DRCR Retina Network

A Randomized Clinical Trial Evaluating Combination Faricimab + PRP vs. Vitrectomy + Endolaser for Treatment of Proliferative Diabetic Retinopathy

Protocol Identifying Number: AP

IND Sponsor: Jaeb Center for Health Research

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Version Number: v1.2

20 JUN 2025

Signature Page

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VERSION HISTORY

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	Carrie Preston	Cynthia Stockdale	Not implemented	Initial
1.1	Carrie Preston	Cynthia Stockdale	20/NOV/2024	Clarifications to VMT eligibility criterion, which visits require OFA, and other miscellaneous inconsistencies.
1.2	Carrie Preston	Cynthia Stockdale	20/JUN/2025	Addition of ancillary procedure to collect vitrectomy videos, miscellaneous clarifications (site sign-off not required if trained on v1.1)

*Version in effect at study initiation

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AI	Artificial Intelligence
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
CC	Coordinating Center
CFR	Code of Federal Regulations
CRF	Case Report Form
CI	Confidence Interval
CST	Central Subfield Thickness
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
DSMC	Data Safety Monitoring Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
E-ETDRS	Electronic ETDRS
EVA	Electronic Visual Acuity
FA	Fluorescein Angiography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
IRB	Institutional Review Board
ITT	Intention-to-treat
IOP	Intraocular Pressure
JCHR	Jaeb Center for Health Research
NIH	National Institutes of Health
OCT	Optical Coherence Tomography
OFA	Objective Field Analyzer
PPV	Pars Plana Vitrectomy
PRP	Pan-Retinal Photocoagulation
RCT	Randomized Controlled Trial
RC	Reading Center
SAE	Serious Adverse Event
SD-OCT	Spectral Domain OCT
SUSAR	Suspected Unexpected Serious Adverse Reaction

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PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	A Randomized Clinical Trial Evaluating Faricimab + PRP vs. Vitrectomy + Endolaser for Treatment of PDR
Précis	This randomized trial will compare treatment strategies for proliferative diabetic retinopathy (PDR). Participants will receive either combination faricimab + PRP or vitrectomy + endolaser. The participants will be followed for 3 years. The study will evaluate long-term visual acuity as well as differences in number of injections, procedures, and complications during follow up (after completion of randomization treatment), and cost.
Investigational Drug	faricimab (Vabysmo, Genentech, Inc.)
Objectives	Primary: • To compare visual acuity at 3 years following initial randomized treatment of either faricimab + PRP or vitrectomy + endolaser. • To compare the number of post-randomization treatments for PDR (injections, PRP, vitrectomy) over 3 years of follow up in each group* Secondary: • To compare the number of visits over 3 years of follow-up in each group • To compare number of complications such as vitreous hemorrhage, recurrent NV, TRD and percent with thresholds of VA loss over 3 years of follow-up in each group • To compare the number of post-randomization in-office treatments (injections or PRP) for PDR over 3 years of follow-up in each group* Additional study objectives: • To share a standardized strategy for combination treatment for PDR and characterize outcomes when using this approach • To share a standardized vitrectomy approach for PDR and characterize outcomes when using this approach • To assess the presence and extent of vitreous adherence on OCT at baseline and over time and its effect on outcomes • Compare cost of treatment in each group over 3 years (economic analysis) • To assess if artificial intelligence (AI) models can be trained to classify specific features of retinal surgery from videos of vitrectomy and endolaser for treatment of PDR * Excludes the initial randomized treatment of anti-VEGF + PRP or vitrectomy + endolaser.
Study Design	Randomized, multi-center clinical trial
Number of Sites	~55
Endpoint	**Primary Efficacy Outcome:** • Change in visual acuity from baseline at 3 years (equivalence test)

PARTICIPANT AREA	DESCRIPTION

	• Number of post-randomization treatments for PDR (injections, laser, vitrectomy) over 3 years*
	
	Key Secondary Efficacy Outcomes:
	• Development of vitreous hemorrhage causing vision loss of at least 5 letters not attributable to another cause during follow-up over 3 years (time-to-event outcome)
	• Presence of active neovascularization on fundus photos and FA over 3 years
	• Presence of macula threatening tractional retinal detachment on fundus photos and FA over 3 years
	• Change in visual acuity from baseline over 3 years (area under the curve)
	• Change in visual acuity from baseline at 1 year
	• Change in visual acuity from baseline at 2 years
	• Number of visits over 3 years (unilateral participants only)
	• Number of in-office procedures for PDR (injections or PRP) following the end of randomized treatment over 3 years (superiority test)*
	• Number of post-randomization injections to treat PDR over 3 years*
	• Number of post-randomization PRP sessions to treat PDR over 3 years*
	• Number of post-randomization vitrectomies to treat PDR over 3 years*
	
	Economic Analysis:
	• Compare cost of treatment in each group over 3 years
	
	Exploratory Outcomes:
	• Cumulative proportion of eyes requiring vitrectomy after initial randomized treatment over 3 years (time-to-event outcome)
	• Development of recurrent neovascularization (i.e., NVD and/or NVE) over 3 years (time-to-event outcome)
	  o Development of recurrent NVD during follow-up over 3 years (time-to-event outcome)
	  o Development of recurrent NVE during follow-up over 3 years (time-to-event outcome)
	• Development of any tractional retinal detachment over 3 years (time-to-event outcome)
	  o Development of macula threatening traction retinal detachment over 3 years (time-to-event outcome)
	• Presence of vitreous hemorrhage on fundus photos and FA over 3 years
	• Percentage with visual acuity 20/20 or better, 20/40 or better, 20/70 or worse, 20/200 or worse at 3 years
	• Loss of 10 or more letters of visual acuity from baseline at 3 years
	• Loss of 15 or more letters of visual acuity from baseline at 3 years
	• Development of DME with vision loss over 3 years (time-to-event outcome)

PARTICIPANT AREA	DESCRIPTION
	• Number of procedures to treat DME over 3 years • Extent of retinal nonperfusion in retina that has not been treated with PRP on FA • Activity of NVE/NVD on FA/fundus photos • Area and density of PRP on fundus photos * Excludes the initial randomized treatment of faricimab + PRP or vitrectomy + endolaser
Population	**Key Inclusion Criteria:** *Individual:* • ≥ 18 years old • Diagnosis of diabetes mellitus (type 1 or type 2) *Study Eye:(A participant can have one or two study eyes if both eyes are eligible at screening.)* • Presence of PDR requiring treatment, defined as moderate PDR or worse on global grading of ultrawide field fundus photos or NV meeting criteria for moderate PDR or worse on global grading of ultrawide field FA, confirmed by a central reading center • Best corrected visual acuity ≥49 letters (20/100 Snellen equivalent or better) **Key Exclusion Criteria:** *Individual:* • Significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant. • Blood pressure > 160/100 (systolic above 160 or diastolic above 100). o If blood pressure is brought below 160/100 by anti-hypertensive treatment, individual can become eligible. • For women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next 3 years. o Women of childbearing potential will be required to have pregnancy testing or use an acceptable method of pregnancy prevention. Women who are potential study participants should be questioned about the potential for pregnancy at baseline and prior to each injection. Pregnancy test is required for all women of childbearing potential at baseline. Investigator judgment is used to determine when a pregnancy test is needed during follow up. *Study Eye: (A participant can have two study eyes.)* • Traction retinal detachment involving the macula • Significant vitreous hemorrhage that would preclude completion of a full PRP • Significant vitreomacular traction • Any prior vitrectomy • Any prior PRP (defined as ≥100 burns outside of the posterior pole)

PARTICIPANT AREA	DESCRIPTION

	• Treatment for DME within the prior 6 months
	• Intravitreal anti-VEGF for any indication, other than DME, within the prior year
	• CI-DME on clinical exam or on OCT
	  o Zeiss Cirrus central subfield: ≥290µm in females or ≥ 305µm in males
	  o Heidelberg Spectralis central subfield: ≥ 305µm in females or ≥320µm in males

Sample Size	426 eyes
Phase	Phase 3 Trial
Treatment Groups	Random assignment (1:1) to faricimab + PRP or vitrectomy + endolaser
Participant Duration	3 years of follow up for each randomized participant
Study Duration (planned)	Approximately 5.5 years from first enrollment until last participant visit
Protocol Overview/Synopsis	1. Informed consent will be obtained. 2. Study eligibility will be assessed, and baseline procedures will be completed. Baseline procedures include: Self-reported demographics, medical and ocular history, visual acuity, SD-OCT using Zeiss Cirrus or Heidelberg Spectralis on the study eye, ultra-widefield digital fundus photographs, ultra-widefield digital FA, ocular examination, , measurement of intraocular pressure, HbA1c testing, blood pressure measurement, and objective field analyzer (OFA; ancillary component at select sites). 3. A central reading center will confirm the fundus photos and FAs for eligibility. Eligible participants will return for a randomization visit within 3 weeks from enrollment and complete an eye exam and E-ETDRS test of best corrected visual acuity. Participants confirmed eligible will be randomized 1:1 to faricimab + PRP or vitrectomy + endolaser. If randomized to faricimab + PRP, the participant will receive their first faricimab injection and return for additional visit to complete the remaining faricimab injections and PRP. If randomized to vitrectomy + endolaser, the participant will have vitrectomy + endolaser within 4 weeks; one injection of faricimab may be given at any time prior to vitrectomy. 4. Participants will return for follow up visits according to the following schedule: Year 1: 16 (-2/+4) wks, 24(±4) wks, 36 (±4) wks, 52(±8) wks Year 2: 68 (±4) wks, 84 (±4) wks, 104 (±8) wks Year 3: 120 (±4) wks, 136 (±4) wks, 156 (±8) wks Follow-up visit procedures include: best corrected E-ETDRS visual acuity, SD-OCT, ocular exam, measurement of intraocular pressure, ultra-widefield digital fundus photographs, ultra-widefield digital FA, HbA1c testing, OFA (ancillary component at select sites), and blood pressure measurement. Surgical videos will also be collected at sites with video capabilities. 5. Additional visits may occur to assess for PDR retreatment, or DME treatment. Protocol criteria will be followed for treatment initiation and retreatment. Participants will be followed for 3 years.

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SCHEDULE OF STUDY VISITS AND PROCEDURES

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

Procedure	Screening Visit	Randomization	1 Month Post-Vitrectomy Visit	Non-Annual Visits*	Annual Visits
Visit Window		Within 3 weeks after screening	± 1 week from target date	-2/+4 weeks from target date for 16 week visit, ± 4 weeks from target date at all other visits	± 8 weeks from target date
Randomization		X			
Visual Acuity[a]	X	X		X	X
OCT	X			X	X
Eye Exam	X	X	X	X	X
UWF Fundus Photography*	X				X
UWF Fluorescein angiography*	X				X
Objective Field Analyzer (at select sites)		X			X
HbA1c	X				X
Pregnancy Test[c]	X				
Blood pressure	X				X
Vitreous/aqueous sampling[b]		X			

***** Photos and FA will be required at the 16-week visit. If the eye is not quiescent at the 16-week visits, photos only will be taken at each subsequent visit until quiescence is achieved (see section 4.1.6.)

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= if investigator has agreed to perform sample collection and participant consents to this ancillary component; participants will be given the option of providing vitreous sample only at time of vitrectomy, both vitreous and aqueous samples (vitreous at the time of vitrectomy, aqueous either at the time of vitrectomy or in clinic), or aqueous sample only in clinic.

c= for women of childbearing potential

Chapter 1: Background Information

1.1 Introduction

1.1.1 Disease Background

The age-adjusted incidence of diabetes mellitus in the United States has reportedly doubled in recent history.[1] Estimates suggest that by the year 2035, approximately 592 million individuals worldwide will be affected by this chronic disease.[2] The increasing global epidemic of diabetes implies an increase in rates of associated vascular complications from diabetes. At present at least 5 million people over the age of 40 in the United States are estimated to have diabetic retinopathy (DR) in the absence of diabetic macular edema (DME), and an additional 800,000 have DME, according to data from the Centers for Disease Control.[3] Despite advances in diagnosis and management of ocular disease in patients with diabetes, eye complications from diabetes mellitus continue to be a leading cause of vision loss and new onset blindness in working-age individuals throughout the United States.[4,5]

Worsening DR is characterized by the development of increasing areas of retinal vascular non-perfusion causing ischemia or infarction of retina tissue. The anatomic sequel of retinal vascular ischemia is retinal neovascularization (NV) or proliferative diabetic retinopathy (PDR), a major cause of preventable and potentially irreversible vision loss in patients with diabetes. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy showed a 25-year cumulative progression rate to PDR of 42% among participants with type 1 diabetes, which suggests that given long enough duration of diabetes, a substantial number of patients with type 1 and type 2 diabetes mellitus develop PDR.[6]

1.1.2 Current Treatments

Protocol S and CLARITY illustrated that either anti-VEGF injections or panretinal photocoagulation (PRP) are viable treatments for PDR. [7,8,9] The disadvantages of PRP alone are greater loss, on average, of visual fields, greater chance of DME development with visual acuity loss warranting anti-VEGF for DME, greater chance of vitreous hemorrhage through 2 years, and likely greater chance of vitrectomy for complications of PDR. The disadvantages of anti-VEGF alone are the greater number, on average, of procedures (mean 18 injections vs 3 injections for eyes without DME in Protocol S) and visits (mean 43 vs. 21 in Protocol S) over 5 years. In addition, there may be greater risks associated with non-compliance with follow-up using anti-VEGF therapy, since neovascularization often recurs with treatment cessation.[10] Eyes receiving ranibizumab in Protocol S needed on average, approximately 3 injections annually from years 2 through 5, after receiving an average of 7 injections in the first year, suggesting that treatment burden may decrease, but may not be completely ameliorated with time.[11] Studies suggest that anti-VEGF treatment does not substantially ameliorate underlying retinal nonperfusion. Thus, patients lost to follow-up who have received only anti-VEGF for their PDR may risk PDR worsening, potentially leading to severe, vision-threatening complications such as neovascular glaucoma or tractional retinal detachment (TRD) more frequently than with non-compliance of follow-up after completion of full PRP.[10]

1.1.3 Proposed Treatments

Anti-VEGF plus Pan Retinal Photocoagulation

Since Protocol S, many physicians now use a combination of anti-VEGF therapy + PRP for PDR, with PRP performed either at baseline or following a series of anti-VEGF injections. In the 2020 ASRS PAT survey, when asked how to manage a patient with high-risk PDR and no DME, the most common approach chosen was PRP + anti-VEGF (52% in US). In the 2021 PAT survey, for high-risk PDR with DME, nearly 70% in US and internationally treat with combination PRP + anti-VEGF.[12] The hoped for, but unproven, goal of this approach is to decrease the number of injections and visits compared with anti-VEGF alone, decrease the rate of DME development causing vision loss and warranting anti-VEGF for DME compared with PRP alone, and assuage some of the concerns regarding poor outcomes associated with poor compliance with follow-up in this cohort. Clinicians using this approach assume that visual acuity outcomes, visual field loss, development of DME with vision loss warranting anti-VEGF therapy, and rates of traction retinal detachment or subsequent vitrectomy will not be worse than those seen with either PRP or anti-VEGF treatment alone.

Additional Rationale for Faricimab

The angiopoietin/tyrosine kinase with immunoglobulin-like domains 2 (Tie2) and VEGF pathways are important signaling pathways involved in multiple retinal diseases. Activation of the Tie2 receptor, a transmembrane receptor tyrosine kinase, controls survival signaling, vascular maturation, and maintenance. Ang-1 is a critical maintenance factor that stabilizes blood vessels in healthy tissue. Ang-1 binds to Tie2 receptors on vascular endothelial cells, leading to Tie2 activation. Elevated Ang-2 levels cause displacement of Ang-1 on Tie2, inhibiting its activation, which modulates immune signaling and inflammation in the vasculature.[13-17]

During certain pathologic conditions like nAMD and DR, stress conditions can lead to a shift in the balance of proangiogenic and antiangiogenic factors. Among these factors are Ang-2 and VEGF-A. Together they work in a synergistic manner to disrupt vascular homeostasis and promote inflammation, vascular leakage, and neovascularization. Ang2 on its own can also promote release of cytokines (e.g., histamine, VEGF-A) and sensitizes blood vessels to these cytokines.[15,18-21] Upregulation of Ang-2 levels in the vitreous has been investigated in multiple pathologic conditions like nAMD, DR, proliferative DR, and retinal vein occlusion (RVO); Ang-2 levels were significantly elevated in all 4 retinal vascular diseases investigated compared with what was observed in the controls.[22]

Based on the novel mechanism of action of faricimab through selective neutralization of both VEGF and Ang-2 and based on the similarities in pathophysiology with other retinal diseases, it is hypothesized that faricimab may lead to better stabilization of the pathological ocular vasculature and improve visual and anatomical outcomes in diabetic retinopathy compared with anti-VEGF alone.

Pars Plana Vitrectomy with Pan Retina Photocoagulation

Another potential approach aimed at effectiveness and durability is vitrectomy for PDR. Vitrectomy allows full PRP to be given while also removing attached hyaloid, which can contribute to PDR worsening, development of TRD and other complications. The removal of vitreous would prevent scaffolding and TRD development with subsequent profound visual loss in diabetic populations. It is anticipated that over the long term, the absence of vitreous and the presence of a complete PRP in this manner would reduce the treatment burden for these patients, with fewer patients needing repeat treatments. There is also evidence that performing vitrectomy may increase intraocular oxygenation.[24,25] In Protocol S, 42% and 46% of eyes in the ranibizumab and PRP groups, respectively, had active NV on photographs at 2 years.[9] In eyes with more severe disease at baseline in Protocol AB that involved vitreous hemorrhage from PDR, only 2% of eyes in the vitrectomy with endolaser group had retinal neovascularization on clinical exam at 2 years, compared with 23% in the aflibercept group.[26] In addition, cataract rates were similar in both groups despite cataract being a known complication of vitreoretinal surgery. Modern techniques have reduced surgical times and complications, making prompt surgery a more viable approach.

1.1.4 Public Health Impact

There are few studies with 10 years of follow-up for PDR. One retrospective multicenter study following over 1000 eyes noted that that supplemental PRP was needed in nearly 90% of eyes, and the average number of PRP sessions over this period was 3.[27] Thirty percent of subjects needed pars plana vitrectomy (PPV) while 60% of subjects needed cataract surgery. These data support what most retina specialists intuitively suspect: diabetic retinopathy is a disease with continued risk for progression despite anti-VEGF and PRP. Additionally, only 3% of the patients with early PDR remained stable at the end of 10 years of follow-up. Thus, a durable treatment strategy is still needed for this disease.

PDR with vision loss is a significant source of preventable blindness in the diabetic population. The increasing global epidemic of diabetes is associated with increasing prevalence of DR and PDR. DRCR studies in PDR suggest poor follow-up rates in this population, even in the context of clinical trials. Patients on anti-VEGF treatment alone who fail follow-up could experience severe vision loss that is often irreversible. Although PRP is an effective treatment, long-term rates of recurrent NV and vitreous hemorrhage remain high. Although a substantial proportion of patients with PDR are likely being treated with a combination of these two therapies, we lack a standardized combination approach and data on outcomes using this treatment strategy. More permanent and durable solutions are needed to reduce treatment burden and complications from PDR long-term.

1.2 Summary of Rationale

Although some combination of anti-VEGF plus PRP is the most common treatment approach for PDR with and without DME,[12] there are currently no long-term data on a standardized approach. Vitrectomy is not currently used as first-line treatment for early PDR but advances in surgical technique have reduced associated complications and the ability to remove the posterior hyaloid

during surgery may have advantages over nonsurgical approaches, especially in the reduction of vitreous hemorrhage and/or traction retinal detachment that may occur later when the hyaloid separates naturally. Protocol S demonstrated both PRP and anti-VEGF alone result in good visual acuity results long-term so it is expected that a combination treatment would also result in good visual acuity results.

This study will evaluate the safety and efficacy of two treatment strategies for PDR: 1) faricimab plus PRP and 2) Vitrectomy with endolaser with the goal to determine whether either approach decreases visit and treatment burden along with decreasing complications compared with the other treatment method while maintaining good visual acuity.

1.3 Study Objectives

The primary objectives of this study are to compare visual acuity at 3 years following vitrectomy with endolaser or faricimab+PRP and to compare number of post-randomization treatments for PDR (i.e., injections, PRP, or vitrectomy) following the end of randomized treatment over 3 years. Key secondary objectives include comparing the number of visits, in-office treatments for PDR (i.e., injections or PRP) following the end of randomized treatment, as well as complications such as vitreous hemorrhage, recurrent NV, TRD, and percent with VA loss.

Additional study objectives include:

- To assess the presence and extent of vitreous adherence on OCT at baseline and over time and its effect on outcomes.
- To share a standardized strategy for combination treatment and characterize outcomes in PDR when using this approach
- To share a standardized vitrectomy approach and characterize outcomes in PDR when using this approach
- To assess if artificial intelligence (AI) models can be trained to classify specific features of retinal surgery from videos of vitrectomy and endolaser for treatment of PDR

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. For fluorescein angiography, there is a small risk of discomfort or phlebitis at the site of the injection. Lightheadedness or nausea after dye injection may occur and is usually transient and resolves after a few minutes without further intervention. An allergic reaction to the dye used to do the fluorescein angiography imaging is rare. A rash or pruritus (itching) can develop, but true anaphylactic reactions are very rare. Fundus photographs

and OCT 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.

1.4.2 Known Potential 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 Faricimab

Faricimab (Vabysmo, Genentech, Inc) is an anti-VEGF/anti-Ang2 agent, injected intravitreally for treatment of diabetic macular edema (DME), neovascular age-related macular degeneration (nAMD), and retinal vein occlusion (RVO). To date, the risks of faricimab have been similar to those of aflibercept, one of the currently used anti-VEGF agents for treatment of DR. Known potential risks of faricimab include intraocular inflammation (uveitis), retinal pigment epithelial (RPE) tear, the intravitreal injection-related risks of infectious endophthalmitis, retinal detachment/tear, iatrogenic traumatic cataracts and increased IOP. Other potential risks include the non-ocular risk of arterial thromboembolic events and immunogenicity. [27] Please see the RO6867461 (faricimab) Investigator's Brochure for more details on the risks of faricimab.

Rarely, the drugs used to anesthetize the eye before Study Drug injections (proparacaine, tetracaine, or xylocaine) can cause an allergic reaction, seizures, and an irregular heartbeat. Subconjunctival hemorrhage or floaters will commonly occur as a result of the intravitreous injection. Discomfort, redness, or itching lasting for a few days is also likely.

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

1.4.4 Known Potential Risks Related to Vitrectomy

The most likely risk of vitrectomy is development of cataract. Other less common risks include corneal edema, retinal tear, or retinal detachment. Rare but serious risks include endophthalmitis, vitreous hemorrhage and vision loss.

1.4.5 Known Potential Risks Related to PRP

The most likely risks of PRP are loss of areas of retinal function, including peripheral, color or night vision. Other less common risks include worsening of macular edema. Rare but serious risks include a laser burn too close to the macula causing permanent vision loss, increase in intraocular pressure, retinal hole, or damage to other parts of the eye, such as the optic nerve, iris, or lens.

1.4.6 Known Potential Benefits

Based on results of the studies described above, both anti-VEGF plus PRP and vitrectomy plus endolaser may help preserve or improve vision in eyes with PDR.

1.4.7 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).

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of at least 426 participants completing the trial. It is anticipated that up to 650 individuals may be consented in the study 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 ~50 clinical centers in the United States and ~5 clinical centers outside the United States. 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. However, the goal is to recruit from a representative population with regard to diversity. There is no restriction on the number of participants to be enrolled by each site toward the overall recruitment goal. If each clinical center enrolls at least one participant per quarter, enrollment will be completed in approximately 2.5 years.

2.1.1 Informed Consent and Authorization Procedures

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. Written IRB-approved consent materials and consent discussions must be in a language understandable to the participants. For example, if the participant's primary language is Spanish, then the Spanish consent form, as well as other participant facing materials (e.g., instruction sheets) must be in Spanish. Also, the use of an approved translator is required to support not only the consent process, but also the participant's understanding and communication for the duration of the study.

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.

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 routine care (i.e., are being done specifically for the study), written informed consent will be obtained.

For potential study participants, 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 sign an 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 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.

A participant may withdraw consent at any time throughout the course of the trial. The rights and welfare of the participant will be protected by emphasizing that the quality of their medical care will not be adversely affected if they decline to participate in this study.

2.2 Participant Inclusion and Exclusion Criteria

Eligibility will be assessed by the investigator, or his or her designee, at the baseline visit. Reading Center confirmation of DR severity level is required prior to Randomization. To be eligible, the study participant must meet all individual-level criteria and have at least one eye meeting all the eye-level criteria. Participants can have one or two study eye(s) if both eyes are eligible at the time of screening.

2.2.1 Individual-Level Criteria

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

1. Age ≥ 18 years
2. Diagnosis of diabetes mellitus (type 1 or type 2)
3. At least one eye meets the study eye criteria listed below.

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

4. Significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant.
5. A condition that, in the opinion of the investigator, would preclude participation in the study and may preclude successful completion of 3 years of follow-up.
6. A condition that, in the opinion of the investigator, would preclude the participant undergoing elective vitrectomy surgery during the study.
7. Participation in an investigational trial that involved treatment within 30 days of randomization with any drug that has not received regulatory approval for the indication being studied.
   - Note: study participants cannot participate in another investigational trial that involves treatment with an investigational drug or device while participating in the study.
8. Known allergy to any component of faricimab injections (including povidone iodine prep).

9. Known allergy to fluorescein dye.
10. Blood pressure > 160/100 (systolic above 160 or diastolic above 100).
    - If blood pressure is brought below 160/100 by anti-hypertensive treatment, individual can become eligible.
11. Myocardial infarction, other acute cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 4 months prior to randomization.
12. Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization.
13. For women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next 3 years.
    a. Women of childbearing potential will be required to have pregnancy testing or use an acceptable method of pregnancy prevention. Women who are potential study participants should be questioned about the potential for pregnancy at baseline and prior to each injection. Pregnancy test is required for all women of childbearing potential at baseline. Investigator judgment is used to determine when a pregnancy test is needed during follow-up.
    b. Childbearing potential is defined as less than 12 months post-menopausal or not surgically sterile.
    c. Acceptable methods of pregnancy prevention are condom with spermicide, hormonal contraception, or IUDs.
14. 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 3 years

2.2.2 Study Eye Criteria

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

Study participants can have two study eyes only if both eyes are eligible at the time of randomization. For study participants with two eligible eyes, the logistical complexities of the protocol must be considered for each individual prior to randomizing both eyes. If both eyes are eligible, but only one eye will be randomized, the study eye will be selected by the investigator and participant before randomization.

The eligibility criteria for a study eye are as follows:

Inclusion:

a. Presence of PDR requiring treatment, defined moderate PDR or worse on global grading of ultrawide field fundus photos or NV meeting criteria for moderate PDR or worse on global grading of ultrawide field FA, confirmed by a central reading center. Moderate PDR is defined as the presence of at least one of the following:
   - Any NVD

- Any NVE greater than ½ disc area in one field
- Any NVE with at least 1 disc area of vitreous or preretinal heme

b. Best corrected E-ETDRS visual acuity letter score ≥49 letters (approximate Snellen equivalent 20/100 or better)

c. Media clarity, pupillary dilation, and study participant cooperation sufficient to administer PRP and 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)*

Exclusion:

d. Traction retinal detachment involving the macula
   - A tractional retinal detachment is not an exclusion if it is not threatening the macula and in the investigator's judgment, is not a contraindication to intravitreal anti-VEGF treatment or PRP (e.g., if greater than 5 disc areas)

e. Significant vitreous hemorrhage that would preclude completion of a full PRP

f. Significant vitreomacular traction (i.e., likely to require surgery within 6 months following randomization)

g. Any prior vitrectomy

h. Any prior PRP (defined as ≥ 100 burns outside of the posterior pole)

i. Treatment for DME within the prior 6 months

j. Intravitreal anti-VEGF for any indication, other than DME, within the prior year
   - Anti-VEGF for prior PDR is not an exclusion if the anti-VEGF was administered more than one year prior to enrollment

k. Center-involved diabetic macular edema on clinical exam or on OCT
   - Zeiss Cirrus central subfield: ≥290µm in females or ≥ 305µm in males
   - Heidelberg Spectralis central subfield: ≥ 305µm in females or ≥320µm in males
   - Investigator must verify accuracy of OCT scan by ensuring it is centered and of adequate quality

l. History of rhegmatogenous retinal detachment

m. An ocular condition is present (other than diabetic retinopathy) that, in the opinion of the investigator, might alter visual acuity during the course of the study (e.g., retinal vein or artery occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc.)

n. History of corticosteroid treatment (intravitreal or peribulbar) at any time in the past 4 months

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

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

q. Aphakia

r. Uncontrolled glaucoma (in investigator's judgment)

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

2.2.3 Non-Study Eye

There are no eligibility or exclusion criteria with respect to the non-study eye. Non-study eyes with PDR at enrollment or non-study eyes that develop PDR during the study will be treated at the discretion of the investigator. However, if the investigator determines that anti-VEGF injections are the best course of treatment for the non-study eye, the investigator will use study faricimab during the duration of their study participation. Non-study eyes with DME at enrollment or non-study eyes that develop DME during the study will use study faricimab during the duration of their participation, unless the investigator believes an alternative anti-VEGF would be a better treatment approach and the alternative has been discussed with and approved by the Protocol Chair or Coordinating Center designee.

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 medical conditions.

All testing does not need to be completed on the same day provided it is within the windows specified below.

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 6 for which testing procedures require certified personnel.

- OCTs meeting DRCR Retina Network criteria for manual grading will be sent to a reading center, but study participant eligibility is determined by the site (i.e., individuals deemed eligible by the investigator will be randomized without pre-randomization reading center confirmation).

- 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.

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 the clinic's usual care method or Electronic-ETDRS visual acuity testing to confirm vision is 20/100 in the study eye *(within 8 days prior to enrollment).*

4. Spectral-domain OCT using Zeiss Cirrus or Heidelberg Spectralis on the study eye *(within 8 days prior to enrollment).*

   - For a given study participant, the same machine should be used for the duration of the study, unless circumstances do not permit (e.g., replacement of damaged machine). If a switch is necessary, the same machine type should be used for the remainder of the study.

5. Ultra-widefield digital fundus photographs on the study eye only. *(Within 8 days prior to enrollment)*

6. Ultra-widefield digital FA on the study eye only. *(Within 8 days prior to enrollment)*

   - The transit eye should be the study eye. For participants with two study eyes, the transit eye at follow-up should be consistent with the transit eye selected at baseline.

7. Ocular examination on each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy *(within 8 days prior to enrollment)*.

2.4 Screen Failures

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

Chapter 3: Randomization

3.1 Randomization Visit Procedures

The randomization visit must be completed within 3 weeks after screening. The screening fundus photos and FA must be graded by the Central Reading Center prior to randomization.

The following procedures are needed to confirm eligibility and/or serve as baseline measures for the randomized trial and must be completed within the windows noted for each procedure:

- The testing procedures are detailed in the DRCR Retina Network procedures manuals. See Chapter 6 for which testing procedures require certified personnel.

1. Electronic-ETDRS visual acuity testing using the Electronic Visual Acuity Tester (including protocol refraction) in both eyes (*on day of randomization*).

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

3. Objective Field Analyzer (OFA) on the study eye only (*on day of randomization*)

   - Only obtained at a subset of sites with OFA capabilities

3.2 Randomization of Eligible Study Participants

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

1. The randomization visit must be completed within 3 weeks after the screening visit and after the screening fundus photos and FA have been graded by a Central Reading Center.
2. Prior to randomization, the participant's understanding of the trial, willingness to accept the assigned treatment group, and commitment to the follow-up schedule should be reconfirmed.
3. The first study injection must be given on the day of randomization and vitrectomy must be performed within 4 weeks, depending on treatment group; therefore, a participant should not be randomized until this is possible.
4. Randomization is completed on the DRCR.net website.

   - Study participants with one study eye will be randomly assigned (stratified by site) with equal probability to one of two treatment groups:
     - Group A: Vitrectomy + Endolaser
     - Group B: 6.0mg faricimab + PRP

- Study participants with two study eyes (both eligible at the time of randomization), the study participant will be randomly assigned with equal probability to receive either:
    - Group A in the right eye and Group B in the left eye
    - Group B in the right eye and Group A in the left eye

3.3 Randomized Treatment

3.3.1 Vitrectomy + Endolaser

If randomized to the vitrectomy + endolaser group, the vitrectomy must occur within 4 weeks of randomization. A single injection of faricimab is allowed at any point prior to the vitrectomy. It is recommended that this injection is within 1 week of the vitrectomy.

Refer to the Site Procedure Manual for details on the standardization of the vitrectomy + endolaser procedure. This procedure will include the following:

- Standard definition of complete PRP
- Requirement of triamcinolone staining to assist in complete elevation and removal of the posterior hyaloid and in removal of as much peripheral vitreous as is safely possible
- 20 gauge not permitted
- Allows subconjunctival steroid at investigator discretion; however sub-tenon's triamcinolone or other long-acting steroid will not be permitted

3.3.2 Faricimab + PRP

If the participant is randomized to the faricimab + PRP group, treatment must be initiated on the day of randomization with one faricimab injection. The remainder of the randomized treatment includes 2 additional q4 week faricimab injections and complete PRP. PRP may be completed in 1-3 sessions, with the timing at investigator discretion. All PRP sessions and faricimab injections must be completed within 90 days of randomization.

Refer to the Site Procedure Manual for the PRP procedure and definition of complete PRP.

Chapter 4: Randomized Trial Procedures

4.1 Study Visits

The schedule of protocol-specified assessment visits is detailed below. All participants will have the protocol visits listed below. All other protocol visits will depend on treatment administered.

4.1.1 Study Protocol Visits

Study visits will occur per the table below.

Visit	Target Day/Week	Target Window (around Target Day/Week)
4 Weeks*	4 weeks	±1 week
16 Week	16 weeks	-2 weeks/+4 weeks
24 Week	24 weeks	±4 week
36 Week	36 weeks	±4 week
52 Week	52 weeks	±8 weeks
68 Week	68 weeks	±4 week
84 Week	84 weeks	±4 week
104 Week	104 weeks	±8 week
120 Week	120 weeks	±4 weeks
136 Week	136 weeks	±4 week
156 Week	156 weeks	±8 week

*Vitrectomy group only

4.1.2 PDR Treatment Assessment Visits

Initial treatments for PDR are based on randomized assignment and described in section 3.3. Following the 16-week visit, additional visits may occur to assess for PDR retreatment based on protocol criteria for retreatment described in Section 4.1.6. If retreatment is given, the next visit is in 8 weeks. Once treatment is deferred at 2 consecutive visits, the follow-up interval is extended by 4 weeks with each subsequent deferral, up to 16 weeks maximum. Otherwise, participants will continue on the set time point visit schedule above.

4.1.3 DME Treatment Assessment Visits

Following the 16 week visit, additional visits may occur for the treatment of DME. Criteria to initiate treatment for DME are described in Section 4.1.7. If faricimab for DME has been initiated, follow-up visits for DME treatment occur every 4 weeks for the first 24 weeks from initial faricimab treatment for DME. After 24 weeks, if the injection is deferred at two consecutive visits, the next study follow-up visit is twice the time since the last visit up to a maximum of 16 weeks between visits. Otherwise, the next study follow-up visit is in 4 weeks.

4.1.4 Additional Protocol Visits

Participants undergoing vitrectomy will have a study visit 1 month (±1 week) post-vitrectomy for safety evaluation only. Investigators may schedule an initial (e.g., 1 day) post-operative visit earlier as standard care.

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

4.1.5 Procedures at Study Visits

The 1-month post-operative visit will include a safety evaluation only. Otherwise, the following procedures will be performed at each protocol-specified visit on the study eye only, unless otherwise specified.

1. E-ETDRS visual acuity testing (best corrected) in each eye.
    - A protocol refraction in the study eye is required at all visits. Refraction in the non-study eye is only required at annual visits. When a refraction is not performed, the most recently performed refraction is used for the testing.
2. SD-OCT on the study eye
    - For a given study participant, the same machine type should be used for the duration of the study, unless circumstances do not permit (e.g., replacement of damaged machine). If a switch is necessary, the same machine type should be used for the remainder of the study.
3. Ocular exam, including slit lamp examination (including lens assessment), measurement of intraocular pressure, and dilated ophthalmoscopy.
    - *Undilated exam of the iris is at the discretion of the investigator; examination of the angle is required if neovascularization of the iris is present or increased IOP (defined as one of the following: a) IOP ≥ 30mm Hg b) first time IOP has increased at least 10mm Hg since baseline c) IOP has increased at least 10mm Hg since last visit or d) IOP lowering medication initiated since last visit).*
4. Ultra-widefield digital fundus photographs at 16 weeks and annual visits only.
    - If the eye is not quiescent at the 16-week visit, photos will be taken at each subsequent visit until quiescence is achieved (see section 4.1.6).
5. Ultra-widefield digital FA at 16 weeks and annual visits only.
    - *The transit eye should be the study eye. For participants with two study eyes, the transit eye at follow-up should be consistent with the transit eye selected at baseline.*
6. Objective Field Analyzer (OFA) on the study eye at annual visits only.
    - *Only obtained at a subset of sites with OFA capabilities.*
7. Laboratory testing - HbA1c at the annual visits only.

8. Measurement of blood pressure at annual visits only.

All the testing procedures do not need to be performed on the same day if they are completed within the time window of a visit and prior to administering any treatment.

4.1.6 Treatment for Recurring PDR in Both Groups

If the eye is not quiescent at the 16-week visit, the eye will be treated according to the options below. Then at each subsequent visit, the eye will have photos only taken until quiescence is achieved. Quiescence is defined as NV is no longer visible, is completely fibrotic, or is persistent and perfused but has been stable over two or more visits on clinical exam or on color fundus photographs.

Once the quiescence is established, either at the 16-week visit or a subsequent visit, study eyes will subsequently be evaluated for retreatment based on appearance of neovascularization and vitreous hemorrhage.

Faricimab and/or PRP

Comparing the study eye to the most recent quiescent images that are available, the eye must be treated if it meets any of the following criteria:

- Worsened NVD or NVE compared to last quiescent image
- New or worsened vitreous hemorrhage

Once criteria are met, treatment must be initiated with a faricimab injection plus fill-in PRP within 4 weeks of the injection.

If there is no room for fill-in PRP, treat with a faricimab injection only.

Regardless of treatment, participants will follow up 8 weeks following the injection.

If an eye has experienced adverse effects from prior intravitreal injection treatment that may require temporary deferral of faricimab, retreatment with intravitreal faricimab is at the discretion of the investigator. In addition, if all future treatment with faricimab is contraindicated based on a previous adverse reaction, and the participant has full PRP, any alternative treatment for PDR must be discussed with and approved by the Protocol Chair or Coordinating Center designee.

Vitrectomy

Vitrectomy will be permitted when the study eye meets any of the following failure criteria:

- Persistent or recurrent vitreous hemorrhage affecting vision and not improving after two or more 8-week visits with injections (i.e. 4 months)
- Worsening traction or traction threatening the macula

4.1.7 Treatment for Diabetic Macular Edema (DME) in Both Groups

Beginning at the 16-week visit, study eyes can be assessed for DME. No DME treatment can be given before the 16-week visit. At and after 16 weeks, if DME is present (OCT CST above sex and OCT machine-specific thresholds and investigator has confirmed thickening is due to diabetic macular edema and not post-surgical macular edema or other cause) and vision is 20/32 or worse, treatment with intravitreous faricimab will be given, using the Protocol T retreatment protocol. If the investigator believes an alternative anti-VEGF would be a better treatment approach for the participant, the investigator must discuss and gain approval of the alternative by the Protocol Chair or Coordinating Center designee.

4.1.8 Treatment for Other Ocular Conditions

Treatment for other ocular conditions is at the discretion of the investigator. However, steroid injections for treatment of post-surgical edema are NOT permitted. Only topical steroid treatment is allowed.

4.1.9 Treatment in the Non-Study Eye

For non-study eyes, treatment for any condition other than PDR or DME is at the discretion of the investigator. Non-study eyes with PDR at enrollment or non-study eyes that develop PDR during the study will be treated at the discretion of the investigator. However, if the investigator determines that anti-VEGF injections are the best course of treatment for the non-study eye, the investigator will use study faricimab during the duration of their study participation. Non-study eyes with DME at enrollment or non-study eyes that develop DME during the study will use study faricimab during the duration of their participation, unless the investigator believes an alternative anti-VEGF would be a better treatment approach and the alternative has been discussed with and approved by the Protocol Chair or Coordinating Center designee. Every effort should be made to maintain separate treatment decisions for the non-study eye.

4.1.10 Unscheduled Visits

Additional visits may occur as required for usual care of the study participant. Testing procedures at unscheduled visits are at investigator discretion. However, it is recommended that procedures that are performed should follow the standard DRCR Retina Network protocol for each procedure.

4.2 Vitrectomy Surgery Video Collection

If an operating room has surgery video capabilities meeting specified criteria, video of the vitrectomy surgery in study eyes will be collected. The videos will be uploaded to the DRCR Retina Network Coordinating Center at the Jaeb Center for Health Research via secure method. The videos will be used to determine whether artificial intelligence (AI) models can be trained, validated, and tested to classify specific features of retinal surgery from videos of vitrectomy and endolaser for treatment of PDR.

4.3 Vitreous and Aqueous Sample Collection

Participation in the ancillary sample collection component is not a requirement for participation in this study. It is expected that sites with the capability to obtain and ship intraocular fluids will participate. At the time of consent into the main study, participants will have the option of signing the ancillary sample collection portion of the informed consent form to indicate their willingness to provide either a vitreous sample only (collected during the vitrectomy procedure) or to provide both vitreous and an additional aqueous sample (requiring an additional anterior paracentesis) at the time of vitrectomy or to provide an aqueous sample only in clinic (requiring an anterior paracentesis). The recommended minimum collection volume is at least 1cc of vitreous and at least 0.1cc of aqueous.

If consent for vitreous and/or aqueous sampling is obtained, the sample(s) will be collected and shipped on dry ice to a central laboratory for storage until analyses are completed. Details regarding collection, sample labeling, storage, and shipment can be found in the ancillary study procedures manual.

4.4 Participant Access to Study Agent at Study Closure

After participation in the study is completed, participants may have access to intravitreal anti-VEGF as part of their usual care, on or off label depending on the anti-VEGF agent, and can discuss with their eye doctor.

Currently, Genentech, a member of the Roche Group does not have any plans to provide Genentech Investigational Medicinal Product (IMP) (faricimab) or any other study treatments to patients who have completed the study. Genentech may evaluate whether to continue providing faricimab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

Genentech Access Solutions and the Genentech Patient Foundation are the U.S. resources for access and reimbursement support after a Genentech medicine has been prescribed, including transitioning from investigational drug to commercial drug after FDA approval, as clinically appropriate. Genentech Access Solutions can help patients understand their insurance coverage and costs related to Genentech medicines (or can help patients navigate the access and reimbursement process for their Genentech medicine). The Genentech Patient Foundation provides free medicine for people who do not have insurance coverage or who have financial concerns about their Genentech medicine and meet certain eligibility criteria. Genentech is committed to helping patients access the Genentech medicines they need.

Chapter 5: Study Drug

5.1 Study Agent and Control Description

5.1.1 Acquisition

Genentech, Inc will provide 6.0 mg faricimab, referred to as Study Drug. The Study Drug will be labeled for investigational use. Each package label will contain an identifying drug number. Select study personnel (e.g., VA testers and imaging technicians) will be masked to the drug assignment. The Study Drug will be shipped to the central pharmacy responsible for drug distribution to clinical sites according to Study Drug accountability procedures.

5.1.2 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, directions for storage and use, and indication that it is an investigational drug.

The physical, chemical, and pharmaceutical properties and formulation of the Study Drug are provided in the Clinical Investigator's Brochure.

5.1.3 Product Storage and Stability

Study drug will be stored at the central pharmacy and each clinical site in a limited access, secure area. Study drug will be stored at 2° to 8° C (36° to 46° F). Sites will be instructed to follow manufacturer recommendations for drug storage.

5.1.4 Preparation

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

5.1.5 Dosing and Administration

Study Drug will be supplied in a single use vial, from which a dose of 6.0 mg of faricimab will be administered. The Study Drug will be injected into the eye in clinic during the study visit using sterile technique. The full injection procedure is described in the protocol-specific study procedures manual. Study drug must not be injected into the eye less than 21 days after the prior injection of Study Drug.

5.1.6 Dose Adjustments/Modifications/Delays

Female study participants of child-bearing potential (i.e., have started menstruation, are not surgically sterile, and are not 1 year post-menopausal) must be questioned regarding the possibility of pregnancy prior to each injection and method of pregnancy prevention. Child-bearing potential and/or pregnancy prevention plans must be documented. In the event of pregnancy, study injections must be discontinued during the pregnancy and any post-partum period of breastfeeding.

5.1.7 Duration of Therapy

Study participants may continue Study Drug for the three-year duration of the study, according to protocol criteria. At and after the 36-month visit, treatment is at investigator discretion as part of usual care. Study Drug should not be given at the final visit.

5.2 Study Agent 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.

Chapter 6: Testing Procedures

6.1 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, coordinator, or technician
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 and masked to treatment at all visits
Visual Acuity – ETDRS	EVA system (preferred) otherwise ETDRS charts if EVA not available	Clinical site personnel certified for ETDRS and masked to treatment at all visits
Ultra-widefield Fundus Photography	Optos, otherwise a digital system certified by the central Reading Center	Clinical site personnel certified for fundus photography and masked to treatment at all visits
Ultra-widefield Fluorescein Angiography	Optos, otherwise a digital system certified by the central Reading Center	Clinical site personnel certified for FA and masked to treatment at all visits
SD-OCT	Zeiss Cirrus or Heidelberg Spectralis	Clinical site personnel certified for specific SD-OCT machine type and masked to treatment at all visits
Objective Field Analyzer (OFA) (only at sites with OFA capabilities)	Objective Field Machine	Clinical site personnel certified for OFA
Sample collection – HbA1c	Central lab collection kit provided by study	Does not need to be performed by study certified personnel*

** Site 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 7: Unanticipated Problem and Adverse Event Reporting

7.1 Unanticipated Problems

Site investigators will promptly report all unanticipated problems meeting the criteria below on an eCRF. Sites overseen by the JCHR IRB must report Unanticipated Problems to the IRB within seven (7) calendar days of recognition. 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 subject 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. These instances must be reported to the JCHR IRB within seven (7) calendar days of recognition. The Director of the Human Research Protection Program (HRPP) will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem that requires further reporting to fulfill the reporting obligations of the HRPP.

7.2 Adverse Events

7.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence (including laboratory findings) associated with study procedures, the use of a device, biologic, or drug in humans, including any comparator used, whether or not the event is considered related (i.e., irrespective of the relationship between the adverse event and the drug(s) under investigation) (referred to as *Adverse Reaction* when caused by a drug).

Serious Adverse Event (SAE): Any untoward medical occurrence that results in any of the following outcomes:

- Death.
- A life-threatening adverse event (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Inpatient hospitalization or prolongation of existing hospitalization.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical and surgical intervention to prevent one of the outcomes listed in this definition.

In general, an ocular adverse event should be reported as serious (considered sight threatening) if it meets one of the following criteria:

1. It causes a decrease of ≥ 30 letters in visual acuity compared with the last visual acuity measurement prior to onset (e.g. central retinal artery occlusion)
2. In the opinion of the investigator, it requires prompt surgical intervention (e.g. vitrectomy, vitreous tap, intravitreous antibiotics) to prevent permanent loss of sight. Examples include endophthalmitis or rhegmatogenous retinal detachment.
3. It is associated with severe intraocular inflammation (i.e., endophthalmitis, 4+ AC cell/flare, or 4+vitritis)

Note: If either the Sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting. See 21 CFR 312 for more information.

Serious and Unexpected Suspected Adverse Reaction (SUSAR): An adverse event that is a suspected adverse reaction, is serious, and is unexpected. This event requires a submission of an IND Safety Report. See 21 CFR 312 for more information.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

7.2.2 Reportable Adverse Events

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

All reportable 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.

7.2.3 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. The Medical Monitor will also make this assessment, which may or may not agree with that of the site investigator. Reporting requirements will be based on the Medical Monitor's assessment as the Sponsor's representative.

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

- **Unrelated:** The AE is clearly not related to a study drug/intervention/procedure and a likely alternative etiology exists such as an underlying disease, environmental or toxic factors or other therapy.
- **Unlikely Related:** The AE does not follow a reasonable temporal sequence during or after use of study drug/intervention/procedure and a more likely alternative etiology exists such as an underlying disease, environmental or toxic factors, or other therapy.
- **Possibly Related:** The AE occurred in a reasonable time during or after use of study drug/intervention/procedure; but could be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a possible, though weak, scientific basis for establishing a causal association between the AE and the study drug/intervention/procedure.
- **Probably Related:** The AE occurred in a reasonable time during or after use of study drug/intervention/procedure; is unlikely to be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a plausible, though not strong, scientific basis for establishing a causal association between the AE and the study drug/intervention/procedure.
- **Definitely Related:** The AE occurred in a reasonable time during or after use of study drug/intervention/procedure; cannot be explained by another factor such as an underlying disease, environmental or toxic factors, or therapy; and there is a strong scientific basis for establishing a causal association between the AE and the study drug/intervention/procedure.

Where these relatedness categories are used, events determined to be Possibly Related, Probably Related, or Definitely Related will be considered to meet the *reasonable possibility* causality standard as related and necessitate reporting as required (see 21 CFR 312.32 for more information).

7.2.4 Severity (Intensity) of Adverse Event

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. The severity (intensity) of adverse events will be rated on a five-grade scale as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to the adverse event.

7.2.5 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 investigator brochure and package insert.

7.2.6 Effect of Adverse Event on Study Drug

If an adverse event leads to a permanent or temporary discontinuation of study drug or a dose reduction, this will be reported on the Adverse Event form.

7.2.7 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. To facilitate coding, the site will enter a preliminary MedDRA code which the Medical Monitor may accept or change (the Medical Monitor's MedDRA coding will be used for all reporting). The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. The assessments of both the investigator and Medical Monitor will be recorded. The Medical Monitor will have the final say in determining the causality as well as whether an event is classified as a serious adverse event and as a serious unanticipated event.

7.2.8 Outcome of Adverse Event

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

- RECOVERED/RESOLVED (COMPLETE RECOVERY) – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – AE/SAE where the subject recuperated but retained pathological conditions resulting from the prior disease or injury. 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.
- ONGOING NOT RECOVERED/NOT RESOLVED – An ongoing AE/SAE is defined as an ongoing event with an undetermined outcome.
    - An ongoing outcome will require follow-up by the site to determine the final outcome of the AE/SAE.
    - 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.

If a participant is lost to follow up and participant outcome cannot be determined, outcome classification will be the last known outcome.

7.3 Timing of Event Reporting

Serious or unexpected adverse events must be reported to the Coordinating Center within twenty-four (24) hours of becoming aware of the event 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 no later than fifteen (15) calendar days after the Coordinating Center becomes aware of the event, and no later than seven (7) calendar days where the event is fatal or life-threatening.

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. Where the JCHR IRB is the overseeing IRB, sites must report all serious, unexpected and related adverse events regardless of whether they are fatal or life-threatening within seven (7) calendar days.

7.4 Safety Oversight

The Medical Monitor will review all adverse events that are reported during the study. SAEs typically will be reviewed within twenty-four (24) hours of reporting. Other AEs typically will be reviewed on a weekly basis. Additionally, the Medical Monitor will review compiled safety data at periodic intervals (generally timed to the review of compiled safety data by the DSMC).

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.

7.5 Stopping Criteria

7.5.1 Participant Discontinuation of Study Drug

Rules for discontinuing study drug use are described below.

- The investigator 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
- 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.

7.5.2 Criteria for Suspending or Stopping Overall Study

There is no plan for formal statistical interim data monitoring for either futility or efficacy, as enrollment will be completed before any participants complete three years of follow up. However, the Data and Safety Monitoring Committee will monitor study data approximately every six months. 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 8: Miscellaneous Considerations

8.1 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).

Medical Conditions during the study: In addition to conditions meeting the reporting requirements for an adverse event or as described above, the following medical conditions should also be reported: (1) new diagnosis of a chronic disease (ie, not present at the time of enrollment), and (2) any medical condition that could affect the participant's ability to carry out any aspect of the protocol or could affect an outcome assessment.

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 preventive treatment also should be recorded.

8.2 Prohibited Medications, Treatments, and Procedures

Alternative treatment for PDR or DME will not be permitted unless protocol treatment is discussed with and approved by the Protocol Chair or Coordinating Center designee.

Steroid injections for treatment of post-surgical edema are NOT permitted. Only topical steroid treatment is allowed.

8.3 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 seven days of notification and to the JCHR IRB as an Unanticipated Problem within seven calendar days. An electronic case report form must be completed for all confirmed pregnancies.

8.4 Participant Compensation

Participant compensation will be specified in the informed consent form.

8.5 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.

8.6 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.

8.6.1 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 per year.

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.

Chapter 9: Statistical Considerations

9.1 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 before the first enrollment.

9.2 Statistical Hypotheses

This study has two primary outcomes that will be tested in a fixed sequence: change in visual acuity from baseline at 3 years, and number of post-randomization treatments for PDR (i.e., injections, PRP, or vitrectomy) over 3 years. Each primary outcome will be compared between vitrectomy with endolaser vs. faricimab + PRP with a hypothesis test. To control the familywise error rate, the fallback procedure will be used. The overall Type I error rate (α) of 5% will be partitioned equally among the two primary outcomes: 2.5% for the equivalence test of the first primary outcome (i.e., change in visual acuity at 3 years), and 2.5% for the superiority test of the second primary outcome (i.e., number of post-randomization treatments for PDR over 3 years).

The first primary outcome will be tested using the confidence interval approach whereby equivalence will be declared if the 95% confidence interval on the treatment difference in change in visual acuity from baseline to 3 years falls entirely within the equivalence margins. This procedure is operationally identical to the Two One-Sided Tests (TOST) procedure that evaluates the two disjoint null hypotheses specified below,[28] which will be used to obtain a p-value for the primary outcome treatment comparison. If the null hypothesis for the first primary outcome is rejected (i.e., the two groups are statistically equivalent), the second primary outcome will be tested with alpha of 5%; if the null hypothesis for the first primary outcome is not rejected (i.e., the two groups are not statistically equivalent), the second primary outcome will be evaluated with alpha of 2.5%.

Visual Acuity Outcome (test of equivalence with an equivalence margin of -5 to +5 letters)

- Null hypothesis: The absolute mean difference in the change in visual acuity from baseline at 3 years between the vitrectomy with endolaser group vs. the faricimab + PRP group is at least 5 letters.
- Alternative hypothesis: The absolute mean difference in the change in visual acuity from baseline at 3 years between the vitrectomy with endolaser group vs. the faricimab + PRP group is less than 5 letters.

Treatment Outcome (test of superiority)

- Null hypothesis: There is no difference in the mean number of post-randomization treatments for PDR over 3 years between the vitrectomy with endolaser group vs. the faricimab + PRP group.
- Alternative hypothesis: There is a difference in the mean number of post-randomization treatments for PDR over 3 years between the vitrectomy with endolaser group vs. the faricimab + PRP group.

Similar hypothesis tests of superiority will be conducted for the secondary outcomes. Treatment-group comparisons will be based on statistics appropriate to the outcomes.

9.3 Sample Size

The sample size calculation is performed for each co-primary outcome separately. The study sample size is determined by the co-primary outcome that requires the larger sample size.

9.3.1 Sample Size Assumptions

In the subset of eyes enrolled in DRCR Retina Network Protocol S without CI-DME at baseline, 85 eyes in the ranibizumab group had a mean visual acuity of 78 letters at 3 years, with a mean of 1 letter improvement from baseline; while 85 eyes in the PRP group had an average of 77.7 letters at 3 years, with a 0.5 letter mean decrease from baseline. With adjustment for baseline visual acuity, the standard deviation for change in visual acuity from baseline at 3 years is 15.2 (95% CI, 13.2 to 17.9) letters for the ranibizumab group and 10.9 (95% CI, 9.4 to 12.8) letters in the PRP group. Combining the two treatment groups, the pooled standard deviation is 13.2 (95% CI, 11.9 to 14.8) letters adjusting for baseline visual acuity. In addition, the mean (SD) total number of study injections, PRP sessions and vitrectomies received between 3 months and 3 years was 9.6 (6.8) in the ranibizumab group and 3.4 (3.9) in the PRP group. Assuming a negative binomial distribution, the estimated model-based dispersion parameter is 0.7 for the overall cohort and 1.2 for the PRP group.

9.3.2 Sample Size Estimates

For the equivalence testing of the visual acuity outcome, the choice of the equivalence margin is based on a minimum clinically important difference (MCID). While there is no clear consensus regarding the precise value of the MCID for visual acuity, a review of non-inferiority margins used in ophthalmology trials supports an MCID of between 3 and 5 letters, under the assumption that the non-inferiority margin represents a lower bound on the MCID.

Since equivalence testing (at a confidence level of $\alpha = 2.5\%$) for the visual acuity outcome will use a confidence interval approach[29]– by determining if the entire two-sided $100(1-2\alpha)\%$ confidence interval for the difference between the two means falls within the predefined equivalence margin – the sample size is estimated based on the precision of the 95% CI for the mean difference. Under this precision-based approach,[30,31] the required sample size is calculated to ensure the full width of the 95% CI associated with the treatment effect does not exceed half the width of the specified equivalence margin, thereby minimizing the risk of obtaining inconclusive results. Table 1 shows the total number of eyes needed to obtain a 95% CI for the mean difference in change in visual acuity with a desired full-width of 3-5 letters with a given standard deviation, assuming equal variance between the two groups.

Table 1: Total Sample Size Projections Based on the Precision of the 95% Confidence Interval for the Difference in Change in Visual Acuity from Baseline

Standard Deviation (Letters)	Full-width of the 95% CI for the Mean Difference in Change in VA from Baseline at 3 Years (Letters)		
	3	4	5
7	338	192	124
9	556	314	202
11	830	468	300
13	1156	652	**418**
16	1752	986	632

Data from Protocol S showed that the ranibizumab group and the PRP group both had minimal improvement in visual acuity from baseline at 3 years. Although there is no prior data available for the treatment groups being evaluated in this study, we expect change in visual acuity from baseline at 3 years would be similar between the vitrectomy with endolaser group vs. the faricimab + PRP group and that the standard deviation for the mean change would be close to the pooled standard deviation from Protocol S. With an equivalence boundary of -5 to +5 letters, a margin that is considered clinically acceptable in retinal studies ,[9,32,33] assuming a standard deviation similar to the pooled standard deviation of 13 letters from Protocol S, the required total sample size is **418** eyes (209 per group) for a desired full-width of 5 letters for the 95% CI for the treatment group difference in the VA outcome.

The Two One-Sided Tests (TOST) procedure was used to project power for the primary outcome comparison, assuming a sample size of 418 eyes, 2.5% Type I error rate, an equivalence margin of ±5 letters, for a range of standard deviations mean treatment differences (Table 2). This sample size has 95% power for an absolute mean difference of 0, and 93.3% power for an absolute mean difference of 0.5 letters under the assumption of SD of 13 letters. It also provides 90% or greater power for absolute mean differences of ≤1.5 letters with SD = 11 letters, and for absolute mean differences of ≤2 letters with SD = 9 letters.

Table 2: Power Projections for Change in Visual Acuity from Baseline at 3 Years Based on a Test of Equivalence and Total Sample Size of 418 eyes

Adjusted Standard Deviation (Letters)*	Absolute Mean Difference in Change in VA from Baseline at 3 Years (Letters)						
	0	0.5	1	1.5	2	2.5	3
7	>99.9%	>99.9%	>99.9%	>99.9%	99.2%	95.4%	83.0%
9	>99.9%	>99.9%	99.5%	97.8%	92.5%	80.9%	62.0%
11	99.3%	98.6%	96.0%	90.1%	79.4%	64.0%	45.8%
13	95.0%	93.3%	87.8%	78.3%	65.3%	50.1%	34.8%
16	78.0%	75.7%	69.1%	59.2%	47.5%	35.5%	24.6%

* Adjusted for the correlation with baseline visual acuity.

For the testing of difference in the number of post-randomization treatments for PDR, the sample size is calculated as the total number of eyes needed to achieve 90% power for a mean difference, assuming 5% or 2.5% two-sided Type I error rate (actual rate will be determined by the fallback procedure), a given mean in the reference group, a dispersion parameter, and a given

mean difference based on the negative binomial distribution.[34] The total sample size of 418 eyes calculated for the VA outcome also accommodates the highlighted combinations of reference mean and mean differences in this PDR treatment outcome.

Table 3: Total Sample Size Projections for Number of Post-Randomization Treatments for PDR Based on a Test of Superiority

Dispersion	Alpha (2-sided)	Mean in Reference Group (Treatments)	Mean Difference (Treatments)*						
			1	2	3	4	5	6	7
0.7	5%	3	472	72	--	--	--	--	--
		4	874	158	44	--	--	--	--
		5	1396	274	90	32	--	--	--
		6	2038	418	146	62	26	--	--
		7	2800	594	218	98	46	22	--
		8	3684	800	302	142	72	38	20
	2.5%	3	558	86	--	--	--	--	--
		4	1032	186	54	--	--	--	--
		5	1648	322	106	38	--	--	--
		6	2408	494	174	72	32	--	--
		7	3308	702	258	116	56	26	--
		8	4350	944	358	166	86	44	22
1.2	5%	3	320	52	--	--	--	--	--
		4	572	106	32	--	--	--	--
		5	894	178	60	24	--	--	--
		6	1286	266	94	40	18	--	--
		7	1748	374	138	62	30	16	--
		8	2280	498	190	90	46	26	14
	2.5%	3	378	62	--	--	--	--	--
		4	674	124	38	--	--	--	--
		5	1056	210	70	28	--	--	--
		6	1518	314	112	48	22	--	--
		7	2064	440	164	74	36	18	--
		8	2694	588	224	106	54	30	16

***** The mean number of treatments in the other group = mean in the reference group – mean difference.

Despite that the two treatment approaches are likely to yield similar visual acuity outcomes at 3 years, being able to detect a significant difference in the total number of post-randomization treatments for PDR over 3 years is meaningful and applicable to clinical practice, as the approach with fewer number of treatments for PDR during follow-up will help alleviate

treatment burden as well as reduce cost for patients and the healthcare system. To account for the potential loss in efficiency arising from missing data due to loss to follow up, the study total sample size is increased by 2% to **426** eyes (213 per treatment group). This sample size is also feasible from a Network recruitment and cost perspective.

9.4 Outcome Measures

Outcomes marked with an asterisk (*) will include descriptive statistics by treatment group only, with no inferential statistics on treatment effect (no point estimation, confidence intervals or p-values for treatment group differences). Outcomes without an asterisk will include a point estimate and 2-sided confidence interval for the treatment group difference. The analysis of safety outcomes will be separately detailed in Section 9.9.

Primary Efficacy Outcomes

- Change in visual acuity from baseline at 3 years
- Number of post-randomization treatments for PDR (injections, PRP, vitrectomy) over 3 years[†]
    - Note: the initial randomized treatment of faricimab + PRP or vitrectomy + endolaser will be excluded

Secondary Efficacy Outcomes

- Development of vitreous hemorrhage during follow-up over 3 years causing vision loss of at least 5 letters not attributable to another cause (time-to-event outcome)
- Presence of active neovascularization on fundus photos and FA over 3 years
- Presence of macula threatening tractional retinal detachment on fundus photos and FA over 3 years
- Change in visual acuity from baseline over 3 years (area under the curve)
- Change in visual acuity from baseline at 1 year
- Change in visual acuity from baseline at 2 years
- Number of visits over 3 years (unilateral participants only)
    - Number of post-randomization injections to treat PDR over 3 years[*†]
    - Number of post-randomization PRP sessions to treat PDR over 3 years[*†]
    - Number of post-randomization vitrectomies to treat PDR over 3 years[*†]

[†]Excluding the initial randomized treatment of faricimab + PRP or vitrectomy + endolaser

Exploratory Outcomes

- Cumulative proportion of eyes requiring vitrectomy after initial randomized treatment over 3 years (time-to-event outcome)
- Development of recurrent neovascularization (i.e., NVD and/or NVE) during follow-up over 3 years (time-to-event outcome)
    - Development of recurrent NVD during follow-up over 3 years (time-to-event outcome) [*]

    - Development of recurrent NVE during follow-up over 3 years (time-to-event outcome) *
- Development of any tractional retinal detachment during follow-up over 3 years (time-to-event outcome)
    - Development of macula threatening tractional retinal detachment during follow-up over 3 years (time-to-event outcome)*
- Presence of vitreous hemorrhage on fundus photos and FA over 3 years
- Percentage with visual acuity 20/20 or better at 3 years*
- Percentage with visual acuity 20/40 or better at 3 years*
- Percentage with visual acuity 20/70 or worse at 3 years*
- Percentage with visual acuity 20/200 or worse at 3 years*
- Loss of 10 or more letters of visual acuity from baseline at 3 years*
- Loss of 15 or more letters of visual acuity from baseline at 3 years*
- Development of DME on OCT CST (based on sex- and machine-specific thresholds) with vision loss (i.e., VA ≤ 78 letters [20/32 or worse]) over 3 years (time-to-event outcome)
- Number of procedures to treat DME over 3 years
- Extent of retinal nonperfusion in retina that has not been treated with PRP on FA
- Activity of NVE/NVD on FA/fundus photos
- Area and density of PRP on fundus photos
- Correlation of change in degree of adherence of the vitreous with visual acuity at 3 years and with number of post-randomization treatments over 3 years

<u>Safety Outcomes</u>

- Endophthalmitis
- Any retinal detachment
    - Rhegmatogenous retinal detachment*
    - Tractional retinal detachment*
- Retinal tear
- Increased intraocular pressure
    - Increase in IOP ≥ 10 mmHg from baseline*
    - IOP ≥ 30 mmHg at a follow-up visit*
    - Initiation of medication to lower IOP that was not in use at baseline*
    - Glaucoma procedure*
- Neovascularization of the iris
- Ocular Inflammation
- Cataract extraction (among eyes that are phakic at baseline)
- Visually significant cataract on clinical exam
- Intraocular hemorrhage
- Death
- Any serious adverse event
- Hospitalization
- APTC event

9.5 Analysis Datasets and Sensitivity Analyses

The primary analysis will be performed by analyzing all randomized participants according to their initial treatment received at randomization, regardless of treatment assignment (Table 4). Supplemental analysis for the primary outcomes will provide additional information on the magnitude of the treatment effect using the intention-to-treat (ITT), per-protocol (PP), and complete case (CC) analysis cohorts. The ITT, PP, and CC analyses will be performed regardless of the number of randomized participants who would be included based on the definitions below. The primary analysis cohort is considered primary; if the ITT, PP and CC analysis are inconsistent with the primary analysis cohort, an exploratory analysis will evaluate possible reasons for the differences. Supplemental analysis will not be performed for any other outcomes besides the primary.

- Primary Analysis Cohort: all randomized participants analyzed according to the actual initial treatment received as detailed in Table 4 below, irrespective of treatment assignment and treatment received during follow-up. Participants who did not receive any treatment during the initial randomization treatment period will be excluded from the analysis.

Table 4: Definitions of treatment group for primary analysis based on the initial treatment(s) the study eye received during randomization treatment period.

Randomized Group	Initial Treatment(s) Received	Analysis Group
Vitrectomy with endolaser	Vitrectomy with or without endolaser	Vitrectomy with endolaser
	Vitrectomy with or without faricimab	Vitrectomy with endolaser
	Faricimab and/or PRP without vitrectomy	Faricimab + PRP
Faricimab + PRP	Faricimab and/or PRP	Faricimab + PRP
	Vitrectomy with or without endolaser	Vitrectomy with endolaser

- Safety Analysis Cohort: all randomized participants analyzed according to the initial treatment received, irrespective of treatment assignment (same as the primary analysis cohort).
- ITT Cohort: all randomized participants irrespective of treatment received, analyzed according to treatment assignment.
- PP Cohort: participants analyzed according to actual treatment received at baseline. Vitrectomy with endolaser group participants who do not receive the vitrectomy within 4 weeks of randomization, and participants in the faricimab + PRP group who do not complete the PRP sessions or the 3 faricimab injections within 90 days of randomization will be excluded. In addition, data from participants in either group that do not receive the treatment for recurrent PDR when the protocol-specified criteria are met will be

excluded after the visit when the criteria are met, and data from participants in either group who receive treatment for recurrent PDR without meeting the criteria will be excluded after the visit when treatment is performed.

- CC Cohort: same participants as the primary analysis cohort but excluding those with missing 3-year outcome data.

The approaches to handle missing data for the primary outcomes will be described separately for each outcome. Descriptive statistics will be estimated using observed data only (no imputed values).

9.6 Analysis of the Primary Outcomes

Estimation for Visual Acuity Outcome

The first primary outcome, change in visual acuity from baseline at 3 years, is a continuous outcome that will be evaluated in the primary analysis cohort. Descriptive statistics will include the mean, standard deviation, median and interquartile range for each analysis group. The test of equivalence will be conducted using the two-sided confidence interval approach, which is operationally equivalent to the two one-sided test (TOST) procedure.[28,29] The treatment effect will be described as a mean difference and 95% confidence interval using a linear mixed model with adjustment for baseline visual acuity and laterality, and a random intercept term for participant to account for the correlations arising from participants contributing two study eyes. The model-based standard error will be used in constructing the confidence interval for the treatment effect. The assumptions of linearity, normality and homoscedasticity will be assessed using graphical methods. If the 95% confidence interval of the treatment group difference is within the equivalence margin of (-5 to +5) letters, the null hypothesis will be rejected at the 2.5% significance level and the two treatment groups are considered equivalent; otherwise, the two treatment groups will not be considered equivalent. Estimand attributes:

- Treatment: Vitrectomy with endolaser vs. faricimab + PRP
- Population: Eyes with PDR requiring treatment (i.e., DRSS level 65 or worse on UWF-photo or NV meeting criteria for level 65 or worse on UWF-FA) and best corrected visual acuity ≥49 letters (20/100 Snellen equivalent or better)
- Variable: Change in visual acuity from baseline at 3 years
- Population-level summary: Mean difference between treatment groups in change in visual acuity from baseline at 3 years.

Missing data will be imputed using Markov Chain Monte Carlo (MCMC) multiple imputation (100 imputations), and variables included in the imputation model will be specified in the statistical analysis plan. The mean treatment group difference and 95% confidence interval for change in VA will be estimated from the imputed datasets. To aid in interpretation, a line plot of visual acuity over time with confidence intervals will be presented by treatment group without imputation for missing data.

Estimation for Post-Randomization PDR Treatments Outcome

The second primary outcome, number of post-randomization treatments for PDR (i.e., injections, PRP, or vitrectomies) over 3 years, is an ordinal outcome that will be evaluated in the primary analysis cohort. For both treatment groups, any faricimab injections or PRP received as part of the randomization treatment will not be included (i.e., the single faricimab injection received prior to vitrectomy among eyes in the vitrectomy with endolaser group, or among eyes in the faricimab + PRP group, the PRP and the 3 faricimab injections received within 90 days of randomization). Descriptive statistics will include the mean, standard deviation, median and interquartile range for each treatment group. The treatment effect will be described as a mean difference, 97.5% (or 95%) confidence interval, and a p-value calculated using a negative binomial regression model with adjustment for laterality, an offset term for the logarithmically transformed length of total follow-up period (in the number of years), and a random intercept term for participant to account for the correlations arising from participants contributing two study eyes. In the presence of zero-inflation, alternative methods such as zero-inflated or hurdle models may be considered.[35] The level of significance will be determined by whether the equivalence test to compare the visual acuity outcome reaches statistical significance (Sections 9.2 and 9.17). Estimand attributes:

- Treatment: Vitrectomy with endolaser vs. faricimab + PRP
- Population: Eyes with PDR requiring treatment (i.e., DRSS level 65 or worse on UWF-photo or NV meeting criteria for level 65 or worse on UWF-FA) and best corrected visual acuity ≥49 letters (20/100 Snellen equivalent or better)
- Variable: Number of post-randomization treatments for PDR over 3 years
- Population-level summary: Mean difference between treatment groups in the number of post-randomization PDR treatments over 3 years.

Missing data due to dropout will not be imputed. However, by scaling the count data to counts per unit of follow-up time (i.e., years), the offset term included in the model incorporates information about follow-up length for each eye, thus helping to mitigate the impact of missing observations.

Table 5 below specifies the types of foreseen intercurrent events, the approaches to handle the primary outcome data after the event, and the strategies for addressing intercurrent events as defined in *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials*.[36]

Table 5. Intercurrent Event Handling for the Primary Outcomes

Event	Variable Value	Strategy
Dropout (due to withdraw, loss to follow-up, or death)	VA outcome: Imputed PDR treatment outcome: Observed	Hypothetical
Receipt of alternative treatment for PDR	Observed	Treatment policy
Receipt of treatment for other conditions	Observed	Treatment policy

Event	Variable Value	Strategy
Treatment discontinuation	Observed	Treatment policy
Development of other conditions/ adverse events	Observed	Treatment policy

Sensitivity analyses will include adjustment for random site effects, ITT analysis, per protocol analysis, complete case analysis, nonparametric analysis, and alternative methods for handling missing data. Additional sensitivity analysis will be performed in the primary analysis cohort with adjustment for baseline factors that appear imbalanced between analysis groups and/or possibly associated with deviations of randomized treatment. Details will be specified in the statistical analysis plan.

9.7 Analysis of the Secondary Outcomes

The primary analysis cohort will be used for the analyses of all secondary endpoints. Treatment group comparisons will be performed with tests of superiority. All secondary outcome analyses will be considered exploratory and hypothesis-generating and therefore will not be used to draw definitive conclusions.

Development of vitreous hemorrhage during follow-up over 3 years causing vision loss of at least 5 letters not attributable to another cause is a time-to-event outcome whose 3-year incidence and 95% confidence interval will be estimated using the Kaplan-Meier method. Data from eyes that did not experience the outcome event will be censored on the date of the last completed visit. All event and censoring times will be grouped according to the visit window in which they occur. Visit windows will be contiguous and defined in the Statistical Analysis Plan. Cox proportional hazards regression will be performed to obtain a hazard ratio, 95% confidence interval, and a p-value for the treatment effect. A robust sandwich estimate of the covariance matrix will be used to account for the correlation between the 2 study eyes of the same participant. The proportional hazards assumptions will be evaluated by testing the interaction of covariates with time and checking Martingale residuals.

Presence of active neovascularization on fundus photos and FA and presence of macula threatening tractional retinal detachment on fundus photos and FA over 3 years are binary outcomes which will be analyzed using generalized linear mixed models with adjustment for time (i.e., 1-, 2-, and 3-year) as a categorical covariate, and a random intercept term for participant to account for the correlations arising from participants contributing two study eyes. The treatment group difference in the overall trend will be tested first; if there is evidence suggesting that the difference varies by time, the treatment group difference will be estimated at each annual time point.

Change in visual acuity from baseline over 3 years area under the curve (AUC) is a continuous outcome which will be calculated by the trapezoidal rule using all protocol visits as detailed in the Statistical Analysis Plan. Change in visual acuity from baseline at 1 year and 2 years are continuous outcomes. The analyses of these VA outcomes will use the imputed data sets created for the primary VA outcome. A linear mixed model similar to the analysis of the primary VA outcome will be performed to obtain an adjusted mean difference, confidence interval, and a P-value for the treatment effect.

Number of visits over 3 years is an ordinal outcome. Only unilateral participants (i.e., participants with only one study eye) will be included. Descriptive statistics will include the mean, standard deviation, median and interquartile range for each treatment group. Missing data will not be imputed. The treatment effect will be described as a mean difference, 95% confidence interval, and a p-value calculated using a negative binomial regression model with the robust sandwich estimator for the variance.

Number of post-randomization in-office procedures for PDR (i.e., injections or PRP), and number of post-randomization treatments for PDR by type (i.e., injection, PRP, or vitrectomy) over 3 years are ordinal outcomes. Descriptive statistics will include the mean, standard deviation, median and interquartile range for each treatment group based on the observed data. Mean difference, confidence interval, and a P-value for the composite outcome will be calculated using a negative binomial regression model similar to the analysis of the primary treatment outcome.

As with the primary outcome, all model assumptions will be verified and appropriate summary statistics for each outcome over time will be plotted by treatment group using observed data to aid in interpretation of data. The robust sandwich estimator will be used in calculating the variance. If model assumptions are not satisfied, data transformation or a nonparametric analysis will be considered. Medians and interquartile ranges and/or means and standard deviations of the outcome by treatment will be reported to describe the distribution of the data and confidence intervals will be constructed where appropriate. All exploratory analyses will be considered exploratory and therefore will not be used to draw definitive conclusions.

9.8 Exploratory Analyses

The analysis of exploratory outcomes will include descriptive statistics appropriate to the distribution by treatment group. The treatment group comparisons will mimic the analysis of primary and secondary outcomes, but no p-values will be included (i.e., only point estimate and 2-sided confidence interval will be reported). Statistical methods for exploratory analyses will be detailed in the Statistical Analysis Plan.

9.9 Safety Analyses

The analysis of safety outcomes will include descriptive statistics by the analysis group assigned according to the initial treatment received among all randomized participants (safety analysis cohort; Section 9.5). All reportable adverse events (AEs) will be categorized as ocular or systemic. All events will be tabulated by treatment group in a listing of each reported Medical Dictionary for Regulatory Activities (MedDRA) term and summarized over each MedDRA System Organ Class. For each ocular AE, the number of events and the number and percentage of eyes that had the event will be reported separately for study and non-study eyes. For each type of ocular adverse events, the percentage of eyes that had at least one event will be compared between treatment groups using logistic regression with conditional standardization and robust variance estimation to obtain odds ratios, 95% confidence intervals, and *P* values. The risk difference and 95% confidence interval will be estimated using the delta method.[37] If the total number of an event is small (i.e., <5 events in each treatment group), Barnard's unconditional

exact test will be performed without adjustment for the correlation between eyes. Outcomes marked with an asterisk (*) will be tabulated without statistical comparisons.

The following ocular adverse events will be assessed:

- Endophthalmitis
- Any retinal detachment
    - Rhegmatogenous retinal detachment*
    - Tractional retinal detachment*
- Retinal tear
- Increased intraocular pressure
    - Increase in IOP ≥ 10 mmHg from baseline*
    - IOP ≥ 30 mmHg at a follow-up visit*
    - Initiation of medication to lower IOP that was not in use at baseline*
    - Glaucoma procedure*
- Neovascularization of the iris
- Ocular Inflammation
- Cataract extraction (among eyes that are phakic at baseline)
- Visually significant cataract on clinical exam
- Intraocular hemorrhage

For each systemic AE, the number of events and the number and percentage of participants that had the event will be reported. Systemic adverse events will be reported in three groups according to initial treatment group assigned to each of the eyes for the primary analysis: 1) unilateral participants in the vitrectomy with endolaser group and bilateral participants with both eyes in the vitrectomy with endolaser group, 2) unilateral participants in the faricimab + PRP group and bilateral participants with both eyes in the faricimab + PRP group, and 3) bilateral participants with one eye in the vitrectomy with endolaser group and one eye in the faricimab + PRP group. For each type of systemic adverse events, the percentage of participants with at least one event will be compared between treatment groups using Fisher's exact test.

The following systemic adverse events will be assessed:

- Death
- Any serious adverse event
- Hospitalization

- Cerebrovascular/cardiovascular events as defined by the Antiplatelet Trialists' Collaboration
    - Includes non-fatal myocardial infarction, non-fatal stroke, death of unknown cause, and death attributed to cardiac, cerebral, hemorrhagic, embolic, or other vascular cause (does not need to be ischemic in origin). Antiplatelet Trialists' Collaboration. BMJ. 1994 Jan 8; 308 (6921):81-106.[38]

9.10 Analysis of Ancillary Outcomes

Analysis of the ancillary outcomes (Objective Field Analyzer) will be described in a separate analysis plan.

9.11 Economic Analysis

The economic analysis aims to compare costs between the treatment groups. The frequencies of clinic visits and diagnostic procedures (e.g., OCT, fundus photography, FA), office procedures (e.g., PRP, study injections), and repeat vitrectomy will be considered. An average medical cost per patient for each treatment arm using the Medicare Fee Schedule will be estimated and an incremental cost-effectiveness ratio (ICER) will be calculated in addition to other summary measures that include non-medical costs.

9.12 Intervention Adherence

Intervention adherence will be defined as receipt of all study treatment required per protocol.

9.13 Protocol Adherence and Retention

Protocol deviations and visit completion rates (excluding participants who die before the end of the visit window) will be tabulated for each treatment group.

9.14 Baseline Descriptive Statistics

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

9.15 Planned Interim Analyses

There is no formal interim analysis planned for this study, as enrollment is expected to be completed before any participants complete three years of follow-up. Furthermore, as both treatments are presumed to have permanent effects, interim trial results will be uninformative regarding the potential benefits or risks to study participants of switching to the other treatment. The Data and Safety Monitoring Committee will review interim study data at approximately 6-month intervals and will have the option to recommend stopping the study. In addition, the cumulative incidence of the following adverse events will be provided at each DSMC meeting for safety monitoring:

- Retinal detachment
- Retinal tear

- Overall and by indication (i.e., pre-existing vs. complication)
- Cataract
- Endophthalmitis
- Vision loss (defined as loss of ≤15 letters at a single visit or ≤10 letters at two consecutive visits)
- Unanticipated inflammatory response (including vasculitis)

9.16 Sub-Group Analyses

Subgroup analyses, i.e., assessments of effect modification, will be conducted for the primary outcomes. These analyses will be considered exploratory. The study is not powered to detect subgroup effects, and a lack of significance is not necessarily an indication that subgroup effects do not exist. Interpretation of the analyses will depend on whether the primary analysis establishes equivalence or demonstrates a significant treatment group difference.

The general approach for subgroup analyses will be to add an interaction term for the subgroup factor by treatment into the primary analysis model. Subgroup analyses will use the complete case cohort. Within-subgroup adjusted mean differences for the treatment effects with confidence intervals (but not p-values) will be estimated from the interaction model and presented as a forest plot.

The subgroups of interest will include:

- Extent of retinal nonperfusion: continuous and categorized by tertiles
- Degree of vitreous adherence on OCT at baseline
-

Details on the subgroup factors, such as hypothesized mechanism for and direction of subgroup differences, will be provided in the Statistical Analysis Plan.

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

To increase statistical precision, subgroup analyses will only be conducted if there are at least 20 eyes per treatment group in each subgroup where 36-month data was available.

9.17 Multiplicity Comparisons/Multiplicity

For the primary analyses, the fixed sequence method with the fallback procedure will be used to control the familywise error rate for the two primary outcomes. Both primary outcomes will be tested. The hypothesis testing for change in visual acuity outcome will be performed first with alpha of 2.5%. If the null hypothesis for the VA outcome is rejected, the number of post-randomization treatments for PDR will be compared with alpha of 5%; if the null hypothesis for the VA outcome is not rejected, the number of post-randomization treatments for PDR will be

compared with alpha of 2.5%. In addition to the estimates of the treatment effect, the associated confidence intervals will be presented for both outcomes.

The testing sequence is as follows:

1. Change in visual acuity from baseline at 3 years
2. Number of post-randomization treatments for PDR over 3 years

For the analyses of the secondary outcomes, the treatment group differences will be estimated regardless of the results from the primary outcome analyses. False discovery rate (FDR) will be controlled using the adaptive Benjamini Hochberg procedure with < .05 as the threshold for statistical significance.[39] The FDR method will be applied for all secondary outcomes.

There will be no formal adjustment for multiplicity in sensitivity, subgroup, or safety analyses. For exploratory analyses, all will be considered exploratory rather than definitive, and p-values will not be reported, irrespective of the results from the analysis of primary and secondary outcomes.

9.18 Additional Tabulations and Analyses

The following outcomes will be presented with summary statistics and no statistical comparisons will be performed:

- For eyes in the vitrectomy with endolaser group:
    - number of eyes with surgical complications
    - number of eyes adhered to the treatment regimen protocol
    - Visual acuity at 3 years by adherence of the hyaloid on baseline OCT
    - Number of eyes that have baseline adherence of vitreous in macular or optic nerve head OCTs and then demonstrate post-surgical absence of vitreous adherence based on reading center grading of OCT parameters that help visualize vitreous interface
- For eyes in the faricimab + PRP group:
    - number of PRP sessions
    - number of burns
    - number of eyes adhered to the treatment regimen protocol
    - number of eyes with presence of vitreous adherence at baseline and over time using OCT parameters that help visualize vitreous interface
    - Number of eyes with changes in vitreous adherence over time using OCT parameters that help visualize vitreous interface

9.19 Outliers

To ensure that statistical outliers do not have undue impact on analyses of the continuous outcome, change in visual acuity from baseline will be truncated to ±3 standard deviations based on the overall mean and standard deviation from the two treatment groups combined at the 3-year visit. Truncation will occur after imputation where applicable.

Chapter 10: Data Collection and Monitoring

10.1 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 (reading centers) will be provided directly to the Coordinating Center. Reading center grading will not be made available to the site.

10.2 Study Records Retention

Each participating site and vendor 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.

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.

10.3 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.

10.4 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. A significant (or major) deviation is any deviation that departs from the established materials in such a way that it poses an increase in the risk to subjects, adversely affects the welfare, rights, or safety of the research subjects, or negatively influences the scientific study integrity. As a result of significant deviations, corrective and preventive 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 11: Ethics/Protection of Human Participants

11.1 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.

11.2 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.

11.3 Informed Consent Process

11.3.1 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 physician(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.

11.3.1.1 Adults that Lack Capacity to Consent

In the event that a potential participant may lack the capacity to consent for oneself, the investigator must obtain documentation of that person's status and assignment to a legally authorized representative (LAR) in accordance with local laws and regulations, and institutional policy and procedures. For example, the investigator and another non-interested party (e.g., other physician that is not an investigator) may be required to make a documented assessment, and a social worker on behalf of the institution may be required to have legal documentation of LAR

designation. When a LAR is consenting on behalf of a participant that lacks capacity to consent, this documentation must be made available for monitoring.

11.3.2 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. Study participant's contact information will be securely stored and will be destroyed at the end of the study at JCHR.

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 JCHR.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained 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.

11.3.3 Future Use of Stored Data

Data collected for this study will be analyzed and stored at JCHR. 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.

Chapter 12: References

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