

**Diabetic Retinopathy
Clinical Research Network
(DRCR.net)**

**PROMINENT-Eye Ancillary Study:
Diabetic Retinopathy Outcomes in a
Randomized Trial of Pemaibrate
Versus Placebo**

**Protocol Amendment 1
Version 2.0**

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Signature Page

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ABBREVIATIONS

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACCORD-Eye	Action to Control Cardiovascular Risk in Diabetes Eye Trial
ALT	Alanine aminotransferase
anti-VEGF	Anti-Vascular Endothelial Growth Factor
AST	Aspartate aminotransferase
bid	Two times per day
CI	Confidence Interval
CK	Creatine kinase
CST	Central Subfield Thickness
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
DRCR.net	Diabetic Retinopathy Clinical Research Network
E-ETDRS	Electronic- Early Treatment Diabetic Retinopathy Study
ETDRS	Early Treatment Diabetic Retinopathy Study
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
HbA1c	Hemoglobin A1c
HR	Hazard Ratio
ICH	International Conference on Harmonization
IRB	Institutional Review Board
JCHR	Jaeb Center for Health Research
NF-kappa B	nuclear factor kappa-light-chain-enhancer of activated B cells
NPDR	Non-Proliferative Diabetic Retinopathy
OCT	Optical Coherence Tomography
PDR	Proliferative Diabetic Retinopathy
PPAR α	Peroxisome Proliferator-Activated Receptor α
PROMINENT	Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes
PRP	Panretinal Photocoagulation
QALY	Quality-Adjusted Life-Year
US	United States
UWF	Ultra-widefield

INTRODUCTION

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 2040, approximately 642 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, almost 8 million people in the United States are estimated to have diabetic retinopathy (DR).³ Despite advances in the 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}

1.2 Preventing DR Onset and Worsening

At this time, the primary method of slowing DR onset and worsening remains that of strict glycemic control and blood pressure control. Results from the Early Treatment Diabetic Retinopathy Study (ETDRS) revealed that better glycemic control inhibits DR worsening among all age groups, type 1 and type 2 diabetes, and all stages of retinopathy.⁶ The United Kingdom Prospective Diabetes Study (UKPDS) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study demonstrated that improved blood glucose control can reduce the risk of developing DR in patients with type 2 diabetes, with the UKPDS additionally showing the benefit of improved blood pressure control.^{7,8} The Diabetes Control and Complications Trial (DCCT) found that intensive therapy, aimed at keeping glycemic levels as close to normal range values as possible, reduced the risk of any DR developing by 76% (95% confidence interval (CI):62% to 85%) among patients with no DR at baseline and slowed the worsening of DR by 54% (95% CI: 39% to 66%) among patients with mild DR at baseline.⁹ The benefits of intensive treatment were sustained for approximately 4 years after the period of intensive glycemic control with a 75% ($P<0.001$) risk reduction in the worsening of DR.¹⁰ This beneficial effect in fact persisted for even as long as 18 and 25 years later in this cohort of study participants with type 1 diabetes.^{11,12} This beneficial effect also persisted in type 2 diabetes.^{13,14}

Despite improvements in systemic glycemic control,¹⁵ there continues to be a substantial proportion of diabetic patients who develop DR and its associated sequelae. In 2005–2008, 28.5% (4.2 million) of Americans with diabetes aged 40 years or older had DR, and of this group, 655,000 individuals had advanced DR that could lead to severe vision loss.¹⁶ Approximately 40-60% of the Wisconsin Epidemiologic Study Diabetic Retinopathy (WESDR) cohort, whose onset of diabetes occurred between 1922 and 1980, developed proliferative diabetic retinopathy (PDR) over time, with rates of visual impairment (vision of 20/40 or less in the better seeing eye) ranging from approximately 5% to 20%.¹⁵

1.3 Limitations of Current Treatments for PDR and DME

Recent advances in therapy for advanced diabetic eye disease include the use of anti-vascular endothelial growth factor (anti-VEGF) agents to prevent vision loss from PDR and also to treat center-involved DME. Anti-VEGF therapy has been shown to be highly effective in treating active ocular neovascularization as well as in increasing visual gain and decreasing visual loss in eyes with center-involved DME.¹⁷⁻¹⁹ However, anti-VEGF treatment does have drawbacks including the need for recurrent intravitreal injections for medication delivery that are performed as often as once a month. These injections have potential associated side effects including the development of endophthalmitis and incremental cost effectiveness ratios when using aflibercept or ranibizumab that are far beyond \$100,000 per Quality-Adjusted Life-Year (QALY) over a 10-year time horizon compared with bevacizumab.²⁰ In addition not all eyes treated with anti-VEGF have resolution of

51 DR or DME.^{19, 21} Scatter laser photocoagulation or panretinal photocoagulation (PRP) is another
52 treatment for PDR that is not invasive and does not need to be repeated as frequently as anti-VEGF
53 injections, but laser treatment has other well-documented adverse effects, including exacerbation or
54 development of macular edema with transient or permanent central vision loss, peripheral visual
55 field defects, night vision loss, loss of contrast sensitivity, potential complications from misdirected
56 or excessive burns, increased risk of vitrectomy compared with anti-VEGF treatment, and
57 worsening of visual loss in nearly 5 percent of individuals despite appropriate treatment.^{19, 22} Thus,
58 there is an ongoing need to identify novel therapies that are both effective for PDR and DME
59 treatment and that also avoid the potential adverse events or costs associated with current ocular
60 interventions. Furthermore, the identification of an oral therapeutic agent that may prevent
61 worsening to PDR or DME might allow treatment of a wider segment of the diabetic population at
62 risk for diabetic eye complications who do not have access to anti-VEGF or laser treatment or who
63 are not suitable candidates for these treatments. This would be a major public health contribution if
64 indeed this potentially effective oral agent could be implemented into clinical care.

65

66 **1.4 Rationale for PPAR α Therapy for DR Worsening**

67 Two major clinical studies in patients with diabetes have demonstrated beneficial effects on ocular
68 outcomes from treatment with oral fenofibrate, which acts via activation of peroxisome proliferator-
69 activated receptor α (PPAR α) and may decrease inflammation through inhibition of NF-kappa B
70 activity.²³ Fenofibrate is an oral medication of the fibrate class with a well-documented and
71 favorable safety profile that is used for treatment of hyperlipidemia. Fenofibrate reduces low-
72 density and very low-density lipoprotein and triglyceride levels while increasing high-density
73 lipoprotein levels. In addition to its agonist effects on the PPAR α pathway, fenofibrate affects
74 human retinal endothelial cells through a PPAR α -independent mechanism. A number of other
75 pathways have also been explored with regards to its effects in diabetic retinopathy. For example,
76 Dr. Lois Smith from Harvard has suggested that fenofibrate may inhibit cytochrome P450
77 epoxygenase 2C activity resulting in reduction in pathological ocular angiogenesis, using her
78 oxygen induced retinopathy in a mouse model. Others have suggested a decrease in NF-kappa B
79 activity may be the potential pathway for reduction of diabetic retinopathy progression. Other
80 mechanisms have also been suggested.²⁴⁻²⁹

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82 The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study randomized 9795
83 patients with type 2 diabetes to fenofibrate 200 mg/day versus placebo.³⁰ A subgroup of this cohort
84 (N=1012) also agreed to undergo fundus photography at baseline, 2 year, 5 year, and end of study in
85 order to document DR severity worsening. The percentage of patients requiring first laser treatment
86 for either DR or DME was significantly lower in the fenofibrate group than in the placebo group
87 (3.4% vs 4.9%; HR for first laser treatment: 0.69, 95% CI 0.56-0.84, $P = 0.0002$). 850 participants
88 (84%; 421 allocated to placebo, 429 allocated to fenofibrate) in the photography substudy were
89 followed to the end of the study. Although a difference between the groups overall for the primary
90 endpoint of 2-step DR worsening in the substudy was not identified, in the subgroup of participants
91 with pre-existing DR (N=193), fenofibrate treatment was associated with a reduction in 2-step DR
92 worsening as compared with placebo (3.1% versus 14.6%, $P = 0.004$).

93

94 The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial enrolled 10,251
95 participants with type 2 diabetes and randomized them to intensive glycemic control (goal HbA1c <
96 6.0%) or standard therapy.⁸ The 5,518 participants with dyslipidemia were further randomized in a
97 2x2 factorial design to receive simvastatin in combination with either fenofibrate (at 160 or 54
98 mg/day depending on renal function) or placebo. The ACCORD Eye study enrolled 3,537
99 individuals from this group of which 82.3% (N = 2,856) achieved both a baseline and year 4 follow-
100 up visit and among which 1,593 were included in the fenofibrate portion of the trial. Among all of

138 ischemic stroke, unstable angina requiring unplanned revascularization and/or cardiovascular death.
 139 The participants are adults with type 2 diabetes who have elevated triglycerides and low high-
 140 density lipoprotein cholesterol, and are at high risk for cardiovascular events, in the context of
 141 adequate background of lipid-lowering therapy (including stable dose moderate or high intensity
 142 statin). Two-thirds of the enrolled study population will have prior evidence of systemic
 143 atherosclerosis (secondary prevention cohort) while one-third will not (high risk primary prevention
 144 cohort, age ≥ 50 years [male] or ≥ 55 years [female]). There are expected to be approximately
 145 2,500 participants enrolled in the U.S. and Canada. The trial is an event-driven trial, anticipated to
 146 involve approximately 10,000 participants to achieve 1,092 cardiovascular events over
 147 approximately 5 years.

149 This protocol is an ancillary study to the main PROMINENT trial in which the DRCR.net and
 150 PROMINENT Study Group will collaborate to evaluate the effect of pemafibrate treatment versus
 151 placebo on long-term rates of DR worsening in patients with type 2 diabetes at risk for
 152 cardiovascular events. Based on data from eyes with baseline retinopathy in the ACCORD Eye
 153 study (see table below), it is anticipated that approximately 50% of PROMINENT study
 154 participants will have diabetic retinopathy in at least one eye and be eligible for this PROMINENT-
 155 Eye Study.

Table 2. Baseline Ocular Characteristics of ACCORD Eye Study Participants

Characteristics	No. Participants (%)
Baseline severity of diabetic retinopathy	
None (level 10, step 1)	1573 (48.0)
Mild nonproliferative only (level 10 to 22, steps 2-3)	778 (21.0)
Mild NPDR (level 23 to 35, steps 4-5)	629 (19.9)
Moderate NPDR (level 36 to 43, steps 6-7)	171 (5.2)
Advanced severe NPDR (level 44 to 54, steps 8-9)	101 (3.5)
Severe NPDR or PDR (level 55 to 63, or advanced steps 10-17)	38 (1.4)
Macular edema (non-cystoid)	
None (LME or DME severity 0A)	2579 (82.1)
Mild (1B-1C)	150 (5.3)
Moderate (2-3B)	46 (1.5)
Severe (4-5C)	25 (0.8)
Soft exudates (no total 1+ person)	
None (0 EA)	3570 (90.7)
Very mild (1 EA and <0.02 EA)	117 (3.1)
Mild (≥ 0.03 and <0.12 EA)	128 (3.5)
Moderate (≥ 0.13 EA)	29 (0.7)
Retinal thickening (total 1+ person)	
None (0 EA)	3611 (91.9)
Very mild (1 EA and <0.40 EA)	75 (2.3)
Mild (≥ 0.41 and <1.59 EA)	75 (2.6)
Moderate (≥ 1.60 and <6.25 EA)	49 (1.7)
Severe (≥ 6.26 EA)	12 (0.3)

ACCORD = Action to Control Cardiovascular Risk in Diabetes; EA = due area; ETDRS = Early Treatment Diabetic Retinopathy Study; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

156
 157 Table taken from Chew EY, Davis MD, Danis RP, et al. The effects of medical management on the progression of
 158 diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes
 159 (ACCORD) Eye Study. *Ophthalmology*. 2014;121(12):2443-51.

161 1.6 Summary of Protocol Rationale

162 Despite improved glycemic and systemic control for many patients with diabetes, over the past
 163 several decades, DR develops and progresses in a large proportion of patients, and visual loss from
 164 diabetic eye complications continues to be a leading cause of blindness in the US and other
 165 developed countries worldwide. Thus, even a modest ability to prevent DR onset or to slow DR
 166 worsening might substantially reduce the number of patients at risk for diabetes-related vision loss

167 worldwide. Widespread use of an oral agent effective at reducing worsening of DR might also
168 decrease the numbers of patients who undergo treatment for DR and DME and who are
169 consequently at risk for side effects that adversely affect visual function. Two major studies of
170 fenofibrate, FIELD and ACCORD-eye, have demonstrated clinically important reduction in
171 progression of retinopathy in patients with diabetes assigned to fibrate compared with placebo.
172 However, despite the positive clinical trial results, fenofibrate has not gained wide acceptance as a
173 preventive agent by either ophthalmologists or primary diabetes care providers. Thus, it is
174 important to provide further evidence demonstrating whether or not selectively increasing PPAR α
175 activity reduces progression of retinopathy in patients with diabetes and non-proliferative diabetic
176 retinopathy at baseline. Pema-fibrate is a more potent and selective PPAR α modulator than
177 fenofibrate. Its efficacy is currently being evaluated in the PROMINENT study for prevention of
178 cardiovascular events in patients with type 2 diabetes. Given the large study cohort with a
179 substantial proportion likely to have DR and the multi-year duration of the PROMINENT trial, this
180 study represents a unique opportunity to assess effects of chronic PPAR α activation through
181 pema-fibrate therapy on DR outcomes.

182

183 **1.7 Study Objective**

184

185 **Primary Objective:**

- 186 1. To assess whether treatment with pema-fibrate (0.2 mg orally BID) compared with placebo
187 reduces the hazard rate of diabetic retinopathy worsening in adults with type 2 diabetes and
188 diabetic retinopathy without neovascularization in at least one eye who are participating in
189 the parent PROMINENT trial.

190

191 **Secondary Objectives:**

- 192 1. To assess whether treatment with pema-fibrate (0.2 mg orally BID) compared with placebo
193 reduces rates of diabetic macular edema development or visual acuity worsening.
- 194 2. To assess whether treatment with pema-fibrate compared with placebo affects safety or
195 tolerability in the cohort of participants with diabetic retinopathy in at least one eye.

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198 **1.8 Study Design and Synopsis of Protocol**

199 **A. Study Design**

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- 200 • Longitudinal ancillary study to the PROMINENT trial.
- 202 **B. Major Eligibility Criteria (see section 2.2 for additional eligibility criteria)**
- 203 • Already randomized at US or Canadian sites in the PROMINENT study
 - 204 a. Enrollment visit into the ancillary study must be conducted within 3 months of
205 randomization into the PROMINENT trial.
 - 206 • Ability to cooperate with dilated ophthalmic examination and imaging procedures
 - 207 • At least one eye meets the following study eye inclusion criteria:
 - 208 a. ETDRS Diabetic Retinopathy Severity level between 20 and 53 (minimal to severe
209 NPDR), inclusive, according to the investigator and confirmed by central Reading
210 Center grading.
 - 211 • Major study eye exclusion criteria are:
 - 212 a. Neovascularization on clinical exam or fundus photographs
 - 213 b. Current central-involved DME based on optical coherence tomography (OCT)
214 central subfield thickness (CST)
 - 215 i. Zeiss Cirrus: CST $\geq 290\mu\text{m}$ in women or $\geq 305\mu\text{m}$ in men
 - 216 ii. Heidelberg Spectralis: CST $\geq 305\mu\text{m}$ in women or $\geq 320\mu\text{m}$ in men

- 217 c. Major non-diabetic intraocular pathology that in the opinion of the investigator
 218 would substantially and adversely affect visual acuity or lead to ocular
 219 neovascularization during the course of the study
 220 d. Anticipated need for intravitreal anti-VEGF, intravitreal corticosteroid, or PRP in
 221 the next 6 months following randomization
 222 e. History of intravitreal anti-VEGF or corticosteroid treatment within the prior year
 223 for any indication.
 224 f. Any history of PRP or vitrectomy
 225

226 Participants may have 1 or 2 study eyes based on how many eyes meet eligibility criteria.
 227

228 **C. Estimated Sample Size**

229 At least 600 individuals are expected to be eligible and to enroll in the study at US and Canadian
 230 DRCR.net clinical sites that have geographic proximity to the parent PROMINENT clinical site.
 231 Recruitment will continue until the PROMINENT trial has completed enrollment, with up to a
 232 maximum of 900 enrolling in PROMINENT-Eye.
 233

234 **D. Protocol Summary**

235 Participants in the parent PROMINENT study will be referred to partnering DRCR.net sites for
 236 comprehensive ophthalmologic examination including visual acuity, fundus photography and
 237 spectral domain optical coherence tomography (OCT) to be performed within 3 months of the
 238 PROMINENT randomization visit. Participants who meet eligibility criteria at this visit will be
 239 eligible for two or three additional study ophthalmic visits through 4 years (see Table in Section E
 240 below). Participants who do not meet ocular eligibility will be discontinued from the ancillary
 241 PROMINENT-Eye Study, but not from the parent study. If intravitreal anti-VEGF or
 242 corticosteroid treatment, PRP, or vitrectomy will be administered to a study eye for any indication
 243 for the first time since entering the study, when possible, all study procedures should be performed
 244 prior to implementing treatment to establish retinopathy severity before therapy is initiated.
 245 Participants who receive treatment will continue follow-up through 4 years.
 246

247 **E. Schedule of Study Visit and Examination Procedures**
 248

Visit and Visit Window	Screening/ Baseline ^a	2 year ^b ± 2 months	4 year ^b ± 2 months ^c	Prior to DME/PDR Treatment Initiation ^d
Best corrected visual acuity	X	X	X	X
Eye Exam ^{e, f}	X	X	X	X
DRCR.net Fundus Photography ^{e, g}	X	X	X	X
Spectral Domain OCT ^e	X	X	X	X
Collection of Adverse Events occurring during the visit	X	X	X	X

249 a. To be performed within 3 months of the PROMINENT randomization visit

250 b. Time from randomization into the PROMINENT trial.

- 251 c. If the PROMINENT trial ends before a participant reaches the 4 year visit, one final visit within 3 months of
252 the PROMINENT trial ending will be completed.
- 253 d. All study procedures should be performed prior to the initiation of treatment for DME or DR in a study eye.
- 254 e. After pupil dilation
- 255 f. Participants may opt out of eye exam particularly if they have recently had an eye exam
- 256 g. The widest camera type available will be used for color fundus photography.

257
258 **F. Outcomes**

259 Primary outcome:

260
261 The primary outcome is diabetic retinopathy worsening or DME development (composite outcome),
262 based on both eyes for bilateral participants and based on the study eye only for unilateral
263 participants. Study eye is defined based on the criteria in section 2.2.2 as the eye(s) having ETDRS
264 Diabetic Retinopathy Severity level between 20 and 53 (minimal to severe NPDR), inclusive,
265 according to the investigator and confirmed by central Reading Center, without definite central
266 subfield involved diabetic macular edema.

267
268 Diabetic retinopathy worsening or DME development is defined as any of the following:

- 269
- 270 • For participants with 2 study eyes: 3-step worsening on the ETDRS Retinopathy Severity Scale
271 for Persons (Table 1 in Section 6) at a protocol visit. This scale takes into account the
272 retinopathy level of both study eyes.
 - 273 • For participants with one study eye: 2-step worsening on the ETDRS Retinopathy Severity
274 Scale for Individual Eyes (Table 2 in Section 6) in the study eye at a protocol visit. This scale
275 only takes into account the retinopathy level of the study eye.
 - 276 • Procedure undertaken for the treatment of PDR at any time (even in the absence of photographic
277 documentation) including PRP, intravitreal anti-VEGF, or vitrectomy in at least one study eye.
 - 278 • Treatment initiated for DME at any time (even in the absence of OCT documentation) including
279 anti-VEGF, corticosteroids, focal/grid laser, or vitrectomy in at least one study eye.
 - 280 • Development of central-involved DME on OCT with vision loss at the 2-year or 4-year visit.
281 Defined as OCT central subfield thickness above the machine and gender-specific thresholds
282 (see Section 2.2.2 for details) with at least a 10% increase in thickness from baseline and visual
283 acuity 20/32 or worse (letter score ≤ 78) in at least one study eye.
- 284

285 Secondary outcomes include a treatment comparison of the following:

286
287 Participant-Level Secondary Outcomes (relates to either eye for bilateral participants and to the
288 study eye for unilateral participants):

- 289
- 290 • Hazard rate of 3-step person-level (for bilateral participants, see Table 1 in Section 6) or 2-step
291 eye-level (for unilateral participants, see Table 2 in Section 6) diabetic retinopathy worsening on
292 the ETDRS Retinopathy Severity Scale or receiving treatment for PDR in at least one study eye
293 at any time (irrespective of DME status or treatment)
 - 294 • Hazard rate of developing central-involved DME on OCT with vision loss (as defined above) or
295 receiving treatment for DME in at least one study eye at any time (irrespective of diabetic
296 retinopathy severity level or treatment)
 - 297 • Person-level diabetic retinopathy severity at 2 years and 4 years
 - 298 • Percentage of participants with at least a 2-line loss in visual acuity from baseline in at least one
299 study eye at 2 years and 4 years

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Eye-Level Secondary Outcomes (evaluated only for study eyes):

- Hazard rate of a composite PDR/DME outcome. Defined as the time to 2-step diabetic retinopathy worsening on the ETDRS Retinopathy Severity Scale for Individual Eyes (see Table 2 in Section 6) at 2 years or 4 years, development of central-involved DME on OCT with vision loss (as defined above) at 2 years or 4 years, or treatment for DME or PDR at any time
- Hazard rate of 2-step diabetic retinopathy worsening or receiving treatment for PDR at any time (irrespective of DME status or treatment)
- Hazard rate of developing central-involved DME on OCT with vision loss at 2 years or 4 years or receiving treatment for DME at any time (irrespective of diabetic retinopathy level or treatment)
- Eye-level diabetic retinopathy severity at 2 years and 4 years
- Change in OCT central subfield thickness from baseline at 2 years and 4 years
- Change in visual acuity letter score from baseline at 2 years and 4 years
- Percentage of eyes with at least 2-line loss in visual acuity from baseline at 2 years and 4 years

Safety Outcomes:

- Adverse events collected as part of this ancillary study including vitreous hemorrhage and retinal detachment
- Changes from randomization in ALT, AST, CK, and creatinine

1.9 General Considerations

The study is being conducted in compliance with the policies described in the DRCR.net Policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and in accordance with ICH E6 Good Clinical Practice. All study investigators will attest to complying with these requirements.

The DRCR.net Procedures Manuals provide details of the imaging procedures.

Retinal images and OCT data will be primary source data, and additional data collected will be directly entered in electronic case report forms, which will be considered the source data.

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

Assessment of adverse events occurring during the Prominent-Eye clinical visit will be obtained through adverse event reporting at the end of each study visit.

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

The risk level for this ancillary research is considered to be no more than minimal risk.

STUDY PARTICIPANT ELIGIBILITY AND ENROLLMENT

2.1 Identifying Eligible Participants and Obtaining Informed Consent

At least 600 participants are expected to be enrolled in this study. Recruitment will continue until the PROMINENT trial has completed enrollment, with up to a maximum of 900 participants enrolling in PROMINENT-Eye. Participants in the PROMINENT trial will be referred to participating DRCR.net sites based on geographic proximity within the U.S. and Canada. The ancillary study brochure providing an overview of the study will be initially discussed with the patient by the PROMINENT investigator and/or coordinator. Interested participants will be provided contact information and encouraged to contact their local PROMINENT-Eye clinical site and (if permitted by the IRB) will consent to having their contact information provided to the local PROMINENT-Eye clinical site and the DRCR.net Coordinating Center. The DRCR.net PROMINENT-Eye clinical site may also contact the participant to facilitate scheduling with participant consent.

At the DRCR.net clinical site, the PROMINENT-Eye study protocol will be discussed with the patient by a DRCR.net study investigator and clinic coordinator. Prior to completing any procedures or collecting any data for this study, informed consent will be obtained. Potential eligibility will be assessed at the screening visit. Patients who are eligible based on the screening visit and Reading Center confirmation of DR severity level will return for additional study imaging visits as outlined below.

2.2 Subject Eligibility and Exclusion Criteria

2.2.1 Eligibility Criteria

- Already randomized at US or Canadian sites in the PROMINENT study
 - a. Enrollment visit into the ancillary study must be conducted within 3 months of randomization into the PROMINENT trial.
- Ability to cooperate with dilated ophthalmic examination and imaging procedures

2.2.2 Study Eye Criteria:

The study participant must have at least one eye meeting all of the inclusion criteria listed below.

The eligibility criteria for a study eye are as follows (both eyes will be considered study eyes if both meet the eligibility criteria at the time of enrollment):

- At least one eye meets the following study eye inclusion criteria:
 - a. ETDRS Diabetic Retinopathy Severity level between 20 and 53 (minimal to severe NPDR), inclusive, on color fundus photographs confirmed by central Reading Center grading.
- Study eye exclusion criteria are:
 - a. Neovascularization present.
 - b. Current central-involved DME based on optical coherence tomography (OCT) central subfield thickness (CST)
 - i. Zeiss Cirrus: $CST \geq 290\mu\text{m}$ in women or $\geq 305\mu\text{m}$ in men
 - ii. Heidelberg Spectralis: $CST \geq 305\mu\text{m}$ in women or $\geq 320\mu\text{m}$ in men
 - c. Known major non-diabetic intraocular pathology that in the opinion of the investigator would substantially and adversely affect visual acuity or lead to ocular neovascularization during the course of the study

- 393 d. Anticipated need for intravitreal anti-VEGF, intravitreal corticosteroid, or PRP in
394 the next 6 months following randomization
395 e. History of intravitreal anti-VEGF or corticosteroid treatment within the prior year
396 for any indication.
397 f. History of intraocular surgery within prior 4 months or anticipated within the next 6
398 months following randomization
399 g. Any history of PRP or vitrectomy
400 h. History of YAG capsulotomy performed within 2 months prior to screening
401 i. Aphakia
402 j. Known substantial media opacities that would preclude successful imaging
403

404 Participants may have 1 or 2 study eyes based on how many eyes meet eligibility criteria.
405

406 **2.3 Screening Evaluation and Baseline Testing**

407 **2.3.1 Ocular Historical Information**

408 An ocular history will be elicited from the potential study participant including prior ocular
409 diseases, surgeries, and treatment.
410

411 **2.3.2 Baseline Testing Procedures**

412 The following procedures will be performed to assess eligibility and/or to serve as baseline
413 measures for the study:

- 414 • The testing procedures are detailed in the DRCR.net Procedures Manuals. Visual acuity
415 testing, ocular exam, fundus photography, and OCT will be performed by DRCR.net
416 certified personnel.
- 417 • The fundus photographs will be sent to a Reading Center for grading.
- 418 • OCT images meeting DRCR.net criteria for manual grading will be sent to a Reading
419 Center.

- 421 1. E-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester (including
422 protocol refraction) in each eye
- 423 2. Ocular examination on each eye including dilated ophthalmoscopy
 - 424 • Participant can opt out of ocular exam (dilation will be required regardless)
- 425 3. Spectral Domain OCT using Zeiss Cirrus or Heidelberg Spectralis OCT machine on both eyes
- 426 4. DRCR.net protocol fundus photography in both eyes
 - 427 • The widest field camera type available will be used for color fundus photography.

FOLLOW-UP VISITS

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3.1 Visit Schedule

Each participant will have protocol specific follow-up visits scheduled at 2 years (\pm 2 months) and at 4 years (\pm 2 months) from the randomization date in the PROMINENT trial. If the PROMINENT study ends prior to a participant's 4-year visit, the participant will have one closeout visit within 3 months of the last PROMINENT visit.

436 Additional retina evaluation visits may occur as required for usual care of the study participant
437 either by the DRCR.net clinical site or by the participant's non-DRCR.net ophthalmologist. If the
438 participant will be examined by a non-DRCR.net ophthalmologist, the participant will be asked to
439 sign a medical records release so any treatment that is documented can be obtained by the
440 DRCR.net site. In addition, participants for whom ocular treatment for DR or DME is planned for
441 the first time during the trial (e.g. anti-VEGF or corticosteroid intravitreal injection, PRP,
442 focal/grid laser, or vitrectomy) will be asked to return to the DRCR.net clinical site to complete the
443 study procedures before the treatment is administered, provided treatment is not urgently needed as
444 determined by the treating physician. If pre-treatment images are not able to be obtained, study
445 images should try to be obtained within 1 month after treatment initiation. Participants who receive
446 treatment will continue follow-up through 4 years.

447
448 Communication between the PROMINENT clinical site and the PROMINENT-Eye clinical site
449 may occur to facilitate compliance with the follow-up schedule if needed.

3.2 Testing Procedures

450
451 The following procedures will be performed at each protocol visit unless otherwise specified. A
452 grid in section 1.3 summarizes the testing performed at each visit.

- 453
454
- 455 1. Visual Acuity:
 - 456 • A protocol refraction followed by E-ETDRS visual acuity testing in both eyes (best
 - 457 corrected).
 - 458 2. Ocular examination on each eye including dilated ophthalmoscopy
 - 459 • Participant can opt out of ocular exam (dilation will be required regardless)
 - 460 3. OCT using Zeiss Cirrus or Heidelberg Spectralis OCT machine on both eyes
 - 461 4. DRCR.net protocol fundus photography in both eyes
 - 462 • The widest field camera type available will be used for color fundus photography.
- 463

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

STUDY PROCEDURES

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4.1 Imaging Procedures

The DRCR.net protocol images will be obtained by a fundus photographer specifically certified by the DRCR.net for these imaging procedures. The images will be first sent to the DRCR.net Coordinating Center (uploaded through the website as available) and then to a Reading Center for further evaluation. During image grading, a map of the ETDRS 7 standard fields will be placed as an overlay on each ultra-widefield (UWF) image with peripheral areas outside the ETDRS fields darkened so that extent and severity of DR lesions can be graded separately for the areas within and outside the ETDRS fields.

OCT will be performed by DRCR.net certified personnel. Only spectral domain machines are permitted. For a given study participant, the same machine type should be used for the duration of the study, unless circumstances do not permit (e.g., replacement of damaged machine). If a switch is necessary, the same machine type should be used for the remainder of the study. The images will be sent to the DRCR.net Coordinating Center (uploaded through the website as available) and may be sent to a Reading Center for further evaluation.

Each digital image must be evaluated to be of adequate quality for submission, according to the study procedures. If photograph quality is judged substandard by the operator, then the imaging should be repeated until a good quality image is obtained.

4.2 Other Procedures

Ocular historical information will be collected, including prior treatment for diabetic retinopathy, prior nondiabetic ocular diseases, surgeries, and treatment.

4.3 Safety Assessments

Assessment of subject safety at the study visit will be obtained through adverse event reporting at the end of each study visit. Any adverse events that occurred during the participant's visit will be documented and communicated to the PROMINENT clinical site, and these adverse events will be entered into the PROMINENT study database.

MISCELLANEOUS CONSIDERATIONS

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5.1 Treatment of DR and DME

Treatment of diabetic retinopathy and/or DME including initiation of PRP or anti-VEGF treatment is at the discretion of the treating physician. However, the first time PRP, intravitreal anti-VEGF or corticosteroid treatment, focal/grid laser, or vitrectomy is planned, the study procedures should be performed prior to treatment initiation, provided treatment is not urgently needed as determined by the treating physician.

5.2 Risks and Benefits

The procedures in this study are part of daily ophthalmologic practice in the United States and pose few known risks. Dilating eye drops will be used as part of the exam. There is a small risk of inducing a narrow-angle glaucoma attack from the pupil dilation. However, all participants will have had prior pupil dilation usually on multiple occasions and therefore the risk is extremely small. Fundus photographs have bright lights associated with the camera flashes, which can be uncomfortable for study participants, but these carry no known risk to the eye or vision.

There may be few direct benefits from participating in this ancillary study other than the awareness of being involved in a large endeavor to answer relevant and timely questions regarding the possible benefit of pemafibrate on diabetic retinopathy progression.

In addition, if proliferative diabetic retinopathy is identified on color fundus photos, the participant's non-DRCR.net ophthalmologist (if applicable) and the PROMINENT investigator will be notified of this diagnosis so that treatment can be initiated if necessary.

5.3 Study Participant Withdrawal and Losses to Follow-up

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

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

Study participants who withdraw will be asked to have a final closeout visit at which the testing described for the protocol visits will be performed.

5.4 Discontinuation of Study

The study may be discontinued by the Executive Committee of the parent PROMINENT study or the Executive Committee of the PROMINENT-Eye study prior to the preplanned completion of follow-up for all ancillary study participants.

5.5 Contact Information Provided to the DRCR.net Coordinating Center

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

Contact from the Coordinating Center may be made for each study participant in the first month after enrollment, and approximately every six months thereafter. Additional contacts from the

547 Coordinating Center will be made if necessary to facilitate the scheduling of the study participant
548 for follow-up visits. A participant-oriented newsletter may be sent once a year. A study logo item
549 may be sent once a year.

550
551 Study participants may be provided with a summary of the study results in a newsletter format after
552 completion of the study by all participants.

553
554 **5.6 Subject Reimbursement**
555 The Coordinating Center will provide each study participant with a \$50 merchandise or money card
556 per completed protocol visit. Additional travel expenses may be paid in cases for participants with
557 higher expenses.

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STATISTICAL CONSIDERATIONS

The approach to sample size and statistical analysis is summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study.

6.1 Primary Outcome

The primary outcome is diabetic retinopathy worsening or DME development (composite outcome), based on both eyes for bilateral participants and based on the study eye only for unilateral participants. From a statistical perspective, the primary outcome is a person-level outcome as data from both eyes of bilateral participants is combined into a single outcome measurement. The primary outcome is defined as any of the following:

- For participants with 2 study eyes: 3-step worsening on the ETDRS Retinopathy Severity Scale for Persons (**Table 1**) at a protocol visit. This scale takes into account the retinopathy level of both study eyes.
- For participants with one study eye: 2-step worsening on the ETDRS Retinopathy Severity Scale for Individual Eyes (**Table 2**) in the study eye at a protocol visit. This scale only takes into account the retinopathy level of the study eye.
- Procedure undertaken for the treatment of PDR at any time (even in the absence of photographic documentation) including PRP, intravitreal anti-VEGF, or vitrectomy in at least one study eye.
- Treatment initiated for DME at any time (even in the absence of OCT documentation) including anti-VEGF, corticosteroids, focal/grid laser, or vitrectomy in at least one study eye.
- Development of central-involved DME on OCT with vision loss at the 2-year or 4-year visit. Defined as OCT central subfield thickness above the machine and gender-specific thresholds (see Section 2.2.2 for details) with at least a 10% increase in thickness from baseline and visual acuity 20/32 or worse (letter score ≤ 78) in at least one study eye.

Table 1: Summary of ETDRS Final Retinopathy Severity Scale for Persons

Level in each eye	Description	Scale step
10/10	No DR	1
20/< 20	Microaneurysms only, one eye	2
20/20	Microaneurysms only, both eyes	3
35/< 35	Mild NPDR, one eye	4
35/35	Mild NPDR, both eyes	5
43/< 43	Moderate NPDR, one eye	6
43/43	Moderate NPDR, both eyes	7
47/< 47	Moderately severe NPDR, one eye	8
47/47	Moderately severe NPDR, both eyes	9
53/< 53	Severe or very severe NPDR, one eye	10
53/53	Severe or very severe NPDR, both eyes	11
60 or 61/< 60	Mild PDR and/or PRP, one eye	12
60 or 61/60 or 61	Mild PDR and/or PRP, both eyes	13
65/< 65	Moderate PDR, one eye	14
65/65	Moderate PDR, both eyes	15
71+/< 71	High-risk PDR, one eye	16
71+/71+	High-risk PDR, both eyes	17

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Table 2: Summary of ETDRS Final Retinopathy Severity Scale for Individual Eyes

Level in the eye	Severity	Scale Step
10	DR absent	1
20	Microaneurysms only	2
35	Mild NPDR (hard exudates, soft exudates, and/or mild hemorrhage)	3
43	Moderate NPDR (mild intraretinal microvascular abnormalities or moderate hemorrhage)	4
47	Moderately severe NPDR (mild venous beading, moderate intraretinal microvascular abnormalities or severe hemorrhage)	5
53	Severe or very severe NPDR (moderate/severe venous beading, severe intraretinal microvascular abnormalities and/or very severe hemorrhage)	6
60, 61	Scars of photocoagulation for PDR (60) or mild PDR (61)	7
65	Moderate PDR	8
71, 75	High-Risk PDR	9
81, 85	High-Risk PDR with vitreous hemorrhage	10

590

591 **6.2 Sample Size Estimation**

592 Based on data from eyes with baseline retinopathy in the ACCORD study, it is anticipated that
 593 approximately 50% of PROMINENT study participants will have minimal to severe NPDR (levels
 594 20-53) in at least one eye. Among participants with minimal to severe NPDR in at least one eye,
 595 the percentage of patients with either a 3-step patient-level progression or photocoagulation was
 596 approximately 5% in the fenofibrate group and 12% in the placebo group. For the entire ACCORD
 597 cohort (i.e. with and without baseline retinopathy), the rate of DME worsening on color
 598 photographs was approximately 3% over 4 years in both the fenofibrate and control groups.
 599 However, the percentage of patients with baseline retinopathy and worsening DME without
 600 worsening retinopathy is not reported. In addition, DME progression in ACCORD was assessed by
 601 color photographs while in the current study it will be assessed by OCT, which has been shown to
 602 be more sensitive at detecting DME.³² Therefore, it is unknown what impact the primary outcome
 603 components, besides retinopathy progression, will have on the projected outcome, resulting in
 604 uncertainty around these estimates.

605

606 The table below shows the required sample size for 80% power with a type I error rate of 5% and a
 607 null hypothesis of no difference between groups (two-tailed test) for a time-to-event outcome (log-
 608 rank test). These calculations were based on the 4-year outcome rate in the placebo group and the
 609 resulting hazard ratio when comparing the outcome rate in the pemafibrate group. The outcome
 610 times are assumed to follow an exponential distribution and the estimates include adjustment for
 611 15% attrition over 4 years, also assumed to follow an exponential distribution.

612

Table 3. Required Number of Participants for Primary Analysis

Hazard Ratio	Placebo Event Rate				
	16%	14%	12%	10%	8%
0.30	270	310	364	438	552
0.40	398	458	536	646	812
0.50	618	710	832	1000	1256

613

614

615
616 The projected 4-year outcome rates of 5% in the pema fibrate group and 12% in the placebo group
617 yield a hazard ratio of approximately 0.4, resulting in a required sample size of 536 participants.
618

619 Assuming 600 participants are enrolled of whom 15% are lost to follow up over 4 years, the
620 detectable hazard ratio with 80% power is 0.49 for a placebo event rate of 16% to 0.32 for a placebo
621 event rate of 8%. In other words, the study is powered for a reduction in the rate of diabetic
622 retinopathy worsening by 1/2 to 2/3, depending on the event rate in the placebo group. The placebo
623 event rate could be higher than 16% because the 12% estimate from ACCORD accounts for events
624 due only to progression of retinopathy on photographs and does not include treatment-related and
625 DME-related events, which are other components of the composite outcome. There are no existing
626 data on which to base estimates for rates of these outcomes. In the event that the outcome rates in
627 the placebo group are higher than projected, the study will be powered to detect smaller reductions
628 in the hazard of diabetic retinopathy worsening. Therefore, the estimates given here are
629 conservative.
630

631 **6.3 Primary Analysis Plan**

632 **6.3.1 Principles for Analysis**

633 The primary treatment group comparison will be based on the hazard ratio from a Cox proportional
634 hazards regression model that adjusts for the baseline person-level retinopathy, which accounts for
635 the retinopathy level in the non-study eye of unilateral participants (see **Table 1**). The primary
636 analysis is an intention-to-treat analysis. Data from participants who are not observed to meet
637 outcome criteria and who are lost to follow up will be censored at the time of the last completed
638 visit. All model assumptions, including proportional hazards, will be verified. If model
639 assumptions are not reasonably satisfied, alternative approaches will be explored.
640

641 **6.3.2 Confounding**

642 Imbalances between groups in important covariates are not expected to be of sufficient magnitude
643 to produce confounding. However, the presence of confounding will be evaluated in regression
644 models by including factors potentially associated with the outcome for which there is an imbalance
645 between groups.
646

647 **6.3.3 Per Protocol Analyses**

648 Per protocol analyses mimicking the primary intention-to-treat analyses will be performed on the
649 following cohorts:
650

- 651 • Participants with no major protocol deviations as defined by the PROMINENT trial.
 - 652 • Participants with $\geq 80\%$ compliance during the treatment period as defined by the
653 PROMINENT trial.
- 654

655 **6.3.4 Sensitivity Analyses**

656 The following sensitivity analyses will be conducted:
657

- 658 • Repeat the primary analysis while censoring data from participants who receive treatment
659 for DME when the OCT central subfield thickness in the treated eye did not meet the
660 outcome criteria for DME with vision loss when the treatment was given. Participants who
661 do not have an OCT scan from the visit at which treatment is given also will be censored in
662 this analysis.
663

664 **6.3.5 Subgroup Analyses**

665 The treatment effect in subgroups defined by baseline factors will be assessed in pre-planned
666 subgroup analyses. These analyses will be conducted to determine whether the treatment effect in
667 any subgroup differs from the overall treatment effect. The study is not expected to have sufficient
668 statistical power for definitive conclusions in subgroups and statistical power will be low to
669 formally test for the presence of subgroup effects. Interpretation of subgroup analyses will depend
670 on whether the overall analysis demonstrates a significant treatment effect. In the absence of a
671 significant treatment effect in the primary analysis, assessment of subgroups will be considered
672 exploratory and used to suggest hypotheses for further investigation in future studies.

673
674 The general approach for these analyses will be to add an interaction term for the subgroup factor
675 by treatment group into the proportional hazards model used for the primary analysis.

676
677 The planned subgroups for analyses are as follows:

- 678 • Baseline person-level retinopathy level: Steps 2-4, Steps 5-6, Steps 7-9, and Steps 10-11

679
680 Statistical analyses will only be conducted for a subgroup if there are at least 20 participants in each
681 treatment group for that subgroup. The above subgroups are considered those of primary interest
682 for which a rationale for a subgroup effect is hypothesized. The hypothesized mechanism and
683 direction of effect are listed in the table below.

Factor	Hypothesized direction/mechanism of association
Retinopathy Level	Participants with more severe retinopathy have higher risk for retinopathy worsening and may have disease that is too advanced for the treatment to work. Therefore, it is possible that the treatment effect is greater in eyes with less severe disease.

684
685
686 The following baseline subgroup factors also will be evaluated in exploratory analyses:

- 687 • Prior DME treatment: yes vs. no
- 688 • Age: < 65 vs. ≥ 65
- 689 • HbA1c: < 7.5% vs. ≥ 7.5%
- 690 • Sex
- 691 • Race/Ethnicity
- 692 • Hyperlipidemia status: ≥ HDL (high-density lipoprotein) median of the sample cohort and ≥
693 TG (triglyceride) median; ≥ HDL median and < TG median; < HDL median and ≥ TG
694 median; < HDL median and < TG median
- 695 • Number of study eyes: 1 vs. 2

696
697
698 There is no known mechanism supporting an interaction of these effects with treatment group. If a
699 significant subgroup effect for any of these factors is found, it will be interpreted as hypothesis
700 generating only and in need of confirmation from further studies. In particular, there are no data to
701 suggest that the treatment effect will vary by sex or race/ethnicity, although both of these factors
702 will be evaluated.

703
704 For all analyses, P-values will be computed for factors based on continuous or ordinal data when
705 available in addition to the categorizations listed above.

706

707 **6.4 Secondary Outcomes and Safety Outcomes for Treatment Group Comparison**

708 Secondary outcomes will be compared at the 2-year and 4-year visits with the exception of time-to-
709 event outcomes in which the hazard rates will be compared over 4 years only. Safety outcomes
710 collected as part of this ancillary study will be compared at 4 years only. To control for potential
711 correlations arising from participants with two study eyes, eye-level outcomes will be compared
712 using linear mixed models (continuous outcomes), logistic regression using generalized estimating
713 equations (binary outcomes), or Cox proportional hazards regression with a robust sandwich
714 estimate of the covariance matrix (time-to-event outcomes).³³ Participant-level outcomes will be
715 compared similarly but without adjustment for inter-eye correlation.

716
717 All analyses will include adjustment for the baseline level of the outcome, where appropriate. In
718 addition, participant-level and eye-level secondary outcomes will be adjusted for baseline person-
719 level diabetic retinopathy severity. The treatment groups will be compared on the following
720 outcomes of interest:

721
722 Participant-Level Secondary Outcomes (relates to either eye for bilateral participants and to the
723 study eye for unilateral participants):

- 724
- 725 • Hazard rate of 3-step person-level (for bilateral participants, **Table 1**) or 2-step eye-level (for
726 unilateral participants, **Table 2**) diabetic retinopathy worsening on the ETDRS Retinopathy
727 Severity Scale or receiving treatment for PDR in at least one study eye at any time (irrespective
728 of DME status or treatment)
 - 729 ○ Percentage of participants with diabetic retinopathy worsening at 2 years and 4 years
730 will be enumerated without statistical comparison
 - 731 ○ Percentage of participants receiving treatment for PDR in at least one study eye at or
732 prior to 2 years and 4 years will be enumerated without statistical comparison
 - 733 • Hazard rate of developing central-involved DME on OCT with vision loss (as defined in Section
734 6.1) or receiving treatment for DME in at least one study eye at any time (irrespective of
735 diabetic retinopathy severity level or treatment)
 - 736 ○ Percentage of participants with central-involved DME on OCT with vision loss in at
737 least one study eye at 2 years and 4 years will be enumerated without statistical
738 comparison
 - 739 ○ Percentage of participants receiving treatment for DME in at least one study eye at or
740 prior to 2 years and 4 years will be enumerated without statistical comparison
 - 741 • Person-level diabetic retinopathy severity at 2 years and 4 years
 - 742 • Percentage of participants with at least a 2-line loss in visual acuity from baseline in at least one
743 study eye at 2 years and 4 years

744
745 Eye-Level Secondary Outcomes (evaluated only for study eyes):

- 746
- 747 • Hazard rate of a composite PDR/DME outcome. Defined as the time to 2-step diabetic
748 retinopathy worsening on the ETDRS Retinopathy Severity Scale for Individual Eyes
749 (**Table 2**) at 2 years or 4 years, development of central-involved DME on OCT with vision
750 loss (as defined in Section 6.1) at 2 years or 4 years, or treatment for DME or PDR at any
751 time
 - 752 ○ Percentage of eyes with 2-step diabetic retinopathy worsening or development of
753 central-involved DME on OCT with vision loss at 2 years and 4 years will be
754 enumerated without statistical comparison

- 755 ○ Percentage of eyes receiving treatment for PDR or DME at or prior to 2 years and 4
- 756 years will be enumerated without statistical comparison
- 757 ● Hazard rate of 2-step diabetic retinopathy worsening or receiving treatment for PDR at any
- 758 time (irrespective of DME status or treatment)
- 759 ○ Percentage of eyes with 2-step diabetic retinopathy worsening at 2 years and 4 years
- 760 will be enumerated without statistical comparison
- 761 ○ Percentage of eyes receiving treatment for PDR at or prior to 2 years and 4 years will
- 762 be enumerated without statistical comparison
- 763 ● Hazard rate of developing central-involved DME on OCT with vision loss at 2 years or 4
- 764 years or receiving treatment for DME at any time (irrespective of diabetic retinopathy level
- 765 or treatment)
- 766 ○ Percentage of eyes with central-involved DME on OCT with vision loss at 2 years
- 767 and 4 years will be enumerated without statistical comparison
- 768 ○ Percentage of eyes receiving treatment for DME at or prior to 2 years and 4 years
- 769 will be enumerated without statistical comparison
- 770 ● Eye-level diabetic retinopathy severity at 2 years and 4 years
- 771 ● Change in OCT central subfield thickness from baseline at 2 years and 4 years
- 772 ● Change in visual acuity letter score from baseline at 2 years and 4 years
- 773 ● Percentage of eyes with at least 2-line loss in visual acuity from baseline at 2 years and 4
- 774 years

775

776 Safety Outcomes:

- 777 ● Adverse events collected as part of this ancillary study including vitreous hemorrhage and
- 778 retinal detachment
- 779 ● Changes from randomization in ALT, AST, CK, and creatinine

780

781 To help control the type I error rate at 5%, P-values for secondary outcomes and safety outcomes

782 will be adjusted using the adaptive false discovery rate method of Benjamini and Hochberg in

783 separate sets (i.e., one adjustment for patient-level secondary outcomes, one adjustment for eye-

784 level secondary outcomes, and one adjustment for safety outcomes).³⁴ It is recognized that this does

785 not completely control the type I error rate.

786

787 All model assumptions will be verified. These include but are not limited to proportional hazards,

788 linearity, normality of residuals, and homoscedasticity. If model assumptions are not reasonably

789 satisfied, then a transformation of the data or an alternative approach may be considered. Methods

790 for handling missing secondary outcome data will be included in the detailed Statistical Analysis

791 Plan.

792

793 Adverse events reported in this ancillary study as defined in section 4.3 will be enumerated in

794 patient listings and summarized in tables by System Organ Class, using MedDRA terms. Changes

795 in ALT, AST, CK, and creatinine will be depicted as shift tables (i.e., as a shift to high, low, or

796 normal) for each parameter at 4 years.

DATA COLLECTION AND MONITORING

7.1 Case Report Forms

The key study data are collected through a combination of electronic case report forms (CRFs) and grading of retinal images.

When data are directly collected in electronic case report forms, this will be considered the source data. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

7.2 Study Records Retention

Study documents should be retained by the investigator for the latest of 3 years following the end of the current DRCR.net grant, 2 years after the last approval of a marketing application, and until there are no pending or contemplated marketing applications, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Jaeb Center for Health Research. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

7.3 Quality Assurance and Monitoring

Designated personnel from the JCHR Coordinating Center will be responsible for maintaining quality assurance and quality control systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

A risk-based monitoring plan will be developed and revised as needed during the course of the study, consistent with the FDA “Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring” (August 2013).

The data of most importance for monitoring at the site are participant eligibility and image outcome data. Therefore, the risk-based monitoring plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data when possible. Elements of the risk-based monitoring will include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

845
846 JCHR Coordinating Center representatives or their designees may visit the study facilities at any
847 time in order to maintain current and personal knowledge of the study through review of the
848 records, comparison with source documents, observation and discussion of the conduct and progress
849 of the study.

850
851 **7.4 Protocol Deviations**

852 A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure
853 requirements. The noncompliance may be either on the part of the participant, the investigator, or
854 the study site staff. As a result of deviations, corrective actions are to be developed by the site and
855 implemented promptly.

856
857 The site principal investigator/study staff is responsible for knowing and adhering to their IRB
858 requirements. Further details about the handling of protocol deviations will be included in the
859 monitoring plan.

ETHICS/PROTECTION OF HUMAN PARTICIPANTS

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8.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

8.2 Institutional Review Boards

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

8.3 Informed Consent Process

8.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

8.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The study monitor, other authorized representatives of the sponsor or, representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital). The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the JCHR Coordinating Center. This will not include a link to the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and

909 study management systems used by clinical sites and by JCHR Coordinating Center research staff
910 will be secured and password protected. At the end of the study, all study databases will be de-
911 identified and archived at the JCHR Coordinating Center.

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