence interval [CI]: -0.5 to $+5.0$). Other, secondary outcomes
150 appeared to favor the ranibizumab-treated group, including mean change in visual acuity letter
151 area under the curve over 2 years (difference $+4.2$, 95% CI: $+3.0$ to $+5.4$, $P < 0.001$), visual field
152 sensitivity loss (mean difference 368 dB; 95% CI: 213 to 531, $P < 0.001$) and rates of vitrectomy
153 (difference in surgical rates 11% ($P < 0.001$)). Ranibizumab was well-tolerated with few ocular
154 events (1 case of endophthalmitis) and no substantial differences identified in rates of systemic
155 adverse events between the treatment groups.¹⁶

156 157 **1.1.3 DME and Its Treatment**

158 DME is another manifestation of DR that produces loss of central vision. DME is currently a
159 leading cause of moderate vision loss in patients with diabetes.¹⁷ Without intervention, 33% of
160 221 eyes included in the ETDRS with center-involved DME (CI-DME) experienced “moderate
161 visual loss” (defined as a 15 or more letter score decrease in visual acuity) over a 3 year period.¹⁸
162 The DRCR.net study “Intravitreal Ranibizumab or Triamcinolone Acetonide in Combination
163 with Laser Photocoagulation for Diabetic Macular Edema” (Protocol I) indicated that treatment
164 for DME with intravitreal anti-VEGF therapy (0.5 mg ranibizumab) with prompt or deferred
165 focal/grid laser provides visual acuity outcomes at 1 year and 2 years that are superior to
166 focal/grid laser alone or focal/grid laser combined with intravitreal corticosteroids,¹⁴ providing
167 definitive confirmation of the important role of VEGF in DME and the superiority of anti-VEGF
168 agents in the treatment of DME. Additional phase 3 studies have since confirmed the superiority
169 of anti-VEGF agents to manage DME.¹⁹⁻²¹

170 171 **1.1.4 Rationale for Prevention of PDR and DME in Eyes at High Risk**

172 Worse baseline NPDR severity is strongly associated with increased risk of worsening to PDR.
173 Data from the ETDRS suggest that eyes with severe non-proliferative diabetic retinopathy
174 (NPDR) have a 52% risk of progressing to PDR within 1 year and a 60% risk of worsening to
175 PDR with high risk characteristics within 5 years.¹⁰ Although PRP is performed in some select
176 cases of severe NPDR, there is no clear treatment mandate generalizable to most eyes with
177 severe NPDR that are at high risk of worsening to PDR. However, the high risk of vision loss
178 from untreated PDR and potential complications from PDR treatment with PRP support a
179 rationale to explore possible therapeutic modalities for prevention of PDR.

180

181 A higher risk of incident DME in eyes with more severe levels of baseline NPDR also has been
182 reported.²² Although there is similarly no clear current mandate to treat eyes with severe NPDR
183 in the hopes of preventing DME, there is scientific rationale to support this approach. It is
184 possible that the prevention of CI-DME onset in eyes at high risk might prevent vision loss
185 associated with the development of CI-DME. Furthermore, it is possible that an initial,
186 infrequently dosed anti-VEGF treatment regimen that prevents CI-DME onset might avoid
187 adverse events associated with more frequent dosing required for treatment once CI-DME is
188 present.

189
190 Multiple studies have implicated VEGF as a major causative factor in human eye diseases
191 characterized by neovascularization including PDR and vascular permeability including DME.²³⁻
192 ³³ Thus, inhibition of VEGF might be expected to reduce the risk of both PDR and DME onset in
193 eyes with DR at high risk for worsening and over the long-term, reduce the risk of vision loss
194 from these conditions. Indeed, as written above, substantial reductions in PDR-related outcomes
195 such as worsening on fundus photographs or clinical examination from NPDR to PDR, having
196 PRP, experiencing vitreous hemorrhage, or undergoing vitrectomy for PDR, have been reported
197 from studies comparing eyes treated with ranibizumab to those given laser or no treatment to
198 manage DME.^{34, 35,19,20} Furthermore, anti-VEGF treatment appears not only to prevent
199 worsening to PDR, but also to result in some improvement in the DR severity level as
200 demonstrated by DRCR.net Protocol I, RIDE/RISE trials with ranibizumab, and VIVID/VISTA
201 trials with aflibercept^{14, 19, 20}

202
203 While there is strong evidence that PDR outcomes are markedly reduced in eyes that are treated
204 with monthly anti-VEGF therapy (RIDE/RISE) and moderately reduced in eyes that received
205 fairly frequent dosing during the 1st year of treatment (DRCR protocol I), it is yet unknown
206 whether or not an earlier but less frequent dosing regimen would result in similar, favorable
207 anatomic outcomes, and whether favorable anatomic outcomes subsequently would result in
208 favorable visual acuity outcomes. Indeed, recently available data reveal that in the open label
209 extension phase that followed the RIDE/RISE core studies, 28% of eyes that did not receive
210 further ranibizumab treatment experienced 2 or more step worsening over the subsequent year,
211 suggesting that the beneficial effects on DR severity of anti-VEGF therapy may not be sustained
212 in all eyes once that therapy is withheld or given at decreasing frequency.³⁶

213
214 The ability of anti-VEGF therapy to prevent DME onset has not been addressed by data from
215 large scale clinical studies, since these studies largely have enrolled eyes with CI-DME at
216 baseline. However, given the efficacy of anti-VEGF therapy in ameliorating retinal thickening
217 in the RIDE/RISE, VIVID/VISTA, and Protocol I trials, as well as the very low rates of DME
218 worsening in patients treated with anti-VEGF in these studies, it is plausible that anti-VEGF
219 injections also might be effective in reducing the onset of and worsening to CI-DME in eyes at
220 risk for CI-DME development and subsequently result in improved vision outcomes. In
221 addition, ranibizumab reduced the rates development of CI-DME with decreased visual acuity in
222 eyes with PDR in DRCR.net Protocol S (10% with ranibizumab vs. 27% with PRP, $P < 0.001$).

223 224 **1.1.5 Aflibercept**

225 The anti-VEGF drug to be used in this trial is intravitreal aflibercept injection, also known as
226 VEGF Trap-Eye or Aflibercept (Eylea[®]), which is a soluble decoy receptor fusion protein that

227 has a high binding affinity to all isoforms of VEGF as well as to placental growth factor.
228 Aflibercept received approval by the United States Food and Drug Administration (FDA) for the
229 treatment of neovascular age-related macular degeneration in 2011³⁷, for treatment of macular
230 edema due to central retinal vein occlusion in 2012³⁸⁻⁴⁰, and for treatment of macular edema due
231 to branch retinal vein occlusion in 2014. In 2014, the FDA approved aflibercept for treatment of
232 DME based on data from two phase III studies, VISTA and VIVID, which included 872 eyes
233 with DME with central involvement that received either intravitreal aflibercept every 4 weeks,
234 intravitreal aflibercept every 8 weeks after 5 initial monthly doses, or macular laser
235 photocoagulation. The mean change in visual acuity letter score at 1 year compared to baseline
236 was 12.5 and 10.7 letters in the aflibercept groups compared with 0.2 letters in the laser group in
237 VISTA ($P < 0.0001$) and 10.5 and 10.7 compared with 1.2 letters in VIVID ($P < 0.0001$). The
238 visual gains in the aflibercept arms as compared with the macular laser arm were sustained
239 through 100 weeks. The FDA further approved aflibercept for treatment of diabetic retinopathy
240 in patients with diabetic macular edema in March 2015 based on VIVID and VISTA data that
241 showed that eyes treated with q4 or q8 week aflibercept had a significantly higher chance of at
242 least a 2 step improvement in Diabetic Retinopathy Severity Scale score as compared to eyes
243 treated with laser control (VIVID: 29.3% and 32.6% vs. 8.2%, respectively; $P < 0.0004$ for
244 q4wk and $P < 0.0001$ for q8wk; VISTA: 37.0% and 37.1% vs. 15.6%, $P < 0.0001$ for both
245 aflibercept vs control comparisons).⁴¹ With regard to safety, the incidences of ocular and non-
246 ocular adverse events were similar across treatment groups. The incidence of APTC-defined
247 thromboembolic events was similar across treatment groups. There were no reported cases of
248 endophthalmitis, and intraocular inflammation occurred in less than 1% of injections.⁴²

249
250 Although there is no currently available head-to-head data on the available anti-VEGF agents for
251 treatment and prevention of PDR, a comparative effectiveness trial in DME reported that
252 aflibercept was more effective than ranibizumab and bevacizumab in improving vision in eyes
253 starting with CI-DME and worse levels of visual acuity (approximately 20/50 or worse).⁴³ No
254 difference in efficacy was identified for eyes with CI-DME and mild visual acuity loss
255 (approximately 20/40 or better).

256

257 **1.1.6 Summary of Study Rationale**

258 The prevention of PDR or DME in eyes that are high risk for PDR and DME onset might prevent
259 vision loss secondary to retinal neovascularization or central retinal thickening and also might
260 avoid potential complications and adverse effects on vision associated with more aggressive
261 treatments for these diabetic ocular complications once established. Although anti-VEGF
262 therapy given for DME improves PDR-related outcomes and results in regression of
263 nonproliferative changes in some eyes with baseline NPDR, these data derive largely from trials
264 of frequent, often monthly dosing of intravitreal anti-VEGF. No study to date has specifically
265 evaluated the role of anti-VEGF in prevention of DME. This study will evaluate the safety and
266 efficacy of an anti-VEGF regimen for prevention of PDR or CI-DME or both in eyes that are at
267 high risk for worsening to PDR or CI-DME. Treatment will be deferred in the control
268 (observation) arm since there is no clear treatment mandate for these eyes at this time. This
269 protocol will evaluate both anatomic outcomes of development of either PDR within the 7-
270 modified ETDRS fields or CI-DME on OCT associated with vision loss as well as whether
271 favorable anatomic outcomes, if identified, result in longer-term beneficial visual outcomes.

272

273 If this study demonstrates that intravitreal aflibercept treatment is effective and safe for
274 reducing the onset of PDR or CI-DME in eyes that are at high risk for these complications, a new
275 strategy to prevent vision threatening complications of diabetes will be available for patients.
276 The application of intravitreal aflibercept earlier in the course of disease (i.e., at the time when
277 an eye has baseline severe NPDR) could help to reduce future potential treatment burden in
278 patients, at the same time resulting in similar or better long-term visual outcomes, if PDR and
279 DME are prevented.

280

281 **1.2 Study Objective**

282 The objectives of this study are to 1) determine the efficacy and safety of intravitreal
283 aflibercept injections versus sham injections (observation) for prevention of PDR or CI-DME in
284 eyes at high risk for development of these complications and 2) compare long-term visual
285 outcomes in eyes that receive anti-VEGF therapy early in the course of disease with those that
286 are observed initially, and treated only if high-risk PDR or CI-DME with vision loss develops.

287

288 **1.3 Study Design and Synopsis of Protocol**

289 **A. Study Design**

- 290 • Phase III, multi-center randomized clinical trial

291

292 **B. Major Eligibility Criteria**

- 293 • Age ≥ 18 years

- 294 • Type 1 or type 2 diabetes

- 295 • Study eye with

- 296 ○ Best corrected Electronic-ETDRS (E-ETDRS) visual acuity letter score in the study
297 eye ≥ 79 (approximate Snellen equivalent 20/25 or better)

- 298 ○ Severe NPDR (based on the 4:2:1 rule) on clinical examination and on digital
299 imaging as judged by the investigator

- 300 • Reading Center grading of less than ETDRS level 43 or greater than 53 is
301 an exclusion

- 302 ○ No evidence of neovascularization on fluorescein angiography within the 7-modified
303 ETDRS fields, confirmed by Reading Center grading.

- 304 ○ No clinical exam evidence of neovascularization including active neovascularization
305 of the iris (small iris tufts are not an exclusion) or angle neovascularization (if the
306 angle is assessed).

- 307 ○ No prior PRP (defined as ≥ 100 burns placed previously outside of the posterior pole)

- 308 ○ No CI-DME on clinical exam and OCT central subfield thickness below the
309 following gender and OCT-machine specific thresholds:

- 310 • Zeiss Cirrus: 290 μ m in women and 305 μ m in men

- 311 • Heidelberg Spectralis: 305 μ m in women and 320 μ m in men

- 312 ○ No history of DME or DR treatment with laser or intraocular injections of medication
313 within the prior 12 months and no more than 4 prior intraocular injections at any time
314 in the past.

315 **C. Treatment Groups**

316 Study eyes will be assigned randomly (1:1) to one of the following two groups:

317

- 318 • Sham injections
- 319 • Intravitreal 2 mg aflibercept injections

320

321 Study participants may have one or two study eyes. Study participants with two study eyes will
322 receive intravitreal aflibercept in one eye and sham injection in the other eye. Further details on
323 randomization are located in section 2.4.

324

325 Injections (intravitreal or sham) will be given at baseline, 1 and 2 months in all participants.
326 Thereafter, injections will be given at each 4-month visit until 2 years. At and after the 2-year
327 visit, retreatment with injections (intravitreal or sham) will be based on DR level, as assessed
328 by the investigator.

329

330 Treatment for DME or PDR, if developed, may only be given once protocol-specified criteria are
331 met and will follow a protocol-specified regimen (see Section 4.4 and 4.5).

332

333 **D. Sample Size**

- 334 • A minimum of 386 eyes (approximately 322 study participants assuming 20% have two
335 study eyes)

336

337 **E. Duration of Follow-up**

- 338 • Primary outcome: 2 years
- 339 • Total follow-up: 4 years

340

341 **F. Follow-up Schedule**

- 342 • All participants will have visits at 1 month, 2 months, and 4 months, followed by visits
343 every 4 months thereafter through 4 years.
- 344 • Eyes may be seen more frequently depending on disease progression and treatment
345 administered. Further details on the follow-up visit schedule are described in Section 3.1.

346

347 **G. Main Efficacy Outcomes**

348

349 *Primary outcome:*

350

351 Development of PDR or DME, defined as the first occurrence of any of the following
352 (composite time-to-event outcome):

- 353 • NV within the 7-modified ETDRS fields on fundus photography or FA, confirmed by
354 a masked grader at the central reading center
 - 355 ○ At non-annual visits, fundus photography and FA will only be submitted to the
356 reading center to assess for this component of the primary outcome if the
357 investigator thinks treatment is necessary.
- 358 • NV of the iris (at least 2 cumulative clock hours), definitive NV of the angle, or
359 neovascular glaucoma on clinical exam (photographic documentation not required)

- 360 • Other outcomes presumed to be from PDR and documented: traction retinal
- 361 detachment, vitreous hemorrhage, or pre-retinal hemorrhage greater than ½ disc area
- 362 • Procedures undertaken for the treatment of PDR (when present or presumed to be
- 363 present): PRP, anti-VEGF, or vitrectomy
- 364 • CI-DME on clinical exam with at least 10% increase in central subfield thickness
- 365 from baseline and either (1) at least a 10-letter decrease in visual acuity from baseline
- 366 at a single visit or (2) 5-to-9-letter decrease in visual acuity from baseline at 2
- 367 consecutive visits at least 21 days apart, with vision loss presumed to be from DME
- 368 • Non-topical treatment for DME performed without meeting the above criteria,
- 369 including focal/grid laser or intravitreal injections for DME

370

371 *The primary outcome analysis will be performed when the last randomized participant reaches 2*
 372 *years of follow up, using all available follow up data. The treatment groups will be compared*
 373 *using the hazard ratio.*

374

375 *Other Key Outcomes:*

- 376 • Development of PDR or DME outcome through 4 years
- 377 • Mean visual acuity change from baseline at 2 years
- 378 • Mean visual acuity change from baseline at 4 years

379

380 See section 7.3 for methods of handling multiplicity.

381

382 *Additional secondary outcomes at 2 and 4 years:*

- 383 • Development of PDR or PDR-related outcome (as defined above within the
- 384 composite time-to-event outcome)
- 385 • Development of CI-DME with visual acuity impairment (as defined above within the
- 386 composite time-to-event outcome)
- 387 • Development of PDR or DME based only on the objective components defined in the
- 388 composite outcome, including OCT, visual acuity, and reading center assessment of
- 389 photos and FA (i.e. not including investigator-only assessments)
- 390 • Development of each component of the composite outcome assessed individually
- 391 • Proportion of eyes with at least 10 or at least 15 letter loss from baseline, or gain or
- 392 loss of at least 5 letters at consecutive study visits, consisting of the visits just before
- 393 and the 2- or 4-year visit
- 394 • Visual acuity area under the curve (AUC) between randomization and the 2- and 4-
- 395 year visits
- 396 • Mean change in OCT central subfield thickness from baseline
- 397 • Mean change in OCT volume from baseline
- 398 • Development of CI-DME on clinical exam with at least 10% increase in central
- 399 subfield thickness and at least a 25-micron increase from baseline, regardless of
- 400 visual acuity change
- 401 • Proportion of eyes with at least 2-step worsening of DR severity level (scale for
- 402 individual eyes) by central reading center from baseline
- 403 • Proportion of eyes with at least 2-step improvement of DR severity level (scale for
- 404 individual eyes) by central reading center from baseline

- 405 • Proportion of eyes with at least 3-step worsening of DR severity level (scale for
- 406 individual eyes) by central reading center from baseline
- 407 • Proportion of eyes with at least 3-step improvement of DR severity level (scale for
- 408 individual eyes) by central reading center from baseline
- 409 • Level of retinopathy on color photos
- 410 • Number of aflibercept injections performed
- 411 • Follow-up costs and patient-centered outcomes from the Workplace Productivity and
- 412 Activity Impairment Questionnaire
- 413

414 **H. Main Safety Outcomes**

415 Ocular: endophthalmitis, inflammation, retinal detachment, traumatic cataract from injection,

416 vitreous hemorrhage

417

418 Systemic: Antiplatelet Trialists’ Collaboration (APTCL) events and hypertension

419

420 **I. Schedule of Assessment Visits and Examination Procedures**

| | Screening | Randomization | Follow-Up Visits* | Annual Visits |
|---|-----------|-----------------------------|-------------------|---------------|
| Visit Window | | within 35 days of screening | (±1to8w) | (±8w) |
| Usual care visual acuity ^a | X | | | |
| E-ETDRS best corrected visual acuity ^b | | X | X | X |
| Questionnaires ^c | | X | | X |
| OCT ^d | X | X | X | X |
| Eye Exam ^e | X | X | X | X |
| Fundus Photography ^f | X | | X ^g | X |
| Fluorescein angiography ^f | X | | X ^g | X |
| Blood pressure | | X | | X |
| HbA1c ^h | | X | | X |
| OCT angiography ⁱ | X | | X ^g | X |

421 *= Assessment Visits at 1 month (±1w), 2 months (±1w), 4 months (±8w) and every 4 months (±8w) thereafter; additional study

422 visits may occur for treatment of DME/PDR as needed

423 a=study eye only; refraction and/or electronic ETDRS testing may be performed at the discretion of the site for usual care visual

424 acuity.

425 b=both eyes including protocol refraction in the study eye at each study visit. Protocol refraction in non-study eye is only

426 required at baseline and annual visits. E-ETDRS refers to electronic ETDRS testing using the Electronic Visual Acuity Tester

427 that has been validated against 4-meter chart ETDRS testing.

428 c= only in participants with one study eye

429 d= study eye only at randomization and annual visits and at other study visits only if evaluating for DME treatment (see section
430 3.2 for more details) or prior to initiating more frequent anti-VEGF treatment for PDR, if the DME outcome was not confirmed
431 previously.

432 e=both eyes at randomization; study eye only at each additional study visit including slit lamp exam, lens assessment,
433 measurement of intraocular pressure, and dilated ophthalmoscopy

434 f= study eye only. Fundus photography is 7MF or 4WF and FA is using the widest approach available at the site.

435 g= fundus photography, FA, and OCTA (if available at the site) is also required in the study eye at 4 months AND 1) the first
436 time traction retinal detachment, vitreous hemorrhage, or preretinal hemorrhage is identified to confirm the primary outcome has
437 been met, or 2) prior to initiating PRP or vitrectomy, if the primary outcome was not confirmed previously or 3) prior to initiating
438 more frequent anti-VEGF treatment for either DME or PDR, if the primary outcome was not confirmed previously. Fundus
439 photography is 7MF or 4WF and FA is using the widest approach available at the site.

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

442 i=study eye only; only at sites with OCT angiography capabilities.

443 **1.4 General Considerations**

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

447
448 The DRCR.net Procedures Manuals (Visual Acuity-Refractive Testing Procedures Manual, OCT
449 procedures manuals, photography and FA procedures manuals, and Study Procedures Manual)
450 provide details of the examination procedures and intravitreal injection procedure.

451
452 Photographers, OCT technicians, and visual acuity testers, including refractionists, will be
453 masked to treatment group at the annual visits. Study participants will be masked to their
454 treatment group assignment and will continue to be masked to their original treatment
455 assignment even once they initiate treatment for PDR or CI-DME. Investigators and study
456 coordinators are not masked to treatment group.

457
458 Data will be directly collected in electronic case report forms, which will be considered the
459 source data.

460
461 There is no restriction on the number of study participants to be enrolled by a site.

462
463 A risk-based monitoring approach will be followed, consistent with the FDA “Guidance for
464 Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring” (August
465 2013).

466
467 The risk level is considered to be research involving greater than minimal risk.

468 **CHAPTER 2. STUDY PARTICIPANT ELIGIBILITY AND ENROLLMENT**

469
470 **2.1 Identifying Eligible Subjects and Obtaining Informed Consent**

471 A minimum of 386 eyes (322 participants assuming 20% have two study eyes) are expected to be
472 enrolled into the randomized trial. As the enrollment goal approaches, sites will be notified of
473 the end date for recruitment. Study participants who have signed an informed consent form can
474 be randomized up until the end date, which means the recruitment goal might be exceeded.

475
476 Potential eligibility will be assessed as part of a routine-care examination. Prior to completing
477 any procedures or collecting any data that are not part of usual care, written informed consent
478 will be obtained. For patients who are considered potentially eligible for the study based on a
479 routine-care exam, the study protocol will be discussed with the potential study participant by a
480 study investigator and clinic coordinator. The potential study participant will be given the
481 Informed Consent Form to read. Potential study participants will be encouraged to discuss the
482 study with family members and their personal physician(s) before deciding whether to participate
483 in the study.

484
485 Consent may be given in two stages (if approved by the IRB). The initial stage will provide
486 consent to complete any of the screening procedures needed to assess eligibility that have not
487 already been performed as part of a usual-care exam. The second stage will be obtained prior to
488 randomization and will be for participation in the study. A single consent form will have two
489 signature/date lines for the study participant: one for a study participant to give consent for the
490 completion of the screening procedures and one for the study participant to document consent for
491 the randomized trial. Study participants will be provided with a copy of the signed Informed
492 Consent Form.

493
494 Once a study participant is randomized, that participant will be counted regardless of whether the
495 assigned treatment is received. Thus, the investigator must not proceed to randomize an
496 individual until he/she is convinced that the individual is eligible and will accept assignment to
497 either of the two treatment groups.

498
499 **2.2 Subject Eligibility Criteria**

500 **2.2.1 Individual-level Criteria**

501 Inclusion

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

- 503 1. Age \geq 18 years
- 504 • *Individuals <18 years old are not being included because DR is so rare in this age group*
 - 505 • *that the diagnosis of NPDR may be questionable.*
- 506 2. Diagnosis of diabetes mellitus (type 1 or type 2)
- 507 • Any one of the following will be considered to be sufficient evidence that diabetes is
 - 508 present:
 - 509 ➤ *Current regular use of insulin for the treatment of diabetes*
 - 510 ➤ *Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes*
 - 511 ➤ *Documented diabetes by ADA and/or WHO criteria (see Procedures Manual for*
 - 512 *definitions)*

513 3. At least one eye meets the study eye criteria listed in section 2.2.2.

514 4. Able and willing to provide informed consent.

515 Exclusion

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

517 5. History of chronic renal failure requiring dialysis or kidney transplant.

518 6. A condition that, in the opinion of the investigator, would preclude participation in the study
519 (e.g., unstable medical status including blood pressure, cardiovascular disease, and glycemic
520 control).

521 7. Initiation of intensive insulin treatment (a pump or multiple daily injections) within 4 months
522 prior to randomization or plans to do so in the next 4 months.

523 8. Participation in an investigational trial that involved treatment within 30 days of
524 randomization with any drug that has not received regulatory approval for the indication
525 being studied.

526 • *Note: study participants cannot participate in another investigational trial that involves*
527 *treatment with an investigational drug while participating in the study.*

528 9. Known allergy to any component of the study drug or any drug used in the injection prep
529 (including povidone iodine prep).

530 10. Known allergy to fluorescein dye.

531 11. Blood pressure > 180/110 (systolic above 180 or diastolic above 110).

532 • *If blood pressure is brought below 180/110 by anti-hypertensive treatment, individual*
533 *can become eligible.*

534 12. Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization.

535 • *These drugs should not be used during the study.*

536 13. For women of child-bearing potential: pregnant or lactating or intending to become pregnant
537 within the next 2 years.

538 • *Women who are potential study participants should be questioned about the potential for*
539 *pregnancy. Investigator judgment is used to determine when a pregnancy test is needed.*

540 14. Individual is expecting to move out of the area of the clinical center to an area not covered by
541 another DRCR.net certified clinical center during the next 2 years.

542

543 **2.2.2 Study Eye Criteria**

544 The potential study participant must have at least one eye meeting all of the inclusion criteria and
545 none of the exclusion criteria listed below.

546

547 A study participant can have two study eyes only if both are eligible at the time of
548 randomization. For study participants with two eligible eyes, the logistical complexities of the
549 protocol must be considered for each individual prior to randomizing both eyes.

550

551 The eligibility criteria for a study eye are as follows:

552

553

554 Inclusion

- 555 a. Best corrected E-ETDRS visual acuity letter score ≥ 79 (approximate Snellen equivalent
556 20/25 or better)
- 557 b. Severe NPDR (based on the 4:2:1 rule) evident on clinical examination and/or on digital
558 imaging as judged by the investigator. Severe NPDR is defined as:
- 559 1. 4 fields show severe hemorrhages or microaneurysms (at least as great as Standard
560 photograph 2A), or
- 561 2. At least 2 fields of definite venous beading or at least 1 field at least as severe as
562 Standard photograph 6A, or
- 563 3. At least 1 field of moderate intraretinal microvascular abnormalities (IRMA), at
564 least as severe as Standard photograph 8A
- 565 c. No evidence of neovascularization on clinical exam including active neovascularization of
566 the iris (small iris tufts are not an exclusion) or angle neovascularization (if the angle is
567 assessed).
- 568 d. No evidence of neovascularization on fluorescein angiography within the 7-modified ETDRS
569 fields, confirmed by the central Reading Center prior to randomization.
- 570 • *The widest method of imaging available at the site must be used to document whether*
571 *there is NV present in the periphery; however, presence of NV outside of the 7-modified*
572 *ETDRS fields on ultra-widfield imaging will not be an exclusion provided treatment is*
573 *not planned.*
- 574 e. No CI-DME on clinical exam and OCT central subfield thickness must be below the
575 following gender and OCT-machine specific thresholds:
- 576 ▪ Zeiss Cirrus: 290 μ in women and 305 μ in men
577 ▪ Heidelberg Spectralis: 305 μ in women and 320 μ in men
- 578 AND investigator and potential participant are comfortable withholding treatment for DME
579 until there is at least a 10% increase in OCT central subfield thickness with confirmed visual
580 acuity loss (10 letter loss at a single visit or 5 to 9 at two consecutive visits).
- 581 f. Prompt PRP or anti-VEGF treatment not required AND investigator and potential participant
582 are willing to wait for development of high-risk characteristics (defined in Section 4.5.2) to
583 treat PDR.
- 584 g. Media clarity, pupillary dilation, and study participant cooperation sufficient to obtain
585 adequate fundus photographs, FA, and OCT.
- 586 • *Investigator must verify accuracy of OCT scan by ensuring it is centered and of adequate*
587 *quality (including segmentation line placement)*

588
589 Exclusion

590 The following exclusions apply to the study eye only (i.e., they may be present for the non-study
591 eye):
592

- 593 h. Central Reading Center grading of DR severity level on fundus photographs less severe than
594 ETDRS level 43 or more severe than level 53.
- 595 • *Enrollment will be limited to a maximum of 50% of the planned sample size with DR*
596 *severity level 47A or 43 by RC grading (with a maximum of 25% of the planned*
597 *sample size with DR severity level 43 by RC grading). Once the number of eyes has*
598 *been enrolled for each severity level, RC grading of that level will be an exclusion*
599 *criterion.*
- 600 i. Exam or photographic evidence of vitreous hemorrhage or preretinal hemorrhage presumed
601 to be from PDR.
- 602 j. History of prior vitreous hemorrhage or preretinal hemorrhage presumed to be from PDR.
- 603 k. History of prior PRP (defined as ≥ 100 burns outside of the posterior pole).
- 604 l. An ocular condition is present (other than DR) that, in the opinion of the investigator, might
605 alter visual acuity during the course of the study (e.g., retinal vein or artery occlusion, uveitis
606 or other ocular inflammatory disease, vitreomacular traction, etc.).
- 607 m. History of DME or DR treatment with laser or intraocular injections of medication within the
608 prior 12 months and no more than 4 prior intraocular injections at any time in the past.
- 609 • *Enrollment will be limited to a maximum of 25% of the planned sample size with any*
610 *history of treatment for DME/DR. Once this number of eyes has been enrolled, any*
611 *history of treatment for DME/DR will be an exclusion criterion.*
612
- 613 n. History of major ocular surgery (including cataract extraction, scleral buckle, any intraocular
614 surgery, etc.) within prior 4 months or anticipated within the next 6 months following
615 randomization.
- 616 o. Any history of vitrectomy.
- 617 p. History of YAG capsulotomy performed within 2 months prior to randomization.
- 618 q. Aphakia.
- 619 r. Exam evidence of severe external ocular infection, including conjunctivitis, chalazion, or
620 substantial blepharitis.
- 621 s. Evidence of uncontrolled glaucoma.
- 622 • *Intraocular pressure must be <30 , with no more than one topical glaucoma*
623 *medication, and no documented glaucomatous field loss for the eye to be eligible.*

624 **2.2.3 Non-Study Eye Criteria**

625 If anti-VEGF treatment is indicated for any condition in the non-study eye at any time during the
626 study, the investigator must be willing to use the study anti-VEGF drug (2 mg aflibercept) for the
627 non-study eye. If the non-study eye is currently being treated with a different anti-VEGF drug
628 for any condition, then the investigator and patient must be willing to switch to aflibercept. If
629 the investigator or patient is unwilling to change anti-VEGF treatment in the non-study eye, the
630 patient should not be enrolled.
631

632 **2.3 Screening Evaluation and Baseline Testing**

633 **2.3.1 Historical Information**

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

638

639 **2.3.2 Baseline Testing Procedures**

640 **2.3.2.1 Screening Visit**

641 The following procedures are needed to assess eligibility at Screening.

- 642 • If a procedure has been performed (using the study technique and by study certified
643 personnel) as part of usual care, it does not need to be repeated specifically for the study
644 if it was performed within the defined time windows specified below.
 - 645 • The testing procedures are detailed in the DRCCR.net Procedures Manuals. Visual acuity
646 testing, ocular exam, fundus photography, fluorescein angiography and OCT will be
647 performed by DRCCR.net certified personnel.
 - 648 • The fundus photographs and fluorescein angiograms will be promptly sent to the central
649 reading center for grading and a participant cannot be randomized until reading center
650 confirmation of eligibility has been received.
 - 651 • OCTs meeting DRCCR.net criteria for manual grading may be sent to a reading center, but
652 study participant eligibility regarding DME status is determined by the site (i.e.,
653 individuals deemed eligible by the investigator will be randomized without pre-
654 randomization reading center confirmation of the OCT central subfield thickness).
- 656 1. Visual acuity using clinic’s usual care method or Electronic-ETDRS visual acuity to
657 confirm vision is 20/25 or better in the study eye (*within prior 8 days*).
 - 658 2. Spectral Domain OCT using Zeiss Cirrus or Heidelberg Spectralis on the study eye (*within*
659 *prior 8 days*).
 - 660 3. Ocular examination on the study eye including slit lamp, measurement of intraocular
661 pressure, lens assessment, and dilated ophthalmoscopy (*on day of Screening*).
 - 662 4. Digital fundus photography in the study eye. (*within prior 8 days*)
 - 663 5. Digital fluorescein angiogram (FA) in the study eye, using the widest approach available at
664 the clinical site (e.g. ultra-widefield imaging device, if available). (*within prior 8 days*)
 - 665 6. OCT angiography on the study eye. (*within prior 8 days*)
 - 666 • Only obtained by a subset of sites with OCT angiography capabilities. If a site has
667 OCT angiography systems from more than one manufacturer, the images should be
668 obtained on each system available.
 - 669 • *See procedure manual for more details on acquisition, including which fields to*
670 *collect on a given OCT angiography system.*

671

672 **2.3.2.2 Randomization Visit**

673 The randomization visit must be completed within 35 days of Screening. The visit should not be
674 completed until Reading Center confirmation of eligibility based on the Screening fundus

675 photographs and FA has been received. The following procedures are needed to confirm
676 eligibility and to serve as baseline measures for the study:

- 677
- 678 1. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester
679 (including protocol refraction) in each eye. (*on day of randomization*)
 - 680 2. Spectral Domain OCT using Zeiss Cirrus or Heidelberg Spectralis on study eye (*on day of*
681 *randomization*)
 - 682 • *The same OCT machine type as Screening should be used.*
 - 683 3. Ocular examination on each eye including slit lamp, measurement of intraocular pressure,
684 lens assessment, and dilated ophthalmoscopy. (*on day of randomization*)
 - 685 4. Workplace Productivity and Activity Impairment (WPAI) Questionnaire (only in participants
686 with one study eye, *on day of randomization*).
 - 687 5. Measurement of blood pressure.
 - 688 6. Laboratory testing of Hemoglobin A1c.
 - 689 • *HbA1c does not need to be repeated if available in the prior 3 months. If not*
690 *available at the time of randomization, the potential study participant may be*
691 *enrolled but the test must be obtained within 3 weeks after randomization.*

692 **2.4 Randomization of Eligible Study Participants**

- 693 1. Prior to randomization, the study participant's understanding of the trial, willingness to
694 accept the assigned treatment group, and commitment to the follow-up schedule should be
695 reconfirmed.
- 696 2. The initial injection must be given on the day of randomization. A study participant should
697 not be enrolled until this is possible
- 698 3. Randomization is completed on the DRCR.net website.
 - 699 • Study participants with one study eye will be randomly assigned (stratified by
700 Reading Center grading of DR severity level [43, 47A, 47B-D, 53 with no NV in the
701 periphery, or 53 with NV in the periphery]) with equal probability to one of the
702 treatment groups:
 - 703 ○ Group A: Sham injections
 - 704 ○ Group B: Intravitreal 2 mg aflibercept injections
 - 705
 - 706 • For study participants with two study eyes (both eyes eligible at the time of
707 randomization), the study participant will be randomly assigned with equal
708 probability to receive either:
 - 709 ○ Group A in the eye with greater DR severity and Group B in the eye with
710 lower DR severity
 - 711 ○ Group B in the eye with greater DR severity and Group A in the eye with
712 lower DR severity

713

714
715

Note: if both eyes have the same DR severity, the right eye will be considered the eye with the greater DR severity.

CHAPTER 3. FOLLOW-UP VISITS AND TESTING

716
717
718

3.1 Visit Schedule

3.1.1 Assessment Visits

720 The schedule of protocol-specified Assessment Visits for all participants is as follows:

721

722

723

724

725

726

727

728

729

- Visits at 1 and 2 months (± 1 week)
 - *Study injections for prevention of PDR and DME must be at least 21 days apart; therefore, follow-up visits should be scheduled accordingly so that the eye is eligible for retreatment.*
- Visits at 4 months and then every 4 months at 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 months (± 8 weeks)
 - *The every 4-month study visits/injections for prevention of PDR and DME must be no closer than 8 weeks apart.*

3.1.2 Additional Study Visits

731

732

733

734

735

736

737

738

739

740

741

742

743

744

745

746

747

748

749

750

751

752

753

754

755

756

757

758

759

1. DME Outcome Visits

- If the eye has not already met the primary outcome and visual acuity has decreased 5 to 9 letters from baseline and the loss is attributable to DME, the participant will return in 4 weeks (± 1 week) to assess whether the eye has met the primary outcome for DME progression and is eligible for treatment.

2. DME Treatment Visits

- Once DME treatment has been initiated, follow-up visits for DME treatment occur every 4 weeks for the first 6 months from initial aflibercept treatment for DME. After 6 months, if the injection is deferred at the current and previous 2 visits (see section 4.4 for retreatment criteria), the next study follow-up visit is in twice the time since the last visit up to a maximum of 16 weeks between visits. Otherwise, the next study follow-up visit is in 4 weeks.

3. PDR Treatment Visits

- Once NV is present, the participant may return sooner than the next scheduled Assessment Visit to evaluate for progression to high-risk, at the discretion of the investigator.
- Once PDR treatment has been initiated, follow-up visits for PDR treatment occur every 4 weeks for the first 6 months from initial aflibercept treatment for PDR. After 6 months, if the injection is deferred at the current and previous 2 visits (see section 4.5.4 for retreatment criteria), the next study follow-up visit is in twice the time since the last visit up to a maximum of 16 weeks between visits. Otherwise, the next study follow-up visit is in 4 weeks.

Note: Regardless of the timing of additional visits for DME/PDR treatment, the participant will return for the protocol-specified Assessment Visits listed above in Section 3.1.1.

760 3.2 Testing Procedures

761 The following procedures will be performed at each study visit (listed in 3.1.1 and 3.1.2) on the
762 study eye only unless otherwise specified. A grid in section 1.3 summarizes the testing
763 performed at each visit. Photographers, OCT technicians, and visual acuity testers, including
764 refractionists, will be masked to treatment group at annual visits.

765

766 1. E-ETDRS visual acuity testing in each eye (best corrected).

767 • A protocol refraction in the study eye is required at all study visits. Refraction in the
768 non-study eye is only required at annual visits. When a refraction is not performed,
769 the most-recently performed refraction is used for the testing.

770 2. Workplace Productivity and Activity Impairment (WPAI) Questionnaire (only in participants
771 with one study eye) at annual visits.

772 3. OCT on the study eye at annual visits and if any of the following are met:

773 • If visual acuity has decreased by at least 5 letters (equivalent to approximately 1 or
774 more line) since baseline in an eye that has not previously met the DME outcome and
775 there is no other apparent cause (e.g. cataract), an OCT must be performed to
776 determine if DME is the cause of vision loss.

777 • If DME treatment is being considered, an OCT must be done to confirm the eye has
778 met the primary outcome before proceeding with treatment.

779 • Once DME treatment has been initiated, an OCT must be done at each subsequent
780 DME Treatment Visit.

781 • Prior to initiating more frequent anti-VEGF treatment for PDR, if DME outcome was
782 not met previously.

783 ➤ *The same OCT machine type as Randomization should be used.*

784 4. Ocular exam on the study eye, including slit lamp examination, lens assessment,
785 measurement of intraocular pressure and dilated ophthalmoscopy

786 • Undilated exam of the iris and examination of the angle is at investigator discretion.

787 5. Digital fundus photographs on the study eye at the 4-month visit and annual visits.

788 • Digital fundus photography must also be performed 1) the first time traction retinal
789 detachment, vitreous hemorrhage, or preretinal hemorrhage is identified to confirm
790 the primary outcome has been met, or 2) prior to initiating PRP or vitrectomy, if the
791 primary outcome was not confirmed previously or 3) prior to initiating more frequent
792 anti-VEGF treatment for either DME or PDR, if the primary outcome was not
793 confirmed previously.

794 6. Digital FA using the widest approach available (e.g. ultra-widefield imaging device, if
795 available) on the study eye at the 4-month visit and annual visits.

796 • Digital FA must also be performed 1) the first time traction retinal detachment,
797 vitreous hemorrhage, or preretinal hemorrhage is identified to confirm the primary
798 outcome has been met, or 2) prior to initiating PRP or vitrectomy, if the primary
799 outcome was not confirmed previously or 3) prior to initiating more frequent anti-

- 800 VEGF treatment for either DME or PDR, if the primary outcome was not confirmed
801 previously.
- 802 ➤ *If a site obtains a new ultra-widefield imaging device during the course of the study,*
803 *the widest approach available should be used for all study visits going forward.*
- 804 ➤ *For participants with two study eyes, the transit eye at follow-up should be consistent*
805 *with the transit eye selected at baseline.*
- 806 7. OCT angiography on the study eye at the 4-month visit and annual visits, as well as the time
807 points above when fundus photographs and FA are obtained for primary outcome
808 documentation.
- 809 • Only obtained by a subset of sites with OCT angiography capabilities. If a site has
810 OCT angiography systems from more than one manufacturer, the images should be
811 obtained on each system available.
- 812 ➤ *See procedure manual for more details on acquisition, including which fields to*
813 *collect on a given OCT angiography system.*
- 814 8. Measurement of blood pressure at annual visits only.
- 815 9. Laboratory testing of Hemoglobin A1c at annual visits only.
- 816 ➤ *HbA1c does not need to be repeated at annual visits if available in the prior 3*
817 *months.*
- 818 All of the testing procedures do not need to be performed on the same day, provided that they are
819 completed within the time window of a visit and prior to initiating any treatment.
- 820 Testing procedures at unspecified visits are at investigator discretion. However, it is
821 recommended that procedures that are performed should follow the standard DRCR.net protocol
822 for each procedure. If a primary outcome criterion is identified at an unspecified visit, the
823 imaging requirements above apply and best-corrected visual acuity testing should be performed
824 whenever possible.

CHAPTER 4. TREATMENT REGIMEN

825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872

4.1 Treatment Groups

The treatment groups are as follows:

- A: Sham injections
- B: Intravitreal 2 mg aflibercept injections

For both groups, the baseline injection (sham or intravitreal) must be given on the day of randomization.

4.2 Injection Procedure

4.2.1 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, macular edema due to central retinal vein occlusion, macular edema due to branch retinal vein occlusion, diabetic macular edema, and diabetic retinopathy in eyes with diabetic macular edema.

Study eyes that receive anti-VEGF will receive a dose of 2 mg aflibercept in 0.05 cc each time a study injection is performed. 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.

4.2.2 Intravitreal Injection Technique

The injection is preceded by a povidone iodine prep of the conjunctiva. In general, topical antibiotics in the pre-, peri-, or post-injection period should not be used.

The injection will be performed using sterile technique. The full injection procedure is described in the protocol-specific study procedures manual.

4.2.3 Sham Injection Technique

The prep will be performed as for an intravitreal injection. A syringe without a needle will be used, with the hub pressed against the conjunctival surface to simulate the force of an actual injection.

4.2.4 Deferral of Injections Due to Pregnancy

Female study participants of child-bearing age must be questioned regarding the possibility of pregnancy prior to each injection. In the event of pregnancy, study injections must be discontinued during the pregnancy and any post-partum period of breastfeeding.

4.2.5 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 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 non-study anti-VEGF medication is desired to be administered by intravitreal injection in the non-study eye, a discussion with the Protocol Chair is required first.

873 **4.3 Follow-Up Treatment Protocol for Prevention of PDR/DME**

874 Injections for prevention of PDR/DME will be given according to the criteria below at each
875 Assessment Visit (listed in 3.1.1). Additional injections must not be given in-between the
876 Assessment Visits, unless criteria are met for PDR or DME treatment (see Sections 4.4 and 4.5).

877
878 If an eye experienced adverse effects from a prior intravitreal injection, retreatment is at the
879 discretion of the investigator.

880
881 **4.3.1 Injections at 4 and 8 Weeks and Each 4-Month Interval Visit until 2 Years**

882 During Years 1 and 2, study eyes receive an injection (sham or intravitreal) at each Assessment
883 Visit (listed in 3.1.1). Group A receives a sham injection and group B receives a 2 mg aflibercept
884 injection.

885
886 **4.3.2 Injections at and After the 2-Year Visit**

887 At and after the 2-year visit, the study eye is evaluated for intravitreal (sham) injection
888 retreatment at each Assessment Visit. Group A receives a sham injection and group B receives a
889 2 mg aflibercept injection.

- 890
- 891 • If the DR level is mild NPDR or better (\leq Level 35) based on the investigator's
892 assessment, the injection should be deferred.
 - 893 ○ Level 35 can be clinically defined as microaneurysms plus venous loops, hard
894 exudates, cotton wool spots and/or mild retinal hemorrhages (less than present in
895 ETDRS Standard photograph 2a).
 - 896 • If the DR level is worse than mild NPDR ($>$ Level 35, defined above), the injection (or
897 sham) is given.
- 898

899 **4.4 Treatment for CI-DME**

900 Treatment for CI-DME must not be given until the following criteria have been met:

- 901 • CI-DME on clinical exam with $\geq 10\%$ increase in central subfield thickness from baseline
902 and either:
- 903 ○ 1) at least 10 letter decrease in visual acuity presumed to be from DME at a single
904 visit or
 - 905 ○ 2) 5 to 9 letter decrease in visual acuity presumed to be from DME at two-
906 consecutive visits at least 21 days apart.

907 Once the above criteria have been met, an injection of 2 mg aflibercept will be given.
908 Thereafter, the eye will be evaluated at each visit for retreatment. In general, an eye will continue
909 to receive an injection if the eye is improving or worsening on OCT or visual acuity. The first
910 time an eye has not improved or worsened, the eye will receive an injection. If the eye has not
911 improved or worsened for at least 2 consecutive 4-week injections and the OCT CSF thickness is
912 less than the gender specific spectral domain OCT threshold (see below) and visual acuity is
913 20/20 or better, then injection will be deferred. If the eye has not improved or worsened for at
914 least 2 consecutive 4-week visits and the OCT CSF thickness is \geq the gender specific spectral
915 domain OCT threshold or visual acuity is worse than 20/20, the following will be done:

- 916 • If less than 24 weeks from the initial injection for DME, an injection will be given.
917 • At and after 24 weeks, the injection will be deferred.

918

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

921
922 Spectral domain OCT central subfield gender-specific threshold:

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

926 **4.4.1 Initiation of Focal/Grid Photocoagulation While Receiving Anti-VEGF Injections**

927 In general, focal/grid laser will be initiated at or after the 24 week visit if 1) the OCT central
928 subfield thickness is greater than the OCT central subfield gender-specific threshold (above) or
929 there is edema that is threatening the fovea and 2) the eye has not improved on OCT or visual
930 acuity from the last two consecutive injections. Once focal/grid laser has been initiated,
931 retreatment with focal/grid laser will be given unless one of the following is present: 1)
932 focal/grid laser has been given in the previous 13 weeks, 2) complete focal/grid laser has already
933 been given in the investigator's judgment, 3) the OCT central subfield thickness is less than the
934 OCT central subfield gender-specific threshold (above) and there is no edema threatening the
935 fovea, 4) the eye has improved since the last laser treatment. The protocol chair or designee must
936 be contacted prior to deviating from the focal/grid laser protocol. See the DRCCR.net Procedure
937 Manual for additional details.

938 939 **4.4.2 Continuation of Prevention Treatment Protocol**

940 Eyes for which the above anti-VEGF treatment regimen is initiated for DME will continue
941 injections as part of the prevention protocol. At each Assessment Visit, if an injection has not
942 been given within the prior 21 days, the eye will be treated per protocol (years 1 and 2) or
943 evaluated for a prevention injection (sham or intravitreal) following section 4.3.2 in years 3 and
944 4, regardless of DME status.

946 **4.5 Treatment for PDR**

947 **4.5.1 Primary Outcome for PDR**

948 An eye will be considered to have met the primary outcome for PDR if any of the following are
949 met:

- 950 • Development of NV within the 7-modified ETDRS fields on fundus photography or
951 FA, confirmed by a masked grader at the central reading center
 - 952 ○ At non-annual visits, fundus photography and FA will only be submitted to the
953 reading center to assess for this component of the primary outcome if the
954 investigator thinks treatment is necessary.
- 955 • NV of the iris (at least 2 cumulative clock hours), definitive NV of the angle, or
956 neovascular glaucoma development on clinical exam (photographic documentation
957 not required)
- 958 • Other outcomes presumed to be from PDR and documented: traction retinal
959 detachment, vitreous hemorrhage, pre-retinal hemorrhage greater than ½ disc area
- 960 • Procedures undertaken for the treatment of PDR (when present or presumed to be
961 present): PRP, anti-VEGF, or vitrectomy

962
963 Once NV develops, the participant may return sooner than the next scheduled Assessment Visit
964 to evaluate for initiation of treatment (see below), at the discretion of the investigator.

965

966 **4.5.2 Initiating Treatment for PDR**

967 If at any point NV of the angle develops, treatment with anti-VEGF and/or PRP is at investigator
968 discretion; otherwise, treatment for PDR must not be given until one of the following criteria has
969 been met:

- 970
- 971 1. The eye has PDR with high-risk characteristics, defined as:
 - 972 ○ NVD greater than Standard photograph 10A (1/4 to 1/3 disc area), or
 - 973 ○ Any NVD with pre-retinal or vitreous hemorrhage, or
 - 974 ○ NVE greater than ½ disc area with pre-retinal or vitreous hemorrhage
 - 975 2. The eye has vitreous hemorrhage requiring treatment that is presumed to be from
976 PDR (either NV identified on FA or unable to assess NV due to density of the
977 hemorrhage but there is no other attributable cause)
 - 978 3. The reading center has confirmed NV is present within the 7-modified fields and
979 protocol chair approval has been received to initiate treatment prior to high-risk
980 characteristics being present.
 - 981 ○ Treatment for NVE outside of the 7-modified fields without the presence of pre-
982 retinal or vitreous hemorrhage is discouraged. If the investigator believes
983 treatment for peripheral NV is necessary, protocol chair approval is required.
- 984

985 If at least 4 study injections have been given in the prior 4 months (for DME) and the eye has
986 developed high-risk PDR as defined above, PRP may be performed at the discretion of the
987 investigator.

988

989 Otherwise, once one of the above criteria for treatment has been met, an injection of 2 mg
990 aflibercept will be given. Thereafter, the eye will be evaluated at each visit for retreatment using
991 the criteria below (Sections 4.5.3 to 4.5.4). If an anti-VEGF injection was already given in the
992 prior 5 weeks for prevention, it will be considered the baseline injection, and retreatment will
993 begin with section 4.5.3.

994

995 **4.5.3 Intravitreal Injection for PDR at 4 weeks, 8 weeks and 12 weeks**

996 All eyes that initiate treatment for PDR will receive injections at 4, 8, and 12 weeks following
997 the initial injection. If an eye experienced adverse effects from a prior intravitreal injection,
998 retreatment with intravitreal aflibercept is at the discretion of the investigator.

999

1000 **4.5.4 Intravitreal Injection for PDR at and after 16 weeks**

1001 Starting at 16 weeks, the eye will be evaluated for retreatment with intravitreal injection for
1002 PDR based on appearance of neovascularization.

1003

1004 If an eye has experienced adverse effects from prior intravitreal injection treatment, retreatment
1005 with intravitreal aflibercept is at the discretion of the investigator. In addition, if any future
1006 treatment with aflibercept is contraindicated based on a previous adverse reaction, treatment with
1007 PRP for PDR is at investigator discretion after discussion with and approval from the Protocol
1008 Chair or Coordinating Center designee. Each eye with no contraindication to additional
1009 injections will be categorized into one of the following 5 categories based on neovascularization
1010 (NV) status:

1011

1012 * Note: examination of the angle is at investigator discretion; however, if the angle is
1013 examined, then the results from this examination should be factored into the
1014 subsequent treatment decision.
1015

1016 • **Resolved**

- NV (of the retina, disc, AND iris/angle*) is absent and visualization of the entire retina is adequate to completely assess for NV. Decision to re-inject is at investigator discretion. In general, if NV is completely regressed the injection should be deferred. PRP should not be given.

1022 • **Improved**

- NV (of the retina, disc OR iris/angle*) still persists, but there is evidence of improvement (improvement defined as a decrease in the size of NV or diminished density of NV) since the last visit and visualization of the entire retina is adequate to completely assess for NV. An injection is given. PRP should not be given.

1028 • **Stable**

- NV (of the retina, disc AND iris/angle*) is clinically unchanged since the last visit and visualization of the entire retina is adequate to completely assess for NV. Once the eye meets criteria for stability, at least 2 more injections must be given, each one month apart (one at the visit at which stability criteria are met and the second at the following study visit one month later if still stable). Further reinjection is then at investigator discretion as long as the eye remains stable. PRP should not be given.

1037 • **Not fully treated**

- Failure/futility criteria not met and recurrent or worsening NV (of the retina, disc OR iris) is present since the last visit in an eye that has had fewer than 4 injections over the previous 4 months or there is vitreous or preretinal hemorrhage preventing adequate visualization of the fundus to assess NV status. An injection is given. PRP should not be given.

1044 • **Failed/futile**

- Failure/futility criteria met. Decision to re-inject is at investigator discretion. PRP may be given at this time (see below for cases that first require discussion with the Protocol Chair or Coordinating Center designee).
 - *Failure criteria are defined as*
 1. *growth of NV or new NV of the retina, disc OR iris since the last visit such that the NV, including fibrosis, is greater in extent than when treatment for NV was initiated and at least 4 study injections have been given over the previous 4 months. The investigator may perform PRP.*

1056 OR

2. *New or worsened NV of the angle* has developed since the last visit. The investigator may perform PRP.*

1060
1061
1062
1063
1064
1065
1066
1067
1068
1069
1070
1071
1072
1073
1074
1075
1076
1077
1078
1079
1080
1081
1082
1083
1084
1085
1086
1087
1088
1089
1090
1091

OR

3. *definite worsening of NV or fibrous proliferation of the retina, disc OR iris at least 1 day after the last injection that the investigator believes is likely to lead to substantial vision loss if PRP is not performed within 1 week. PRP may only be performed after discussion with and approval from the Protocol Chair or Coordinating Center designee.*

- *Futility criteria are defined as continued persistence or recurrence of NV at least 1.5 years from initial study aflibercept injection that is equal to or greater than the extent of the NV when treatment for NV was initiated and at least 5 study injections performed over the preceding 6 months. PRP may only be performed after discussion with and approval from the Protocol Chair or Coordinating Center designee.*

4.5.5 Continuation of Prevention Treatment Protocol

Eyes for which the above anti-VEGF treatment regimen is initiated for PDR will continue injections as part of the prevention protocol. At each Assessment Visit, if an injection has not been given within the prior 21 days, the eye will be treated per protocol (years 1 and 2) or be evaluated for a prevention injection (sham or intravitreal) following section 4.3.2 in years 3 and 4, regardless of whether the injection can be deferred according to the PDR treatment criteria.

4.6 Panretinal Photocoagulation Technique

An eye may receive PRP only if failure/futility criteria for intravitreal injection for PDR above are met. Study eyes that receive panretinal photocoagulation should have 1200 to 1600 burns with a spot size on the retina of approximately 500 microns (or the equivalent area treated with a PASCAL) given over 1 to 3 sittings and completed within 8 weeks (56) days of initiation.

The burn characteristics for non-automated photocoagulation will be as follows:

| | |
|----------------------------------|---|
| Size (on retina) | 500 microns [e.g. argon laser using 200 micron spot size with Rodenstock lens (or equivalent) or 500 micron spot size with 3 mirror contact lens] |
| Exposure | 0.1 seconds recommended, 0.05 to 0.2 allowed |
| Intensity | mild white (i.e. 2+ to 3+ burns) |
| Distribution | edges 1 burn width apart |
| No. of Sessions/Sittings | 1 to 3 |
| Nasal proximity to disk | No closer than 500 microns |
| Temp. proximity to center | No closer than 3000 microns |
| Superior/inferior limit | No further posterior than 1 burn within the temporal arcades |

| | |
|-------------------------|---|
| Extent | Arcades (~3000 microns from the macular center) to at least the equator |
| Total # of burns | 1200 to 1600: <i>There may be instances where 1200 burns are not possible such as development of vitreous hemorrhage or study participant inability to complete a sitting precluding completion of the PRP session. Similarly, there may be clinical situations in which more than 1600 burns are needed such as initial difficulty with laser uptake due to media opacity.</i> |
| Wavelength | Green or yellow (red can be used if vitreous hemorrhage is present precluding use of green or yellow) |

1092
1093 An anesthetic injection (retrobulbar, peribulbar or sub-Tenon's) can be used at investigator
1094 discretion.

1095
1096 An indirect laser approach can be used at investigator discretion.

1097
1098 If a laser is used that has the capability of producing an automated pattern (e.g. the PASCAL),
1099 the automated pattern producing mode is permissible. Guidelines for use of the automated
1100 pattern are included in the study procedure manual.

1101
1102 **4.7 Surgery for Vitreous Hemorrhage, Traction Detachment, and Other Complications**
1103 **of DR**

1104 A study eye could develop a vitreous hemorrhage or traction detachment that may cause visual
1105 impairment. In these cases, vitrectomy may be performed at the discretion of the investigator;
1106 however, vitrectomy for hemorrhage alone should not be performed without first confirming
1107 presence of neovascularization on color photographs and/or FA. If NV has not been confirmed
1108 by the investigator in the setting of vitreous hemorrhage alone, review with the Protocol Chair or
1109 Coordinating Center designee must occur prior to proceeding with vitrectomy.

1110
1111 **CHAPTER 5.**
1112 **MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP**
1113

1114 **5.1 Endophthalmitis**

1115 Diagnosis and treatment of endophthalmitis is based on investigator's judgment. Obtaining
1116 cultures of vitreous and aqueous fluid is highly recommended prior to initiating antibiotic
1117 treatment for presumed endophthalmitis.

1118
1119 **5.2 Treatment in Non-study Eye**

1120 Treatment of PDR or DME in the non-study eye is at investigator discretion. However, if anti-
1121 VEGF treatment will be given in the non-study eye, study aflibercept must be used.

1122
1123 **5.3 Diabetes Management**

1124 Diabetes management is left to the study participant's medical care provider.

1125
1126 **5.4 Study Participant Withdrawal and Losses to Follow-up**

1127 A study participant has the right to withdraw from the study at any time. If s/he is considering
1128 withdrawal from the study, the principal investigator should personally speak to the individual
1129 about the reasons, and every effort should be made to accommodate the study participant to
1130 allow continued participation if possible.

1131
1132 The goal for the study is to have as few losses to follow-up as possible. The Coordinating Center
1133 will assist in the tracking of study participants who cannot be contacted by the site. The
1134 Coordinating Center will be responsible for classifying a study participant as lost to follow-up.

1135
1136 Study participants who withdraw will be asked to have a final closeout visit at which the testing
1137 described for the annual study visits will be performed. Study participants who have an adverse
1138 effect attributable to a study treatment or procedure will be asked to continue in follow-up until
1139 the adverse event has resolved or stabilized.

1140
1141 Study participants who withdraw or are determined to have been ineligible post-randomization
1142 will not be replaced.

1143
1144 **5.5 Discontinuation of Study**

1145 The study may be discontinued by the Executive Committee (with approval of the Data and
1146 Safety Monitoring Committee) prior to the preplanned completion of follow-up for all study
1147 participants.

1148
1149 **5.6 Contact Information Provided to the Coordinating Center**

1150 The Coordinating Center will be provided with contact information for each study participant.
1151 Permission to obtain such information will be included in the Informed Consent Form. The
1152 contact information may be maintained in a secure database and will be maintained separately
1153 from the study data.

1154
1155 Phone contact from the Coordinating Center will be made with each study participant in the first
1156 month after enrollment, and approximately every six months thereafter. Additional phone
1157 contacts from the Coordinating Center will be made if necessary to facilitate the scheduling of

1158 the study participant for follow-up visits. A study participant-oriented newsletter will be sent at
1159 least twice a year. A study logo item may be sent once a year.

1160

1161 Study participants will be provided with a summary of the study results in a newsletter format
1162 after completion of the study by all study participants.

1163

1164 **5.7 Study Participant Reimbursement**

1165 The study will be providing the study participant with a \$25 merchandise or money card per
1166 completed non-annual study visit and \$100 in merchandise or money cards per annual visit.

1167 Additional travel expenses will be paid in select cases for study participants with higher
1168 expenses.

1169 **CHAPTER 6.**
1170 **ADVERSE EVENTS**

1171
1172 **6.1 Definition**

1173 An adverse event is any untoward medical occurrence in a study participant, irrespective of
1174 whether or not the event is considered treatment-related. An adverse event can therefore be any
1175 unfavorable and unintended sign (including an abnormal lab finding), symptom or disease
1176 temporally associated with the use of the treatment, whether or not related to the treatment. This
1177 includes preexisting medical conditions (other than the condition being studied) judged by the
1178 investigator to have worsened in severity or frequency or changed in character.

1179
1180 **6.2 Recording of Adverse Events**

1181 Throughout the course of the study, all efforts will be made to remain alert to possible adverse
1182 events or untoward findings. The first concern will be the safety of the study participant, and
1183 appropriate medical intervention will be made.

1184
1185 All adverse events whether volunteered by the subject, discovered by study personnel during
1186 questioning, or detected through physical examination, laboratory test, or other means will be
1187 reported on an adverse event form online. Each adverse event form is reviewed by the Medical
1188 Monitor to verify the coding and the reporting that is required.

1189
1190 The study investigator will assess the relationship of any adverse event to be related or unrelated
1191 by determining if there is a reasonable possibility that the adverse event may have been caused
1192 by the treatment.

1193
1194 To ensure consistency of adverse event causality assessments, investigators should apply the
1195 following general guideline when determining whether an adverse event is related:

1196
1197 **Yes**

1198 There is a plausible temporal relationship between the onset of the adverse event and
1199 administration of the study treatment, and the adverse event cannot be readily explained by the
1200 subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event
1201 follows a known pattern of response to the study treatment; and/or the adverse event abates or
1202 resolves upon discontinuation of the study treatment or dose reduction and, if applicable,
1203 reappears upon re-challenge.

1204
1205 **No**

1206 Evidence exists that the adverse event has an etiology other than the study treatment (e.g.,
1207 preexisting medical condition, underlying disease, intercurrent illness, or concomitant
1208 medication); and/or the adverse event has no plausible temporal relationship to study treatment
1209 administration (e.g., cancer diagnosed 2 days after first dose of study drug).

1210
1211 The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3)
1212 severe. It is emphasized that the term severe is a measure of intensity: thus, a severe adverse
1213 event is not necessarily serious. For example, itching for several days may be rated as severe,
1214 but may not be clinically serious.

1215
1216 Adverse events will be coded using the MedDRA dictionary.

1217
1218 Definitions of relationship and intensity are listed on the DRCRnet website data entry form.
1219
1220 Adverse events that continue after the study participant’s discontinuation or completion of the
1221 study will be followed until their medical outcome is determined or until no further change in the
1222 condition is expected.

1223 1224 **6.3 Reporting Serious or Unexpected Adverse Events**

1225 A serious adverse event is any untoward occurrence that:

- 1226 • Results in death
- 1227 • Is life-threatening; (a non-life-threatening event which, had it been more severe, might have
1228 become life-threatening, is not necessarily considered a serious adverse event)
- 1229 • Requires inpatient hospitalization or prolongation of existing hospitalization
- 1230 • Results in persistent or significant disability/incapacity or substantial disruption of the ability
1231 to conduct normal life functions (sight threatening)
- 1232 • Is a congenital anomaly/birth defect
- 1233 • Is considered a significant medical event by the investigator based on medical judgment (e.g.,
1234 may jeopardize the participant or may require medical/surgical intervention to prevent one of
1235 the outcomes listed above)

1236
1237 Unexpected adverse events are those that are not identified in nature, severity, or frequency in
1238 the current Eylea® Clinical Investigator’s Brochure, protocol, or informed consent form.

1239
1240 Serious or unexpected adverse events must be reported to the Coordinating Center immediately
1241 via completion of the online serious adverse event form.

1242
1243 The Coordinating Center will notify all participating investigators of any adverse event that is
1244 both serious and unexpected. Notification will be made within 10 days after the Coordinating
1245 Center becomes aware of the event.

1246
1247 Each principal investigator is responsible for informing his/her IRB of serious study-related
1248 adverse events and abiding by any other reporting requirements specific to their IRB.

1249 1250 **6.4 Data and Safety Monitoring Committee Review of Adverse Events**

1251 A Data and Safety Monitoring Committee (DSMC) will advise the Coordinating Center
1252 regarding the protocol, template informed consent form, and substantive amendments and will
1253 provide independent monitoring of adverse events. Cumulative adverse event data are semi-
1254 annually tabulated for review by the DSMC. Following each DSMC data review, a summary
1255 will be provided to institutional review boards. A list of specific adverse events to be reported to
1256 the DSMC expeditiously, if applicable, will be compiled and included as part of the DSMC
1257 Standard Operating Procedures document.

1258

1259 **6.5 Risks**

1260 **6.5.1 Potential Adverse Effects of Aflibercept**

1261 The most common adverse reactions ($\geq 5\%$) reported in patients receiving aflibercept were
1262 conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and
1263 vitreous detachment.

1264
1265 Serious adverse reactions related to the injection procedure have occurred in $<0.1\%$ of
1266 intravitreal injections with aflibercept including endophthalmitis and retinal detachment.

1267
1268 The DA VINCI study, a phase II study evaluating aflibercept for treatment of DME, reported
1269 common adverse events that were consistent with those previously seen with intravitreal
1270 injections. Over one year of follow-up, two cases of endophthalmitis and one case of uveitis
1271 occurred (all in aflibercept treatment groups). Seven deaths (4.0%) occurred in the groups
1272 randomized to aflibercept treatment as compared with 1 (2.3%) in the group treated with laser.
1273 Myocardial infarction or cerebrovascular accident occurred in 6 (3.4%) participants treated with
1274 aflibercept as compared with 1 (2.3%) participant treated with laser alone.⁴⁴ Percentages of
1275 study participants that experienced events meeting APTC criteria were 5.1% (N = 9) in the
1276 combined aflibercept groups and 4.5% (N = 2) in the laser group.⁴⁵

1277
1278 The DRCCR.net Protocol T study assessed ocular and systemic adverse events in eyes with
1279 central-involved DME treated with aflibercept over 1 year.⁴³ In the aflibercept-treated study
1280 eyes, there were no cases of endophthalmitis and 2 cases of ocular inflammation. Non-study eyes
1281 treated with aflibercept had 1 case of endophthalmitis and 3 cases of ocular inflammation.
1282 Systemic adverse events were infrequent with only 6 APTC events (4 nonfatal myocardial
1283 infarctions, 2 deaths from a potential vascular cause or unknown cause, 6% of participants) over
1284 the 1 year period in the aflibercept group.

1285
1286 Additional safety data were published from phase III studies VISTA and VIVID, which included
1287 872 eyes with DME with central involvement that received either intravitreal aflibercept every 4
1288 weeks, intravitreal aflibercept every 8 weeks after 5 initial monthly doses, or macular laser
1289 photocoagulation. Overall, the incidences of ocular and non-ocular adverse events were similar
1290 across treatment groups at 52 weeks.⁴² The incidence of APTC-defined thromboembolic events
1291 was similar across treatment groups. There were no reported cases of endophthalmitis, and
1292 intraocular inflammation occurred in less than 1% of injections. Through 100 weeks, an
1293 integrated safety analysis found that the most frequent serious ocular adverse event was cataract
1294 (2.4% and 1.0% in the aflibercept groups compared with 0.3% in the laser group).⁴¹

1295
1296 There may be side effects and discomforts that are not yet known.

1297

1298 **6.5.2 Potential Adverse Effects of Intravitreal Injection**

1299 Rarely, the drugs used to anesthetize the eye before the study drug injections (proparacaine,
1300 tetracaine, or xylocaine) can cause an allergic reaction, seizures, and an irregular heartbeat.

1301
1302 Subconjunctival hemorrhage or floaters will commonly occur as a result of the intravitreal
1303 injection. Discomfort, redness, or itching lasting for a few days is also likely.

1304
1305 Immediately following the injection, there may be elevation of intraocular pressure. It usually
1306 returns to normal spontaneously, but may need to be treated with topical drugs or a

1307 paracentesis to lower the pressure. The likelihood of permanent loss of vision from elevated
1308 intraocular pressure is less than 1%.

1309
1310 As a result of the injection, endophthalmitis (infection in the eye) could develop. If this occurs, it is
1311 treated by intravitreal injection of antibiotics, but there is a risk of permanent loss of vision including
1312 blindness. The risk of endophthalmitis is less than 1%.

1313
1314 As a result of the injection, a retinal detachment could occur. If this occurs, surgery may be
1315 needed to repair the retina. The surgery is usually successful at reattaching the retina.
1316 However, a retinal detachment can produce permanent loss of vision and even blindness. The
1317 risk of retinal detachment is less than 1%.

1318
1319 The injection could cause a vitreous hemorrhage. Usually the blood will resolve
1320 spontaneously, but if not, surgery may be needed to remove the blood. Although the surgery
1321 usually successfully removes the blood, there is a small risk of permanent loss of vision and
1322 even blindness. The risk of having a vitreous hemorrhage due to the injection is less than 1%.

1323 1324 **6.5.3 Risks of Eye Examination and Tests**

1325 There is a rare risk of an allergic response to the topical medications used to anesthetize the eye
1326 or dilate the pupil. Dilating drops rarely could cause an acute angle closure glaucoma attack, but
1327 this is highly unlikely since the study participants in the study will have had their pupils dilated
1328 many times previously.

1329
1330 There are no known risks associated with OCT or fundus photographs. The bright flashes used
1331 to take the photographs may be annoying, but are not painful and cause no damage.

1332
1333 For fluorescein angiography, both the skin and urine are expected to turn yellow/orange for up to
1334 24 hours after the injection of fluorescein dye. There is a small risk of discomfort or phlebitis at
1335 the site of the injection. Patients occasionally experience lightheadedness or nausea after dye
1336 injection which are usually transient and resolve after a few minutes without further intervention.
1337 An allergic reaction to the dye used to do the fluorescein angiography imaging is rare. A rash or
1338 pruritus (itching) can develop, but true anaphylactic reactions are very rare.

1339
1340
1341
1342
1343
1344
1345
1346

CHAPTER 7. STATISTICAL METHODS

1342 The approach to sample size and statistical analyses are summarized below. A detailed statistical
1343 analysis plan will be written and finalized prior to the first assessment of 2-year outcome data.
1344 The analysis plan synopsis in this chapter contains the framework of the anticipated final
1345 analysis plan.

1347 **7.1 Primary Objectives and Key Outcomes**

1348 This study has two objectives. First, to determine the efficacy and safety of intravitreal
1349 aflibercept injections versus sham injections (observation) for prevention of PDR and CI-DME
1350 in eyes at high risk for development of these complications. Second, to compare long-term vision
1351 outcomes in eyes that receive anti-VEGF therapy early in the course of disease with those that
1352 are initially observed and treated only if high-risk PDR or CI-DME with vision loss develops.

1353
1354 *Primary outcome:* development of PDR or DME defined as the first occurrence of any of the
1355 following (composite time-to-event outcome):

- 1356 • NV within the 7-modified ETDRS fields on fundus photography or FA, confirmed by
1357 a masked grader at the central reading center
 - 1358 ○ At non-annual visits, fundus photography and FA will only be submitted to the
1359 reading center to assess for this component of the primary outcome if the
1360 investigator thinks treatment is necessary.
- 1361 • NV of the iris (at least 2 cumulative clock hours), definitive NV of the angle, or
1362 neovascular glaucoma on clinical exam (photographic documentation not required)
- 1363 • Other outcomes presumed to be from PDR and documented: traction retinal
1364 detachment, vitreous hemorrhage, or pre-retinal hemorrhage greater than ½ disc area
- 1365 • Procedures undertaken for the treatment of PDR (when present or presumed to be
1366 present): PRP, anti-VEGF, or vitrectomy
- 1367 • CI-DME on clinical exam with at least 10% increase in central subfield thickness
1368 from baseline and either (1) at least a 10-letter decrease in visual acuity from baseline
1369 at a single visit or (2) a 5-to-9-letter decrease in visual acuity from baseline at 2
1370 consecutive visits at least 21 days apart, with vision loss presumed to be from DME
- 1371 • Non-topical treatment for DME performed without meeting the above criteria,
1372 including focal/grid laser or intravitreal injections for DME

1373
1374 The primary outcome analysis will be performed when the last enrolled participant reaches 2
1375 years of follow up, using all available follow up data. The treatment groups will be compared
1376 using the hazard ratio.

1377
1378 *Other Key Outcomes:*

- 1379 • Development of PDR or DME outcome through 4 years
- 1380 • Mean visual acuity change from baseline at 2 years
- 1381 • Mean visual acuity change from baseline at 4 years

1382
1383 The overall type 1 error for the primary outcome and all key outcomes will be controlled at 5%.
1384 To control the type 1 error for each time point, 2.5% type I error will be allocated to the 2-year

1385 analysis, and 2.5% will be allocated to the 4-year analysis. To control the type 1 error for the
1386 multiple key outcomes, a hierarchical approach will be used. The visual acuity outcome will be
1387 formally compared (i.e., with a *P* value) only if there is a significant treatment group difference
1388 in the anatomic outcome at the same time point ($P \leq .025$). If not, only point estimates and
1389 confidence intervals for within and between group changes in visual acuity from baseline will be
1390 computed.

1391
1392 See Section 7.4 for secondary outcomes to be evaluated at 2 and 4 years.

1393 1394 **7.2 Sample Size**

1395 The sample size has been computed for the primary outcome at 2 years. The primary analysis
1396 will consist of a treatment group comparison based on the hazard ratio for the composite time-to-
1397 event outcome, as defined in Section 7.1, estimated using the marginal Cox proportional hazards
1398 model (see Section 7.3).

1399 1400 **7.2.1 Projected Control Group Proportion**

1401 Data from the ETDRS, the Protein Kinase C β Inhibitor Diabetic Retinopathy Study (PKC-
1402 DRS), Diabetic Retinopathy Study (DRS)-2, prior DRCR.net studies, and RIDE/RISE were used
1403 to estimate progression rates in the control group. Estimates for this study are based largely on
1404 PDR development, although approximately 4% of eyes in ETDRS developed CI-DME prior to
1405 PDR, which would increase the expected progression rate.

1406
1407 It should be noted that eligibility for this study is based primarily on investigator assessment of
1408 DR severity as severe NPDR (level 53). The data below are presented by DR severity level as
1409 assessed by central reading center grading of fundus photographs; however, it is unknown
1410 whether features of severe NPDR were evident on clinical exam or FA in these cohorts

1411
1412 Fifty-nine percent (N=249), 43% (N=461), and 23% (N=499) of eyes in the ETDRS assigned to
1413 observation with DR Severity levels graded on fundus photography of 53, 47, and 43,
1414 respectively, with no DME on fundus photography at baseline, progressed to PDR on fundus
1415 photography at 2 years (personal communication, Adam Glassman).

1416
1417 More recent data for longer-term progression rates are available from 2 separate phase 3 trials of
1418 the protein kinase C inhibitor, ruboxistaurin, which demonstrated rates of PDR progression of
1419 approximately 40% and 60% in the 2 trials, respectively, over 3 years with lower levels of DR
1420 (47A) being included in the first trial.^{7,8}

1421
1422 Data from DRCR.net Protocol A and Protocol B include eyes with baseline DME treated with
1423 laser alone and having DR severity levels 43 to 53 at baseline (Table 1, personal communication,
1424 Adam Glassman). Data from RIDE/RISE include eyes with DME and diabetic retinopathy less
1425 severe than active PDR on clinical exam that were treated with sham (Table 2).³⁴

1426

1427 **Table 1. Proportion of Eyes with PDR* at 2 years by Baseline Level of Retinopathy (Laser**
 1428 **group only; DME at Baseline)**

| Protocol A – A Pilot Study of Laser Photocoagulation for Diabetic Macular Edema | | |
|---|----------|---|
| DR Severity | N | Proportion of eyes with PDR at 2 years |
| Level 43 | 27 | 7% |
| Level 47A | 62 | 13% |
| Level 47B-47D | 22 | 32% |
| Level 53 | 26 | 58% |
| Protocol B – A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Laser Photocoagulation for Diabetic Macular Edema | | |
| DR Severity | N | Proportion of eyes with PDR at 2 years |
| Level 43 | 41 | 10% |
| Level 47A | 59 | 15% |
| Level 47B-47D | 23 | 13% |
| Level 53 | 27 | 55% |

* Defined as ETDRS DR Severity Score \geq 60 (i.e. includes eyes with PRP prior to 2 years)

1429
 1430
 1431 **Table 2. RIDE/RISE Cumulative Proportion with PDR Events in Sham Eyes (includes**
 1432 **eyes with DME)**

| RIDE/RISE | N | 1 Year | N | 2 Year |
|------------------|----------|---------------|----------|---------------|
| Sham | 135 | 18% | 116 | 30% |

1433
 1434 Based on these data and the expected proportion of eyes enrolled in each DR severity level, we
 1435 estimate the overall outcome proportion in the control group to be 30%. This estimate includes
 1436 approximately 5% that are expected to meet the outcome by development of CI-DME prior to
 1437 PDR.

1438
 1439 **7.2.2 Projected Treatment Group Rate**

1440 Pooled data from the RIDE/RISE Open-Label Extension include only eyes with DME and
 1441 diabetic retinopathy less severe than active PDR on clinical exam (Table 3).³⁴

1442
 1443 **Table 3. RIDE/RISE Cumulative Proportion with PDR Events in the Anti-VEGF Treated**
 1444 **Groups**

| RIDE/RISE | N | 1 Year | N | 2 Year |
|--------------------|----------|---------------|----------|---------------|
| 0.3 mg Ranibizumab | 164 | 5% | 152 | 12% |
| 0.5 mg Ranibizumab | 154 | 6% | 147 | 10% |

1445
 1446 The cumulative proportions of eyes with progression from RIDE/RISE are supported by
 1447 unpublished data of PDR progression in eyes with DR severity levels of 43 to 53 treated with
 1448 anti-VEGF from DRCR.net Protocol T (personal communication, Adam Glassman). Based on
 1449 these data, the projected cumulative outcome proportion for the treatment group is estimated to
 1450 be no more than one-half the rate in the control group (10-15%).

1451

1452 **7.2.3 Sample Size Estimates**

1453 Table 4 shows sample size estimates under varying assumptions for primary outcome
 1454 proportions in the treatment and control groups at 2 years. These calculations assume a type I
 1455 error rate of 5% with 90% power, and a null hypothesis of no difference between groups.
 1456

1457 **Table 4: Total Sample Size for Various Outcome Rates of PDR/DME Development**

| Treatment Group Rate | Control Group Rate | | |
|----------------------|--------------------|------------|-----|
| | 20% | 30% | 40% |
| 10% | 564 | 180 | 94 |
| 15% | 2496 | 346 | 144 |
| 20% | -- | 822 | 236 |

1458
 1459 For true outcome rates of 30% vs. 15%, a sample of N=346 (173 per group) gives 90% power to
 1460 reject the null hypothesis of no difference for a 2-sided test with a type I error rate of 5%.
 1461 Sample size is increased by 10% for possible dropouts giving **N=386 (193 per group)**. Sample
 1462 size was selected based on the original study design, which included the parameters above.
 1463 Considering that the study is sufficiently powered for the current design (see below), no change
 1464 to sample size will be made.
 1465

1466 Given the approach to control type 1 errors, the alpha allocation at 2 years will be 2.5%. Using
 1467 the assumptions above, with a sample size of 386 and an alpha level of 2.5%, the study will have
 1468 89% power to reject the null hypothesis of no difference. As this power calculation does not
 1469 include estimates for person-time beyond 2 years, which will be included in the primary analysis,
 1470 and is not adjusted for the correlation between eyes of participants with two study eyes, power is
 1471 expected to be greater than this projection.
 1472

1473 **7.2.4 Power for the Visual Acuity Outcome**

1474 Table 5 shows the expected statistical power to detect a difference in the mean change in visual
 1475 acuity from baseline if the true difference between the groups is 3, 4, or 5 letters under varying
 1476 assumptions for standard deviation, using the estimated sample size for 2 and 4 years.

1477 **Table 5. Expected Statistical Power for Mean Change in Visual Acuity Outcome Adjusted**
 1478 **for Baseline Visual Acuity**

| Standard Deviation* | N [†] | Difference in Letter Score | | |
|---------------------|----------------|----------------------------|------|------|
| | | 3 | 4 | 5 |
| 6 | 346 | >99% | >99% | >99% |
| | 306 | 98% | >99% | >99% |
| 8 | 346 | 89% | >99% | >99% |
| | 306 | 85% | 98% | >99% |
| 10 | 346 | 71% | 93% | >99% |
| | 306 | 65% | 89% | 98% |

1479 Alpha = 0.025 for a 2-sided hypothesis test.

1480 * For reference, the adjusted standard deviation from the DRCR.net Protocol T aflibercept group

1481 (baseline visual acuity 20/32 to 20/40) of change in visual acuity from baseline at 2 years, adjusted for
1482 baseline visual acuity, was 7.7 (personal communication, Adam Glassman)

1483 † Based on 5% annual lost to follow-up

1484

1485 **7.3 Primary Analysis Plan**

1486 **7.3.1 Principles for Analysis**

1487 The primary analysis consists of a treatment group comparison based on the hazard ratio for the
1488 PDR/DME composite time-to-event outcome when the last participant reaches 2 years.

1489

1490 Other key analyses include a treatment group comparison of (1) the development of PDR/DME
1491 composite time-to-event outcome when the last participant reaches 4 years, (2) the difference in
1492 the mean change in visual acuity from baseline at 2 years, and (3) the difference in the mean
1493 change in visual acuity from baseline at 4 years. Note that (2) and (3), the comparisons of mean
1494 change in visual acuity, will only be conducted if there is a significant difference ($P \leq .025$) in
1495 the PDR/DME composite outcome at the corresponding time point. The 2-year analysis will be
1496 conducted when the last enrolled participant reaches 2 years of follow up and include all of the
1497 data collected through that point. The 4-year analysis will be conducted at the end of the study.

1498

1499 *PDR/DME Outcome*

1500 The comparison of the PDR/DME composite time-to-event outcome will be based on the hazard
1501 ratio from a marginal Cox regression model that accounts for the correlation within study
1502 participants having two study eyes, and adjusts for randomization stratification factors.⁴⁶ The
1503 primary analysis is an intention-to-treat analysis. Data from participants not observed to meet
1504 outcome criteria who are lost to follow up will be censored at the time of the last completed visit.
1505 If there is evidence that assumptions are not reasonably satisfied, an alternative analysis method
1506 will be considered.

1507

1508 *Visual Acuity Outcome*

1509 If there is a significant difference ($P \leq .025$) in the PDR/DME composite outcome, a treatment
1510 group comparison of the difference in the mean change in visual acuity from baseline to the
1511 outcome visit will be conducted. A linear mixed effects model will be used to estimate the
1512 treatment group difference. The analysis will adjust for baseline visual acuity and randomization
1513 stratification factors. This will also be an intention-to-treat analysis that includes all randomized
1514 eyes. Multiple imputation will be used to impute missing data. The correlation between eyes of
1515 participants having two study eyes will be modeled using random intercepts. If model
1516 assumptions are not reasonably satisfied, a transformation or non-parametric analysis will be
1517 considered.

1518

1519 Imbalances between groups in important covariates are not expected to be of sufficient
1520 magnitude to produce confounding. However, the presence of confounding will be evaluated in
1521 a sensitivity analysis by including factors potentially associated with the outcome for which there
1522 is an imbalance between groups as covariates in the mixed effects model.

1523

1524 Pre-planned subgroup analyses will be described in the detailed Statistical Analysis Plan. There
1525 are no data to suggest that the treatment effect will vary by gender or race/ethnicity. However,
1526 both of these factors will be evaluated in exploratory subgroup analyses.

1527

1528 **7.3.2 Per-protocol Analysis**

1529 A per-protocol analysis for the 2- and 4-year outcomes will be performed including only eyes
1530 that received at least 80% of injections (sham or intravitreal) according to protocol and no other
1531 treatment for DR or DME. If the intention-to-treat and per-protocol analyses yield similar results,
1532 the per-protocol analyses will be used to provide supportive evidence of the magnitude of
1533 treatment effect among subjects who received the treatment. If the results of the methods differ,
1534 exploratory analyses will be performed to evaluate the factors that may have contributed to the
1535 differences.

1536 **7.3.3 Interim Analysis Plan**

1537 The DSMC will review tabulated safety and efficacy data at semi-annual meetings to assess the
1538 risk-benefit ratio of adverse events against benefits, if any, of anti-VEGF as compared with
1539 sham. No formal statistical analysis is planned during these reviews.

1540 It is not expected that the trial will be stopped early for efficacy, based on the following reasons:

- 1541 • Even if there is a significant difference in the primary outcome at 2 years, this may not
1542 translate to a long-term visual acuity difference.
- 1543 • Even if there is a significant difference in mean visual acuity change from baseline at 2
1544 years, it is important to know whether in the long term, treatment when progression
1545 occurs results in worse, equal, or better visual acuity outcome compared with treatment to
1546 prevent progression, and the relative differences in amount of treatment required with the
1547 two approaches to DR management.

1548 **7.4 Secondary Outcomes for Treatment Group Comparison**

1549 The treatment groups will be compared on the following outcomes of interest at the time of the
1550 2- and 4-year analyses of the primary outcome:

- 1551 • Development of PDR or PDR-related outcome (as defined above within the
1552 composite time-to-event outcome)
- 1553 • Development of CI-DME with visual acuity impairment (as defined above within the
1554 composite time-to-event outcome)
- 1555 • Development of PDR or DME based only on the objective components defined in the
1556 composite outcome, including OCT, visual acuity, and reading center assessment of
1557 photos and FA (i.e. not including investigator-only assessments)*
- 1558 • Development of each component of the composite outcome assessed individually*
- 1559 • Proportion of eyes with at least 10 or at least 15 letter loss from baseline, or gain or
1560 loss of at least 5 letters at consecutive study visits, consisting of the visits just before
1561 and the 2- or 4-year visit[†]
- 1562 • Visual acuity area under the curve (AUC) between randomization and the 2- and 4-
1563 year visits[†]
- 1564 • Mean change in OCT central subfield thickness from baseline
- 1565 • Mean change in OCT volume from baseline
- 1566 • Development of CI-DME on clinical exam with at least 10% increase in central
1567 subfield thickness and at least a 25-micron increase from baseline, regardless of
1568 visual acuity change*
- 1569 • Proportion of eyes with at least 2-step worsening of DR severity level (scale for
1570 individual eyes) by central reading center from baseline

- 1574 • Proportion of eyes with at least 2-step improvement of DR severity level (scale for
1575 individual eyes) by central reading center from baseline
- 1576 • Proportion of eyes with at least 3-step worsening of DR severity level (scale for
1577 individual eyes) by central reading center from baseline*
- 1578 • Proportion of eyes with at least 3-step improvement of DR severity level (scale for
1579 individual eyes) by central reading center from baseline*
- 1580 • Level of retinopathy on color photos*
- 1581 • Number of aflibercept injections performed*

1582
1583 * Outcomes will include descriptive statistics only with no statistical comparisons of treatment
1584 groups.

1585 † If the statistical comparison of the mean change in visual acuity is not performed because the
1586 anatomic outcome comparison is not statistically significant, any analysis on visual acuity
1587 outcomes will be considered exploratory.

1588
1589 Descriptive statistics for the outcomes listed above will also be presented for the 1- and 3-year
1590 visits, with no statistical analyses conducted.

1591
1592 Binary outcomes will be analyzed using logistic regression with generalized estimating equations
1593 (GEE). Continuous outcomes will be analyzed using a linear mixed model. Time-to-event
1594 outcomes will be analyzed using the marginal Cox regression model. Analyses will be adjusted
1595 for baseline measure, correlation within study participants having two study eyes, and
1596 randomization stratification factors, where appropriate. If model assumptions are not reasonably
1597 satisfied, a transformation, nonparametric approach, or alternative method will be considered.
1598 Methods for handling missing secondary outcome data will be included in the detailed Statistical
1599 Analysis Plan.

1600
1601 **7.5 Economic Analysis**

1602 The purpose of the economic analysis is to compare the treatment groups with respect to cost and
1603 workplace productivity loss. Data from the clinical trial on number of clinic visits completed,
1604 number of procedures performed (e.g., OCT, fundus photographs), and number of aflibercept
1605 injections will be used to estimate an average cost per patient for each treatment arm, using the
1606 Medicare Fee Schedule to estimate medical costs. The cost estimates, in combination with the
1607 percentage of productivity loss for each treatment arm, will be incorporated into the analysis.

1608 The following will be analyzed by treatment group:

- 1609 • Mean change from baseline in the percentage of work time missed due to vision problems
1610 over the past week (Absenteeism score)
 - 1611 ○ Tabulated without statistical comparison
- 1612 • Mean change from baseline in the percentage of impairment while working due to vision
1613 problems over the past week (Presenteeism score)
 - 1614 ○ Tabulated without statistical comparison
- 1615 • Mean change from baseline in the percentage of overall work impairment due to vision
1616 problems over the past week (Work Productivity Loss score)
- 1617 • Mean change from baseline in the percentage of activity impairment due to vision
1618 problems over the past week (Activity Impairment score)

1619
1620 For functional outcomes measured at the participant level, bilateral participants are non-
1621 informative with respect to the treatment comparison and will not be included in the analyses.
1622

1623 **7.6 OCT Angiography Ancillary Study**

1624 At a subset of sites with OCT angiography capabilities, images will be taken at baseline and at
1625 least one annual visit. Features evident on OCT angiography alone will not be used for the
1626 primary outcome determination. Exploratory analyses of OCT angiography may include, but are
1627 not limited to, the following:

- 1628 1. Comparison with current imaging modalities for detection of diabetic retinopathy
1629 pathology.
- 1630 2. Identification of biomarkers at baseline that are associated with retinopathy
1631 progression.
- 1632 3. Comparison of different OCT angiography systems at sites with more than one
1633 available.

1634

1635 **7.7 Safety Analysis Plan**

1636 **7.7.1 Ocular Adverse Events**

1637 The following ocular adverse events are of primary interest:

- 1638 ○ Endophthalmitis
- 1639 ○ Retinal detachment
- 1640 ○ Traumatic cataract
- 1641 ○ Vitreous hemorrhage
- 1642 ○ Inflammation
- 1643 ○ Neovascular glaucoma
- 1644 ○ Iris neovascularization

1645

1646 The ocular adverse events of primary interest will be tabulated by treatment group. In addition, a
1647 tabulation will be made for non-study eyes receiving study aflibercept. The frequency of the
1648 event occurring at least once per eye will be calculated. Eye-level outcomes will be compared
1649 between treatment groups using logistic regression with GEE to account for the potential
1650 correlation within participants having two study eyes.

1651

1652 **7.7.2 Systemic Adverse Events**

1653 Systemic adverse events will be reported in three groups: (1) unilateral participants randomized
1654 to sham, (2) unilateral participants randomized to aflibercept, and (3) bilateral study participants.
1655 The frequency of the event occurring at least once per participant will be calculated. However,
1656 statistical comparisons for systemic adverse events will only include unilateral participants
1657 randomized to sham and unilateral participants randomized to aflibercept. Analysis of
1658 participant-level adverse events will be conducted with Barnard's Unconditional Exact Test.

1659

- 1660 ○ Primary systemic adverse events of interest:
 - 1661 ■ Death
 - 1662 ■ Serious adverse event (proportion of participants with at least one)
 - 1663 ■ Hospitalization (proportion of participants with at least one)
 - 1664 ■ Cardiovascular and cerebrovascular events according to Antiplatelet Trialists'
1665 Collaboration (excerpted from BMJ Jan 8, 1994):

- 1666 • Non-fatal myocardial infarction
- 1667 • Non-fatal stroke (counted only if symptoms lasted at least 24 hours)
- 1668 • Death of unknown cause
- 1669 • Death attributed to cardiac, cerebral, hemorrhagic, embolic, or other
- 1670 vascular cause (does not need to be ischemic in origin)

1671
1672 Note that transient ischemic attack, angina, possible myocardial infarction, and possible stroke
1673 are not counted. Non-fatal myocardial infarction and non-fatal stroke require that the participant
1674 is alive at the end of the study. If not, then only the death is counted.

- 1675
- 1676 ○ Secondary systemic adverse events of interest to be tabulated without statistical
- 1677 comparison:
- 1678 ▪ Hypertension
- 1679 ▪ Frequency of at least one event per participant in each Medical Dictionary for
- 1680 Regulatory Activities (MedDRA) system organ class

1681
1682 Sensitivity analyses will replicate the analyses above within two groups: (1) participants who
1683 received study aflibercept in either eye and (2) participants who did not receive study aflibercept
1684 in either eye.

1685
1686 A tabulation of all study eye ocular, non-study eye ocular, and systemic adverse events by
1687 primary treatment groups will be created.

1688 **7.8 Additional Tabulations and Analyses**

- 1689 The following will be tabulated according to treatment group:
- 1691 1) Baseline demographic and clinical characteristics
 - 1692 2) Visit completion rate
 - 1693 3) Treatment adherence

CHAPTER 8. REFERENCES

1694
1695

- 1696 1. Centers for Disease Control and Prevention. State-specific incidence of diabetes among
1697 adults--participating states, 1995-1997 and 2005-2007. *MMWR Morb Mortal Wkly Rep.*
1698 2008;57(43):1169-73.
- 1699 2. International Diabetes Federation: Facts and figures.
1700 <http://www.idf.org/worlddiabetesday/toolkit/gp/facts-figures> Accessed Accessed June 19,
1701 2014.
- 1702 3. Varma R, Bressler NM, Doan QV, et al. Prevalence of and risk factors for diabetic
1703 macular edema in the United States. *JAMA Ophthalmol.* 2014;132(11):1334-40.
- 1704 4. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. *N Engl J Med.*
1705 2012;366(13):1227-39.
- 1706 5. Aiello LP. Angiogenic pathways in diabetic retinopathy. *N Engl J Med.* 2005;353:839-
1707 41.
- 1708 6. Klein R, Klein BE, Moss SE. A population-based study of diabetic retinopathy in insulin-
1709 using patients diagnosed before 30 years of age. *Diabetes Care.* 1985;8 Suppl 1:71-6.
- 1710 7. The PKC-DRS Study Group. The effect of ruboxistaurin on visual loss in patients with
1711 moderately severe to very severe nonproliferative diabetic retinopathy: initial results of
1712 the Protein Kinase C beta Inhibitor Diabetic Retinopathy Study (PKC-DRS) multicenter
1713 randomized clinical trial. *Diabetes.* 2005;54(7):2188-97.
- 1714 8. The PKC-DRS2 Group. Effect of ruboxistaurin on visual loss in patients with diabetic
1715 retinopathy. *Ophthalmology.* 2006;113(12):2221-30.
- 1716 9. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of
1717 photocoagulation therapy. *Am J Ophthalmol.* 1976;81(4):383-96.
- 1718 10. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for
1719 diabetic retinopathy. ETDRS report number 9. *Ophthalmology.* 1991;98(5 suppl):766-
1720 85.
- 1721 11. The Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating short-
1722 term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema
1723 following focal/grid laser for diabetic macular edema in eyes also receiving panretinal
1724 photocoagulation. *Retina.* 2011;31(6):1009-27.
- 1725 12. Ferris F. Early photocoagulation in patients with either type I or type II diabetes. *Trans*
1726 *Am Ophthalmol Soc.* 1996;94:505-37.
- 1727 13. AAO Preferred Practice Patterns: Diabetic retinopathy [≤http://one.aao.org/preferred-](http://one.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp--september-2008-4th-print)
1728 [practice-pattern/diabetic-retinopathy-ppp--september-2008-4th-print](http://one.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp--september-2008-4th-print)>. Accessed
1729 Accessed: 27 February 2014.
- 1730 14. Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating
1731 ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic
1732 macular edema. *Ophthalmology.* 2010;117(6):1064-77 e35.
- 1733 15. Elman MJ, Qin H, Aiello LP, et al. Intravitreal ranibizumab for diabetic macular edema
1734 with prompt versus deferred laser treatment: three-year randomized trial results.
1735 *Ophthalmology.* 2012;119(11):2312-8.
- 1736 16. Gross JG, Glassman AR, Jampol LM, et al. Diabetic Retinopathy Clinical Research
1737 Network. Panretinal Photocoagulation vs Intravitreal Ranibizumab for Proliferative
1738 Diabetic Retinopathy: A Randomized Clinical Trial. *JAMA.* 2015;Submitted.

- 1739 17. International Diabetes Federation: Diabetes and blindness due to DME Q&A.
1740 http://www.idf.org/sites/default/files/Toolkit%2520Q%2526A_FINAL.pdf. Accessed
1741 Accessed June 19, 2014.
- 1742 18. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for
1743 diabetic macular edema: ETDRS report number 4. *Int Ophthalmol Clin*. 1987;27(4):265-
1744 72.
- 1745 19. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for Diabetic Macular Edema:
1746 Results from 2 Phase III Randomized Trials: RISE and RIDE. *Ophthalmology*.
1747 2012;119(4):789-801.
- 1748 20. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic
1749 macular edema. *Ophthalmology*. 2014;121(11):2247-54.
- 1750 21. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study ranibizumab
1751 monotherapy or combined with laser versus laser monotherapy for diabetic macular
1752 edema. *Ophthalmology*. 2011;118(4):615-25.
- 1753 22. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic
1754 Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema
1755 in persons with type 1 diabetes. *Ophthalmology*. 2009;116(3):497-503.
- 1756 23. Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor
1757 levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol*.
1758 1994;118(4):445-50.
- 1759 24. Adamis AP, Shima DT, Tolentino MJ, et al. Inhibition of vascular endothelial growth
1760 factor prevents retinal ischemia-associated iris neovascularization in a nonhuman
1761 primate. *Arch Ophthalmol*. 1996;114(1):66-71.
- 1762 25. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid
1763 of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med*.
1764 1994;331(22):1480-7.
- 1765 26. Aiello LP, Pierce EA, Foley ED, et al. Suppression of retinal neovascularization in vivo
1766 by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor
1767 chimeric proteins. *Proc Natl Acad Sci USA*. 1995;92(23):10457-61.
- 1768 27. Amano S, Rohan R, Kuroki M, Tolentino M, Adamis AP. Requirement for vascular
1769 endothelial growth factor in wound- and inflammation-related corneal
1770 neovascularization. *Invest Ophthalmol Vis Sci*. 1998;39(1):18-22.
- 1771 28. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med*. 1971;285:1182-
1772 6.
- 1773 29. Krzystolik MG, Afshari MA, Adamis AP, et al. Prevention of experimental choroidal
1774 neovascularization with intravitreal anti-vascular endothelial growth factor antibody
1775 fragment. *Arch Ophthalmol*. 2002;120(3):338-46.
- 1776 30. Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial
1777 growth factor is a secreted angiogenic mitogen. *Science*. 1989;246(4935):1306-9.
- 1778 31. Malecaze F, Clamens S, Simorre-Pinatel V, et al. Detection of vascular endothelial
1779 growth factor messenger RNA and vascular endothelial growth factor-like activity in
1780 proliferative diabetic retinopathy. *Arch Ophthalmol*. 1994;112(11):1476-82.
- 1781 32. Schwesinger C, Yee C, Rohan RM, et al. Intrachoroidal neovascularization in transgenic
1782 mice overexpressing vascular endothelial growth factor in the retinal pigment epithelium.
1783 *Am J Pathol*. 2001;158(3):1161-72.

- 1784 33. Tolentino MJ, Miller JW, Gragoudas ES, Chatzistefanou K, Ferrara N, Adamis AP.
 1785 Vascular endothelial growth factor is sufficient to produce iris neovascularization and
 1786 neovascular glaucoma in a nonhuman primate. *Arch Ophthalmol*. 1996;114(8):964-70.
- 1787 34. Ip MS, Domalpally A, Hopkins JJ, Wong P, Ehrlich JS. Long-term effects of
 1788 ranibizumab on diabetic retinopathy severity and progression. *Arch Ophthalmol*.
 1789 2012;130(9):1145-52.
- 1790 35. Bressler SB, Qin H, Melia M, et al. Exploratory analysis of the effect of intravitreal
 1791 ranibizumab or triamcinolone on worsening of diabetic retinopathy in a randomized
 1792 clinical trial. *JAMA Ophthalmol*. 2013;131(8):1033-40.
- 1793 36. Sun JK, P W, A F. Impact of treatment delay and durability of diabetic retinopathy
 1794 improvement with PRN ranibizumab during the RIDE/RISE open-label extension (OLE).
 1795 Presented at: 38th Annual Macula Society Meeting; 2015 Feb 25-28; Scottsdale, AZ.
- 1796 37. US FDA approves EYLEA (aflibercept) injection for the treatment of we age-related
 1797 macular degeneration.
 1798 <http://www.press.bayer.com/baynews/baynews.nsf/0/EB1AAB6D8405A0BDC125794A0056C856>. Accessed
 1799 January 1, 2012.
- 1800 38. Holz FG, Roeder J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to
 1801 central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J*
 1802 *Ophthalmol*. 2013;97(3):278-84.
- 1803 39. Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept injection for macular
 1804 edema secondary to central retinal vein occlusion: 1-year results from the phase 3
 1805 COPERNICUS study edema secondary to central retinal vein occlusion: 1-year results
 1806 from the phase 3 COPERNICUS study. *Am J Ophthalmol*. 2013;155(3):429-37.
- 1807 40. Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for
 1808 macular edema secondary to central retinal vein occlusion: six-month results of the phase
 1809 3 COPERNICUS study. *Ophthalmology*. 2012;119(5):1024-32.
- 1810 41. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal Aflibercept for Diabetic
 1811 Macular Edema: 100-Week Results From the VISTA and VIVID Studies.
 1812 *Ophthalmology*. 2015.
- 1813 42. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic
 1814 macular edema. *Ophthalmology*. 2014;121(6):2247-54.
- 1815 43. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for
 1816 diabetic macular edema. *N Engl J Med*. 2015;372(13):1193-203.
- 1817 44. Do DV, Nguyen QD, Boyer D, et al. One-year outcomes of the DA VINCI Study of
 1818 VEGF Trap-Eye in eyes with diabetic macular edema. *Ophthalmology*.
 1819 2012;119(8):1658-65.
- 1820 45. Regeneron Pharmaceuticals Inc. Investigator's brochure: VEGF Trap-Eye Intravitreal
 1821 aflibercept injection (IAI) intravitreal administration. Tarrytown, NY; 2012.
- 1822 46. Lee EW, Wei LJ, Amato DA. *Cox-type regression analysis for large numbers of small*
 1823 *groups of correlated failure time observations* Dordrecht: Kluwer Academic; 1992.