DRCR Retina Network

A Randomized Clinical Trial Evaluating Fenofibrate for Prevention of Diabetic Retinopathy Worsening (Protocol AF)

Sponsor: Jaeb Center for Health Research (JCHR)

Version 6.0

October 18, 2023

A Randomized Clinical Trial Evaluating Fenofibrate for Prevention of Diabetic Retinopathy Worsening

Protocol Identifying Number: Protocol AF

IND Sponsor: Jaeb Center for Health Research

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VERSION HISTORY

The following table lists effective versions of the protocol:

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
2.0	Cynthia Stockdale	Adam Glassman	16NOV2020	Initial (IRB approved but not implemented)
3.0	Cynthia Stockdale, Wesley Beaulieu	Adam Glassman	08FEB2021	Removal of DME components from the primary outcome, subsequent revisions to secondary outcomes, clarification of when testing is required for treatment initiation.
4.0	Crystal Franklin, Cynthia Stockdale, Wesley Beaulieu	Adam Glassman	14DEC2021	Clarification of data collection procedures prior to initiation of intraocular treatment for DR or DME at annual and non-annual visits. Clarified that one dose of study drug is one pill. Modified eligibility criteria for eGFR from ≥ 60 to ≥ 45 at screening, with eGFR 45 to <60 starting on the reduced dose. Modified eligibility to include participants with one study eye. Extended allowable window for lab draw at screening. Changed criteria for diabetic retinopathy worsening on photos from 3 or more steps on person scale to 2 or more steps on an eye scale. The unit of analysis for the primary outcome has been changed from a participant to a study eye; statistical methods have been updated accordingly. Added whether a participant has one or two study eyes as a randomization stratification factor.
4.1	Crystal Franklin	Cynthia Stockdale	20JUL2022	Updated FA transit eye instructions; revision to how renal function safety outcomes are defined; miscellaneous revisions to the statistical methods; minor typos and formatting corrections. Since changes are minor, sign-off not required by study personnel.
5.0	Crystal Franklin	Cynthia Stockdale	13APR2023	Expanded allowable windows for select screening procedures; pregnancy test to be completed at randomization visit in-clinic if >30 days since screening; updated visual acuity, liver, and glaucoma eligibility criteria; truncation of continuous outcomes updated to be truncated to ± 3 standard deviations
6.0	Crystal Franklin, Kristin Josic	Cynthia Stockdale	18OCT2023	Sample size reduced to 560; follow-up visits added through up to 6 years for new participants, with option to extend for past 4 years for participants enrolled at time of amendment; procedures updated throughout for visits and phone calls beyond 48 months; Informed consent addendum process added for participants enrolled prior to protocol v6.0; replaced Unknown with 'Ongoing (Medically Stable)' as an AE outcome

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACCORD	Action to Control Cardiovascular Risk in Diabetes
AMD	Age-Related Macular Degeneration
AE	Adverse Event
ALT	Alanine Transaminase
APTC	Antiplatelet Trialists' Collaboration
anti-VEGF	anti-Vascular Endothelial Growth Factor
AST	Aspartate Transaminase
CBC	Complete Blood Count
CGM	Continuous Glucose Monitor
CRF	Case Report Form
CI-DME	Center-Involved Diabetic Macular Edema
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatine Kinase
DSMC	Data and Safety Monitoring Committee
DVT	Deep Vein Thrombosis
DCCT	Diabetes Control and Complications Trial
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
ETDRS	Early Treatment Diabetic Retinopathy Study
E-ETDRS	Electronic ETDRS
EVA	Electronic Visual Acuity
eGFR	Estimated Glomerular Filtration Rate
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
FA	Fluorescein Angiography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HDL	High Density Lipoproteins

ABBREVIATION	DEFINITION
ICGA	Indocyanine Green Angiography
IRB	Institutional Review Board
ITT	Intention-to-Treat
IOP	Intraocular Pressure
IND	Investigational New Drug
JCHR	Jaeb Center for Health Research
LFT	Liver Function Tests
LENS	Lowering Events in Non-proliferative Retinopathy in Scotland
NIH	National Institutes of Health
NPDR	Non-Proliferative Diabetic Retinopathy
NV	Neovascularization
NVD	Neovascularization of the Disc
NVE	Neovascularization Elsewhere
OCT	Optical Coherence Tomography
OCTA	Optical Coherence Tomography Angiography
PRP	Panretinal (Scatter) Photocoagulation
PPARα	Peroxisome Proliferator-Activated Receptor α
PCP	Primary Care Provider
PDR	Proliferative Diabetic Retinopathy
PE	Pulmonary Embolus
RCT	Randomized Controlled Trial
RC	Reading Center
RR	Relative Risk
RNFL	Retinal Nerve Fiber Layer
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD-OCT	Spectral Domain OCT
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIR	Time-In-Range
VA	Visual Acuity

ABBREVIATION	DEFINITION
VF	Visual Field

PROTOCOL SUMMARY

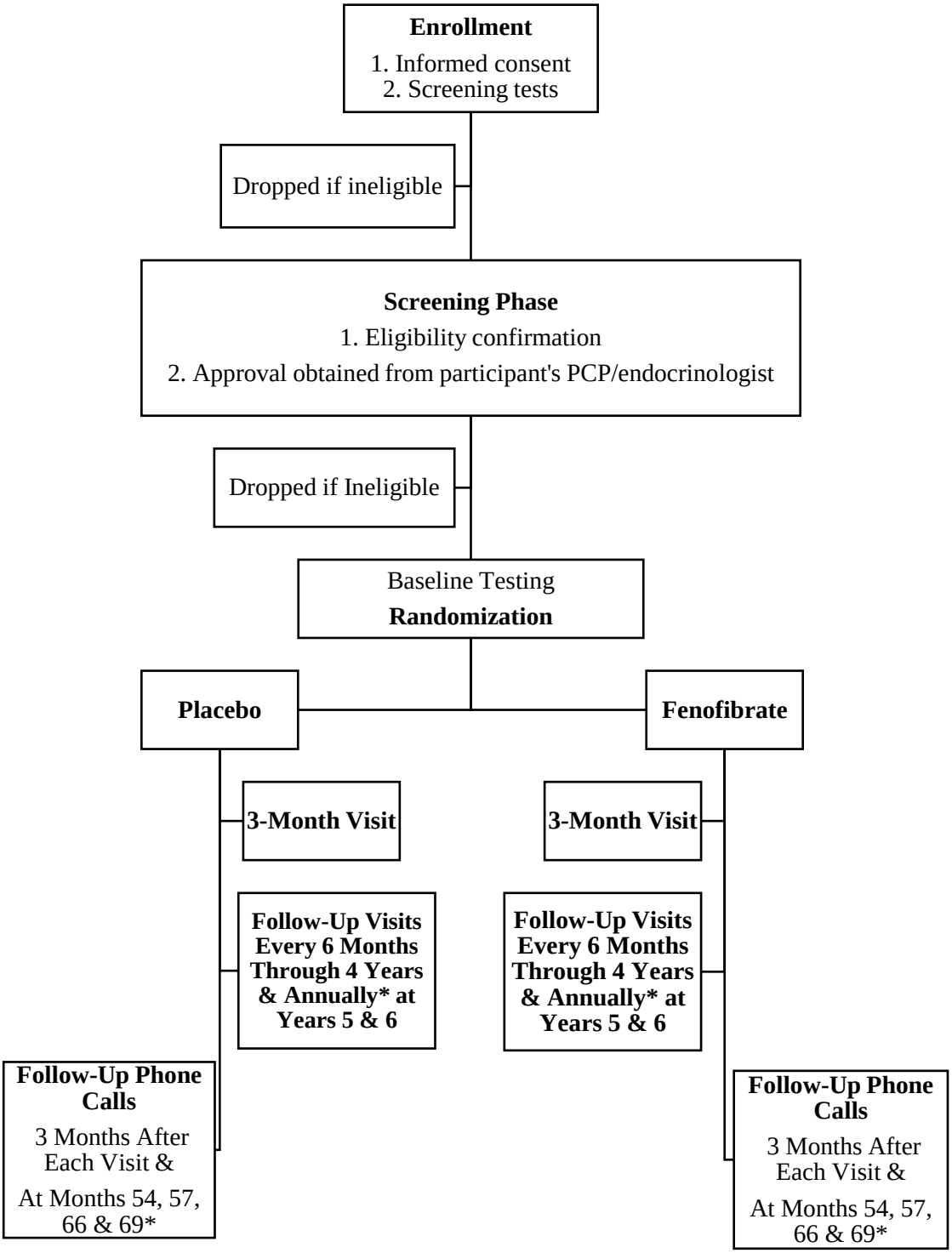
ITEM	DESCRIPTION
Title	A Randomized Clinical Trial Evaluating Fenofibrate for Prevention of Diabetic Retinopathy Worsening
Précis	This randomized trial will evaluate the effect of fenofibrate compared with placebo for prevention of diabetic retinopathy (DR) worsening through at least 4 but up to 6 years of follow-up in eyes with mild to moderately severe non-proliferative DR (NPDR) and no CI-DME at baseline. In addition to evaluating efficacy, this study aims to evaluate the feasibility of a model for ophthalmologists to prescribe or collaborate with a primary care provider such as an internist/endocrinologist to prescribe and monitor the drug safely. If this study demonstrates that fenofibrate is effective for reducing the onset of proliferative diabetic retinopathy (PDR) and the results are adopted by the community of retina specialists, a new strategy to prevent vision threatening complications of diabetes could be widely adopted. Widespread use of an oral agent effective at reducing worsening of DR would decrease the numbers of patients who undergo more invasive and much more expensive treatment for DR and who are consequently at risk for side effects that adversely affect visual function. This study will also assess the relationship of glycemic variability, as measured by continuous glucose monitoring, with DR outcomes. Ancillary studies will characterize functional and structural outcomes in this cohort.
Investigational Drug	Fenofibrate (new indication)
Objectives	The primary objective is to determine if fenofibrate is effective at preventing DR worsening in eyes with mild to moderately severe non-proliferative DR and no CI-DME at baseline. Additional goals of the study are to 1) provide a model for ophthalmologists to prescribe or collaborate with a primary care provider to prescribe and monitor the drug safely, 2) disseminate standardized prescribing guidelines with the aim to encourage broader use, and 3) collect information on potential predictive biomarkers of DR progression via blood sampling, functional, and structural testing as well as glucose levels from CGM.
Study Design	Randomized, double-masked, placebo-controlled clinical trial

ITEM	DESCRIPTION
Number of Sites	Approximately 80
Endpoint	**Primary Efficacy Outcome:** Worsening of DR through 6 years (time-to-event composite outcome) defined as any of the following in a study eye (see details in Section 10.4.1): • 2 or more step worsening on ETDRS DR severity on fundus photographs. • Development of NV within the 7-modified ETDRS fields on fluorescein angiography. • Intraocular procedure undertaken to treat DR including PRP, intraocular anti-VEGF, corticosteroid, or vitrectomy. **Key Safety Outcomes:** Myopathy, rhabdomyolysis, renal disease (eGFR decreased below 30, dialysis, or renal transplant), cholelithiasis, increased liver function tests (ALT or AST), low HDL, muscle pain or weakness, easy bruising or bleeding, death, APTC events
Population	**Key Inclusion Criteria** • Age ≥18 years and < 80 years. • Type 1 or type 2 diabetes. • At least one eye with the following: o Mild to moderately severe NPDR (defined by ETDRS DR severity level 35 to 47), confirmed by central Reading Center grading of fundus photographs. o Best-corrected E-ETDRS visual acuity letter score of ≥74 (approximate Snellen equivalent 20/32 or better). • If only one eye is eligible, the non-study eye must have at least microaneurysms only (DR severity level 20) **Key Exclusion Criteria** ***Eye-level exclusion criteria (the eye is ineligible if any of the following is met):*** • Current CI-DME based on clinical exam or OCT central subfield thickness (CST) o Zeiss Cirrus: CST ≥290 µm in women or ≥ 305 µm in men o Heidelberg Spectralis: CST ≥305 µm in women or ≥320 µm in men

ITEM	DESCRIPTION
	• Any prior treatment for DME or DR, other than focal/grid laser. *If the eye has a history of focal/grid laser, it must be at least 12 months prior.* • History of intraocular anti-VEGF or corticosteroid treatment within the prior year for any indication ***Participant-level exclusion criterion (the participant is ineligible if the following criterion is met):*** • Decreased renal function, defined as requiring dialysis or central laboratory eGFR value < 45 mL/min/1.73 m^2
Sample Size	560 participants
Treatment Groups	Random assignment (1:1) to fenofibrate or placebo
Participant Duration	At least 4 but up to 6 years of follow-up for each randomized participant.
Protocol Overview/Synopsis	1. Informed consent will be obtained. a. Participants enrolled after effective date of Protocol v6.0 will be in the study up to 6 years. b. Participants enrolled prior to Protocol v6.0 will be followed for at least 4 years, and will be asked to continue through up to 6 years if the outcome has not yet been met. Consent will be collected via an ICF addendum. 2. Study eligibility will be assessed by the site. 3. Potentially eligible participants will complete a Screening visit after which: a. Eligibility will be confirmed via lab results and RC grading of DR severity level. b. Approval to participate in the study will be obtained from the participant's health care provider responsible for primary systemic management (e.g., endocrinologist or primary care provider). 4. Eligible participants will be randomly assigned 1:1 to fenofibrate or placebo. 5. Participants will return for a follow-up visit at 3 months, 6 months, and every 6 months thereafter through at least 4 years. Participants meeting criteria for additional follow-up after 4 years could have visits annually through 6 years, depending on the timing of their enrollment into the study. 6. Phone calls to the participant will be made at 3-month intervals in-between 6-month interval visits, starting after the 6-month visit, and every 3 months after the 48-month visit.

ITEM	DESCRIPTION
	7. Participation in the study will be considered completed upon completion of either: a. the 4-year (48-month) visit if the participant has met the definition of the primary efficacy outcome or does not consent to visits beyond 4 years b. OR the last completed visit approximately 4 years after the final study participant's enrollment. Participants will return for a final completion visit if their prior visit was more than 6 months before the completion of the trial. c. OR the 6-year (72-month) visit

SCHEMATIC OF STUDY DESIGN



* For participants who meet criteria for follow-up beyond 4 years; the last visit for each participant will depend on when the last enrolled participant completes their 4-year visit.

SCHEDULE OF STUDY VISITS AND PROCEDURES

In addition to the visits listed below, phone calls will be made from the site at 3-month intervals in between in-person visits, starting after the 6-month visit (months 9, 15, 21, 27, 33, 39, 45) and at months 51, 54, 57, 63, 66 and 69 following for participants enrolled through 6 years. All procedures will be performed on both eyes, unless otherwise indicated in the footnotes.

Visit	**Screening Visit**	**Randomization Visit**	**3-Month Safety Visit**	**6-Month Visit**	**Annual Visits (12, 24, 36, 48-Months) ***	**18, 30, 42-Month Visits**	**60 and 72 Months, Completion Visit**
Visit Window		*<60 days from Screening*	*±2 weeks*	*±4 weeks*	*±8 weeks*	*±4 weeks*	*±8 weeks*
Randomization		X					
Visual acuity[a]	X	X		X	X	X	X
OCT	X			X	X	X	X
Eye Exam [b]	X	X		X	X	X	X
Fundus Photography[c]	X				X		X
Fluorescein Angiography[c]	X				X		X
Blood Pressure	X	X	X	X	X		X
Urine sample for creatinine, albumin, and pregnancy test (if female of child-bearing potential)	X	Pregnancy test only (if > 30 days from screening) [k]	X	X	X	Pregnancy test only (Central Lab)	X
Whole blood sample for CBC and HbA1c[d]	X		CBC only	X	X		X
Serum sample for LFTs, serum creatinine, eGFR, CK, and lipid panels[e]	X		X	X	X		X
Safety assessment[f]			X	X	X	X	X
Assess Compliance with Study Drug Regimen			X	X	X	X	X
CGM Insertion[g]		X		X	X	X	X
Ancillary Components – *the following tests will only be performed at select sites and/or on select participants*							
OCT Angiography[i]		X		X		X	X
Humphrey Visual Field[h]		30-2 & 60-4		30-2	60-4	30-2	30-2 & 60-4
Contrast sensitivity[j]		X			X		X
Biomarker serum sample	X		X	X	X		X

RNA sample	X		X	X	X		X

*= If treatment with intraocular medication, PRP, or vitrectomy is initiated in a study eye at a non-annual or non-study visit, all annual visit ocular testing and all study ancillary components (OCTA, visual field, and contrast sensitivity) will be completed in the eye(s) to be treated. For testing that is to be performed pre-dilation, post-dilation testing will be accepted if the decision to treat is made after dilation.

a= Usual care vision acceptable at Screening Visit; otherwise, visual acuity testing includes protocol refraction at each visit followed by electronic-ETDRS testing using the Electronic Visual Acuity Tester that has been validated against 4-meter chart ETDRS testing.

b= Includes slit lamp exam (including assessment of lens), measurement of intraocular pressure, and dilated ophthalmoscopy.

c= Using the widest approach available (e.g. ultrawide field imaging device).

d= CBC = complete blood count; for HbA1c, central laboratory value preferred but value available from within the prior 3 months may be used if central lab sample cannot be analyzed. CBC only at 3-month visit.

e= LFTs = liver function tests; eGFR = estimated glomerular filtration rate; CK = creatine kinase; fasting required for lipid panels at screening and the 48, 60 & 72-month visits.

f= safety assessments include questions related to symptoms of myopathy/rhabdomyolysis or cholelithiasis.

g= a "masked" CGM sensor will be placed and worn for approximately 10 days. The CGM will then be mailed back to the Coordinating Center for processing of the data.

h= HVF 30-2 and 60-4 performed on both eyes at randomization and the 60 & 72 month visits.
30-2 on study eye(s) only at months 6, 18 &30, and on non-study eye also at month 42.
60-4 on study eye(s) only at months 12, 24 & 36, and on non-study eye also at month 48.

i= OCTA is performed on the study eye(s) at all visits indicated, but is performed on the non-study eye also at randomization and the 42, 60, and 72-month visits.

j= Contrast Sensitivity is performed on the study eye(s) at all visits indicated, but is performed on the non-study eye also at randomization and the 48, 60 and 72-month visits.

k= At randomization, a pregnancy test must be completed at the site (for females who are premenopausal and are not surgically sterile) if randomization visit >30 days from screening. Pregnancy testing at all other visits must be performed by central lab.

Chapter 1: Background Information

1.1 Introduction

1.1.1 Diabetic Retinopathy Complications and Public Health Impact

The number of adults with diabetes mellitus worldwide has more than tripled over the past 20 years, with over 400 million people estimated to be living with diabetes today. Estimates suggest that by the year 2045, approximately 700 million individuals worldwide will be affected by this chronic disease.[1] The increasing global epidemic of diabetes implies an increase in rates of associated vascular complications. 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 and Prevention.[2] 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.[3]

1.1.2 Preventing DR Onset and Worsening

Currently, the primary method of preventing DR onset and worsening remains that of strict glycemic 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.[4] 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.[5,6] 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.[7] 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.[8] This beneficial effect persisted in type 2 diabetes[9,10] and in fact persisted for even as long as 18 and 25 years later for type 1 diabetes.[11,12]

Despite improvements in systemic glycemic control,[13] there continues to be a substantial proportion of patients with diabetes that 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.[14] In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) cohort, participants with type 1 and type 2 diabetes with diabetes duration greater than 15 years had a PDR prevalence of 49% and 15% respectively, with rates of visual impairment ranging from 16% to 24%.[13]

The use of anti-vascular endothelial growth factor (anti-VEGF) agents for prevention of DR complications is currently being studied in eyes at highest risk of progression: those with moderate to severe non-proliferative diabetic retinopathy (DRCR Retina Network Protocol W NCT02634333).[15] The one-year results from the Phase 3 PANORAMA trial conducted by

Regeneron Pharmaceuticals showed the percentage of patients who developed a vision-threatening event was reduced from 41% in the sham group to 10% and 11% in the every 16 week and every 8 week aflibercept-treated groups, respectively.[15] Although these results are positive, longer term data are still needed, including whether starting with early intervention with injections is superior with respect to visual acuity results compared with waiting and treating after PDR or DME develop. The results of DRCR Retina Network's Protocol W will provide much needed longer-term visual acuity data in this cohort. Even if these results suggest early anti-VEGF is beneficial for eyes with severe NPDR, there are currently no guidelines for treating eyes with mild to moderate NPDR.

1.1.3 Limitations of Current Treatments for DR and 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 vision loss in eyes with center-involved DME.[16-18] However, anti-VEGF treatment does have drawbacks including the need for recurrent intravitreous 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. Intravitreal injections are also associated with high 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, which is not FDA-approved for the treatment of PDR or DME.[19,20] In addition, not all eyes treated with anti-VEGF have resolution of DR or DME.[21,22] Scatter laser photocoagulation or panretinal photocoagulation (PRP) is another treatment for PDR that is not invasive and does not need to be repeated as frequently as anti-VEGF injections, but laser treatment has other well-documented adverse effects, including exacerbation or development of macular edema with transient or permanent central vision loss, peripheral visual field defects, night vision loss, loss of contrast sensitivity, potential complications from misdirected or excessive burns, increased risk of vitrectomy compared with anti-VEGF treatment, and severe vision loss in nearly 5 percent of individuals despite appropriate treatment.[18,23] Thus, there is an ongoing need to identify novel therapies that are both effective for PDR treatment and that also avoid the potential adverse events or costs associated with current ocular interventions. Furthermore, the identification of an oral therapeutic agent that prevents worsening to PDR might allow treatment of a wider segment of the diabetic population at risk for diabetic eye complications who do not have access to anti-VEGF or laser treatment or who are not suitable candidates for these treatments.[24] This would be a major public health contribution if an effective preventive oral agent can be implemented into clinical care.

1.1.4 Rationale for Fenofibrate Therapy for DR Worsening

Fenofibrate is an oral medication of the fibrate class that is used for treatment of hyperlipidemia. Fenofibrate reduces low-density and very low-density lipoprotein and triglyceride levels while increasing high-density lipoprotein levels. It acts via activation of peroxisome proliferator-activated receptor α (PPARα) and may decrease inflammation through inhibition of NFκB activity,[25,26] increased neuroprotection through improved mitochondrial function,[27] and possibly impacting telomere length.[28] In addition, fenofibrate affects human retinal endothelial cells

through a PPARα-independent mechanism. Two major clinical studies have evaluated the effect of oral fenofibrate treatment on ocular outcomes in patients with diabetes.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study randomized 9795 patients with type 2 diabetes to fenofibrate 200 mg/day versus placebo.[29] The percentage of participants requiring first laser treatment for either DR or DME was significantly lower in the fenofibrate group than in the placebo group (HR 0.69, 95% CI 0.56-0.84, $P = 0.0002$), although the absolute risk reduction was small (1.5%, 95% CI 0.7-2.3). A subgroup of the overall cohort also underwent fundus photography to document DR severity worsening throughout the study (N=1012). Although a difference between the groups for the primary endpoint of 2-step eye-level DR worsening was not identified in the full cohort with fundus photographs, in the subgroup of participants with pre-existing DR, fenofibrate treatment was associated with a reduction in 2-step eye-level DR worsening compared with placebo (3.1% versus 14.6%, $P = 0.004$). This suggests that the treatment may be of value among individuals with pre-existing DR if proven in a subsequent trial of such a cohort for the primary endpoint.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial enrolled 10,251 participants with type 2 diabetes and randomly assigned them to intensive glycemic control (goal HbA1c < 6.0%) or standard therapy.[6] The 5,518 participants with dyslipidemia were further randomized in a 2x2 factorial design to receive simvastatin in combination with either fenofibrate (at 160 or 54 mg/day depending on renal function) or placebo. The ACCORD Eye study enrolled 3,472 individuals from this group of which 85% of survivors (N = 2,856) completed both a baseline and 4-year follow-up visit. At 4 years, DR worsening was significantly less likely with intensive glycemic control as compared with standard therapy. DR worsening also was significantly less frequent in the fenofibrate group compared with the placebo group (6.5% versus 10.2%, adjusted OR, 0.60, 95% CI, 0.42-0.86, $P = 0.0056$). The benefit of fenofibrate therapy was seen primarily in study participants with DR at baseline (see table below). In participants with microaneurysms in only 1 or both eyes or with mild NPDR in only 1 eye, the odds ratio for ≥3 step progression on a patient level was 0.27 (95% CI: 0.12-0.63, p = 0.0009).[30] No significant relationship was seen between fenofibrate use and DR worsening in eyes with no DR. Among participants with mild NPDR to severe NPDR (N = 279) the rates of progression were 9% to 17%. Fenofibrate treatment did not appear to affect the rate of at least moderate vision loss (fenofibrate group: 23.7%, placebo group: 24.5%, $P = 0.57$), nor did it affect changes in macular edema status between baseline and year 4.[6]

Table 5. Four-Year Rates of Diabetic Retinopathy Severity Progression Overall and in Subgroups

Outcome	Glycemia Trial			Lipid Trial			Blood Pressure Trial		
	Intensive	*Standard*	*OR (95% CI) P*	*Fenofibrate*	*Placebo*	*OR (95% CI) P*	*Intensive*	*Standard*	*OR (95% CI), P*
Original total with progression (≥3 steps, PC, or vitrectomy)	0.073 (104/1429)	0.104 (149/1427)	0.67 (0.51–0.87) $P = 0.0025$	0.065 (52/806)	0.102 (80/787)	0.60 (0.42–0.86) $P = 0.0056$	0.104 (67/647)	0.088 (64/616)	1.23 (0.84–1.79) $P = 0.29$
Revised total with progression (≥3 steps or PC)	0.068 (97/1429)	0.102 (145/1427)	0.64 (0.49–0.84) $P = 0.0010$	0.061 (49/806)	0.098 (77/787)	0.59 (0.40–0.86) $P = 0.0049$	0.099 (64/647)	0.084 (52/616)	1.21 (0.82–1.78) $P = 0.33$
Baseline step* 1 no DR	0.057 (39/683)	0.071 (49/687)	0.78 (0.50–1.21) $P = 0.27$	0.062 (25/401)	0.059 (22/375)	1.12 (0.61–2.03) $P = 0.72$	0.067 (21/314)	0.071 (20/280)	1.00 (0.53–1.92) $P = 0.99$
Baseline steps 2–4: Ma or mild DR 1 eye, no DR or Ma only in other	0.027 (12/439)	0.084 (38/453)	0.30 (0.15–0.59) $P = 0.0002$	0.030 (8/264)	0.101 (26/258)	0.27 (0.12–0.63) $P = 0.0009$	0.046 (8/173)	0.041 (8/197)	1.22 (0.44–3.40) $P = 0.71$
Baseline steps 5–6: mild/moderate NPDR	0.090 (19/210)	0.119 (21/176)	0.69 (0.35–1.36) $P = 0.28$	0.068 (6/88)	0.135 (14/104)	0.41 (0.14–1.18) $P = 0.09$	0.081 (8/99)	0.126 (12/95)	0.61 (0.23–1.62) $P = 0.32$
Baseline steps 7–9: moderate/moderately severe NPDR	0.198 (16/81)	0.256 (22/86)	0.74 (0.33–1.62) $P = 0.45$	0.128 (6/47)	0.250 (10/40)	0.44 (0.12–1.62) $P = 0.21$	0.310 (13/42)	0.237 (9/38)	2.23 (0.64–7.74) $P = 0.20$
Baseline steps 10–17: severe NPDR or PDR	0.667 (10/15)	0.583 (14/24)	†	0.667 (4/6)	0.5 (5/10)	†	0.706 (12/17)	0.5 (3/6)	†

ACCORD = Action to Control Cardiovascular Risk in Diabetes; DR = diabetic retinopathy; Ma = microaneurysms; NPDR = nonproliferative diabetic retinopathy; PC = photocoagulation; PDR = proliferative diabetic retinopathy.
*See Ref. 7 in the Supplementary Appendix.
†Model did not converge because some cells had too few people.

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

In the 8-year follow-up study of ACCORD, 4 years following the cessation of the fenofibrate, the rate of DR progression was 11.8% (N=399) and 10.2% (N=363) in the fenofibrate group and placebo group, respectively, (adjusted OR 1.13, 95% CI0.71 to 1.79, P=0.60). This suggests that fenofibrate's protective effect may be dependent on continued dosing.[10]

A recent systematic review was conducted of randomized trials evaluating either statin, fibrate or combination statin/fibrate among patients with either type 1 or type 2 diabetes with or without NPDR. 1453 studies were initially screened and 8 met the defined eligibility criteria. Of the studies assessing effects of fibrates, there were four included that compared fibrate alone to placebo and one that examined fibrate plus statins. Two RCTs assessed incidence of macular edema development and meta-analysis found a risk reduction with fibrate use (RR 0.55, 95% CI 0.38 to 0.81, N=1309). Four RCTs assessed DR progression using ETDRS or similar and meta-analysis found no statistically significant benefit with fibrate-use neither when unit of analysis was the eye (RR 0.44, 95% CI 0.19 to 1.01) nor the individual patient (RR 0.79, 95% CI 0.55 to 1.14). Similar results were reported when assessing an outcome of progression to presence of NV or need for laser. For all data reported, the authors acknowledged imprecision in the estimates and risk of bias. It should also be noted that the RCTs that were included evaluated multiple types of fibrates (not just fenofibrate). The authors concluded that there is uncertainty regarding the effects of fibrates for DR and that there is a need for well-designed clinical trials to properly identify the role of fibrates for DR.[31]

1.1.5 Ongoing Multicenter Studies Evaluating Fenofibrate and DR

A fenofibrate study is currently recruiting in Scotland: Lowering Events in Non-proliferative Retinopathy in Scotland (LENS).[32] The study aims to recruit approximately 1600 participants with diabetes and observable retinopathy or maculopathy, who will be randomized to fenofibrate or placebo, and followed for at least 4 years. The primary objective is to evaluate the effect of fenofibrate on progression to clinically significant DR/maculopathy. All follow-up data will be

collected via telephone or computer questionnaire with outcome and safety data collected via National Health Service Scotland registries.

Although the LENS trial will potentially contribute additional efficacy data regarding the role of fenofibrate in preventing DR worsening, there is still rationale to pursue a fenofibrate study in the DRCR Retina Network since the LENS trial PIs are general medicine/cardiovascular/nutrition practitioners (not retina or ophthalmology) and data collection involves using usual care eye exams/imaging for follow-up (not standardized data collection). In contrast, the DRCR Retina Network proposed study will include standardized imaging protocols as well as multiple vision function tests to collect additional data on the natural history of DR progression, such as visual fields and contrast sensitivity. Furthermore, the Network's study design will help facilitate the ultimate objective to increase use of fenofibrate in the retina community (assuming the drug is confirmed to be effective for DR prevention).

An additional JDRF-supported study of fenofibrate in individuals with type 1 diabetes is also ongoing in Australia.[33] Recruitment of 450 participants began in 2016 and is ongoing. Enrolling sites include endocrinologists or primary care providers rather than retina physicians. Given the current recruitment rate it is unclear whether or in what timeframe enrollment of the full cohort will be achieved and when results will be available.

1.2 Summary of Study Rationale

Despite improved glycemic and systemic control for many patients over the past several decades, DR develops and progresses in a large proportion of patients with diabetes, and vision loss from diabetic eye complications continues to be a leading cause of blindness in the US and other developed countries worldwide. Thus, even a modest ability to prevent DR onset or to slow DR worsening might reduce the number of patients at risk for diabetes-related vision loss worldwide substantially. Widespread use of an oral agent effective at reducing worsening of DR might also decrease the numbers of patients who undergo treatment for DR and who are consequently at risk for side effects that adversely affect visual function. If the true progression rate over 4 years without treatment is 20% compared with 10% when treated with fenofibrate, the number needed to treat would be 10. In other words, 10 patients would need to be treated with daily fenofibrate to save 1 patient from DR progression that might require treatment with laser or intravitreous anti-VEGF. Even a true rate of 10% vs 5% equates to a number needed to treat of 20. Given the low cost and expected safety profile of fenofibrate, a number needed to treat of 10 to 20 would likely be in the acceptable range for many clinicians. Based on the reported five-year results from the Age-Related Eye Disease Study (AREDS),[34] the number needed to treat with antioxidants + zinc supplementation to prevent development of advanced AMD is 13.2, and this preventive treatment is widely recommended by ophthalmologists for those with intermediate AMD.

Secondary endpoints in prior clinical studies with relatively small sample sizes of eyes with NPDR have shown that fenofibrate can reduce the risk of DR worsening; however, a definitive clinical trial specifically in eyes with baseline NPDR that are at higher risk for progression is necessary to confirm these results. Treatment with fenofibrate has not been adopted by the retina community, perhaps due to lack of better communication and established mechanisms for coordinating the

prescription of fenofibrate with primary care providers and resulting uncertainty as to how to best monitor patients on fenofibrate for systemic complications. This effort has been somewhat hampered by the lack of beneficial effect of fenofibrate on the cardiovascular end points in prior trials, making this less appealing to the primary care physicians and diabetologists who may also be unaware of the results of the DR sub-studies. It is possible that the results from a study designed specifically for retina specialists to evaluate the effect of fenofibrate on DR, if positive, might have better opportunity to permeate into the community and affect change in practice patterns in a way that would benefit patients. In addition, by conducting this study in the DRCR Retina Network, over 300 retina specialists will gain experience using fenofibrate for this indication, which may help fenofibrate use permeate into practice, if the treatment is successful in this trial. This study will evaluate the long-term effects of fenofibrate on prevention of DR worsening in a large cohort of patients with type 1 and type 2 diabetes, as well as provide guidance to physicians for its use.

1.3 Rationale for Ancillary Components

Procedures to evaluate efficacy and monitor safety of fenofibrate are detailed in subsequent sections and include ocular exam, OCT, fundus photography, fluorescein angiography, visual acuity, blood pressure, and laboratory measurements. In addition to evaluating fenofibrate, this study will enroll a large cohort of participants with DR in which contemporary natural history data can be obtained. As such, a secondary objective is to collect information on potential predictive biomarkers via blood sampling, functional, and structural testing as well as glucose levels from CGM over the course of DR progression. Ancillary procedures will be performed at select sites/and or select participants for the reasons described below. Site participation for the ancillary components will depend on site capabilities.

1.3.1 Biomarker Samples

At sites with dry ice capabilities, extra blood samples will be collected and used for serum extraction. The samples will be de-identified and be stored at the central laboratory for future research. The DRCR Retina Network or its collaborators might conduct proteomic or other analyses on the serum samples, including all samples obtained at screening regardless of eligibility. The collection, storage and analysis of the serum samples could facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future. Data generated from serum samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future biological discoveries.

Objectives could potentially include but are not limited to the following:

- To study the association of biomarkers with DR progression or efficacy of fenofibrate.
- To identify safety biomarkers that are associated with susceptibility to developing adverse events.
- To increase knowledge and understanding of disease biology and drug safety.

- To study treatment response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.
- To understand the relationship of biomarker data with available clinical data (e.g. laboratory, imaging etc.) obtained at any time points, including data at screening from subjects that are not randomized.

For participants who consent, an additional whole blood sample will be collected for RNA extraction as part of a collaboration with the Roche Group. The sample will not include any directly identifiable information, and the Roche Group will not make any attempt to re-identify participants in accordance with an agreement with the JCHR. At the direction of the Roche Group, the sample may be sent to one or more external national or international laboratories for genome wide transcriptional or targeted analysis of expression of individual genes utilizing, e.g., whole transcriptome sequencing, targeted transcriptome sequencing or other transcriptomic analysis methods.

1.3.2 Visual Function and Anatomy

The placebo-treated cohort will allow for assessment of factors that may be important in understanding the progression of DR. The data from visual function assessments such as contrast sensitivity and visual field (VF) testing as well as structural data from OCT and OCT angiography (OCTA) will provide valuable information on potential predictive biomarkers of functional outcomes over the natural history of DR progression.

1.3.2.1 Visual Field Testing

In DRCR Retina Network Protocol S,[18] 234 of 394 eyes (59.4%) had at least one VF test pattern (either Humphrey Field Analyzer 30-2 or 60-4) available at baseline, and 143 (36.3%) had at least one test at follow-up. At baseline, the mean (SD) combined total point score was 3487 (659) in the PRP group and 3365 (759) in the ranibizumab group while corresponding values for mean deviation were -6.4 (4.6) dB and -7.0 (5.2) dB. This indicates that, on average, these eyes with PDR had VF defects at study entry. In the ranibizumab group, the mean (SD) total point score change was -36 (486) at 1 year, -23 (410) at 2 years, and -330 (645) at 5 years. One possible explanation for loss of field sensitivity in the ranibizumab group is that the progression of the underlying DR impacted VF sensitivity. Increasing retinal ischemia associated with PDR may cause further deterioration of VF sensitivity despite laser or anti-VEGF. By collecting visual field data in a subset of this cohort, we aim to:

1. Quantify VF deficits at baseline in eyes with DR and assess relationship with baseline DR severity level, potentially including non-study eyes and participants not randomized.
2. Evaluate the relationship of DR progression and VF changes through at least 4 years.
3. Explore whether fenofibrate treatment has an effect on VF changes over 4 years.

1.3.2.2 Contrast Sensitivity

Contrast sensitivity is reduced among patients with diabetes, often before signs of DR develop. Mean levels of contrast sensitivity decrease with more severe levels of DR and with macular edema.[35-39] Contrast sensitivity is important for several aspects of visual function important in daily life including driving,[40-42] recognizing faces,[43,44] reading,[44,45] identifying objects,[46] and mobility.[44] Although VA and contrast sensitivity are correlated strongly within eyes of people who do not have systemic or ocular disease, the correlation is weaker among people with diabetes.[47] A method of measuring contrast sensitivity developed by Adaptive Sensory Technology (AST) will obtain the full contrast sensitivity curve across a spectrum of spatial frequencies. By collecting contrast sensitivity in a subset of this cohort of eyes with mild to moderately severe NPDR, we aim to:

1. Quantify contrast sensitivity at baseline in eyes with DR and assess relationship with baseline DR severity level, potentially including non-study eyes and participants not randomized.

2. Evaluate the relationship of DR progression and contrast sensitivity changes through at least 4 years.

3. Explore whether fenofibrate treatment has any effect on contrast sensitivity (potential to detect treatment differences even if central vision is similar).

1.3.2.3 OCTA

OCTA is to be a promising alternative to fluorescein angiography (FA) and ICGA in visualizing blood vessels and the dynamic changes within the retinal vasculature. OCTA technology compares consecutive, repeated scans and assumes that the sole moving objects in the retina are the blood cells inside the vessels. These changing contrasts are translated to blood vessels in the final images. Thus, OCTA allows for a 3-dimensional visualization of retinal and optic nerve capillary networks and allows for visualization of different retinal layers, whereas FA and ICGA do not. Additionally, OCTA is non-invasive, depth-resolved, and is unaffected by signal blur from vascular leakage.[48]

OCTA reports have consistently shown important pathophysiological findings in DR in small scale clinical studies that hold the potential for meaningful clinical trial endpoints.[49,50] One review of current literature of OCTA in DR concluded that there have been several advances using OCTA imaging in diabetic eyes, with an earlier detection of diabetic changes, better grading of DR, and more reliable quantitative measurements. Morphological and qualitative assessment of vascular changes adds to knowledge about the pathophysiology of DR. However, further studies are warranted to determine the role of OCTA in the routine clinical management of DR.[51] The objectives of including OCT angiography are to compare with current imaging modalities for detection of DR pathology as well as identify biomarkers at baseline that are associated with retinopathy progression.

1.3.3 Continuous Glucose Monitor (CGM) Sub-Study

As part of the study, participants will wear a Dexcom G6 Pro Continuous Glucose Monitor (CGM) for up to 10 days approximately every 6 months (annually during years 5 & 6). By utilizing CGM in this cohort, we will be able to better understand how metrics of glycemia, such as mean blood glucose and time-in-range (TIR), are associated with retinopathy outcomes.

As noted previously, there is evidence from the DCCT that improved glycemic control prevents DR worsening among all age groups, type 1 and type 2 diabetes, and all stages of retinopathy.[4-6] Despite improvements in systemic glycemic control as measured by HbA1c,[13] there continues to be a substantial proportion of diabetic patients that develop DR and its associated sequelae. HbA1c became the gold standard for assessing glycemic management after the landmark DCCT trial demonstrated the strong association between HbA1c levels and the risk of chronic diabetic vascular complications and laboratory methods were developed so that A1C levels could be readily measured with a high degree of precision. Although its important role in diabetes management, as a clinical trials outcome, and as a predictor of long-term diabetic complications cannot be overstated, HbA1c does have certain limitations.[52] It is a measure of hyperglycemia over 2-3 months, but it provides no indication of hypoglycemia, glycemic variability, or daily patterns of glycemia. Notably, considerable inter-individual variability exists in the relationship between HbA1c and mean glucose concentration within and between race-ethnicities,[53] so that for an individual patient with diabetes, HbA1c may or may not be a good indicator of glycemia. This is not necessarily important when comparing groups in a clinical trial or computing population averages, but it can be important in the management of an individual patient. There are certain well-known causes of HbA1c-mean glucose discordance such as hemoglobinopathy, hemolytic anemia, and chronic renal failure; but even when there is no known condition affecting red blood cells present, there is a wide range of possible mean glucose concentrations for a given HbA1c level.[52] This is likely due, at least in part, to inter-individual variation in red-blood-cell life span. The frequent discordance between mean glucose and HbA1c has been known for many years, but awareness has increased in recent years as continuous glucose monitoring (CGM) has become more prevalent.

A CGM system includes a disposable sensor inserted under the skin that measures the interstitial fluid glucose concentration every 5-15 minutes, which closely reflects blood glucose concentration. A transmitter attached to the sensor either stores the glucose values or sends the values to a receiver, smart phone, or smart watch, any of which may in turn be connected to and subsequently share data securely to the cloud. Some CGM devices, such as the Dexcom G6 Professional and the Abbott Libre Pro, provide the ability for the glucose concentrations to be measured but not be visible to the user. These devices will be referred to as "masked" CGM. Such devices provide the ability to collect glucose data without directly affecting user behavior, which could impact the glucose levels. Recently, a consensus statement has been published on specific CGM metrics to use for assessing hyperglycemia, hypoglycemia, and glycemic variability.[54] The CGM measure that has gained the most attention from patients with diabetes and health care providers is the percentage of time glucose values are between 70 and 180 mg/dL, referred to as "time in range" (TIR).[55] TIR measured with CGM has been shown to be strongly correlated with HbA1c, with as few as 7-14 days of data.[56]

Despite the rapidly increasing use of CGM, particularly in type 1 diabetes, and the recognition by clinicians of its value, the Food and Drug Administration (FDA) has not accepted CGM metrics as outcomes for making efficacy claims in clinical trials conducted for the approval of a new drug or device. The FDA has indicated the need to demonstrate the clinical relevance of CGM outcomes, similar to the DCCT's demonstration of the association of HbA1c levels with retinopathy progression and other vascular complications. As a step in this direction, Beck et al utilized blood glucose measurements from the DCCT publicly available dataset in which blood glucose concentrations were measured at a central lab from 7 fingerstick samples collected during one day every 3 months. From these glucose data, TIR was computed and then used to assess the association of TIR with the development or progression of retinopathy. A strong association between TIR and retinopathy was found, similar in magnitude to the association of HbA1c and retinopathy, despite the fact that the glucose data represented only 7 measurements every 3 months; for each 10 percentage points lower TIR, the rate of retinopathy progression was increased by 64%.[57] Additional evidence for the value of CGM-measured TIR was shown in a recent cross-sectional study of individuals with type 2 diabetes that demonstrated an association of TIR with the presence of retinopathy.[58]

To date, there has not been a prospective, longitudinal study assessing the association of TIR and other CGM metrics with retinopathy progression. The CGM data collected in this study will become extremely important for developing an understanding of the continued importance of HbA1c compared with other glycemic metrics as CGM use becomes more widespread.

The primary objective of the CGM study is to evaluate the relationship of TIR and other glycemic parameters measured by CGM (mean glucose, hyperglycemia metrics, hypoglycemia metrics, and variability metrics) with DR progression. Secondary objectives include:

1. To compare the strength of association of CGM-measured glycemic parameters with DR progression versus the strength of association of HbA1c with DR progression.

2. To assess the association of CGM metrics with renal outcomes (eGFR).

3. To explore whether fenofibrate treatment has any effect on measures of glycemia.

1.4 Potential Risks and Benefits of the Study

1.4.1 Known Potential Risks Related to Common Procedures

Many of the procedures in this study are part of daily ophthalmologic practice in the United States and pose few if any 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. Possible risks from blood draws include the following: bruising, arm discomfort, clotting, excess bleeding, infection, or fainting. Please note that although these are possible risks, they are unlikely.

1.4.2 Risks Related to Confidentiality

The risk of disclosure of protected health information is very small. Efforts are taken to assure that this does not occur, in compliance with HIPAA.

1.4.3 Known Potential Risks Related to Fenofibrate

Fenofibrate, the most frequently used medication in the fibrate class, was developed in the 1980s and achieved FDA approval in 1993.[59] Several decades of clinical experience with this agent have demonstrated that it is generally well tolerated. A 2019 systematic review reported that incidences of adverse events were similar between fibrate and placebo when combining four RCTs, although the estimates around the adverse event rates were imprecise.[31] According to the package insert, adverse events reported by 2% or more of participants in clinical trials of fenofibrate and at rates at least 1% greater than in placebo-treated participants, include increases in abnormal liver function tests (7.5% vs 1.4%), aspartate transaminase (AST: 3.4% vs 0.5%), alanine transaminase (ALT: 3.0% vs 1.6%), creatinine phosphokinase (3.0% vs 1.4%) and rhinitis (2.3% vs 1.1%).[60] Rarely, (less than 1% of the time) the following have also been reported with fenofibrate use: gallstones, pancreatitis, changes in blood counts, hypersensitivity reactions of the skin, blood clots and decreases in 'good' cholesterol (HDL or high density lipoproteins). Increases in levels of anticoagulants such as warfarin in patients who are taking these medications with fenofibrate have also been documented.[60]

Rare cases of myopathy and rhabdomyolysis have also been reported, with increased risks for these complications in patients with diabetes, renal failure, or hypothyroidism. The risk for rhabdomyolysis was increased in observational studies of a particular fibrate, gemfibrozil, administered with an HMG-GoA reductase inhibitor (statin).[60] However, this was not observed when fenofibrate was used in combination with simvastatin in more than 2500 patients in ACCORD.[61] In addition, a 2012 meta-analysis including data from 1,628 participants from 6 studies did not reveal significantly higher rates of discontinuation attributed to any adverse events, adverse events related to study drug, or serious adverse events when fenofibrate was co-administered with a statin compared with fenofibrate alone.[62]

In the FIELD trial, there were higher numbers of patients with pulmonary embolus (PE) and deep vein thrombosis (DVT) in the fenofibrate group than in the placebo group (DVT: 48 events (1%) placebo vs 67 (1%) fenofibrate; PE: 32 (0.7%) vs 53 (1%) fenofibrate).[60] Paradoxical decreases in high density lipoproteins (HDL) have also been reported in post-marketing reports.

During the ACCORD Study, serum creatinine increased by 20% or more in 48% of participants randomized to fenofibrate. Of those, the dose was decreased to adjust for the creatinine increase in 26%.[63] Following careful renal function surveillance and dosing adjustments, there was no increase in renal disease. A post hoc analyses showed that fenofibrate was associated with an overall decrease in incident albuminuria and a slower eGFR (estimated glomerular filtration rate) decline but no difference in incidence of chronic kidney disease or kidney failure in ACCORD. [64]

Additionally, in ACCORD, a difference in the primary cardiovascular outcome was observed in men vs women in which there was an increased risk for females.[61] This finding was not observed

in the FIELD trial and could be attributed to the lower number of women participants and lower event rates in ACCORD. Although the difference was also observed during extended follow-up in ACCORDION, the study investigators concluded it may be a chance finding. [65]

Unlike the ACCORD study, in which participants at highest risk for cardiovascular outcomes were specifically included, the eligibility criteria for this study have been developed with the goal to limit those at higher risk for systemic side effects. Systemic effects of fenofibrate will be monitored via lab testing and safety evaluations at each follow-up visit. Guidelines for stopping or titrating a participant's treatment based on follow-up lab testing and safety evaluations have been developed by a panel of internists a priori based on the renal function surveillance performed in ACCORD (see section 6.1.7). This central panel will also be consulted during the study as needed. For all participants, post-visit updates including lab results will be sent to the participant's health care provider responsible for their primary systemic management (e.g. endocrinologist or primary care provider; hereafter referred to as "PCP") with their consent. The PCP will be asked to consult with the study's central panel before recommending any changes in study treatment. A summary of how often the pre-specified safety protocol was used and how often the panel was consulted will be reported with the study results.

1.4.4 Risks if Pregnant

The effects of fenofibrate on a human fetus (unborn baby) or nursing (breast feeding) infant are unknown. It is possible that use of these drugs may be associated with unknown risks to a pregnancy or fetus. Therefore, patients will not be allowed to participate in this study if pregnant, planning to become pregnant within the next 6 years, or if nursing an infant. During the study, females who are capable of bearing children must agree to use an effective method of birth control to prevent pregnancy. In the event of pregnancy during the study, fenofibrate/placebo will be discontinued, but the participant will remain in the study and followed for safety.

1.4.5 Known Potential Benefits

Based on results from the FIELD and ACCORD studies, fenofibrate may reduce the risk of DR worsening in eyes with NPDR. Preventing DR worsening may help preserve vision in some participants. However, there is no guarantee that the treatment with fenofibrate will be successful.

Depending upon the results of this study, the benefits to society may be substantial. Patients with diabetes are at high risk of developing advanced diabetic eye complications, such as PDR and DME, as they live with longer durations of diabetes. Indeed, it is estimated that nearly 60% of patients with type 1 diabetes will develop PDR, after living with diabetes for 20-30 years. DME is also a common complication, affecting approximately 746,000 persons in the United States aged 40 years and older. Future patients may benefit from this medical research if fenofibrate is demonstrated to be effective in this cohort with an acceptable safety profile, and its use becomes more widespread. By preventing progression to vision-threatening PDR, patients may avoid the potential adverse events and costs associated with the frequent injections necessary to treat these complications of advanced diabetic eye disease.

If this study demonstrates that fenofibrate is effective for preventing DR progression and the results are adopted by the community of retina specialists, a new strategy to prevent vision threatening complications of diabetes will be available for patients. In addition to evaluating efficacy, this study aims to provide a model for ophthalmologists to prescribe and/or collaborate with a primary care provider to prescribe and monitor the drug safely. The ability to prevent PDR onset or to slow DR worsening with an oral agent might reduce the number of patients at risk for diabetes-related vision loss worldwide substantially. Widespread use of an oral agent effective at reducing worsening of DR would decrease the numbers of patients who undergo more invasive and much more expensive treatment for DR and DME and who are consequently at risk for side effects that adversely affect visual function.

1.4.6 Known Potential Risks Related to CGM

There is a low risk for developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies.

Sensors may fracture in situ on rare occasions. In the rare instances when this has occurred in the past, consulting physicians and surgeons have recommended not to remove the wire fragment from beneath the skin as long as there are no symptoms of infection or inflammation. If signs and/or symptoms of infection or inflammation arise such as redness, swelling, and pain, participants should consult with the investigator or a primary care provider for the best course of action. If there is no portion of the broken sensor wire fragment visible above the skin, attempts to remove it without medical guidance are not advised.

1.4.7 Known Potential Risks Related to Ranibizumab

For study eyes requiring treatment with an anti-VEGF agent during the study, ranibizumab will be provided. Intravitreal ranibizumab is well tolerated. According to the package insert, the most common adverse reactions are conjunctival hemorrhage, eye pain, vitreous floaters, and increased IOP.[66] As a result of the injection, endophthalmitis, retinal detachment, or vitreous hemorrhage could develop (less than 1% risk for each). There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. There may be side effects and discomforts that are not yet known.

1.4.8 Risk Assessment

The protocol risk assessment for this study has been categorized as greater than minimal risk.

1.5 General Considerations

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

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

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

A minimum of 560 participants with at least one study eye are expected to be randomized. It is anticipated that up to 2,000 participants may be enrolled in the study (defined as signing informed consent form) in order to achieve this goal. Participants who have signed consent and started the screening process may be permitted to continue into the trial, if eligible, even if the randomization goal has been reached.

Study participants will be recruited from approximately 80 clinical centers in the United States and approximately 5 sites in Canada. It is expected that most potential participants are already being seen at the clinical center as part of usual patient care. Potential referral sources (e.g., physicians and other health care providers) may also be sent an announcement about the study from a clinical center that is recruiting patients. All eligible participants will be included without regard to gender, race, or ethnicity. There is no restriction on the number of participants to be enrolled by each site towards the overall recruitment goal.

Protocol v6.0 was implemented in October 2023 to reduce the sample size from 910 to 560. It is anticipated that enrollment will be completed within 22 months of the effective date of v6.0.

2.1.1 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination. Before completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained.

The study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

As part of the informed consent process, each participant will be asked to provide authorization for release of personal information. The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization. A separate signature section will be used to collect consent for optional blood samples and whether the participant agrees to receive text message reminders (text messaging available for United States participants only).

A participant is considered enrolled when the informed consent form has been signed. Screening visit data may be used for cross-sectional analyses even for participants not randomized. Once a study participant is randomized, that participant will be counted in the primary analysis regardless of whether the assigned treatment is received. Thus, the investigator must not proceed to randomize an individual until he/she is convinced that the individual is eligible, will accept assignment to either of the two treatment groups, and will be compliant with daily medication use.

For participants who enroll in the trial after Protocol v6.0 is implemented, the follow-up period of up to 6 years will be explained as part of the informed consent process.

Participants enrolled prior to Protocol v6.0 (which extended follow-up from 4 to up to 6 years) initially agreed to a follow-up period of 4 years. At the 4-year visit, these participants will be asked to remain in the study up to 6 years (i.e. up to 2 additional years). A verbal explanation of the study procedures and timeline will be presented along with a written informed consent addendum.

2.2 Participant Inclusion Criteria

A participant may have one or two study eyes, but must meet the individual-level and study eye-level eligibility criteria in sections 2.2.1 and 2.2.2.

2.2.1 Individual-level Criteria

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

1. Age ≥ 18 and < 80 years
   - *Individuals <18 years old are not being included because DR is so rare in this age group that the diagnosis of NPDR may be questionable. Individuals ≥80 years old are excluded to limit co-morbidities and mortality over this long-term trial.*
2. Diagnosis of diabetes mellitus (type 1 or type 2)
   - Any one of the following will be considered to be sufficient evidence that diabetes is present:
     - *Current regular use of insulin for the treatment of diabetes.*
     - *Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes.*
     - *Documented diabetes by American Diabetes Association and/or the World Health Organization criteria.*
3. At least one eye meets the eye-level criteria listed in Section 2.2.2.
4. Able and willing to provide informed consent.
5. Able and willing to wear a CGM device (for United States participants only).

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

6. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status that may preclude successful completion of follow-up).
7. Initiation of intensive insulin treatment (a pump or multiple daily injections) within 3 months prior to screening or plans to do so in the next 3 months.
8. Participation in an investigational trial that involved treatment within 30 days of screening with any drug that has not received regulatory approval for the indication being studied.
9. Known allergy or hypersensitivity to any component of fenofibrate.
10. Known allergy to fluorescein dye.

11. History of treatment with a prescription fibrate medication (e.g. bezafibrate, fenofibrate, gemfibrozil, fenofibric acid) within 12 months prior to screening or anticipated need for fibrate medication for another indication (e.g. lipid management).
12. Any prior systemic treatment for DME or DR.
13. Decreased renal function, defined as requiring dialysis or central laboratory eGFR value < 45 mL/min/1.73 m^2
14. Active liver disease (defined as any LFT >3x upper limit of normal based on central laboratory value), or known history of Hepatitis C or alcoholic liver disease.
15. Pre-existing symptomatic gallbladder disease including gallstones; however, prior gallbladder removal is not an exclusion.
16. Triglycerides >400mg/dL on treatment or >700mg/dL on no treatment based on central laboratory value.
17. Current use of any of the following medications:
    - Coumarin anticoagulants (Coumadin/Warfarin).
    - Immunosuppressants that affect kidney function, such as cyclosporine and tacrolimus
    - Colchicine (Colcrys)
18. History of severe myalgia requiring discontinuation of lipid lowering treatment.
19. Blood pressure > 160/100 (systolic above 160 or diastolic above 100).
20. HbA1c > 11.0% based on central laboratory value or if lab sample cannot be analyzed, recent result within 3 months
21. Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to screening or anticipated use during the study.
22. For women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next 6 years.
23. Participant is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the next four years.

2.2.2 Study Eye Criteria

The potential study participant must have at least one eye meeting all of the inclusion criteria and none of the exclusion criteria listed below. A study participant can have two study eyes only if both are eligible at the time of randomization.

The eligibility criteria for a <u>study eye</u> are as follows:

a. Mild to moderately severe NPDR (defined by ETDRS DR severity level 35 to 47), confirmed by central Reading Center grading of fundus photographs
b. Best-corrected E-ETDRS visual acuity letter score ≥74 (approximate Snellen equivalent 20/32 or better)

- *If BCVA letter score is 74-78, investigator must verify that vision loss is not due to the presence of CI-DME, cataract, or other condition that may affect visual acuity during the course of the study.*

c. Media clarity, pupillary dilation, and study participant cooperation sufficient to obtain adequate fundus photographs, FA, and OCT.

- *Investigator must verify accuracy of OCT scan by ensuring it is centered and of adequate quality (including segmentation line placement)*

The following exclusions apply to a study eye:

d. Evidence of definite neovascularization according to the investigator or central Reading Center grading of fluorescein angiography.
   - *Includes presence of NV outside of the 7-modified ETDRS fields on ultra-widefield imaging, which is an exclusion.*

e. Current CI-DME based on clinical exam or OCT central subfield thickness (CST), defined as:
   - Zeiss Cirrus: CST ≥290 µm in women or ≥ 305 µm in men.
   - Heidelberg Spectralis: CST ≥ 305 µm in women or ≥320 µm in men.

f. 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 study.

g. Any prior treatment for DME or DR, other than focal/grid laser.
   - *If the eye has a history of focal/grid laser, it must be at least 12 months prior.*

h. History of major ocular surgery within prior 4 months or anticipated within the next 6 months following randomization.

i. Anticipated need for intraocular anti-VEGF or PRP in the next 6 months following randomization.

j. History of intraocular anti-VEGF or corticosteroid treatment within the prior year for any indication other than DME or DR.

k. Any history of vitrectomy.

l. History of YAG capsulotomy performed within 2 months prior to screening.

m. Aphakia.

n. Evidence of uncontrolled glaucoma
   - *Intraocular pressure must be <30, with no more than two topical glaucoma medications, and no documented glaucomatous field loss for the eye to be eligible*

2.2.3 Non-Study Eye Criteria

If only one eye is eligible, the non-study eye must have at least microaneurysms only (DR severity level 20). If pathology or other image quality precludes Reading Center grading in the non-study eye, the Protocol Chair will review images to confirm presence of at least level 20. There is no upper limit on DR severity in the non-study eye.

2.3 Screening Procedures

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history and performance of an ocular examination by study personnel to screen for exclusionary conditions.

Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion.

All testing does not need to be completed on the same day provided it is within the windows specified below. The screening visit should be scheduled early in the day to accommodate fasting requirements for blood samples.

2.3.1 Data Collection and Testing

The following procedures are needed to confirm eligibility and/or serve as baseline measures for the randomized trial:

- If a procedure has been performed using the study technique and by study certified personnel as part of usual care, then it does not need to be repeated specifically for the study if it was performed within the defined time windows specified below.
- The testing procedures are detailed in the DRCR Retina Network procedures manuals. See Chapter 7 for which testing requires certified personnel.
- The fundus photographs and fluorescein angiograms will be promptly sent to the central reading center for grading and a participant cannot be randomized until reading center confirmation of eligibility has been received.
    - Separately, automated grading may be done as an ancillary component to evaluate the accuracy of automated grading systems. However, those results will not be considered for eligibility.
- Screening procedures will last approximately 4 hours.

1. Self-reported demographics (date of birth, sex, race and ethnicity)
2. Medical history (pre-existing medical conditions, concomitant medications, as well as ocular diseases, surgeries, and treatment)
    - ➢ Medical history will be obtained by medical charts if available at the enrolling site; otherwise, it will be self-reported
3. Visual acuity using clinic's usual care method or electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester in both eyes *(within 8 days of ocular examination).*
4. Spectral-domain OCT using Zeiss Cirrus or Heidelberg Spectralis in both eyes *(within 8 days of ocular examination).*

- All OCTs at screening will be sent to a reading center for manual grading, but eligibility in the study eye(s) regarding DME status is determined by the site (i.e., individuals deemed eligible by the investigator will be randomized without pre-randomization reading center confirmation of the OCT central subfield thickness).

- Includes additional optic nerve head scan to obtain Retinal Nerve Fiber Layer (RNFL) thickness data.

5. Digital fundus photographs on both eyes using the widest approach available (e.g. ultra-widefield imaging device, if available). *(within 8 days of ocular examination)*

6. Digital FA on both eyes using the widest approach available (e.g. ultra-widefield imaging device, if available). *(within 8 days of ocular examination)*

- *If only **one eye** is being evaluated as a study eye, the study eye will be considered the transit (rapid series) eye.*

- *If **both eyes** are being evaluated as a study eye, the right eye will be considered the transit (rapid series) eye.*

7. Ocular examination on each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy *(on day of screening visit).*

8. Physical examination to include:

- Weight and height
- Blood pressure

9. ***Fasting*** blood draw (*up to 30 days before or 30 days after screening visit*)* for:

- HbA1c, liver function tests (LFTs), serum creatinine (used for estimated glomerular filtration rate [eGFR]), Creatine kinase (CK), complete blood counts (CBC), and lipid panels
  - *The central laboratory must be used – see study procedure manual for collection procedure. Includes one sample for HbA1c and CBC tests and one sample for extraction of serum for remaining tests above.*
  - *If HbA1c value is not obtained from central laboratory because sample cannot be analyzed, it does not need to be repeated if available in the prior 3 months.*
  - *A small snack will be available for the participant after blood draws are performed.*

* *with* prior *Coordinating Center approval, labs may be drawn beyond* 30 days *after the* screening visit, *but site must ensure there is adequate time to obtain results and PCP approval prior to randomization.*

10. Urine sample (*up to 30 days before or 30 days after screening visit*)* for:

- Creatinine and albumin

- Pregnancy test for all females who are premenopausal and are not surgically sterile
  - *The central laboratory must be used – see study procedure manual for collection procedure. If pregnancy test cannot be analyzed by the central laboratory, it may be repeated or performed locally prior to randomization.*

    ** with prior Coordinating Center approval, labs may be drawn beyond 30 days after the screening visit, but site must ensure there is adequate time to obtain results and PCP approval prior to randomization.*

Additional ancillary procedures (only obtained by a subset of sites or participants) include:

1. Serum sample (all participants at sites with dry ice capabilities)
   - *Includes approximately 20mL of blood collected in SST tubes that will be centrifuged for serum extraction and shipped on dry ice. See laboratory procedure manual for details regarding collection, processing, handling, and shipping procedure.*
2. Whole blood for RNA sample (optional for the participant)
   - *Includes one Pax Gene tube. See laboratory procedure manual for the collection, processing, handling, and shipping procedure.*

2.3.2 Ancillary Samples

At sites with dry ice capabilities, the above serum samples will be collected as part of the study. For participants who consent, an optional RNA sample will also be collected. These samples also will be taken at the specified timepoints in section 5.3.

The serum samples for future use will be sent to a central laboratory to be divided into aliquots and stored in a locked freezer for an indefinite amount of time, identified by a barcode number only. The sample is stored such that no automated links exist between the patient's sample and information that would identify them. De-identified samples and associated study data will be provided to national and international academic and/or industry collaborators under an agreement with the Jaeb Center for Health Research. Under such agreement, collaborators may send serum samples to one or more laboratories for external analyses. Requests for access will be reviewed and approved by a DRCR Retina Network committee.

For the optional RNA sample, consent is recorded on the eCRF upon obtaining a participant ID. The sample will be sent to the central laboratory until a sufficient number have been collected to provide to the Roche Group. Once provided to the Roche Group, the samples may be stored, maintained and used for future research. They may also provide samples to other researchers and industry collaborators. The RNA samples may be sent to one or more external national or international laboratories for genome wide transcriptional or targeted analysis of expression of individual genes utilizing, e.g., whole transcriptome sequencing, targeted transcriptome sequencing or other transcriptomic analysis methods. The sample may not be used to re-identify participants in accordance with an agreement with Roche Group.

Chapter 3: Screening Phase

3.1 Eligibility Confirmation

The clinical center will receive notification regarding DR eligibility and laboratory values for eligibility. If the participant is not eligible, they will be notified, and the participant will be exited from the study. However, the obtained baseline data and samples may still be analyzed and contribute to the additional objectives of the study. If the participant is eligible, the randomization visit may be scheduled provided PCP or endocrinologist approval is obtained as outlined below. In both cases, a copy of the laboratory values will be provided to the participant. If a participant is eligible but had a screening eGFR value between 45 to <60 mL/min/1.73 m^2, the site will need to confirm there is sufficient inventory of reduced dose Study Drug prior to scheduling the randomization visit.

If eligibility cannot be assessed due to a missing central laboratory value a participant may be asked to return for a repeat of select labs. Likewise, if images for eligibility are not of sufficient quality for reading center grading, sites may be asked to repeat the procedure(s) for eligibility determination.

3.2 PCP Approval

Before being scheduled for randomization, the participant must also obtain written confirmation from the participant's PCP that there are no contraindications to participate in the trial. The screening visit lab results will be provided and written confirmation from the PCP must be obtained. The contact information for the participant's PCP also must be provided to the Coordinating Center so that follow-up laboratory values can be provided to the PCP during the study.

If a potential participant does not have a PCP, then the site will help provide a local PCPs contact information for evaluation and approval to enroll. Visits to the PCP are not part of this study. Prior to beginning enrollment, each site will identify a partner PCP who is willing to evaluate patients without their own PCP who are potentially eligible for this study and monitor follow-up lab results.

Chapter 4: Randomization Visit

4.1 Randomization Visit Procedures

The randomization visit must be completed within 60 days of the Screening visit. The visit should not take place until Reading Center and Central Laboratory eligibility confirmation has been received and PCP or endocrinologist approval has been obtained. If a participant is eligible but had a screening eGFR value between 45 to <60 mL/min/1.73 m^2, the site will need to confirm there is sufficient inventory of reduced dose Study Drug prior to scheduling the randomization visit. The following procedures are needed to re-confirm eligibility on the study eye(s) and/or to serve as baseline measures for the study:

2. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester (including protocol refraction) in each eye. *(on day of randomization)*
3. Ocular examination on each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy. *(on day of randomization)*
4. Measurement of blood pressure. *(on day of randomization)*
5. Urine pregnancy test for females who are premenopausal and are not surgically sterile (*prior to randomization <u>if > 30 days from screening</u>*)
    - *Pregnancy test is conducted at the site and must be negative before proceeding to randomization. The central lab is NOT used if pregnancy test is indicated during the randomization visit.*
6. Additional ancillary testing procedures on each eye (only obtained by a subset of sites) include:
    - OCT angiography
    - Humphrey visual field testing using 30-2 and 60-4 test patterns
    - Contrast sensitivity

4.2 Randomization of Eligible Study Participants

1. Prior to randomization, the study participant's understanding of the trial, willingness to accept the assigned treatment group, and commitment to the follow-up schedule should be reconfirmed.
2. The initial 3-month supply of medication (fenofibrate or placebo) will be provided on the day of randomization. The fenofibrate and placebo pills will be provided in masked bottles by the Coordinating Center, or designee, to the clinical sites for distribution to the study participants. A study participant should not be randomized without both types of medication available in inventory.
3. Randomization is completed on the DRCR.net website.
    - Study participants will be randomly assigned (stratified by site and whether a participant has one or two study eyes) with equal probability to one of the treatment groups:
        - Fenofibrate (one pill once a day)

- Placebo (one pill once a day)

The starting study drug dose of either 160 mg or 54 mg is based on the participant's eGFR value at screening as discussed in the starting dose schedule in section 6.1.7.1.

Each group will be asked to start the daily supplementation of one pill once a day (fenofibrate or placebo), with their first dose (one pill) being taken while at the clinical site on the day of randomization.

4.3 CGM Procedures

A masked sensor (CGM data not displayed) will be applied according to the manufacturer's instructions and continuously worn by participants for 10 days, unless it gets dislodged. Participants currently using a CGM device for real-time glucose management may continue to do so with the understanding that the study-provided device will be worn separately.

The participant will be instructed to remove the masked sensor and mail it to the Coordinating Center at the end of the 10 days, using a pre-addressed, pre-paid envelope.

This will be repeated at each 6-month and annual visit, unless an adverse event precludes CGM insertion or the participant refuses. CGM readings will be made available for participants to share with their health care provider at the end of the participant's participation in the study.

If the study-provided CGM is not approved for use in the participant's country (e.g. Canada), the CGM component is not required for study participation.

Chapter 5: Randomized Trial Procedures

5.1 Home Procedures

All participants will be instructed verbally regarding medication administration (one pill once a day) and be provided with a Study Medication Use instruction sheet to take home. All participants are randomized to either the Fenofibrate or placebo group. The masked Study Drug pill should be administered with food (recommended with the morning meal). Since bile acid binding resins may bind other drugs given concurrently, patients should take the Study Drug pill at least 1 hour before or 4 to 6 hours after a bile acid binding resin to avoid impeding its absorption.

The initial 3-month supply will be provided by the site on the day of randomization. Thereafter, study drug supply will be provided at each subsequent follow-up visit. Details regarding study drug accountability are included in the coordinator manual. See Chapter 6 for additional details regarding study drug, including the starting dose and dose adjustment protocol during follow-up.

An identification card will be provided to participants informing other healthcare professionals that they are in a fenofibrate trial.

5.2 Text Message Reminders

For participants in the United States who agree to receive text message reminders, periodic messages will be sent by the Coordinating Center with a reminder to comply with the study drug.

5.3 Study Visits and Phone Contacts

The schedule of protocol-specified assessment visits and phone calls is detailed below. Ocular study procedures also will be performed prior to initiating intraocular medication, PRP or vitrectomy for the first time on a study eye (see additional details in section 5.6).

5.3.1 Study Visits

Study visits will occur at:

Visit	Target Day/Week	Target Window (around Target Day/Week)	Allowable Window (around Target Day/Week)
3 Month	13 Weeks	±2 weeks	±4 weeks
6 Month	26 Weeks	±4 weeks	±8 weeks
12 Month	52 Weeks	±8 weeks	±12 weeks
18 Month	78 Weeks	±4 weeks	±8 weeks
24 Month	104 Weeks	±8 weeks	±12 weeks
30 Month	130 Weeks	±4 weeks	±8 weeks
36 Month	156 Weeks	±8 weeks	±12 weeks
42 Month	182 Weeks	±4 weeks	±8 weeks
48 Month*	208 Weeks	±8 weeks	-12 weeks/+16 weeks
60 Month**	260 Weeks	±8 weeks	-12 weeks/+16 weeks
72 Month**	313 Weeks	±8 weeks	-12 weeks/+16 weeks

** The 48-month visit will be the final visit for participants who have met the primary outcome at or prior to 4 years, for the last enrolled participant,* ***or*** *for participants who only consent to stay enrolled in the trial through 48 months.*
*** The end of the study will occur approximately 4 years after the last participant is enrolled. For participants in follow-up beyond 48 months, a final visit should be scheduled around the same projected timepoint if more than 6 months have passed since the participant's prior 48 or 60-month visit (irrespective of the target and allowable windows for the next scheduled visit).*

The goal will be for all participants to complete all scheduled visits. However, participants who (because of unforeseen circumstances) are unable or unwilling to return for all follow-up visits will be permitted to return for key visits only as an alternative to withdrawal from the study. When a participant is placed into this status, missed visits will not be recorded as protocol deviations (since they would not be recorded as protocol deviations if the participant was dropped from the study).

Additional office visits may occur as needed.

5.3.2 Procedures at Study Visits

3-Month Safety Visit

At the 3-month safety visit, only safety and compliance assessments will be conducted including:

1. Measurement of blood pressure.
2. Blood draw (fasting *not* required) for:
   - LFTs, serum creatinine (used for eGFR), CK, and CBC
   - Biomarker serum and/or RNA sample (only for sites/participants who participate)
     - *The central laboratory must be used – see study procedure manual for collection procedure.*
3. Urine sample for:
   - Creatinine and albumin Pregnancy test for all females who are premenopausal and are not surgically sterile
     - *The central laboratory must be used – see study procedure manual for collection procedure.*
4. Safety assessment of symptoms of myopathy/rhabdomyolysis or cholelithiasis
5. Compliance assessment

6-Month Interval Visits

The following procedures will be performed at each *6-month interval* study visit.

1. E-ETDRS visual acuity testing in each eye (best corrected).
   - A protocol refraction in both eyes is required at all study visits.
2. Ocular exam on both eyes, including slit lamp examination, lens assessment, measurement of intraocular pressure and dilated ophthalmoscopy

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

3. Spectral-domain OCT in each eye:
   - Includes additional optic nerve head scan to obtain RNFL thickness data.
   - *The same OCT machine type as Randomization should be used.*
4. Measurement of blood pressure (first 6-month visit only or if fenofibrate is discontinued at that visit).
5. Blood draw (first 6-month visit only or if fenofibrate is discontinued at that visit, fasting *not* required) for:
   - HbA1c, LFTs, serum creatinine (used for eGFR), CK, and CBC
   - Biomarker serum and/or RNA sample (only for sites/participants who participate)
     - *The central laboratory must be used – see study procedure manual for collection procedure.*
6. Urine sample for:
   - Creatinine and albumin (first 6-month visit only or if fenofibrate is discontinued at that visit)
   - Pregnancy test for all females who are premenopausal and are not surgically sterile
     - *The central laboratory must be used – see study procedure manual for collection procedure.*
7. Safety assessment of symptoms of myopathy, rhabdomyolysis or cholelithiasis
8. Compliance assessment
9. CGM insertion (refer to CGM procedures in section 4.3)
10. Additional ancillary testing procedures (obtained only by a subset of sites) are performed on both eyes at randomization and the 42-month visit, but on the study eye(s) only during interim visits, including:
    - Humphrey visual field testing using 30-2 test pattern
    - OCT angiography

    *Note: Visual field 30-2 and OCTA are performed on the **study** eye(s) at randomization and every subsequent 6-month interval visit (6, 18, 30, 42-months); however, these tests are also required for the **non-study** eye at the randomization and 42-month visits.*

Year 1-4 Annual Visits

The following procedures will be performed at the year 1 through 4 *annual* study visits. Ocular procedures are performed on both eyes.

1. E-ETDRS visual acuity testing in each eye (best corrected).
   - A protocol refraction in both eyes is required at all study visits.

2. Spectral-domain OCT in each eye:
    - Includes additional optic nerve head scan to obtain RNFL thickness data.
    - ➢ *The same OCT machine type as Randomization should be used.*
3. Ocular exam on both eyes, including slit lamp examination, lens assessment, measurement of intraocular pressure and dilated ophthalmoscopy
    - Undilated exam of the iris and examination of the angle is at investigator discretion.
4. Digital fundus photographs on both eyes using the widest approach available (e.g. ultra-widefield imaging device, if available)
    - *Whenever possible, the same imaging system should be used throughout the duration of the study. However, if a site obtains a new ultra-widefield imaging device during the course of the study, the widest approach available should be used for all study visits going forward.*
5. Digital FA on both eyes using the widest approach available (e.g. ultra-widefield imaging device, if available)
    - ➢ *Whenever possible, the same imaging system should be used throughout the duration of the study. However, if a site obtains a new ultra-widefield imaging device during the course of the study, the widest approach available should be used for all study visits going forward.*
    - ➢ *If only **one eye** was eligible as a study eye at randomization, the <u>study eye</u> will be considered the transit (rapid series) eye.*
    - ➢ *If **both eyes** were eligible at randomization, the <u>right eye</u> will be considered the transit (rapid series) eye.*
6. Physical examination to include:
    - Weight
    - Blood pressure
7. Blood draw for:
    - HbA1c, LFTs, serum creatinine (used for eGFR), CK, and CBC at all visits, as well as lipid panels at the 48-month visit
    - Biomarker serum and/or RNA sample (only for sites/participants who participate)
        - ➢ *The central laboratory must be used – see study procedure manual for collection procedure.*
        - ➢ ***Note: must be <u>fasting</u> at 48-month visit only.***
8. Urine sample for:
    - Creatinine and albumin
    - Pregnancy test for all females who are premenopausal and are not surgically sterile

- *The central laboratory must be used – see study procedure manual for collection procedure.*

9. Safety assessment of symptoms of myopathy, rhabdomyolysis or cholelithiasis
10. Compliance assessment
11. CGM insertion (refer to CGM procedures in section 4.3)
12. Additional ancillary testing procedures (only obtained by a subset of sites) are performed on both eyes at randomization and the 48-month visit, and on the study eye(s) only at the 12, 24, and 36-month visits, including:
    - Humphrey visual field testing using 60-4 test pattern
    - Contrast sensitivity

    *Note: Visual field 60-4 and contrast sensitivity are performed on the **study** eye(s) at randomization and <u>every</u> subsequent annual visit (12, 24, 36, 48-months); however, these tests are also required for the **non-study** eye at the baseline and <u>48-month</u> visits.*

<u>Years 5 & 6 Annual Visits</u>

The following procedures will be performed at year 5 and 6 study visits for participants who meet criteria for additional follow-up (see Section 5.3). Ocular procedures are performed on both eyes.

1. E-ETDRS visual acuity testing in each eye (best corrected).
    - A protocol refraction in both eyes is required at all study visits.
2. Spectral-domain OCT in each eye:
    - Includes additional optic nerve head scan to obtain RNFL thickness data.
    - *The same OCT machine type as Randomization should be used.*
3. Ocular exam on both eyes, including slit lamp examination, lens assessment, measurement of intraocular pressure and dilated ophthalmoscopy
    - Undilated exam of the iris and examination of the angle is at investigator discretion.
4. Digital fundus photographs on both eyes using the widest approach available (e.g. ultra-widefield imaging device, if available)
    - *Whenever possible, the same imaging system should be used throughout the duration of the study. However, if a site obtains a new ultra-widefield imaging device during the course of the study, the widest approach available should be used for all study visits going forward.*
5. Digital FA on both eyes using the widest approach available (e.g. ultra-widefield imaging device, if available)
    - *Whenever possible, the same imaging system should be used throughout the duration of the study. However, if a site obtains a new ultra-widefield imaging device during the course of the study, the widest approach available should be used for all study visits going forward.*

- *If only **one eye** was eligible as a study eye at randomization, the study eye will be considered the transit (rapid series) eye.*
- *If **both eyes** were eligible at randomization, the right eye will be considered the transit (rapid series) eye.*

6. Physical examination to include:
   - Weight
   - Blood pressure
7. Blood draw for:
   - HbA1c, LFTs, serum creatinine (used for eGFR), CK, and CBC at all visits, as well as lipid panels at the 48-month visit
   - Biomarker serum and/or RNA sample (only for sites/participants who participate)
     - *The central laboratory must be used – see study procedure manual for collection procedure.*
     - ***Note: must be fasting***
8. Urine sample for:
   - Creatinine and albumin
   - Pregnancy test for all females who are premenopausal and are not surgically sterile
     - *The central laboratory must be used – see study procedure manual for collection procedure.*
9. Safety assessment of symptoms of myopathy, rhabdomyolysis or cholelithiasis
10. Compliance assessment
11. CGM insertion (refer to CGM procedures in section 4.3)
12. Additional ancillary testing procedures on each eye (only obtained by a subset of sites) include:
    - OCT angiography
    - Humphrey visual field testing using 30-2 and 60-4 test patterns
    - Contrast sensitivity

All of the testing procedures do not need to be performed on the same day, provided that they are completed within the time window of a visit and prior to initiating any treatment. A small snack will be available for the participant after blood draws are performed, although participants are only required to be fasting for the screening and 48, 60 and 72-month visits.

5.3.3 Compliance Assessment

At each visit (3-month visit, 6-month visits, annual visits), the participant will receive a new supply of medication. The participant will be instructed to bring their remaining pills to the

clinic for compliance assessment. If a visit is missed, the participant may be sent a limited supply via mail and asked to return all remaining pills at their next visit. Additional pills may not be provided to a participant if more than 16 months have lapsed since their last visit with a safety assessment. Site personnel will count the remaining pills for each returned bottle and enter the number on an eCRF, which will calculate the compliance level.

5.3.4 Communication with PCP

When laboratory results are obtained at a follow-up visit, they will be sent to the PCP or endocrinologist. If any of the values necessitate further action according to the Dose Titration Schedule in section 6.1.7 this will be communicated to the PCP by the site.

5.3.5 Phone Contacts

A phone contact will be completed by certified site personnel (investigator or coordinator) at the following times:

Phone Call	Target Day/Week	Target Window (around Target Day/Week)	Allowable Window (around Target Day/Week)
9 Month	39 Weeks	±2 weeks	-4 weeks/+8 weeks
15 Month	65 Weeks	±2 weeks	-4 weeks/+8 weeks
21 Month	91 Weeks	±2 weeks	-4 weeks/+8 weeks
27 Month	117 Weeks	±2 weeks	-4 weeks/+8 weeks
33 Month	143 Weeks	±2 weeks	-4 weeks/+8 weeks
39 Month	169 Weeks	±2 weeks	-4 weeks/+8 weeks
45 Month	195 Weeks	±2 weeks	-4 weeks/+8 weeks
51 Month	221 Weeks	±2 weeks	-4 weeks/+8 weeks
54 Month*	234 Weeks	±2 weeks	-4 weeks/+8 weeks
57 Month	247 Weeks	±2 weeks	-4 weeks/+8 weeks
63 Month	273 Weeks	±2 weeks	-4 weeks/+8 weeks
66 Month*	286 Weeks	±2 weeks	-4 weeks/+8 weeks
69 Month	299 Weeks	±2 weeks	-4 weeks/+8 weeks

*Phone calls are performed every 3 months following the year 4 and 5 visits for participants still in follow-up, since in-person visits only occur annually

The purpose of the phone contact will be to:

- Emphasize compliance with daily medication and answer any questions
- Assess symptoms of myopathy/rhabdomyolysis or cholelithiasis

Additional phone contacts may be performed as needed. If the participant is in for an unscheduled visit during the call window, the call procedures can be completed at that time.

5.4 Early Termination Visit

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

5.5 Unscheduled Visits

Additional visits may occur as required for usual care of the study participant. Testing procedures at unscheduled visits are at investigator discretion, provided DR or DME treatment is not planned (see section 5.6 below).

5.6 Study Eye Treatment Initiation Visit

Prior to the first time administration of intraocular treatment for DR or DME in the study eye(s) (e.g., anti-VEGF or corticosteroid intraocular injection, PRP, focal/grid laser, or vitrectomy), participants will be asked to complete the ocular study procedures performed at an annual visit plus completion of all ancillary procedures performed at the study site (visual field, OCTA, and contract sensitivity) *only in the study eye(s) receiving treatment*. Participants will be asked to complete all visit procedures in the study eye(s) receiving treatment regardless of whether the treatment is administered at an annual, non-annual (e.g., 6-month), or unscheduled visit.

If a participant has only one study eye, the ocular procedures do not need to be conducted on the non-study eye prior to initiation of treatment in the study eye. If a participant has two study eyes but needs treatment in only one of the eyes, the ocular procedures only need to be performed on the eye receiving treatment.

Usual care vision (e.g. Snellen charts) will be acceptable if the eye is already dilated when treatment is planned.

Participants will be asked to complete at minimum visual acuity, fundus photos, FA, and OCT to confirm the primary outcome has been met, followed by the ancillary components (visual field, OCTA, and contrast sensitivity) prior to treatment initiation.

5.6.1 Study Eye Treatment for CI-DME

Treatment for CI-DME must not be given in the study eye(s) unless the following criteria have been met:

- CI-DME on clinical exam with ≥10% increase in central subfield thickness from baseline and either:
  1) at least 10-letter decrease in visual acuity presumed to be from DME at a single visit
  or
  2) 5 to 9-letter decrease in visual acuity presumed to be from DME at 2 consecutive visits at least 21 days apart.

The investigator is responsible for determining whether the scan is of sufficient quality to obtain an accurate central subfield thickness for determination of the outcome. If the OCT has artifacts, boundary line, or centration issues that may invalidate the automatic measurement, the OCT should be sent to the central reading center for manual grading prior to initiating treatment.

The protocol chair or designee must be contacted for approval to initiate treatment prior to meeting the above criteria.

Otherwise, once the above criteria have been met in the study eye(s), treatment for DME in that eye is at investigator discretion as part of usual care. If anti-VEGF is indicated for DME treatment, ranibizumab should be given. If the investigator believes that an alternative anti-VEGF agent is medically indicated, then that anti-VEGF may be given at investigator discretion.

Regardless of treatment, fenofibrate will still be continued through completion of the 4-year (48 month) visit, unless the laboratory results or PCP indicate that fenofibrate should be stopped as described further in Section 6.

5.6.2 Study Eye Treatment for PDR

Treatment for NPDR in the absence of CI-DME as defined above must not be given in a study eye without prior protocol chair approval.

Treatment for PDR must not be given in a study eye until at least one of the following criteria has been met:

1. Definite neovascularization of the angle or neovascular glaucoma is present.
2. The eye has PDR with high-risk characteristics, defined as:
   - NVD greater than Standard photograph 10A (1/4 to 1/3-disc area), or
   - Any NVD with pre-retinal or vitreous hemorrhage, or
   - NVE greater than ½ disc area with pre-retinal or vitreous hemorrhage
3. The eye has vitreous hemorrhage requiring treatment that is presumed to be from PDR (either NV identified on FA or unable to assess NV due to density of the hemorrhage but there is no other attributable cause).
4. In the absence of the criteria above, the Reading Center has confirmed NV is present and protocol chair approval has been received to initiate treatment prior to high-risk characteristics being present.

Once one or more of the above criteria have been met, treatment for PDR in a study eye is at investigator discretion as part of usual care. If anti-VEGF is indicated for PDR treatment, ranibizumab should be given. If the investigator believes that an alternative anti-VEGF agent is medically indicated, then that anti-VEGF may be given at investigator discretion. Additionally, if ranibizumab is not approved by the regulatory authorities for treatment of DR without DME, another anti-VEGF agent may be given at investigator discretion.

Regardless of treatment, fenofibrate will still be continued through completion of the 4-year (48 month) visit, unless the laboratory results or PCP indicate that fenofibrate should be stopped as described further in section 6.

5.7 Participant Access to Study Agent at Study Closure

Any remaining study drug must be returned at the end of the study (i.e. the last required follow-up visit for each participant, depending on their course in the study). Participants who withdraw from the study will be asked to return the remaining drug for a final compliance assessment. Participants may have access to fenofibrate as part of their usual care and can discuss with their PCP.

Chapter 6: Study Drug

6.1 Study Drug and Accountability

6.1.1 Acquisition

Sharp Clinical Services, Inc. will obtain commercially available 160 mg and 54 mg fenofibrate pills and will make a placebo to match each dose of the drug (referred to collectively as Study Drug).

The Study Drug will be bottled and labeled by Sharp. Each bottle label will contain an identifying drug number. Both study participants and study personnel will be masked to the drug assignment, although it will be clear whether the participant is receiving the full dose (160 mg) or reduced dose (54 mg) Study Drug. The Study Drug will be shipped to a central pharmacy responsible for drug distribution to clinical sites according to Study Drug accountability procedures. If necessary, Study Drug may also be mailed directly to the participant from the central pharmacy.

6.1.2 Formulation, Appearance, Packaging, and Labeling

All study drug dispensed to the participants will be labeled and identified with the study name, drug name, lot number, expiration date, drug number, dose (full 160 mg or reduced 54 mg), daily dose directions (one pill once a day), directions for storage and use, and indication that it is an investigational drug. Placebo packaging will be identical in order to keep study personnel and participants masked. The type of medication (fenofibrate vs. placebo) will be tracked by drug number only, but the dose (full 160 mg or reduced 54 mg) is clearly marked on the bottle.

6.1.3 Product Storage and Stability

Study drug will be stored at the central pharmacy and each clinical site in a room temperature, limited access, secure area. Sites and participants will be instructed to follow manufacturer recommendations for drug storage.

6.1.4 Dispensing Study Drug

At each visit, participants who have not discontinued Study Drug use will be provided a sufficient number of bottles of Study Drug to last until the next visit (beyond the end of the window of the next visit). If a follow-up visit is missed, study drug may be mailed directly to the participant.

6.1.5 Study Drug Return and Compliance Assessment

At each follow-up visit or end of study, the participants will be asked to return the prior medication (including any unused pills) to the clinical site. The clinical site will check-in the Study Drug and perform a compliance assessment based on the number of pills remaining compared with the number expected, which will be calculated on the study website.

6.1.6 Dosing and Administration

Fenofibrate and placebo are taken orally, one pill once daily. The masked medication should be administered with the morning meal.

6.1.7 Starting Dose and Dose Titration Schedule

6.1.7.1 Starting Dose

Participants will start with an assigned dose of either 160 mg or 54 mg of the study drug. Guidelines for the starting dose (160 mg vs. 54 mg) are determined by the participant's estimated GFR during the screening visit as follows:

- If the participant's estimated GFR is ≥60 mL/min/1.73m^2, the participant will start with the 160 mg dose of study drug.
- If the participant's estimated GFR falls between 45 and <60 mL/min/1.73m^2, the participant will start with the reduced 54 mg dose.
- If the estimated GFR is below 45 mL/min/1.73m^2 at screening, the participant is ineligible for participation in the study.

6.1.7.2 Dose Titration Schedule

Guidelines for stopping or titrating a participant's treatment based on follow-up lab testing is as follows:

- If the participant's estimated GFR falls between 30 and <60 mL/min/1.73m^2 and there is no other attributable cause, the 160 mg dose will be down-titrated to the reduced 54 mg dose.
    - The clinical site will be notified, and participants will be informed by the clinical site to take one 160 mg pill every other day until the new dose (54 mg) is provided via mail. The original dose bottle will be returned at the next in-person visit.
- If the estimated GFR falls below 30 mL/min/1.73m^2 at any time, the clinical site will be notified and a confirmatory blood draw for repeat estimated GFR will be required within 4 weeks. In addition, the participant's PCP will be contacted by the clinical site to determine if there is another cause. If the confirmatory estimated GFR is below 30mL/min/1.73m^2 and there is no other attributable cause, the masked study drug will be permanently discontinued, regardless of fenofibrate or placebo assignment. The participant will remain in follow-up.
- If at any time the clinical site becomes aware of an elevated creatinine value from a usual care blood draw for which there is no other attributable cause as confirmed by the PCP, the participant will be asked to obtain a confirmatory blood draw using the central laboratory. Dose-titrations will be made accordingly using the eGFR central laboratory value.
- The masked study drug will also be permanently discontinued for the following after confirmation from the primary care provider that there is no other attributable cause and a

confirmatory blood draw within 4 weeks (provided there are not substantial symptoms necessitating immediate discontinuation):

- ALT > 3x the upper limit of normal (provided there is no other attributable cause)
- CK > 5x the upper limit of normal (provided there is no other attributable cause, such as recent high intensity exercise)
- >50% reduction in HDL from baseline (provided there is no other attributable cause)
- Presence of gallstones

- If a fibrate drug is clinically indicated (e.g. for lipid management) and prescribed by another health care provider, the Study Drug will be discontinued.

- All central laboratory values will be provided to the participant's PCP following each visit. If the PCP recommends a change to study treatment, the central panel of internists described below will be consulted first if possible.

6.1.8 Safety Evaluation

A central panel of internists will be consulted during the study as needed. A summary of how often the pre-specified safety protocol was used and how often the panel was consulted will be reported with the study results.

For all participants, post-visit updates including lab results will be sent to the participant's PCP. If at any time, the participant's PCP recommends a change to study treatment, the central panel will be consulted first if possible.

Ultimately, either the medical monitor, central panel or the participant's PCP can recommend lowering the dose or discontinuing the medication for safety.

6.1.9 Study Drug Accountability Procedures

The pharmacy and applicable Coordinating Center staff will follow detailed drug accountability procedures. Drug accountability procedures for sites will be detailed in the coordinator manual.

6.2 Unmasking Procedure

In general, all study personnel and participants will remain masked to the treatment assignment throughout the duration of the study. This applies even if the participant's dose is lowered or discontinued. In certain circumstances, a site may request that the participant and/or care provider be unmasked to the treatment group assignment during the study if medically necessary. In general, unmasking is only permitted in cases where site/participant knowledge of the treatment group assignment is necessary for the safety or care of the participant. CC approval is required, after consultation with the Protocol or Network Chair. The medical monitor also will be notified of the request.

6.3 Ranibizumab

0.3 mg Ranibizumab (Lucentis®) will be made available to sites for use when anti-VEGF is needed for an approved indication. Ranibizumab is made by Genentech, Inc. and is approved by the FDA and Health Canada for the treatment of age-related macular degeneration, macular edema secondary to retinal vein occlusion, and DME, and additionally for DR without DME by the FDA only. Study covered ranibizumab is only permitted for on-label indications and therefore is not considered an investigational product. The physical, chemical, and pharmaceutical properties and formulation of ranibizumab are provided in the Package Insert.

Chapter 7: Testing Procedures

7.1 Testing Procedures

The testing procedures are detailed in the DRCR Retina Network (or "DRCR.net") procedures manuals. An overview of the equipment and certification requirements for all testing are as follows.

Study Procedures	Equipment Required (if applicable)	Who can Perform
Ocular Exam (including slit lamp examination, lens assessment, and dilated ophthalmoscopy)	Any equipment is acceptable	Certified investigator
Physical examination (height and weight)	Any equipment is acceptable	Certified investigator or coordinator
Blood pressure	Proper size blood pressure cuff	Certified investigator or coordinator
Intraocular pressure IOP	A Goldmann tonometer should be used if available	Does not need to be performed by study certified personnel*
Visual Acuity – Refraction	EVA refraction chart and trial frames	Clinical site personnel certified for protocol refraction
Visual Acuity – ETDRS	EVA system (preferred) otherwise ETDRS charts if EVA not available	Clinical site personnel certified for ETDRS
Fundus Photography	Optos, if available, otherwise a digital system certified by the central Reading Center	Clinical site personnel certified for fundus photography
FA	Optos, if available, otherwise a digital system certified by the central Reading Center	Clinical site personnel certified for FA
SD-OCT including RNFL	Zeiss Cirrus or Heidelberg Spectralis	Clinical site personnel certified for specific SD-OCT machine type
Central Lab Sample collection and processing	Centrifuge required; Central lab collection kit provided by study	Does not need to be performed by study certified personnel*
Central Lab Sample shipment	Shipping materials provided by study; dry ice required for biomarker samples	IATA trained personnel*
Randomization Visit Urine Pregnancy Test (in-office)	Urine sample and HCG testing kit (testing in-office at Randomization if >30 days since screening visit)	Does not need to be performed by study certified personnel*

CGM insertion	N/A- provided by study	Clinical site personnel trained for CGM insertion
Ancillary components (select sites only):		
OCT angiography	Zeiss AngioPlex, Optovue AngioVue, or additional system approved by central Reading Center	Clinical site personnel certified for specific OCTA machine type
Visual Fields	Humphrey Field Analyzer (Zeiss HFA II/II-I and Zeiss HFA 3)	Clinical site personnel certified for visual field testing
Contrast Sensitivity	AST Manifold Contrast Vision Meter (Adaptive Sensory Technology, San Diego, CA, USA)	Does not need to be performed by study certified personnel*
** Personnel who will be performing procedure must be documented in the Study Staff Delegation Log. The Principal Investigator (PI) is responsible for verifying individual qualifications and training specific to performing each type of procedure and ultimate accuracy and integrity of such data*		

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Chapter 8: Unanticipated Problem and Adverse Event Reporting

8.1 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center all unanticipated problems meeting the criteria below. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized **(**including physical, psychological, economic, or social harm)

The Coordinating Center also will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur at the Coordinating Center or at another participating entity such as a pharmacy or laboratory.

8.2 Adverse Events

8.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the drug(s) under investigation.

Serious Adverse Event (SAE): Any untoward medical occurrence that:

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

8.2.2 Reportable Adverse Events

For this protocol, a reportable adverse event includes all events meeting the definition of an adverse event.

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

8.2.3 Relationship of Adverse Event to Study (Investigational) Drug or Study Procedure

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

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

Yes

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

No

Evidence exists that the adverse event has an etiology other than the study drug/intervention/procedure (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study drug/intervention/procedure.

8.2.4 Severity (Intensity) of Adverse Event

The severity (intensity) of an adverse event will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. A severity assessment is a clinical determination of the intensity of an event. Thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- MODERATE: Usually causes a low level of inconvenience, discomfort or concern to the participant and may interfere with daily activities but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.

SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study drug, and generally requires systemic drug therapy or other treatment.

8.2.5 Expectedness

For a serious adverse event that is considered possibly related to study drug, the Medical Monitor will classify the event as unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the package insert.

8.2.6 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality.

8.2.7 Outcome of Adverse Event

The outcome of each reportable adverse event will be classified by the investigator as follows:

- RECOVERED/RESOLVED: The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE: The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL: A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- NOT RECOVERED/NOT RESOLVED (ONGOING): An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
    - An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
    - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- ONGOING (MEDICALLY STABLE) – AE/SAE is ongoing, but medically stable. For example, a chronic condition where no further change is expected.

If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified as suspected, unexpected serious adverse reactions (SUSARs) will be followed until they are either resolved, or have no prospect of improvement or change, even after the participant has completed all applicable study visits/contacts. For all other adverse events, data collection will end at the time the participant completes the study. Note: participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

8.3 Timing of Event Reporting

Serious or unexpected adverse events must be reported to the Coordinating Center within 24 hours via completion of the online serious adverse event form.

Other reportable adverse events will be reported within 3 days of the investigator becoming aware of the event by completion of an electronic case report form.

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

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee.

The Coordinating Center will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after initial receipt of the information. In addition, the Coordinating Center will notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after JCHR determines that the information qualifies for reporting.

8.4 Independent Safety Oversight

A Data and Safety Monitoring Committee (DSMC) will advise the Coordinating Center regarding the protocol, template informed consent form, and protocol amendments and will provide independent monitoring of adverse events. Cumulative adverse event data are semi-annually tabulated for review by the DSMC. Following each DSMC data review, a summary will be provided to institutional review boards. A list of specific adverse events to be reported to the DSMC expeditiously, if applicable, will be compiled and included as part of the DSMC Monitoring Plan. The DSMC can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available.

8.5 Stopping Criteria

8.5.1 Participant Discontinuation of Study Drug

See section 6.1.7 for per-protocol dose adjustments. Additional rules for discontinuing study drug use are described below.

- The investigator or PCP believes it is unsafe for the participant to continue to receive the drug. This could be due to the development of a potential side effect of the drug, a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the drug that imposes on the participant's safety. Whenever possible, the central panel of internists should be consulted prior to discontinuation of the drug.
- The participant requests that the treatment be stopped
- Participant pregnancy

Even if the study drug is discontinued, the participant will be encouraged to remain in the study through the final study visit.

8.5.2 Criteria for Suspending or Stopping Overall Study

A formal plan for interim data monitoring for both futility and efficacy will be established in consultation with the Data and Safety Monitoring Committee. In addition, the DSMC may request suspension of study activities or termination of the study if deemed necessary at any time based on the totality of safety data available. Review of serious, unexpected, and related AEs by the Medical Monitor, DSMB, IRB, or the FDA or relevant local regulatory authorities may also result in suspension of further study agent administration. The FDA and study sponsor(s) retain the authority to suspend additional enrollment and study agent for the entire study, as applicable. The study may be discontinued by the Executive Committee (with approval of the DSMC) prior to the preplanned completion of follow-up for all study participants.

Chapter 9: Miscellaneous Considerations

9.1 Collection of Medical Conditions and Medications

Pre-Existing Condition: Any medical condition that is either present at screening, a chronic disease, or a prior condition that could impact the participant's health during the course of the study (e.g., prior myocardial infarction or stroke).

Medications: All medication for the treatment of chronic pre-existing conditions, medical conditions, and/or adverse events that the participant is currently taking at screening and during the course of the study should be recorded. Nutraceuticals and preventative treatment also should be recorded.

9.2 Prohibited Medications, Treatments, and Procedures

Alternative treatment for DR or DME in a study eye will not be permitted unless protocol criteria in section 5.6 are met or treatment is discussed with and approved by the Protocol Chair or Coordinating Center designee.

9.3 Precautionary Medications, Treatments, and Procedures

Participants will be cautioned regarding the use of warfarin (Coumadin), colchicine (Colcrys), and immunosuppressants that affect kidney function such as cyclosporine and tacrolimus. If any of these are considered, their prescribing health care provider should be made aware that the participant may be taking fenofibrate and be instructed to consider adjusting the dose as necessary.

Since bile acid binding resins may bind other drugs given concurrently, patients should take the Study Drug at least 1 hour before or 4 to 6 hours after a bile acid binding resin to avoid impeding its absorption.

If a fibrate drug is clinically indicated (e.g. for lipid management) and prescribed by another health care provider, the Study Drug will be discontinued but follow-up will continue until completion of the 4-year (48-month) visit.

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

9.4 Prophylactic Medications, Treatments, and Procedures

Not applicable.

9.5 Rescue Medications, Treatments, and Procedures

If criteria are met, alternative treatment for DR or DME in the study eye(s) is considered part of usual care.

9.6 Treatment in Non-study Eye

Treatment of DR or DME in a non-study eye is at investigator discretion. Study-provided ranibizumab may be used, based on availability, if the investigator believes that an anti-VEGF agent is medically indicated in a non-study eye.

9.7 Pregnancy Reporting

If pregnancy occurs, study intervention will be discontinued while continuing safety follow-up. The occurrence of pregnancy must be reported to the Coordinating Center within 7 days of notification. An electronic case report form must be completed for all confirmed pregnancies.

9.8 Participant Compensation

Participant compensation will be specified in the informed consent form.

9.9 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. For participants who withdraw, their data will be used up until the time of withdrawal.

9.10 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the study.

9.10.1 Contact Information Provided to the Coordinating Center

If approved by the overseeing IRB/ethics board, the Coordinating Center will be provided with contact information for each study participant. Permission to obtain such information will be included in the Informed Consent Form. The contact information will be maintained in a secure database and will be maintained separately from the study data.

When contact information is provided, phone contact from the Coordinating Center will be made with each study participant in the first month after enrollment. Additional phone contacts from the Coordinating Center will be made if necessary, to facilitate the scheduling of the study participant for follow-up visits. A participant-oriented newsletter and a study logo item may be sent once. For participants who agree to text message reminders, periodic messages will be sent by the Coordinating Center with a reminder to comply with the study medication schedule.

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

In addition, name and mailing address may be provided to the central pharmacy for study drug distribution if needed between visits.

Chapter 10: Statistical Considerations

10.1 Statistical and Analytical Plans

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

10.2 Statistical Hypotheses

A test of superiority will be used in evaluating the following hypotheses for the primary outcome:

Null Hypothesis (H_0): There is no difference in the hazard of DR worsening (composite outcome) between the fenofibrate and placebo groups over 6 years.

Alternative Hypothesis (H_a): There is a difference in the hazard of DR worsening (composite outcome) between the fenofibrate and placebo groups over 6 years.

Similar hypothesis tests of superiority will be conducted for other outcomes. The comparisons will be based on statistics appropriate to the outcome.

10.3 Sample Size

10.3.1 Outcome Projections

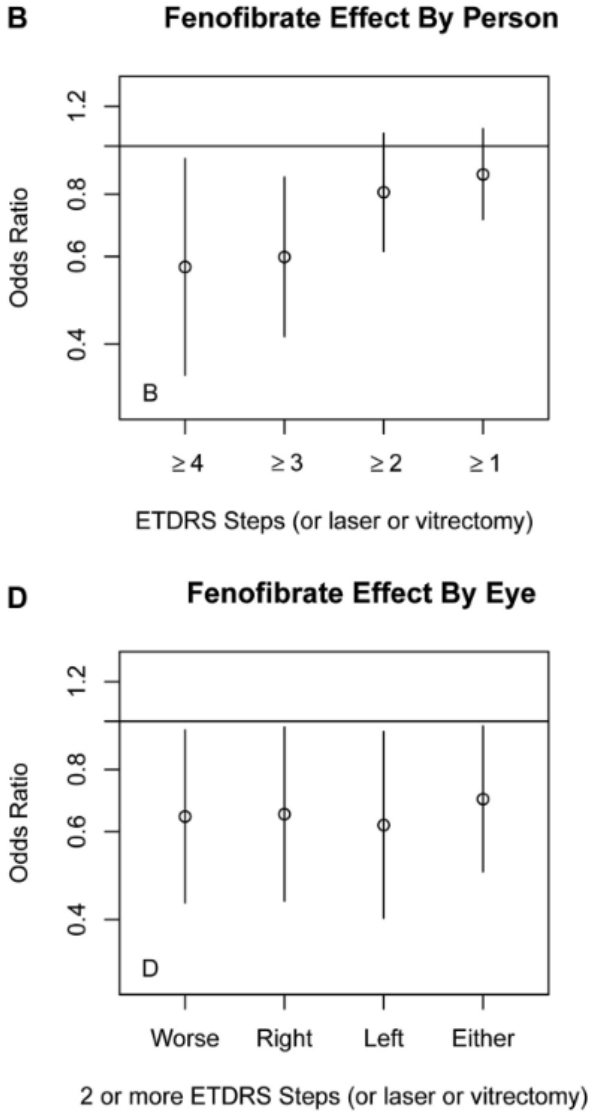
Progression of Diabetic Retinopathy

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial enrolled 10,251 participants with type 2 diabetes and randomized them to intensive glycemic control or standard therapy.[6] The 5518 participants with dyslipidemia were further randomized in a 2 × 2 factorial design to receive simvastatin in combination with either fenofibrate or placebo. The ACCORD Eye sub-study enrolled 3472 individuals of whom 1593 were enrolled in the Lipid study comparing fenofibrate with placebo, completed 4 years of follow-up, and provided data on DR worsening.[30] The rates of DR worsening (≥3-step increase on person scale or receipt of photocoagulation for diabetic retinopathy) by baseline person-level retinopathy over 4 years are displayed below. In addition, the figure shows the odds ratio of DR worsening associated with fenofibrate use at the patient level (panel B) and eye level (panel D).[30]

Table 1. Rates of diabetic retinopathy worsening over 4 years in ACCORD.

Cohort	Fenofibrate	Placebo	Relative Risk
All eyes	6% (49 of 806)	10% (77 of 787)	0.62
Baseline steps 2 – 9: Microaneurysms only in one eye (20/<20) to moderately severe NPDR in both eyes (47/47)	5% (20 of 399)	12% (50 of 402)	0.40
Baseline steps 5 – 6: Mild NPDR in both eyes (35/35) to moderate NPDR in one eye (43/<43)	7% (6 of 88)	13% (14 of 104)	0.51
Baseline steps 5 – 9: Mild NPDR in both eyes (35/35) to moderately severe NPDR in both eyes (47/47)	9% (12 of 135)	17% (24 of 144)	0.53
Baseline steps 7 – 9: Moderate NPDR in both eyes (43/43) to moderately severe NPDR in both eyes (47/47)	13% (6 of 47)	25% (10 of 40)	0.51

Figure 1. Odds ratio of diabetic retinopathy worsening at the patient (B) and eye (D) level in ACCORD.



The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study randomized 9795 participants with type 2 diabetes to fenofibrate versus placebo.[29] A subgroup of this cohort (N=1012) also underwent fundus photography to document worsening of DR. In the subgroup of participants with pre-existing DR (≥ level 20 in the worse eye) over 5 years, the rate of 2 or more step DR worsening in the eye that was more severe at baseline was 3.1% (3 participants) in the fenofibrate group compared with 14.6% (14 participants) in the placebo group (the denominators were not provided).

Protocol Amendment to Re-evaluate Sample Size (Protocol v6.0)

As of February 2023, the distribution of baseline retinopathy among enrolled study eyes suggested higher severity for the cohort in AF compared with ACCORD (Table 2) and FIELD (Table 3). For

example, 45% of the participants with baseline DR in FIELD had only minimal, non-proliferative DR (level 20) in the worse eye, which is below the eligibility requirement for AF (Table 3). In Protocol AF, all study eyes have NPDR of levels 35-47, and all non-study eyes have level 20 or more severe (no upper bound for non-study eyes). Therefore, because baseline retinopathy will likely be higher in AF than FIELD and ACCORD, it is reasonable to assume that DR progression rates will also be higher.

Hence, rates of DR worsening observed in the DRCR Retinal Network Protocol AA clinical trial were examined in conjunction with the baseline DR enrolled in Protocol AF. The Kaplan-Meier estimate of DR worsening, weighted to reflect the baseline distribution of DR severity in Protocol AF (as of February 2023), was 33% [95% confidence interval (CI): 26% to 42%] (Table 4). Based on these figures, an amended rate of 20% was used to recalculate the sample size originally proposed for this study. This amended rate is lower than the lower confidence limit of 26% based on Protocol AA and is a conservative estimate of the likely outcome rate in Protocol AF.

Table 2. Baseline diabetic retinopathy in ACCORD compared with Protocol AF

Baseline Diabetic Retinopathy (Person-level in ACCORD, person-level among study eyes only in AF)	**ACCORD (N = 817 Participants with Baseline DR)**		**Protocol AF (N = 133 Participants as of February 2023)**	
	N	**%**	**n**	**%**
Steps 2-4 Ma or mild DR one eye, no DR or Ma only other (20/<20 to 35/<35)	522	64%	na	na
Steps 5-6 mild - moderate NPDR (35/35 to 43/<43)	192	24%	93	70%
Steps 7-9 moderate- moderately severe NPDR (43/43 to 47/47)	87	11%	40	30%
Steps 10-17 Severe NPDR or PDR (53/<53 to 71+/71+)	16	2%	na	na

Table 3. Baseline diabetic retinopathy in FIELD compared with Protocol AF

Baseline Diabetic Retinopathy (ETDRS grading of worse eye in FIELD, worse eye among study eyes only in AF)	**FIELD (N = 208 Participants with Baseline DR)**		**Protocol AF (N = 133 Participants as of February 2023)**	
	N	**%**	**n**	**%**
Minimal, non-proliferative (level 20)	93	45%	na	na
Mild, non-proliferative (level 35)	73	35%	84	63%
Moderate, non-proliferative (level 43)	35	17%	36	27%
Moderately severe non-proliferative or worse (levels 47-99)	7	3%	13	10%

Table 4. Rates of diabetic retinopathy worsening over 4 years by baseline retinopathy subgroups in Protocol AA, and rates of worsening in AA weighted by the baseline retinopathy distribution in Protocol AF (as of February 2023)

Protocol AF (N = 185 study eyes as of February 2023)			Protocol AA 4-Year DR Worsening[b] by BL ETDRS			by BL UWF Masked		
Baseline Diabetic Retinopathy	**n**	**%[a]**	**EST**	**(LCL**	**UCL)**	**EST**	**LCL**	**UCL**
Mild NPDR (Level 35)	125	68%	31%	(24%	39%)	45%	(37%	54%)
Moderate NPDR (Level 43)	44	24%	37%	(27%	48%)	40%	(32%	49%)
Moderately Severe NPDR (Level 47)	16	9%	43%	(34%	54%)	26%	(17%	38%)
Weighted Sum			33%	(**26%**	42%)	42%	(34%	51%)

EST=estimated rate of DR worsening at 4-years; LCL=lower limit of 95% confidence interval (CI), UCL=upper limit of 95% CI.

[a] Percentage of DR levels in AF are weights for the weighted sum

[b] DR worsening of 2 or more steps on UWF-color images masked within the 7 standard ETDRS fields, or treatment for DR, irrespective of baseline level (including PRP, anti-VEGF, steroid, or vitrectomy.

10.3.2 Sample Size Estimates

The table below shows sample size estimates under varying scenarios for the composite outcome rate in the placebo group and the hazard ratio of fenofibrate versus placebo. Assumptions include 20% loss to follow up, a type 1 error rate of 0.05 (2-sided), 90% power, and a null hypothesis of no difference between groups. Sample size was calculated based on a log-rank test assuming an exponential distribution of outcome and loss to follow-up times with no adjustment for baseline covariates; inclusion of baseline covariates in the final analysis will likely increase power. Additionally, the calculations assume that each participant contributes only one eye to the analysis, however, many participants will contribute 2 eyes, which will increase the final power.

Table 5. Total sample size (number of participants) required for 90% power with 5% type 1 error.

Hazard Ratio	Placebo			
	25%	**20%**	**15%**	**10%**
0.40	342	434	586	890
0.50	536	**676**	910	1378
0.60	900	1136	1526	2306

For a 20% event rate in the placebo group and a hazard ratio of 0.50 (4-year event rate of 10.6% in the fenofibrate group), the required sample size is 676 participants (338 per group) if all participants were followed for only 4 years.

The sample size will be further reduced to 536 participants by extending follow-up time for a maximum of 6 years (with all participants followed for at least 4 years, details in the statistical analysis plan). The extended follow-up assumes a constant outcome event rate over 6 years

(cumulative rate of 28.4% in the placebo group and 15.4% in fenofibrate at 6 years) and loss to follow-up (28.4% at 6 years).

Participants enrolled before sample size adjustment (protocol v6.0) will be reconsented at 4 years for follow-up beyond 4 years. Therefore, the sample size of 536 participants is rounded up to 560 participants under the assumption that 10% of participants will not reconsent to follow-up beyond 4 years (Table 6).

Table 6. Reconsent Adjustment for Sample Size Amendment (Protocol v6.0)

No. of Participants Enrolled before Amendment[a]	No. of Participants for Reconsent Adjustment[b]
215 to 225	20
226 to 236	21
237 to 247	22
248 to 258	23
259 to 270	24
271 to 280	25

[a] There were 191 participants enrolled by June 2023 (time of amendment proposal). It is assumed 259 to 270 participants will have been enrolled when the protocol amendment is implemented.

[b] Adjustment = N*(1-dropout%)*(1/(reconsent%) - 1) where N = No. enrolled before amendment, dropout = 20% and reconsent = 90%.

The total planned sample size is **560 participants (280 participants per group, 1 or 2 study eyes per participant)**. Summary of the sample size assumptions:

- Primary outcome event rates: 20% in placebo group; 10.6% in fenofibrate group at 4 years (28.4% in placebo group; 15.4% in fenofibrate group at 6 years); Hazard ratio = 0.5
- Participants will continue to be followed for a maximum of 6 years until the last participant reaches 4 years, resulting in most participants having follow-up beyond 4 years.
- Loss to follow up rate: 20% at 4 years (28.4% at 6 years)
- Loss to reconsent for follow-up beyond 4 years: 10% of 4-year completers
- Power: 90%
- Type 1 error: 5%

10.4 Outcome Measures

10.4.1 Primary Efficacy Outcome

Worsening of DR through 6 years (time-to-event composite outcome) defined as the occurrence of any of the following in a study eye:

- 2 or more step worsening in ETDRS DR severity on fundus photographs.
- Development of NV within the 7-modified ETDRS fields on fluorescein angiography.
- Intraocular procedure undertaken to treat DR including PRP, intraocular anti-VEGF, corticosteroid, or vitrectomy.

10.4.2 Secondary Efficacy Outcomes

1. Intraocular procedure undertaken to treat DR or DME including PRP, intraocular anti-VEGF, corticosteroid, focal/grid laser or vitrectomy (time-to-event composite outcome)
2. Development of CI-DME (time-to-event composite outcome):
    a. Defined as i, ii, and iii or iv:
        i. At least a 10% increase in OCT central subfield thickness from baseline
        ii. OCT central subfield thickness greater than sex and machine-specific threshold values (Zeiss Cirrus: CST ≥ 290 μm in women or ≥ 305 μm in men; Heidelberg Spectralis: CST ≥ 305 μm in women or ≥ 320 μm in men)
        iii. Investigator determination that thickening cannot be attributed to any cause other than CI-DME
        iv. Intraocular DME treatment including focal/grid laser, intraocular anti-VEGF, intraocular corticosteroid, or vitrectomy
3. Development of CI-DME with vision loss (time-to-event composite outcome):*
    a. Defined as i, ii, iii, and iv or v (note that i, ii, iii, and v are identical to the criteria in the outcome above):
        i. An increase in OCT central subfield thickness of 10% or more from baseline
        ii. OCT central subfield thickness greater than sex and machine-specific threshold values (Zeiss Cirrus: CST ≥ 290 μm in women or ≥ 305 μm in men; Heidelberg Spectralis: CST ≥ 305 μm in women or ≥ 320 μm in men)

iii. Investigator determination that thickening cannot be attributed to any cause other than DME

iv. A decrease in visual acuity from baseline of 10 or more letters at a single visit or 5 to 9 letters at 2 consecutive visits at least 21 days apart with vision loss presumed to be from DME

v. Intraocular DME treatment including focal/grid laser, anti-VEGF injection, corticosteroid injection, or vitrectomy

4. A decrease in visual acuity from baseline of 10 or more letters at a single visit or a 5 to 9-letter decrease at 2 consecutive visits at least 21 days apart regardless of whether vision loss is presumed to be from DME or any other cause (time-to-event outcome)

* To control the type 1 error rate for multiple secondary outcomes, statistical comparison of this outcome will be conducted only if there is a significant treatment group difference in "Development of CI-DME" after adjustment for multiplicity. If a statistical comparison is made it will be evaluated at the same alpha level as "Development of CI-DME". Otherwise, an estimate of the treatment effect and 95% confidence interval will be presented without a P value and this outcome will be considered exploratory.

10.4.3 Exploratory Efficacy Outcomes

- Change in non-perfusion index on fluorescein angiography from baseline to 4 years
- Change in area of leakage on fluorescein angiography from baseline to 4 years
- Presence of predominantly peripheral lesions (PPL) on ultra-widefield imaging to 4 years

In addition, if new scales or variables for categorizing DR severity level are developed during the study, exploratory analyses will be performed to evaluate the effect of fenofibrate on DR progression using the new scales or variables.

10.5 Analysis Datasets and Sensitivity Analyses

- Intention-To-Treat (ITT) Analysis Cohort: all randomized participants irrespective of treatment received, analyzed according to treatment assignment.
- Safety Analysis Cohort: all randomized participants that received treatment (participant took at least one pill).
- Per-Protocol Analysis Cohort: participants who complete the last follow-up visit , achieve at least 75% compliance with the assigned study drug when required to be taken (prior to protocol-allowed discontinuation), and do not receive DR or DME treatment without meeting protocol-specified criteria.

The primary analysis will follow the ITT principle. It will include all randomized participants. The data from the ITT cohort will be analyzed according to the group to which the participants were assigned through randomization, regardless of treatment received.

A per-protocol analysis will be performed to provide additional information regarding the magnitude of the treatment effect. The per-protocol analysis will only be performed if more than 10% of randomized participants would be excluded by per-protocol criteria.

The ITT analysis is considered the primary analysis. If the results of the per-protocol and ITT analyses are inconsistent, the per-protocol analysis will be interpreted with caution. In this scenario, exploratory analyses will be performed to evaluate possible factors contributing to the differences.

If more than 10% of participants in the placebo group receive fenofibrate, then an additional safety analysis will be conducted in which participants will be analyzed according to treatment received rather than treatment assigned.

10.6 Analysis of the Primary Efficacy Outcome

The primary outcome is a time-to-event outcome over 6 years that will be evaluated using the ITT analysis cohort. Marginal Cox proportional hazards regression with robust variance estimation via the sandwich estimator will be used to compare treatment groups while controlling for the correlation between eyes of the same participant.[67,68] The treatment group comparison will be based on the hazard ratio, which will be presented alongside the corresponding 95% confidence interval and P value. Baseline eye-level DR severity will be included as a covariate because eyes with more advanced retinopathy at baseline are expected to be more likely to meet the primary outcome than eyes with less advanced retinopathy. Data from eyes that did not meet the outcome will be censored at the last completed visit (regardless of whether the participant is lost to follow up, withdraws from study, completes the last follow-up visit prior to 6 years, or dies).

All event and censoring times will be grouped according to the visit window in which they occur (all visit windows will be contiguous). For example, an event occurring in the 1-year analysis window will have the event time set to 12 months. To help interpret the hazard ratio, a Kaplan-Meier curve will be constructed and corresponding cumulative probabilities with 95% confidence intervals will be calculated.

The proportional hazards assumption will be assessed by visual inspection of Kaplan-Meier curves and using cumulative sums of martingale residuals.[69,70] If the proportional hazards assumption is violated, then an alternative approach, such as analysis of restricted mean survival time, may be undertaken. Sensitivity analyses (to be outlined in the statistical analysis plan) will explore the effect of anti-VEGF treatment for non-DR indications during follow-up on the randomized treatment effect.

The primary analysis will be conducted at the end of the study unless the interim analysis of the primary outcome results in overwhelming evidence of superiority for one of the treatment groups. Provided strong evidence of superiority is not demonstrated in the interim, the cumulative error spent will be .001 (interim stage) and .05 (final stage), which corresponds to statistical significance determined by 2-sided p-value thresholds of 0.001 (interim stage) and 0.0498 (final stage) using the cumulative error spending method for a two-stage sequential study design.

10.6.1 Interim Analysis

Interim analysis of the primary outcome will be conducted using all available data at the time approximately half of the expected number of events are observed. The counting of events and timing of the analysis will be described in the statistical analysis plan. If the null hypothesis of no difference in the hazards between groups is not rejected at the 0.001 significance level (2-sided p-value not <0.001) then the study will continue as planned and the primary analysis for the primary efficacy outcome will be conducted at the end of the study. Conversely, if the interim analysis results in overwhelming evidence of superiority for either the fenofibrate group or the placebo group (null hypothesis is rejected with 2-sided p-value <0.001) then the interim analysis will be considered the primary analysis of primary efficacy outcome, and participants may be unblinded and/or discontinue randomized treatment. Interim analysis conducted at 50% information time is estimated to have approximately 16% probability of stopping for efficacy under the alternative hypothesis (assuming true HR = 0.5, see statistical analysis plan for details). All participants will be followed for at least 4 years, irrespective of the interim analysis results. A formal interim analysis for futility will not be conducted.

10.7 Analysis of the Secondary Outcomes

Each of the secondary outcomes are time-to-event outcomes and will be analyzed in a similar manner as the primary efficacy outcome. Secondary outcomes will only be analyzed using the ITT analysis cohort at the end of the study unless the interim analysis of the primary outcome results in overwhelming evidence of superiority for one of the treatment groups. In that case, supplemental analysis for the secondary outcomes as described in the statistical analysis plan will also be conducted.

The table below shows which baseline variables will be included as covariates for adjustment in the secondary analyses.

Table 3. Secondary Outcomes and Adjustment Covariates

Outcome	Baseline Covariates
Intraocular procedure undertaken to treat DR or DME	• Eye-level ETDRS DR severity • OCT CST
Development of CI-DME	• Eye-level ETDRS DR severity • OCT CST
Development of CI-DME with vision loss	• Eye-level ETDRS DR severity • OCT CST • Visual acuity letter score
A decrease in visual acuity from baseline of 10 or more letters at a single visit or a 5 to 9-letter decrease at 2 consecutive visits at least 21 days apart	• Eye-level ETDRS DR severity • Visual acuity letter score

10.8 CGM Sub-Study and Ancillary Studies

Analyses for the CGM sub-study will be described in a separate statistical analysis plan. The primary objective is to evaluate the relationship between glycemic parameters (e.g., time-in-range) with DR progression.

Analysis of ancillary study data involving biomarker samples, OCT angiography, Humphrey visual fields, and contrast sensitivity also will be described in a separate statistical analysis plan.

10.9 Safety Analyses

All reportable adverse events in the safety analysis cohort will be tabulated by treatment group according to Medical Dictionary for Regulatory Activities (MedDRA) term and summarized over each MedDRA System Organ Class. In the unlikely event there is a delay in treatment initiation, any events occurring between randomization and treatment initiation will be included in reported event totals, but the number of such events will be specifically noted.

The number and percentage of participants having a systemic adverse event occurring at least once will be calculated for each reportable event. The following systemic adverse events will be tabulated (precise definitions of each outcome will be specified in the statistical analysis plan):

- Myopathy
- Rhabdomyolysis
- Change in renal function defined as any of the following:
    - eGFR reduced from ≥ 60 to < 60
    - eGFR reduced from ≥ 30 to < 30
    - Dialysis
    - Renal transplant
- Increased liver function tests (ALT or AST)
- Low HDL
- Cholelithiasis
- Muscle pain or weakness
- Easy bruising or bleeding
- Death
- Cardiovascular and cerebrovascular events according to the Antiplatelet Trialists' Collaboration:[71]
    - Nonfatal myocardial infarction
    - Nonfatal stroke (counted only if symptoms lasted at least 24 hours)

- Death attributed to cardiac, cerebral, hemorrhagic, embolic, other vascular (does not need to be ischemic in origin), or unknown cause
- At least one event (nonfatal myocardial infarction, nonfatal stroke, or death attributed to potential vascular or unknown cause)

- Hospitalization
- Serious systemic adverse event

The following also will be tabulated by treatment group without formal statistical comparison:

- Number of adverse events
- Number of serious adverse events
- Number of hospitalizations
- Number of adverse events thought by the investigator to be related to the study drug
- Percentage of participants who stopped the intervention in response to an adverse event

10.10 Intervention Adherence

The clinical site will perform a compliance assessment each time study drug is returned. Non-compliance will be calculated as the proportion of pills remaining out of the number expected to have been taken.

10.11 Protocol Adherence and Retention

Protocol deviations and visit completion rates (excluding deaths) will be tabulated for each treatment group.

10.12 Baseline Descriptive Statistics

Baseline characteristics will be tabulated by treatment group and summary statistics appropriate to the distribution will be reported.

10.13 Interim Monitoring

The Data and Safety Monitoring Committee will review tabulated safety and efficacy data at regular intervals and can recommend stopping the trial early at their discretion.

10.14 Subgroup Analyses

Subgroup analyses, i.e., assessments of effect modification, will be conducted for the primary outcome. These analyses will be considered exploratory. Interpretation of the analyses will depend on whether the primary analysis demonstrates a significant treatment group difference; in the absence of a significant difference, subgroup analyses will be interpreted with caution.

The general approach for subgroup analyses will be to add an interaction term for the subgroup factor by treatment into the primary analysis model. Within-subgroup hazard ratios for the

treatment effect with 95% confidence intervals (but not P values) will be estimated from the interaction model and presented as a forest plot.

The baseline factors to be evaluated in pre-planned exploratory subgroup analyses will be specified in the statistical analysis plan.

There are no data known to suggest that the treatment effect will vary by any factor. Sex and race/ethnicity will be included in the list of exploratory subgroup analyses as mandated by National Institutes of Health (NIH) guidelines.

Subgroup analyses will only be conducted if there are at least 20 eyes in each subgroup for each treatment group.

10.15 Multiple Testing

There is only one primary efficacy outcome. If the primary analysis demonstrates a significant treatment group difference, in the interim or final stage, then all 4 secondary efficacy outcomes will be tested accordingly. The Hochberg method will be used to provide strong control of alpha at 0.05 for secondary outcome analyses.[72]

If the primary analysis fails to show a significant difference, then outcomes will be described with summary statistics and between-group 95% confidence intervals without a P value. There will be no formal adjustment for multiplicity in exploratory or subgroup analyses. For subgroup analyses, the number of significant results expected by chance given the number of comparisons will be noted.

Methods for error control in statistical testing for the CGM and other ancillary studies will be outlined in separate statistical analysis plans.

10.16 Exploratory Analyses

Change in nonperfusion index and leakage on fluorescein angiography from baseline to 4 years are continuous outcomes that will be analyzed with a linear mixed model that contains the baseline level of the variable (nonperfusion or leakage) as a covariate and a random intercept for participant to control for correlations between eyes of the same participant. The treatment effect will be summarized with an adjusted mean difference, 95% confidence interval, and *P* value.

Presence of PPL at 4 years is a binary outcome that will be analyzed with mixed effects logistic regression. Baseline presence of PPL will be included as a covariate. The correlation between eyes of the same participant will be modeled with a random intercept term. The treatment effect will be summarized with an adjusted risk difference, 95% confidence interval, and *P* value.[73-75]

10.17 Additional Tabulations and Analyses

The following outcomes are considered exploratory. Summary statistics and between-group 95% confidence intervals for the treatment group effect will be presented without P values. Baseline person- or eye-level DR severity will be included as a covariate for analyses of person- or eye-level DR severity outcomes, respectively. In addition, person-level outcomes also will include whether a participant has one or two study eyes as an adjustment covariate. For outcomes involving visual acuity, OCT central subfield thickness, or OCT volume, the baseline level of the variable(s)

will be included as covariates. Baseline person- or eye-level DR severity will be included as appropriate and consistent with the primary and secondary outcomes described above.

For time-to-event outcomes, hazard ratios and confidence intervals will be obtained using the marginal Cox proportional hazards model. The marginal Cox proportional hazards model accounts for correlation between eyes of the same participant in analyses of eye-level time-to-event outcomes.[67,68]

For binary outcomes, risk differences and confidence intervals will be calculated via mixed effects logistic regression.[73] Participant will be included as a random intercept to account for correlation between eyes of the same participant in analyses of eye-level outcomes.

For continuous outcomes, mean differences and 95% confidence intervals will be calculated using mixed effects linear regression. Participant will be included as a random intercept to account for correlation between eyes of the same participant in analyses of eye-level outcomes.

For visual acuity, OCT central subfield thickness, and OCT retinal volume eye-level outcomes evaluated at annual visits, missing data will be imputed using Markov chain Monte Carlo multiple imputation with 100 imputations. The imputation model will include baseline eye-level DR severity, treatment group, and level of the outcome (e.g., visual acuity, OCT central subfield thickness, or OCT retinal volume) at 0, 6, 12, 18, 24, 30, 36, 42, and 48 months. All other analyses will used observed data only (complete case analysis).

10.17.1 Participant-Level Outcomes (Evaluated in All Participants)

- At any time through 6 years (time-to-event outcomes):
- DR outcomes:
    - Worsening of DR on fundus photographs (defined as a 3-or-more step worsening on the person-level scale if the participant has 2 study eyes, or a 2-or-more step worsening on the eye-level scale if the participant has 1 study eye or if the participant has 2 study eyes and one eye lacks gradable photos)
    - Development of neovascularization within the 7-modified ETDRS fields on fluorescein angiography in a study eye
    - Receipt of intraocular treatment for DR in a study eye
    - Any of the 3 outcomes above (worsening on fundus photographs, development of NV on fluorescein angiography, or intraocular treatment for DR)
    - Worsening of DR on fundus photographs, development of neovascularization within the 7-modified ETDRS fields on fluorescein angiography, vitreous hemorrhage, traction retinal detachment, or intraocular treatment for DR in a study eye

- DME outcomes:
    - Development of CI-DME in a study eye (as defined in the secondary outcome but without the treatment component)
    - Development of CI-DME with vision loss in a study eye (as defined in the secondary outcome but without the treatment component)
    - Development of CI-DME in a study eye (as defined in the secondary outcome)
    - Development of CI-DME with vision loss in a study eye (as defined in the secondary outcome)
    - Receipt of intraocular treatment for DME in a study eye (as defined in the secondary outcome)
- Composite DR/DME outcomes:
    - Worsening of DR on fundus photographs, development of neovascularization within the 7-modified ETDRS fields on fluorescein angiography, development of CI-DME, or intraocular treatment for DR or DME in a study eye
    - Worsening of DR on fundus photographs, development of neovascularization within the 7-modified ETDRS fields on fluorescein angiography, development of CI-DME with vision loss, or intraocular treatment for DR or DME in a study eye

10.17.2 Eye-Level Outcomes (Evaluated in All Study Eyes)

At any time through 6 years (time-to-event outcomes):

- DR outcomes:
    - Worsening of DR on fundus photographs (as defined in the primary outcome)
    - Development of neovascularization within the 7-modified ETDRS fields on fluorescein angiography
    - Worsening of DR on fundus photographs (as defined in the primary outcome) or development of neovascularization within the 7-modified ETDRS fields on fluorescein angiography
    - Receipt of intraocular treatment for DR
    - Worsening of DR on fundus photographs (as defined in the primary outcome), development of neovascularization within the 7-modified ETDRS fields on

fluorescein angiography, vitreous hemorrhage, traction retinal detachment, or intraocular treatment for DR in either eye

- DME outcomes:
    - Development of CI-DME (as defined in the secondary outcome but without the treatment component)
    - Development of CI-DME with vision loss (as defined in the secondary outcome but without the treatment component)
    - Receipt of intraocular treatment for DME
- Composite DR/DME outcomes:
    - Worsening of DR on fundus photographs (as defined in the primary outcome), development of neovascularization within the 7-modified ETDRS fields on fluorescein angiography, development of CI-DME, or intraocular treatment for DR or DME
    - Worsening of DR on fundus photographs (as defined in the primary outcome), development of neovascularization within the 7-modified ETDRS fields on fluorescein angiography, development of CI-DME with vision loss, or intraocular treatment for DR or DME

Evaluated (1) at annual visits and (2) either the last-completed study visit or time of first treatment with intraocular anti-VEGF, intraocular corticosteroid, PRP, or vitrectomy, whichever occurs first:

- Mean change in visual acuity from baseline
- Percentage with visual acuity loss of 5 or more letters from baseline
- Percentage with visual acuity loss of 10 or more letters from baseline
- Percentage with visual acuity loss of 15 or more letters from baseline
- Mean change in OCT central subfield thickness from baseline
- Percentage with an increase in OCT central subfield thickness of 10% or more from baseline
- Percentage with OCT central subfield thickness greater than machine-specific threshold
- Mean change in OCT volume from baseline

10.17.3 Economic Analysis

Depending on the results of the primary outcome, an economic analysis may be performed. The purpose of the economic analysis is to compare the treatment groups with respect to cost effectiveness. An incremental cost effectiveness ratio will be calculated. Data from the clinical trial on the number of clinic visits completed, number of diagnostic procedures performed (e.g., OCT, fundus photographs), and number of treatments given (e.g., fenofibrate, intraocular treatments such as intravitreal anti-VEGF) will be used to estimate an average cost per patient for each treatment arm. The Medicare Fee Schedule will be used to estimate medical costs.

10.18 Assessment of Confounding

Imbalances between groups in important covariates are not expected to be large enough to produce confounding; however, a sensitivity analysis will be conducted that mimics the primary analysis but includes covariate adjustment for baseline factors known to be associated with risk of DR progression: baseline HbA1c, mean arterial blood pressure, duration of diabetes, sex, and race/ethnicity. If there is an imbalance between treatment groups in additional covariates, they will be added to the sensitivity analysis. Imbalance by treatment group will not be judged using statistical testing; instead, imbalance will be judged by whether the imbalance is large enough to have a clinically important effect on the primary outcome.

10.19 Outliers

To ensure that statistical outliers do not have an undue impact on analyses of continuous outcomes, continuous outcomes will be truncated to ± 3 standard deviations. Truncation will occur after imputation, where applicable. If the assumptions of normality and homogeneity of variance are seriously violated in an analysis of a continuous outcome, then robust regression with M estimation may be used.

Chapter 11: Data Collection and Monitoring

11.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (eCRFs). When data are directly collected in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g., lab results that are transcribed from a printed report into the eCRF), the original source documentation must be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a participant must be recorded (e.g., office note, visit record, etc.).

Data from central vendors (laboratory, reading centers) will be provided directly to the Coordinating Center. As indicated in the informed consent form, the Coordinating Center will provide the lab results to the participant's PCP. The site will also have access to print the lab results from the study website. Reading center grading will not be made available to the site.

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.

11.2 Study Records Retention

Study documents should be retained for a minimum of 3 years following the NIH grant cycle for which the last visit was completed or 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, whichever is later. 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 JCHR, if applicable. It is the responsibility of JCHR to inform the investigator when these documents no longer need to be retained.

11.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) 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, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) 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). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 312. This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM 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. Elements of the RBM may 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
- Drug accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of records, comparison with source documents, observation and discussion of the conduct and progress of the study. The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by JCHR, and inspection by local and regulatory authorities.

11.4 Protocol Deviations

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

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

Chapter 12: Ethics/Protection of Human Participants

12.1 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.

12.2 Institutional Review Boards

The protocol, informed consent form(s), 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.

12.3 Informed Consent Process

12.3.1 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 family members and their personal physicians(s) 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.

For participants who enrolled in the trial prior to protocol v6.0, which extended follow-up from 4 to up to 6 years, an informed consent addendum will be presented to ask if the participant wishes to continue in the trial beyond 4 years. A verbal explanation of the procedures and expected timeline for the individual participant will be presented along with the written informed consent addendum since total expected duration of follow-up will depend on when the participant was enrolled in the trial.

12.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and JCHR and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of JCHR.

The study monitor, other authorized representatives of JCHR, representatives of the IRB, regulatory agencies or company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. 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 the reviewing IRB, institutional policies, or JCHR requirements. Separately from any research data, JCHR, will be provided with participant contact information to aid in study retention efforts. Name and mailing address will be provided to the central pharmacy for study drug distribution. Study participant's contact information will be securely stored and will be destroyed at the end of the study at both the JCHR and central pharmacy.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at JCHR. This will be stored separately from the participant's contact or identifying information. For research purposes, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by JCHR research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the JCHR.

To further protect the privacy of study participants, a Certificate of Confidentiality will be available from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

12.3.3 Future Use of Stored Data

After the study is completed, the de-identified, archived data will be made publicly available for use by other researchers including those outside of the study. In addition, OCT scans, fundus photographs, and fluorescein angiograms will be made publicly available. These images of the retina are considered identifiable information but are only identifiable if they can be matched to a database that already includes retinal images for identification purposes (directly identifiable

information will be removed). Permission to make data and retinal images publicly available will be included in the informed consent form.

In addition, serum samples will be stored indefinitely and the de-identified samples made available to collaborators as described above. Data generated from optional serum samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future biological discoveries.

For participants who consent, the optional RNA sample collected as part of this study will be provided to the Roche Group and they will store, maintain and use those samples for future research. They may also provide samples to other researchers and industry collaborators. The samples and information could be used for publications, other research, to help design future studies, and to help discover new ways for personalized treatments.

Chapter 13: References

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