Official Title: A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab in Patients With Macular Edema Secondary to Central Retinal or Hemiretinal Vein Occlusion

NCT Number: NCT04740931

Document Date: Protocol Version 2: 17-November-2020

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FARICIMAB IN PATIENTS WITH MACULAR EDEMA SECONDARY TO CENTRAL RETINAL OR HEMIRETINAL VEIN OCCLUSION**
PROTOCOL NUMBER:	GR41986
STUDY NAME:	COMINO
VERSION NUMBER:	*2*
EUDRACT NUMBER:	2020-000441-1*3*
IND NUMBER:	119225
NCT NUMBER:	To be determined
TEST PRODUCT:	Faricimab (RO6867461)
MEDICAL MONITOR:	[redacted], M.B.B.S., M.S.
SPONSOR:	F. Hoffmann-La Roche Ltd
***APPROVAL* DATE:**	See electronic date stamp below.

PROTOCOL *AMENDMENT* APPROVAL

Date and Time (UTC)	Title	Approver's Name
17-Nov-2020 03:42:01	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
1	3 April 2020

PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

Protocol GR41986 has been amended primarily to increase the patient sample size and to correct the best-corrected visual acuity (BCVA) stratification error. Changes to the protocol, along with a rationale for each change, are summarized below:

- Language has been added to allow the Sponsor to propose exploratory substudies associated with protocol GR41986 (Section 2.6).
- Due to extenuating circumstances, such as the COVID-19 pandemic, patients may not have the ability to complete certain trial activities, therefore, in order to ensure adequate power for the primary endpoint, the sample size has been increased to mitigate the loss of patients, loss of data, and the potential impact of protocol deviations affecting efficacy analyses (Sections 3.1.1, 3.1.1.1, 4.1, 6, 6.1, 9.5).
- To correct the BCVA stratification error (Sections 3.1.1.1, 4.2.1, 6.5).
- It has been clarified that missed mandatory pharmacokinetic, pharmacodynamic, or anti-drug antibody samples may be obtained at the next scheduled visit the patient attends (Section 3.1.2 and Appendix 1).
- Language has been added to indicate that sites can confirm that appropriate temperature conditions have been maintained during investigational medicinal product transit either by time monitoring (shipment arrival date and time) or temperature monitoring (Section 4.3.3).
- Administration of the National Eye Institute 25-Item Visual Functioning Questionnaire (NEI VFQ-25) was clarified (Section 4.5.8.1).
- The Medical Monitors and Emergency Medical Contacts have been updated (Section 5.4.1).
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- The faricimab-pooled safety population has been clarified (Section 6.2.5).
- The immunogenicity analysis population has been clarified (Section 6.2.7).
- The name of a Roche policy on data sharing has been corrected (Section 9.6).
- Pages have been updated and added to the NEI VFQ-25 (Appendix 10).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL *AMENDMENT* ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FARICIMAB IN PATIENTS WITH MACULAR EDEMA SECONDARY TO CENTRAL RETINAL OR HEMIRETINAL VEIN OCCLUSION**
PROTOCOL NUMBER:	GR41986
STUDY NAME:	COMINO
VERSION NUMBER:	*2*
EUDRACT NUMBER:	2020-000441-13
IND NUMBER:	119225
NCT NUMBER:	To be determined
TEST PRODUCT:	Faricimab (RO6867461)
MEDICAL MONITOR:	[redacted], M.B.B.S., M.S.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FARICIMAB IN PATIENTS WITH MACULAR EDEMA SECONDARY TO CENTRAL RETINAL OR HEMIRETINAL VEIN OCCLUSION**
PROTOCOL NUMBER:	GR41986
STUDY NAME:	COMINO
VERSION NUMBER:	*2*
EUDRACT NUMBER:	2020-000441-13
IND NUMBER:	119225
NCT NUMBER:	To be determined
TEST PRODUCT:	Faricimab (RO6867461)
PHASE:	III
INDICATION:	Macular edema secondary to central retinal or hemiretinal vein occlusion
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of faricimab compared with aflibercept in patients with macular edema due to central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO) up to the primary endpoint at Week 24. Efficacy, safety, and pharmacokinetics of faricimab administered according to the personalized treatment interval (PTI) dosing regimen (i.e., from every 4 weeks [Q4W] to every 16 weeks [Q16W]) will be assessed during the study period from Weeks 24 to 72. Specific objectives and corresponding endpoints for the study are outlined below.

EFFICACY OBJECTIVES

For efficacy endpoint evaluation, best-corrected visual acuity (BCVA) will be assessed on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart at a starting test distance of 4 meters.

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of faricimab 6 mg intravitreal (IVT) Q4W compared with aflibercept 2 mg IVT Q4W on the basis of the following endpoint:

- Change from baseline in BCVA at Week 24

Secondary Efficacy Objectives

The secondary efficacy objective for Part 1 of this study (i.e., through Week 24) is to evaluate the efficacy of faricimab compared with aflibercept on the basis of the following endpoints:

- Change from baseline in BCVA at specified timepoints through Week 24
- Proportion of patients *gaining* ≥15 letters in BCVA *from baseline* at Week 24

- Proportion of patients *gaining* $\geq 15, \geq 10, \geq 5$, or > 0 letters in BCVA *from baseline* at specified timepoints through Week 24
- Proportion of patients avoiding a loss of $\geq 15, \geq 10, \geq 5$, or > 0 letters in BCVA from baseline at specified timepoints through Week 24
- Proportion of patients achieving ≥ 84 letters (20/20 Snellen equivalent) in BCVA at specified timepoints through Week 24
- Proportion of patients with BCVA Snellen equivalent of 20/40 or better at specified timepoints through Week 24
- Proportion of patients with BCVA Snellen equivalent of 20/200 or worse at specified timepoints through Week 24
- Change from baseline in central subfield thickness (CST) at specified timepoints through Week 24
- Change from baseline in National Eye Institute 25-Item Visual Functioning Questionnaire (NEI VFQ-25) composite score at specified timepoints through Week 24

The secondary efficacy objective for Part 2 of this study (i.e., Week 24 through Week 72) is to evaluate the efficacy of faricimab administered according to the PTI dosing regimen on the basis of the following endpoints*:*

- Change from baseline in BCVA at specified timepoints from Week 24 through Week 72
- Proportion of patients *gaining* ≥ 15 letters in BCVA *from baseline* at Week *72*
- Proportion of patients *gaining* $\geq 15, \geq 10, \geq 5$, or > 0 letters in BCVA *from baseline* at specified timepoints from Week 24 through Week 72
- Proportion of patients avoiding a loss of $\geq 15, \geq 10, \geq 5$, or > 0 letters in BCVA from baseline at specified timepoints from Week 24 through Week 72
- Proportion of patients achieving ≥ 84 letters (20/20 Snellen equivalent) in BCVA at specified timepoints from Week 24 through Week 72
- Proportion of patients with BCVA Snellen equivalent of 20/40 or better at specified timepoints from Week 24 through Week 72
- Proportion of patients with BCVA Snellen equivalent of 20/200 or worse at specified timepoints from Week 24 through Week 72
- Change from Week 24 in BCVA at specified timepoints through Week 72
- Proportion of patients avoiding a loss of $\geq 15, \geq 10, \geq 5$, or > 0 letters in BCVA from Week 24 through Week 72
- Proportion of patients on a Q4W, every 8 weeks (Q8W), every 12 weeks (Q12W), or Q16W treatment interval at Week 72
- Number of study drug injections received from Week 24 through Week 72
- Change from baseline in CST at specified timepoints from Week 24 through Week 72
- Change from baseline in NEI VFQ-25 composite score at specified timepoints from Week 24 through Week 72

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of faricimab on the basis of the following endpoints*:*

- Proportion of patients with absence of retinal ischemia on fundus fluorescein angiography (FFA) and on optical coherence tomography angiography (OCT-A) (optional) over time (at specified timepoints)
- Change from baseline in area of retinal ischemia on FFA and on OCT-A (optional) over time
- Proportion of patients with vascular leakage on FFA and on OCT-A (optional) over time
- Change from baseline in area of vascular leakage on FFA, and on OCT-A (optional) over time

- Change from baseline in foveal avascular zone and other exploratory outputs defined in the Statistical Analysis Plan (SAP) on OCT-A (optional) over time
- Proportion of patients with absence of retinal neovascularization over time (per investigator assessment)
- Proportion of patients with absence of vitreal, preretinal, or subretinal hemorrhage over time (per investigator assessment)
- Proportion of patients with absence of anterior segment (iris and anterior chamber angle) neovascularization over time
- Proportion of patients requiring panretinal photocoagulation at any time during the study
- Proportion of patients with absence of macular edema, defined as CST of ≤325 μm for Spectralis spectral-domain optical coherence tomography (SD-OCT), or ≤315 μm for Cirrus SD-OCT or Topcon SD-OCT, over time
- Proportion of patients with absence of intraretinal fluid over time
- Proportion of patients with absence of subretinal fluid over time
- Proportion of patients with absence of both intraretinal fluid and subretinal fluid over time
- Proportion of patients with absence of intraretinal cysts over time
- Change from baseline in NEI VFQ-25 near activities–subscale score and distance activities–subscale scores over time

SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of faricimab on the basis of the following endpoints:

- Incidence and severity of ocular adverse events, with severity determined according to Adverse Event Severity Grading Scale
- Incidence and severity of non-ocular adverse events, with severity determined according to Adverse Event Severity Grading Scale

PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to characterize the faricimab PK profile on the basis of the following endpoint:

- Plasma concentration of faricimab over time

The exploratory PK objective for this study is to explore the concentration–effect relationship for visual acuity and other endpoints (e.g., anatomic measures) on the basis of the following endpoint:

- Concentration of faricimab and the change in BCVA or other endpoints (e.g., anatomical markers) over time

IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the antibody immune response to faricimab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

EXPLORATORY BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to faricimab (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of faricimab activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers in plasma (listed in Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., the frequency of faricimab administration) over time
- Relationship between anatomic measures and visual acuity

EXPLORATORY SUBSTUDY

At selected sites, the Sponsor may propose exploratory substudies associated with the Study GR41986 protocol. Each substudy will be documented in a separate substudy protocol and will have a separate associated Informed Consent Form.

STUDY DESIGN

DESCRIPTION OF STUDY

This is a Phase III, multicenter, randomized, double-masked, active comparator–controlled, parallel-group study evaluating the efficacy, safety, and pharmacokinetics of faricimab administered by IVT injection at 4-week intervals until Week 24, followed by a double-masked period of study without active control to evaluate faricimab administered according to a PTI dosing regimen in patients with macular edema due to CRVO or HRVO.

This study is comprised of two parts: Part 1 (Day 1 through Week 24) will compare faricimab Q4W versus aflibercept (active comparator) Q4W; Part 2 (Weeks 24–72) will evaluate faricimab administered at masked treatment intervals of Q4W to Q16W based on PTI dosing criteria.

The study will consist of a screening period of up to 28 days (Days –28 to –1) and an approximately 68-week treatment period (Parts 1 and 2), followed by the final study visit at Week 72. All patients will complete scheduled study visits Q4W for the entire study duration (72 weeks). To preserve the masking of faricimab treatment intervals for Week 24 through Week 68, a sham procedure will be administered during study visits at which (according to the PTI dosing regimen) no faricimab treatment is administered.

Only one eye will be assigned as the study eye. If both eyes are considered eligible, the eye with the worse BCVA, as assessed at screening, will be selected as the study eye, unless the investigator deems the other eye to be more appropriate for treatment in the study.

There will be a minimum of two investigators per site to fulfill the masking requirements of the study. At least one investigator will be designated as the assessor physician who will be masked to each patient's treatment assignment and who will evaluate ocular assessments. At least one other investigator will be unmasked and will perform study treatments.

Patient recruitment is expected to take longer in China; therefore, a specific China enrollment plan may be established. After the global enrollment phase of the study has been completed, additional patients may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. The China extension may include current residents of mainland China, Hong Kong, or Taiwan enrolled at National Medical Products Administration (NMPA)-recognized sites. All Chinese patients enrolled in the global enrollment phase of the study will be included in the primary analysis of the study. Data from patients enrolled during the China extension will not be included in the primary analyses.

NUMBER OF PATIENTS

Approximately *750 patients* with macular edema due to CRVO or HRVO will be enrolled during the global enrollment phase of this study.

TARGET POPULATION

Inclusion Criteria

General Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 3 months after the final dose of study treatment. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For patients enrolled in the extended China enrollment phase at NMPA-recognized sites: current resident of mainland China, Hong Kong, or Taiwan, and of Chinese ancestry

Ocular Inclusion Criteria for Study Eye

Patients must also meet the following ocular criteria for study entry:

- Foveal center–involved macular edema due to CRVO or HRVO diagnosed no longer than 4 months prior to the screening visit and confirmed by central reading center (CRC) based on SD-OCT (or SS-OCT) images

  CRVO or HRVO is defined by retinal hemorrhages, telangiectatic capillary bed, dilated venous system or other biomicroscopic evidence of retinal vein occlusion (RVO; neovascularization, vitreous hemorrhages) in the entire retina (CRVO) or two quadrants of the retina (HRVO)
- BCVA of 73 to 19 letters, inclusive (20/40 to 20/400 approximate Snellen equivalent), as assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters (see the BCVA manual for additional details) on Day 1
- CST ≥325 μm, as measured on Spectralis SD-OCT, or ≥315 μm, as measured on Cirrus SD-OCT or Topcon SD-OCT at screening (SS-OCT acceptable after confirmation with CRC)
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

Exclusion Criteria

General Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Any major illness or major surgical procedure within 1 month before screening
- Active cancer within the 12 months prior to Day 1 except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤ 6 and a stable prostate-specific antigen for > 12 months
- Requirement for continuous use of any medications and treatments indicated in Section 4.4.2 (Prohibited Therapy)
- Systemic treatment for suspected or active systemic infection on Day 1

  Ongoing use of prophylactic antibiotic therapy may be acceptable if approved after discussion with the Medical Monitor.
- Any systemic corticosteroid use (e.g., oral or injectable) within 1 month of the screening visit
- Uncontrolled blood pressure, defined as systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg while a patient is at rest on Day 1

  If a patient's initial reading exceeds these values, a second reading may be taken later on the same day or on another day during the screening period. If the patient's blood pressure is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1.
- Stroke (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1
- History of other disease, metabolic dysfunction, physical examination finding, or historical or current clinical laboratory findings giving reasonable suspicion of a condition that contraindicates the use of the investigational drug or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator
- Pregnant or breastfeeding, or intending to become pregnant during the study

  Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to initiation of study drug. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab or aflibercept injections, study- related procedure preparations (including fluorescein), dilating drops, or any of the anesthetic and antimicrobial preparations used during the study
- Participation in an investigational trial that involves treatment with any drug or device (with the exception of vitamins and minerals) within 3 months prior to Day 1

Ocular Exclusion Criteria for Study Eye

Patients who meet any of the following ocular exclusion criteria for the study eye will be excluded from study entry:

- History of previous episodes of macular edema due to RVO or persistent macular edema due to RVO diagnosed more than 4 months before screening
- Increase of ≥ 10 letters in BCVA ETDRS score between screening and Day 1
- Any current ocular condition which, in the opinion of the investigator, is currently causing or could be expected to contribute to irreversible vision loss due to a cause other than macular edema due to RVO in the study eye (e.g., ischemic maculopathy, Irvine-Gass syndrome, foveal atrophy, foveal fibrosis, pigment abnormalities, dense subfoveal hard exudates, or other non-retinal conditions)
- Current visually significant vitreous hemorrhage on Day 1
- History of retinal detachment or macular hole (Stage 3 or 4)
- Tractional retinal detachment, vitreomacular traction, full thickness macular hole or epiretinal membrane involving the fovea or disrupting the macular architecture in the study eye, as evaluated by the CRC and described in the CRC manual

- Diagnosis of diabetic retinopathy (DR) moderate non-proliferative or worse, proliferative DR, diabetic macular edema (DME), neovascular age-related macular degeneration (nAMD), geographic atrophy, myopic choroidal neovascularization as assessed by the investigator
- Active rubeosis, angle neovascularization, neovascular glaucoma
- Aphakia or implantation of anterior chamber intraocular lens
- Any cataract surgery or treatment for complications of cataract surgery with steroids or YAG (yttrium-aluminum-garnet) laser capsulotomy within 3 months prior to Day 1
- Any other intraocular surgery (e.g., pars plana vitrectomy, scleral buckle, glaucoma surgery, corneal transplant, or radiotherapy)
- Any prior or current treatment for macular edema due to RVO, including anti–vascular endothelial growth factor (VEGF) IVT for macular edema due to RVO
- Macular laser (focal/grid) in the study eye at any time prior to Day 1
- Panretinal photocoagulation in the study eye within 3 months prior to Day 1 or anticipated within 3 months of study start on Day 1
- Any IVT treatment for any other retinal diseases that can lead to macular edema complication
- Any prior or current treatment for macular edema; macular neovascularization, including DME and nAMD; and vitreomacular-interface abnormalities, including, but not restricted to, IVT treatment with anti-VEGF, steroids, tissue plasminogen activator, ocriplasmin, C3F8, air or periocular injection
- Any prior intervention with verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or vitreo-retinal surgery including *sheathotomy*
- Any prior steroid implant use including dexamethasone intravitreal implant (Ozurdex®) and fluocinolone acetonide intravitreal implant (Iluvien®)
- Prior periocular pharmacological or IVT treatment (including anti-VEGF medication) for other retinal diseases

Ocular Exclusion Criteria for Fellow (Non-Study) Eye

Patients who meet the following ocular exclusion criterion for the fellow (non-study) eye at both screening and Day 1 will be excluded from study entry:

- Non-functioning fellow eye, defined as either one of the following:
  - BCVA 20/320 or worse
  - No physical presence of fellow eye (i.e., monocular)

Ocular Exclusion Criteria for Both Eyes

Patients who meet any of the following ocular exclusion criteria for both eyes will be excluded from study entry:

- Prior IVT administration of faricimab in either eye
- History of idiopathic or autoimmune-associated uveitis in either eye
- Active periocular, ocular or intraocular inflammation or infection (including suspected) in either eye on Day 1

END OF STUDY

The study consists of two enrollment phases: the global enrollment phase, during which patients are recruited globally; and an optional China extension phase, during which additional patients may be recruited in China to support registration in China.

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, including patients from the optional China extension. The end of the study is expected to occur approximately 72 weeks after the last patient is randomized.

The Sponsor may decide to terminate the study at any time.

LENGTH OF STUDY

The total length of the study (excluding the China extension) from screening of the first patient to the LPLV for patients from the global enrollment phase is expected to be approximately 34 months.

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCT (INVESTIGATIONAL DRUG)

In Part 1 of the study, patients randomly assigned to Arm A will receive faricimab 6 mg IVT Q4W from Day 1 through Week 20, for a total of 6 injections.

In Part 2 of the study, patients randomly assigned to both Arms A and B will receive faricimab 6 mg IVT administered according to a PTI dosing regimen in intervals between Q4W and Q16W. At faricimab dosing visits, treatment intervals will be maintained or adjusted (i.e., increased by 4 weeks or decreased by 4, 8, or 12 weeks), based on CST and BCVA values. Patients will therefore receive between 3 and 12 injections during the period from Week 24 through Week 68.

COMPARATOR

In Part 1 of the study, patients randomly assigned to Arm B will receive aflibercept 2 mg IVT Q4W from Day 1 through Week 20, for a total of 6 injections.

SHAM PROCEDURE

During Part 2 of the study, to preserve the masking of faricimab treatment intervals, the sham procedure will be administered to patients in both Arms A and B during study visits at which (according to the PTI dosing regimen) no faricimab treatment is administered. The sham vial is empty and will remain empty throughout the sham treatment. The sham is a procedure that mimics an IVT injection and involves the blunt end of an empty syringe (without a needle) being pressed against the anesthetized eye.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary and secondary efficacy analyses will be based on the intent-to-treat (ITT) population, unless otherwise specified, with patients grouped according to the treatment assigned at randomization. Additional analysis based on the per-protocol population will also be conducted for the primary endpoint.

The primary comparison will be between the active comparator (aflibercept Q4W) and faricimab Q4W at Week 24. The following hypothesis will be tested:

- Non-inferiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population (at a 1-sided 0.025 significance level)
- Superiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population (at a 2-sided 0.05 significance level)

The primary analysis will be performed using the mixed-effect model with repeated measures (MMRM) based on all available data up to Week 24. All observed measurements will be included in the analysis regardless whether or not a patient has an intercurrent event. Missing data will be implicitly imputed by the MMRM model, assuming a missing at random mechanism.

The MMRM model will include the change from baseline at Weeks 4–24 as the response variable and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, the continuous baseline value for the response variable (in this case, baseline BCVA), as well as randomization stratification factors as fixed effects. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, a heterogeneous compound symmetry or an AR(1) covariance structure may be fitted.

DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on patients enrolled in the global enrollment phase. The global enrollment phase will enroll approximately $750\ patients$. Patients will be randomized in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B).

A sample size of approximately $375\ patients$ in each arm will provide $>$90% power to show non-inferiority of faricimab to aflibercept in the change in BCVA at Week 24 in the ITT population, using a non-inferiority margin of 4 letters, and under the following assumptions:

- No difference in the mean change from baseline in BCVA between the two treatment arms
- SD of 13 letters for the change from baseline in BCVA at Week 24
- Two-sample $t\text{-}tests$
- 2.5% one-sided type I error rate
- 10% dropout rate

Furthermore, a sample size of approximately $375\ patients$ per arm will provide greater than 80% power to show a 3.5-letter superiority of faricimab over aflibercept in the ITT population, under the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 5%.

INTERIM ANALYSES

There are no prospectively planned interim efficacy or futility analyses.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
BCVA	best-corrected visual acuity
BRVO	branch retinal vein occlusion
CFP	color fundus photograph
CNV	choroidal neovascularization
CRC	central reading center
CRVO	central retinal vein occlusion
CST	central subfield thickness
DME	diabetic macular edema
DR	diabetic retinopathy
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FFA	fundus fluorescein angiography
HIPAA	Health Insurance Portability and Accountability Act
HRVO	hemiretinal vein occlusion
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intent-to-treat (population)
IVT	intravitreal
IxRS	interactive web-based response system
LPLV	last patient, last visit
MMRM	mixed model for repeated measures
nAMD	neovascular age-related macular degeneration
NEI VFQ-25	National Eye Institute 25-Item Visual Functioning Questionnaire
NIMP	non-investigational medicinal product
NMPA	(China) National Medical Products Administration
OCT	optical coherence tomography

Abbreviation	Definition
OCT-A	optical coherence tomography–angiography
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient-reported outcome
PTI	personalized treatment interval
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
Q16W	every 16 weeks
RBR	Research Biosample Repository
RVO	retinal vein occlusion
SAP	Statistical Analysis Plan
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SmPC	Summary of Product Characteristics
SS-OCT	swept-source optical coherence tomography
Tie2	TEK receptor tyrosine kinase-2
ULN	upper limit of normal
USPI	U.S. Package Insert
UWF	ultrawide field
VA	visual acuity
VEGF (-A)	vascular endothelial growth factor (–A)
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON RETINAL VEIN OCCLUSION

Retinal vein occlusion (RVO) is one of the most common retinal vascular disorders and is associated with varying degrees of visual loss (Hayreh and Zimmerman 1994). RVO has been reported as the second leading cause of blindness for patients with retinal vascular disease, following diabetic retinopathy (DR) (Cugati et al. 2006; Klein et al. 2008; Rogers et al. 2010; Yasuda et al. 2010). The main types of RVO include branch retinal vein occlusion (BRVO), hemiretinal vein occlusion (HRVO), and central retinal vein occlusion (CRVO).

The most common presenting complaint of RVO is an abrupt, painless decrease of central vision due to macular edema. Less frequently, patients may present with a history of transient vision loss, lasting a few seconds to minutes, with complete recovery of vision. These symptoms may recur over several days to weeks, followed by a permanent decrease in vision. Metamorphopsia and visual field defects have also been described (Achiron et al. 2015; Manabe et al. 2017).

The pathogenesis of macular edema in these patients starts with an increase in intraluminal pressure due to vascular obstruction, which causes areas of reduced perfusion and ischemia. Ischemia leads to up-regulation and secretion of vascular endothelial growth factor (VEGF) (Boyd et al. 2002; Noma et al. 2006) and angiopoietin-2 (Ang-2), both well-known proangiogenic and vessel hyperpermeability cytokines with Ang-2 contributing additional pro-inflammatory and vessel destabilization properties (Maisonpierre at al. 1997; Hackett et al 2000; Fiedler et al 2006). Patients with RVO were found to have the highest vitreous levels of both Ang-2 and VEGF among all retinal vascular diseases (Aiello et al 1994; Regula et al. 2016). Increased levels of Ang-2 and VEGF in retinal tissue result in pathological changes in the retina, and in many patients also *leads to* macular edema *that is* accompanied with *a* decrease in vision. A hallmark of RVO is the characteristic pattern of retinal hemorrhages, tortuous and dilated retinal veins across the affected area of retina (one quadrant in BRVO, two quadrants in HRVO and the entire retina in CRVO). In more severe cases, patients can develop retinal ischemia with subsequent retinal neovascularization, hemorrhages, neovascularization in the anterior segment leading to rubeosis or neovascular glaucoma, and some patients may develop optic disc edema.

Although macular edema due to RVO and diabetic macular edema (DME) have different origins, they share a common pathophysiology. Both are characterized by a thickening of the macula due to fluid accumulation consequent to breakdown of the blood-retinal barrier and a pathological increase of retinal vessel permeability, which can lead to irreversible vision loss in both diseases.

Anti-VEGF pharmacotherapy is the current mainstay of treatment in macular edema due to RVO and has demonstrated efficacy across several pivotal, randomized clinical studies, although macular laser and intravitreal (IVT) steroids—especially steroid implants—are also used in some cases. Despite anti-VEGF being the most effective therapy for macular edema due to RVO, data from anti-VEGF clinical trials showed that many patients do not achieve optimal best-corrected visual acuity (BCVA) and anatomical outcomes, and many require frequent long-term injections to maintain the gains achieved during initial intensive treatment. Moreover, real-world data analyses suggested that many patients with RVO do not achieve the gains reached in clinical trials due to suboptimal injection frequency (Vaz-Pereira et al. 2017; Wecker et al. 2017; Jumper et al. 2018; LUMINOUS and OCEAN unpublished data). The data suggest that many patients with macular edema due to BRVO and the majority of patients with macular edema due to CRVO require close monitoring and treatment for longer *periods* of time and that more durable and efficacious treatment options are needed (Bhisitkul et al. 2012; Scott et al. 2019).

1.2 BACKGROUND ON FARICIMAB

Faricimab is a humanized full-length bispecific IgG1 monoclonal antibody that selectively binds to all isoforms of VEGF-A (hereafter referred to as "VEGF") and Ang-2, key factors involved in mediating the pathophysiology of macular edema due to RVO. The Ang-2– and VEGF-binding variable regions of faricimab bind to Ang-2 and VEGF independently and simultaneously with high affinity. The Fc portion of faricimab was engineered for ophthalmic use through inactivation of the effector function (FcRγ) and elimination of binding to the neonatal receptor (FcRn), which has the potential to reduce systemic exposure following IVT injection.

Nonclinical studies have shown that Ang-2 and VEGF act in concert to regulate the vasculature and to increase retinal endothelial cell permeability in vitro. Simultaneous inhibition of Ang-2 and VEGF with the bispecific monoclonal antibody faricimab led to a greater reduction in the leakiness and severity of choroidal neovascularization (CNV) lesions in a laser-induced CNV model in non-human primates compared with the molar equivalent of anti–VEGF (ranibizumab) or anti–Ang-2 alone. Earlier experiments using a mouse model of spontaneous CNV showed that dual inhibition of Ang-2 and VEGF consistently outperformed monotherapeutic inhibition of either target alone in terms of reduction in vascular growth, leakage, edema, leukocyte infiltration, and photoreceptor loss (Regula et al. 2016).

In addition, aqueous and vitreous concentrations of both Ang-2 and VEGF were shown to be upregulated in patients with neovascular age-related macular degeneration (nAMD), DR, and RVO (Tong et al 2006; Penn et al. 2008; Kinnunen et al. 2009; Tuuminen and Loukovaara 2014; Regula et al. 2016; Ng et al. 2017). Therefore, simultaneous neutralization of both targets, Ang-2 and VEGF, may further normalize the pathological ocular vasculature compared with anti-VEGF therapy alone. Data from the

completed Phase II studies in DME and nAMD (see below) also support the hypothesis that targeting Ang-2 has the potential to extend the durability of effect beyond anti-VEGF therapy alone in diseases affecting the retinal vasculature.

Faricimab has been studied for the treatment of nAMD and DME in two Phase I studies (BP28936 in nAMD and JP39844 in nAMD and DME) and in three Phase II studies (BP29647 [AVENUE] and CR39521 [STAIRWAY] for nAMD and BP30099 [BOULEVARD] for DME). Four global Phase III studies are ongoing: GR40349 (YOSEMITE) and GR40398 (RHINE) in DME and GR40306 (TENAYA) and GR40844 (LUCERNE) in nAMD.

Based on the mechanism of action of faricimab, data from nonclinical and clinical trials, and the pathophysiology of macular edema due to RVO, it is hypothesized that faricimab may lead to stabilization of the pathological ocular vasculature and to improved visual and anatomical outcomes in RVO compared with anti-VEGF monotherapies.

Refer to the Faricimab (RO6867461) Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Over the past decade, the use of anti-VEGF therapies (for example, ranibizumab [Lucentis®] and aflibercept [Eylea®]) in macular edema due to RVO has greatly improved visual outcomes and prognosis for patients. Despite this, some patients still do not achieve sufficient vision gains to enable reading or driving. Data from the clinical trials with anti-VEGF agents in RVO and analyses of RVO outcomes in the real world suggest an unmet need for 1) treatments that would more fully address the underlying disease pathology by targeting molecular pathways beyond VEGF and deliver better efficacy, and 2) more durable treatments that would address the current requirement for frequent and often long-term administration to maintain vision gains (Wecker et al. 2016; Spooner et al. 2019). Addressing both potentially better efficacy through novel multi-targeting molecules and the real-world issue of suboptimal dosing with more durable treatment options would have a positive impact for patients, caregivers, and the entire health care system.

Therefore, clinical evaluation of therapies with additional mechanisms of action is warranted to further improve upon the clinical benefit of currently approved anti-VEGF therapies. In addition, many patients require frequent IVT injections for prolonged periods of time to maintain their vision, placing a significant burden on patients, caregivers, and healthcare providers. Real-world outcomes do not mirror the optimal outcomes observed in clinical trials, which also underscores the clear clinical need for therapies with a more sustained effect, which would require less frequent office visits and offer dosing intervals tailored to individual need, while still providing visual acuity outcomes comparable to those observed in clinical trials.

The objective of the current Phase III study is to address the existing unmet need of improved efficacy and extended durability of treatment, both of which would represent an important advance for patients with macular edema due to CRVO or HRVO.

1.3.1 Benefits

The elevated levels of both Ang-2 and VEGF in vitreous samples from patients with macular edema due to RVO are among the highest in retinal vascular diseases (Aiello et al. 1994; Regula et al. 2016). The effect of Ang-2 and VEGF inhibition in the nonclinical models of angiogenesis and inflammation (Regula et al. 2016) and the data from Phase I and Phase II faricimab studies in patients with nAMD and DME provide the evidence of efficacy on pathological pathways that are common to all three retinal vascular diseases: nAMD, DME/DR, and macular edema due to RVO (Phase I study BP28936 in nAMD; Phase II studies AVENUE in nAMD, STAIRWAY in nAMD, and BOULEVARD in DME).

Data from the Phase II BOULEVARD study is reported here due to parallels in pathophysiology between DME and macular edema due to RVO. While the trigger for macular edema in diabetic and RVO patients is different, the downstream pathophysiology of hypoxia-driven macular edema with subsequent vision loss is similar and driven by the same proangiogenic, pro-inflammatory, vessel destabilization and vessel permeability factors, including Ang-2, VEGF, and interleukin-6 (IL-6).

The BOULEVARD study provided preliminary evidence of a positive benefit–risk profile for the use of 6-mg IVT injections of faricimab for patients with DME and supported further evaluation of faricimab in the Phase III DME studies. The study met its primary efficacy endpoint, demonstrating statistically significant improvement in the mean change from baseline in BCVA at Week 24 in patients naive to anti-VEGF treatment who were treated with 6 mg faricimab compared with 0.3 mg ranibizumab.

The outcomes in the off-treatment study observation period provided evidence of prolonged duration of effect with faricimab compared with anti-VEGF monotherapy. Assessment of time to disease reactivation up to 16 weeks after the last dose showed an improvement in the duration of the effect of faricimab over ranibizumab, as measured by the time to loss of ≥ 5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters because of DME and an increase ≥ 50 μm in central subfield thickness (CST), in the treatment-naive patient population in a dose-dependent manner. This improvement in the duration of effect of faricimab over ranibizumab was also seen in the previously treated group and the overall patient group.

Based on the totality of this nonclinical and clinical evidence, it is anticipated that the well-established anti-VEGF mechanism of action combined with anti-Ang-2 targeting in the bispecific faricimab molecule could lead to improved efficacy over anti-VEGF standard of care in patients with macular edema due to RVO. Additionally, this study will investigate a less frequent treatment administration schedule tailored to individual need

(up to every 16 weeks) that could provide BCVA outcomes comparable to those of more frequently administered anti-VEGF monotherapy (e.g., every 4 to 8 weeks). Together, these would represent an important and meaningful advance relative to currently available therapies.

1.3.2 Risks

Nonclinical toxicology studies did not reveal any adverse effects that require specific warnings and precautions that are different from those applicable to any anti-VEGF agents currently used in clinical practice for the treatment of RVO.

In Phase I and II clinical studies in nAMD and DME, more than 400 patients have been exposed to at least one dose of faricimab. More than 1600 patients have been exposed to faricimab in ongoing Phase III studies in the same indications. No new or unexpected safety signals have been observed to date.

In the Phase I study (BP28936), faricimab was well tolerated up to the highest dose tested of 6 mg in previously treated patients with nAMD (Chakravarthy et al. 2017). No dose-limiting events or unexpected ocular adverse events were observed, and no non-ocular study drug–related serious adverse events or severe adverse events were reported.

The Phase II studies in nAMD (AVENUE and STAIRWAY) and DME (BOULEVARD) demonstrated that faricimab has an acceptable tolerability and safety profile, with no new or unexpected safety signals. The ocular and non-ocular safety findings for faricimab were generally consistent with the safety profile of approved intravitreally administered anti-VEGF products in patients with nAMD or DME. The safety profile of faricimab in patients with macular edema due to RVO is anticipated to be comparable to that in nAMD and DME.

Refer to the Faricimab (RO6867461) Investigator's Brochure for details on safety results from nonclinical and clinical Phase I and Phase II studies.

1.3.3 Conclusions

The available data from nonclinical studies and available Phase I and II efficacy and safety data in nAMD and DME support the positive benefit–risk assessment for the initiation of this Phase III study to establish the efficacy, safety, pharmacokinetics, and personalized treatment interval (PTI) dosing of faricimab administered every 4 weeks (Q4W) until Week 24 and in the intervals from Q4W up to every 16 weeks (Q16W) thereafter in patients with macular edema due to RVO.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of faricimab compared with aflibercept in patients with macular edema due to CRVO or HRVO (as defined in Section 4.1.1.2) up to the primary endpoint at Week 24. Efficacy, safety, and pharmacokinetics of faricimab administered according to the PTI dosing regimen (i.e., from Q4W to Q16W) will be assessed during the study period from Week 24 to Week 72. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study drug" refers to faricimab or aflibercept and "study treatment" refers to faricimab, aflibercept, or the sham procedure (see Section 4.3.1 for further details).

2.1 EFFICACY OBJECTIVES

For efficacy endpoint evaluation, BCVA will be assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters (see Section 4.5.5).

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of faricimab 6 mg IVT Q4W compared with aflibercept 2 mg IVT Q4W on the basis of the following endpoint:

- Change from baseline in BCVA at Week 24

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objective for Part 1 of this study (i.e., through Week 24) is to evaluate the efficacy of faricimab compared with aflibercept on the basis of the following endpoints:

- Change from baseline in BCVA at specified timepoints through Week 24
- Proportion of patients *gaining* ≥ 15 letters in BCVA *from baseline* at Week 24
- Proportion of patients *gaining* ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA *from baseline* at specified timepoints through Week 24
- Proportion of patients avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline at specified timepoints through Week 24
- Proportion of patients achieving ≥ 84 letters (20/20 Snellen equivalent) in BCVA at specified timepoints through Week 24
- Proportion of patients with BCVA Snellen equivalent of 20/40 or better at specified timepoints through Week 24

- Proportion of patients with BCVA Snellen equivalent of 20/200 or worse at specified timepoints through Week 24
- Change from baseline in CST at specified timepoints through Week 24
- Change from baseline in National Eye Institute 25-Item Visual Functioning Questionnaire (NEI VFQ-25) composite score at specified timepoints through Week 24

The secondary efficacy objective for Part 2 of this study (i.e., Week 24 through Week 72) is to evaluate the efficacy of faricimab administered according to the PTI dosing regimen on the basis of the following endpoints:

- Change from baseline in BCVA at specified timepoints from Week 24 through Week 72
- Proportion of patients *gaining* ≥ 15 letters in BCVA *from baseline* at Week *72*
- Proportion of patients *gaining* ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA *from baseline* at specified timepoints from Week 24 through Week 72
- Proportion of patients avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline at specified timepoints from Week 24 through Week 72
- Proportion of patients achieving $\geq$ 84 letters (20/20 Snellen equivalent) in BCVA at specified timepoints from Week 24 through Week 72
- Proportion of patients with BCVA Snellen equivalent of 20/40 or better at specified timepoints from Week 24 through Week 72
- Proportion of patients with BCVA Snellen equivalent of 20/200 or worse at specified timepoints from Week 24 through Week 72
- Change from Week 24 in BCVA at specified timepoints through Week 72
- Proportion of patients avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from Week 24 through Week 72
- Proportion of patients on a Q4W, every 8 weeks (Q8W), every 12 weeks (Q12W), or Q16W treatment interval at Week 72
- Number of study drug injections received from Week 24 through Week 72
- Change from baseline in CST at specified timepoints from Week 24 through Week 72
- Change from baseline in NEI VFQ-25 composite score at specified timepoints from Week 24 through Week 72

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of faricimab on the basis of the following endpoints:

- Proportion of patients with absence of retinal ischemia on fundus fluorescein angiography (FFA) (as specified in Section 4.5.5) and on optical coherence tomography angiography (OCT-A) (optional) over time (at specified timepoints)

- Change from baseline in area of retinal ischemia on FFA and on OCT-A (optional) over time
- Proportion of patients with vascular leakage on FFA and on OCT-A (optional) over time
- Change from baseline in area of vascular leakage on FFA, and on OCT-A (optional) over time
- Change from baseline in foveal avascular zone and other exploratory outputs defined in *the* Statistical Analysis Plan *(SAP)* on OCT-A (optional) over time
- Proportion of patients with absence of retinal neovascularization *over time* (per investigator assessment)
- Proportion of patients with absence of vitreal, preretinal, or subretinal hemorrhage over time (per investigator assessment)
- Proportion of patients with absence of anterior segment (iris and anterior chamber angle) neovascularization over time
- Proportion of patients requiring panretinal photocoagulation at any time during *the* study
- Proportion of patients with absence of macular edema, defined as CST of $\leq$325 μm for Spectralis SD-OCT, or $\leq$315 μm for Cirrus SD-OCT or Topcon SD-OCT, over time
- Proportion of patients with absence of intraretinal fluid over time
- Proportion of patients with absence of subretinal fluid over time
- Proportion of patients with absence of both intraretinal fluid and subretinal fluid over time
- Proportion of patients with absence of intraretinal cysts over time
- Change from baseline in NEI VFQ-25 near activities–subscale score and distance activities–subscale scores over time

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of faricimab on the basis of the following endpoints:

- Incidence and severity of ocular adverse events, with severity determined according to Adverse Event Severity Grading Scale (see Table 2)
- Incidence and severity of non-ocular adverse events, with severity determined according to Adverse Event Severity Grading Scale (see Table 2)

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to characterize the faricimab PK profile on the basis of the following endpoint:

- Plasma concentration of faricimab over time

The exploratory PK objective for this study is to explore the concentration–effect relationship for visual acuity and other endpoints (e.g., anatomic measures) on the basis of the following endpoint:

- Concentration of faricimab and the change in BCVA or other endpoints (e.g., anatomical markers) over time

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the *antibody* immune response to faricimab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

2.5 EXPLORATORY BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to faricimab (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of faricimab activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers in plasma (listed in Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., the frequency of faricimab administration) over time
- Relationship between anatomic measures and visual acuity

2.6 *EXPLORATORY SUBSTUDY*

At selected sites, the Sponsor may propose exploratory substudies associated with the Study GR41986 protocol. Each substudy will be documented in a separate substudy protocol and will have a separate associated Informed Consent Form.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, multicenter, randomized, double-masked, active comparator–controlled, parallel-group study evaluating the efficacy, safety, and pharmacokinetics of faricimab administered by IVT injection at 4-week intervals until Week 24, followed by a double-masked period of study without active control to evaluate faricimab administered according to a PTI dosing regimen in patients with macular edema due to CRVO or HRVO.

3.1.1 Overview of Study Design

This study is comprised of two parts: Part 1 (Day 1 through Week 24) will compare faricimab Q4W versus aflibercept (active comparator) Q4W; Part 2 (Weeks 24–72) will evaluate faricimab administered at masked treatment intervals of Q4W to Q16W based on PTI dosing criteria.

In Part 1 (Q4W Dosing), approximately $750\ patients$ will be randomized during the global enrollment phase of the study in a 1:1 ratio to one of two treatment arms, with treatment defined as follows:

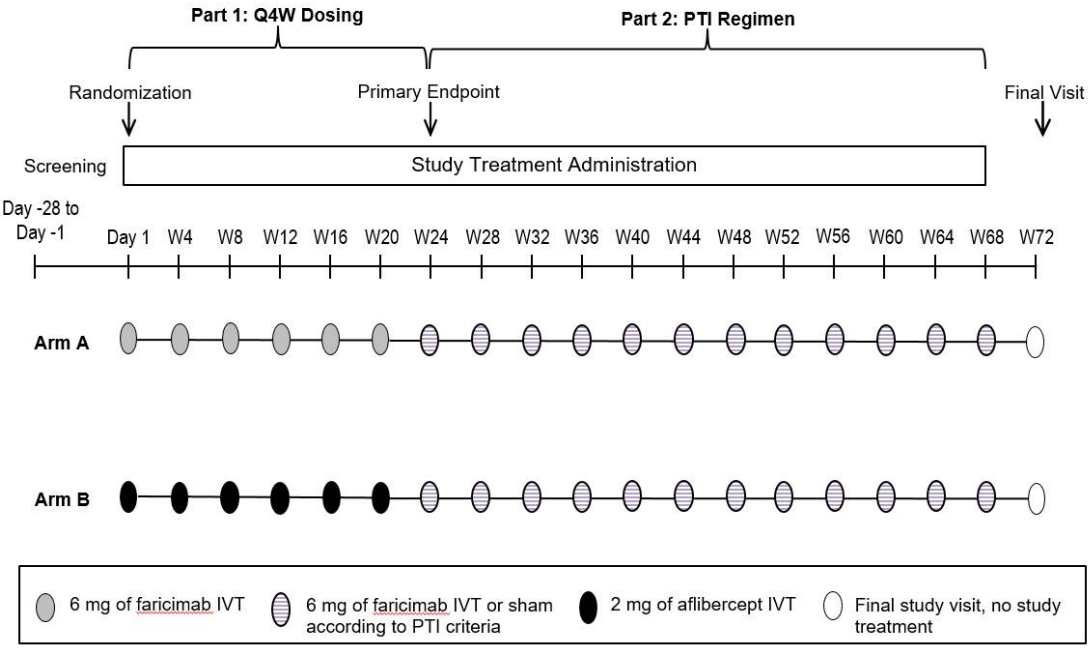
- Arm A (n=375): Patients randomly assigned to Arm A will receive faricimab 6 mg IVT Q4W from Day 1 through Week 20 (6 injections).
- Arm B (comparator arm, n=375): Patients randomly assigned to Arm B will receive aflibercept 2 mg IVT Q4W from Day 1 through Week 20 (6 injections).

In Part 2 (PTI Regimen), patients in both Arms A and B will receive faricimab 6 mg IVT according to a PTI dosing regimen from Week 24 through Week 68 (see Section 3.1.4.1 for the PTI dosing criteria).

All patients will complete scheduled study visits Q4W for the entire study duration (72 weeks). To preserve the masking of faricimab treatment intervals for Week 24 through Week 68, a sham procedure will be administered during study visits at which (according to the PTI dosing regimen) no faricimab treatment is administered.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



IVT = intravitreal; PTI = personalized treatment interval; Q4W = every 4 weeks; W = Week.

Only one eye will be assigned as the study eye. If both eyes are considered eligible, the eye with the worse BCVA, as assessed at screening, will be selected as the study eye, unless the investigator deems the other eye to be more appropriate for treatment in the study.

There will be a minimum of two investigators per site to fulfill the masking requirements of the study. At least one investigator will be designated as the assessor physician who will be masked to each patient's treatment assignment and who will evaluate ocular assessments. At least one other investigator will be unmasked and will perform study treatments (see Section 4.2.2 for additional details on masking).

The study will consist of a screening period of up to 28 days (Days −28 to −1) and an approximately 68-week treatment period, followed by the final study visit at Week 72. A unique screening number will be assigned to each screened patient through a web-based response system (IxRS).

3.1.1.1 Screening

Informed consent must be administered and signed by patients before any study-specific screening procedure is performed. Each consented patient must satisfy the eligibility criteria as applicable at screening and/or the Day 1 visit (see Sections 4.1.1 and 4.1.2).

Some patients may require an extended screening period (more than 28 days) as a result of repeated evaluation of images or other circumstances. Upon agreement with the Medical Monitor, the screening period may be extended by up to 5 business days in such cases.

In some countries or regions, the screening and Day 1 (randomization) visits may occur as a combined visit if all assessments (with the exception of informed consent, which may be obtained earlier) are completed and evaluated within 2 business days. Prior discussion with and approval from the central reading center (CRC) will be required, to allow evaluation of the images to be performed in an expedited manner.

During screening, a patient's eligibility will be assessed, including a CRC review of color fundus photographs (CFP) and spectral-domain optical coherence tomography (SD-OCT) (or swept-source optical coherence tomography [SS-OCT]). The diagnosis of macular edema due to RVO must be confirmed by the CRC. Note that the investigator will determine unilateral versus bilateral disease status at screening. For patients with bilateral RVO, CFP and SD-OCT images of fellow eye may be captured and stored at the CRC. No ocular images of the fellow eye will be captured or stored at screening for patients with unilateral RVO.

When screening and Day 1 visits are completed as a combined visit, the assessments listed for both visits should be conducted only once (see Appendix 1). Prior discussion with and approval from the CRC is required before this combined visit, to enable an expedited evaluation of CFP and SD-OCT (or SS-OCT) images for an objective, masked assessment of patient eligibility.

If the screening and Day 1 visits are not completed on the same day, but rather within 2 business days, the following safety assessments must be repeated on the day of the patient's randomization and first study treatment administration: urine pregnancy test (if appropriate), slitlamp examination, indirect ophthalmoscopy, and predose IOP measurements. These assessments should be recorded on the Day 1 electronic Case Report Form (eCRF) and dated accordingly.

After screening and predose Day 1 assessments have been completed, eligible patients will have a randomization identification number assigned through the IxRS and will be randomized in a 1:1 ratio, with approximately $375\ patients$ randomized to each of the two treatment arms. Randomization will be stratified by baseline BCVA ETDRS letter score, as assessed on Day 1 ($\leq 34\ letters,\ 35–54\ letters,\ and \geq 55$ letters), and region (United States and Canada, Asia, and the rest of the world).

3.1.1.2 Re-Screening

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities within a 3-month period (for a total of three screenings per participant) at the investigator's discretion. Patients are not

required to re-sign the consent form if they are re-screened within 30 days after previously signing the consent form. If more than 30 days have elapsed between signing the most recent consent form and the date of re-screen, then the consent form must be re-signed. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1).

At re-screening, a new screening number will be assigned to each patient through the IxRS and all screening visit assessments will be performed. At the Day 1 visit, fundus FFA images do not have to be repeated, provided that the same eye is selected for the study eye at re-screening and acceptable FFA images were taken within 28 days prior to the new Day 1 visit (randomization) date.

3.1.1.3 Randomization and Visit Schedule

The first study treatment will be administered on the same day as randomization (i.e., at the Day 1 visit).

If a site has an unexpected issue (e.g., the IxRS is not able to assign the study kit), a patient's randomization and first study treatment may be administered within 2 business days of the Day 1 visit assessments, after consultation with the Medical Monitor. The following assessments will be repeated on the day of randomization and study treatment: urine pregnancy test (if applicable), slitlamp examination, indirect ophthalmoscopy, predose IOP measurements (recorded on the Day 1 eCRF and dated accordingly), and any new concomitant medications.

Randomized patients will have the first study treatment administered by the unmasked investigator on Day 1, followed by the safety assessments (finger-counting test, hand-motion and/or light-perception tests [if applicable], and postdose IOP measurement). Afterward, all study patients will also have a safety assessment visit on Day 7 (±3 days) evaluated by the masked investigator. At subsequent scheduled visits, patients will have predose safety assessments evaluated by the masked investigator prior to receiving study treatment administered by the unmasked investigator.

Study treatment administration and study-related assessments will occur Q4W (starting from Day 1), as outlined in the schedule of activities (see Appendix 1). The sham procedure will be delivered to patients from Weeks 24 through 68, as applicable to maintain treatment interval masking (see Section 4.3.1.3).

Patients will be instructed to contact the study site at any time if they have health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 2).

All study visits will be scheduled 28 (±7) days relative to the randomization date as registered in IxRS. All assessments for a scheduled visit, including study treatment, are

to be performed on the same day, except those performed during the screening period. All assessments are to be performed prior to study treatment, unless otherwise specified.

Patients who are prematurely discontinued from study treatment but who agree to continue to participate in the study will be encouraged to undergo as many scheduled visits as possible, with emphasis on completing the Week 24 and Week 72 visits.

Patients who discontinue from the study prior to completion will be asked to return for an early termination visit a minimum of 28 days after their final study treatment for monitoring of adverse events and early termination visit assessments (see Appendix 1).

Patients who complete study treatment (i.e., through the Week 68 visit) will return for the final study visit (Week 72) a minimum of 28 days after their final study treatment for monitoring of adverse events and final study visit assessments (see Appendix 1).

3.1.2 Compliance with Study Visits, Handling of Missed Visits, and Timely Reporting

Sites will report all missed study treatment visits and study treatment interruptions to the IxRS for all patients (Arms A and B) to preserve masking.

Study treatment visits cannot occur earlier than 21 days after the previous study treatment visit. Missed study treatments will not be made up.

After the Day 1 visit, if a patient misses a study visit when ocular CFP and FFA images are to be obtained (see Appendix 1) or these images are not taken at the scheduled visit (e.g., equipment is broken), they must be obtained at the next scheduled visit the patient attends. *Missed mandatory PK, PD, or ADA samples may be obtained at the next scheduled visit the patient attends.*

If a patient misses more than two consecutive study treatment visits within any 24-week treatment period, the investigator and the Medical Monitor may consider discontinuing the patient from study treatment.

3.1.2.1 Timely Forwarding of OCT Images to *the* Central Reading Center or Reporting of Missed OCT Images

Starting at the Day 1 visit, the following must occur:

- Forward OCT images obtained at each study treatment visit to the CRC immediately so they can be evaluated for CST value and the data transferred by the CRC to IxRS prior to the patient's next study visit.
- If the OCT image was missed due to a missed visit or not taken, notify the CRC immediately so they can inform IxRS that the expected data will not be available.

3.1.2.2 IxRS Reporting of Visual Acuity Score, Study Treatment Interruption, and Missed Study Treatment Visits

Sites must enter the following information in IxRS at the time the study treatment kit assignment is requested:

- Patient visual acuity score from the current study treatment visit (final score as calculated on the Visual Acuity Worksheet)
- Study treatment interruption information (if applicable) so that the correct study treatment (study drug or sham) is assigned by the system for a future study treatment visit
- Missed study treatment visits

3.1.3 Treatment Schedule for Part 1 (Q4W Dosing)

In Part 1 of the study, patients will receive treatment as follows:

- Patients randomly assigned to Arm A will receive faricimab Q4W from Day 1 through Week 20
- Patients randomly assigned to Arm B will receive aflibercept Q4W from Day 1 through Week 20

3.1.4 Treatment Schedule for Part 2 (PTI Regimen)

In Part 2 of the study, all patients will visit the clinic Q4W from Week 24 through Week 68 and receive either sham treatment or faricimab 6 mg IVT, depending on their PTI dosing regimen. Faricimab PTI decisions will be automatically calculated by the IxRS based on the PTI criteria described in this section. Faricimab dosing visits are defined as those visits when the patient receives faricimab 6 mg IVT per IxRS assignment.

Starting at Week 24, patients will receive faricimab at a frequency of Q4W until CST meets the predefined reference CST threshold ($<325\ \mu m$ for Spectralis SD-OCT or $<315\ \mu m$ for Cirrus SD-OCT and Topcon SD-OCT), as determined by the CRC. The reference CST (as defined in Figure 2) is used by the IxRS at faricimab dosing visits to determine the faricimab dosing interval. After a patient's initial reference CST is established, the patient is eligible to have the faricimab dosing interval increased in 4-week increments by the IxRS if the CST value is stable (i.e., has not increased or decreased by $>10\%$) with no associated loss of vision of ≥ 10 letters with respect to reference BCVA (as defined in Figure 2).

The maximum and minimum treatment intervals that may be assigned will be Q16W and Q4W, respectively. Patients whose dosing interval had been previously extended and who experience disease worsening that triggers interval reduction will not be allowed to extend the interval again, with the exception of patients whose dosing intervals were reduced to Q4W; their interval may be extended again but only to an interval that is 4 weeks less than their original maximum extension. For example, if a patient's interval is reduced from Q12W to Q8W, this patient's interval will not be

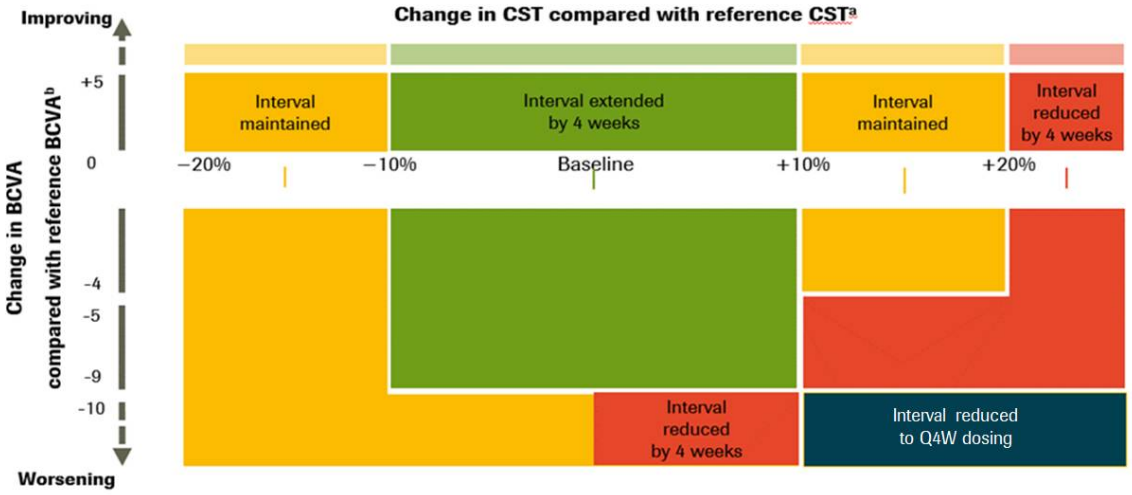
extended beyond Q8W for the remainder of the treatment period. If a patient's interval is reduced from Q16W to Q4W, this patient's interval can be extended up to Q12W, but cannot be extended back to Q16W.

3.1.4.1 Faricimab Interval Determination

The algorithm used by the IxRS for interval decision-making, which is based on the relative change of the CST and BCVA at faricimab dosing visits compared with the reference CST and reference BCVA, is outlined below and in Figure 2. The faricimab dosing interval will be extended, maintained, or reduced as follows.

- Interval extended by 4 weeks
  - If the CST value is increased or decreased by $\leq$ 10% without an associated $\geq$ 10-letter BCVA decrease
- Interval maintained if any of the following criteria are met:
  - If the CST value is decreased by $>$ 10%
  - If the CST value is decreased $\leq$ 10% with an associated $\geq$ 10-letter BCVA decrease
  - If the CST value is increased between $>$ 10% and $\leq$ 20% without an associated $\geq$ 5-letter BCVA decrease
- Interval reduced by 4 weeks if any of the following criteria are met:
  - If the CST value is increased between $>$ 10% and $\leq$ 20% with an associated $\geq$ 5-to $<$ 10-letter BCVA decrease
  - If the CST value is increased by $>$ 20% without an associated $\geq$ 10-letter BCVA decrease
  - If the CST value is increased by $\leq$ 10% with an associated BCVA decrease of $\geq$ 10-letters
- Interval reduced to Q4W
  - If the CST value is increased by $>$ 10% with an associated $\geq$ 10-letter BCVA decrease

Figure 2 Algorithm for IxRS-Determined Faricimab Personalized Treatment Interval Dosing Intervals



BCVA = best-corrected visual acuity; CST = central subfield thickness; IxRS = interactive web-based response system; Q4W = every 4 weeks.

[a] Initial reference CST = CST value when the initial CST threshold criteria are met, but no earlier than Week 20. Reference CST is adjusted if CST decreases by > 10% from the previous reference CST for two consecutive faricimab dosing visits and the values obtained are within 30 μm. The CST value obtained at the latter visit will serve as the new reference CST, starting immediately at that visit.

[b] Reference BCVA = mean of the three best BCVA scores obtained at any prior dosing visit.

3.1.4.2 Missed Faricimab Dosing Visits Starting from Week 20

If a patient misses a faricimab dosing visit, the IxRS will assign the patient to receive faricimab dosing at the next scheduled study visit the patient attends. A decision regarding the subsequent faricimab dosing interval will be made by IxRS based on CST and BCVA assessments completed at the visit when faricimab is administered, and any changes in the faricimab dosing interval will be based from the last assigned interval prior to the missed faricimab dosing visit.

For example, if a patient was on a Q12W drug dosing interval prior to missing the faricimab dosing visit, the IxRS decision to maintain, extend, or reduce the dosing interval will be made on the basis of the previously assigned drug interval (Q12W), along with CST and BCVA data obtained at the visit when the patient receives faricimab. If the data indicate that the patient should maintain the Q12W interval, the patient will receive faricimab 12 weeks after that visit.

If the Week 20 visit is missed, the patient (regardless of Part 1 treatment arm assigned) will receive a faricimab dose at Week 24. At this point, if the patient meets CST and BCVA extension criteria, the patient's faricimab dosing interval will be extended to Q8W by the IxRS, skipping the dose at Week 28.

3.1.4.3 Faricimab Interruption at Faricimab Dosing Visits Starting from Week 20

If a patient's dosing has to be interrupted at a faricimab dosing visit (e.g., because of an adverse event), the IxRS will assign the patient to receive faricimab at the earliest subsequent study visit when the patient is permitted to resume faricimab dosing. The IxRS will be used to determine the next faricimab dosing based on a Q8W interval unless the patient was treated on a Q4W interval prior to dose interruption. In that case, the patient will be evaluated on the basis of the Q4W interval.

3.1.4.4 Missing CST Value at Faricimab Dosing Visits Starting from Week 20

If a patient attends a faricimab dosing visit, but the CST value is not available for any reason (e.g., OCT machine is not available or is inoperative), the IxRS will assign the patient to receive faricimab at that visit. Generally, the IxRS will maintain the previous drug dosing interval. However, in the event of a concurrent $\geq$10-letter decrease relative to the reference BCVA at that faricimab dosing visit, the IxRS will reduce the faricimab dosing interval by 4 weeks.

3.1.4.5 Missing BCVA Value at Faricimab Dosing Visits Starting from Week 20

If a patient attends a faricimab dosing visit, but the BCVA value is not available for any reason, the IxRS will assign the patient to receive faricimab at that visit. The IxRS will base the faricimab dosing interval determination on CST value only.

3.1.5 China Enrollment Plan

Patient recruitment is expected to take longer in China; therefore, a specific China enrollment plan may be established. After the global enrollment phase of the study has been completed, additional patients may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. The China extension may include current residents of mainland China, Hong Kong, or Taiwan enrolled at National Medical Products Administration (NMPA)-recognized sites. All Chinese patients enrolled in the global enrollment phase of the study will be included in the primary analysis of the study. Data from patients enrolled during the China extension will not be included in the primary analyses (see Section 6.11 for details).

3.1.6 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will monitor safety and study conduct on an ongoing basis. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the iDMC's roles and responsibilities.

The iDMC will meet approximately every 6 months (frequency may be adjusted if required) to evaluate unmasked ocular and systemic (non-ocular) safety events with an emphasis on the evaluation of the rate of ocular inflammation, increased IOP, endophthalmitis, arterial thromboembolic events, and clinically significant decreases in BCVA and rates of neovascularization, which will be prepared for the committee by an independent Data Coordinating Center (iDCC). The iDMC may recommend stopping the study early for safety reasons. There are no prospectively planned interim efficacy or futility analyses.

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor.

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics Committees (IRBs/ECs).

3.2 END OF STUDY AND LENGTH OF STUDY

The study consists of two enrollment phases: the global enrollment phase, during which patients are recruited globally; and an optional China extension phase, during which additional patients may be recruited in China to support registration in China.

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, including patients from the optional China extension. The end of the study is expected to occur approximately 72 weeks after the last patient is randomized.

The total length of the study (excluding the China extension) from screening of the first patient to the LPLV for patients from the global enrollment phase is expected to be approximately 34 months.

The Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

A multicenter, double-masked, randomized, comparator-controlled design trial for Part 1 was selected to minimize the bias in the evaluation of faricimab as a treatment for patients with CRVO or HRVO. Part 2 of the study is designed to assess the efficacy and safety of faricimab PTI dosing.

To ensure the safety of all patients during the study, several safety assessments have been included (e.g., regular ophthalmic monitoring and imaging assessments, adverse event monitoring [ocular and systemic], and laboratory safety tests) (see Section 4.5 and Appendix 1 for a description of study assessments).

3.3.1 Rationale for Faricimab Dose

The 6-mg dose of faricimab will be administered to patients in Arm A of Part 1 and to all patients in Part 2 of the study, as outlined in Section 3.1.1.

The 6-mg dose of faricimab selected for this study is based on data from nonclinical in vivo and toxicology models and clinical outcomes from Phase I and Phase II studies, and is supported by clinical PK and PD assessments.

The first-in-human study (BP28936) evaluated the safety and tolerability of single and multiple administration of faricimab to 24 patients with nAMD, at doses ranging from 0.5 mg to 6 mg. The selection of these doses was based on nonclinical findings and absolute IVT doses administered in toxicology studies. The 6-mg dose of faricimab was the highest feasible dose of faricimab, and single and multiple doses of up to 6 mg were well tolerated.

In the Phase II studies (BOULEVARD in DME and AVENUE and STAIRWAY in nAMD), the ocular and non-ocular safety findings in patients receiving faricimab 1.5-mg and 6-mg doses were consistent with the safety profile of anti-VEGF products licensed for nAMD and DME with no new or unexpected events.

The data from BOULEVARD suggest a dose-related benefit favoring the 6-mg dose of faricimab relative to the 1.5-mg dose, as measured by both the efficacy outcomes and duration of effect. Based on these results, the 6-mg dose of faricimab was chosen for further clinical development in Phase III studies in patients with DME.

While the underlying disease etiologies are different (e.g., diabetes in DME versus a vascular occlusion in RVO), the downstream pathophysiology of hypoxia-driven macular edema with subsequent vision loss is similar. DME and macular edema due to RVO are both characterized by a thickening of the macula due to fluid accumulation consequent to breakdown in the blood-retinal barrier and pathological increase of retinal vessel permeability, which can lead to irreversible vision loss. Both Ang-2 and VEGF were increased in aqueous and vitreous samples from patients with diabetic eye disease or RVO (Adamis et al. 1994; Aiello et al 1994; Funatsu et al. 2002; Regula et al. 2016).

Considering the similar pathophysiology of macular edema and vision loss in patients with DME and macular edema due to RVO and based on the data from BOULEVARD, the 6-mg dose of faricimab has been chosen for clinical development in Phase III studies in patients with macular edema due to RVO.

Refer to the Faricimab (RO6867461) Investigator's Brochure for details about efficacy and safety results from nonclinical and clinical studies of faricimab.

3.3.2 Rationale for Faricimab Schedule

In this proposed Phase III study, patients in Arm A of Part 1 of the study will receive the 6-mg faricimab dose Q4W up to Week 20 for a total of 6 injections, as outlined in Section 3.1.1.

The initial six faricimab IVT Q4W doses are proposed for this study provide the opportunity for maximum efficacy against an active comparator (aflibercept) dosed Q4W. This dosing regimen is also consistent with the dosing studied in all the pivotal anti-VEGF trials and is consistent with global recommended dosing posologies (e.g., in the United States, the European Union, and Japan) for Eylea (aflibercept) and Lucentis (ranibizumab) RVO product labeling (Eylea E.U. Summary of Product Characteristics (SmPC), Eylea and Lucentis U.S. Package Inserts (USPI), Eylea Japan local prescribing information).

In Part 2 of the study, all patients will receive faricimab (from Week 24 through Week 68) according to the PTI dosing regimen (intervals ranging from Q4W to Q16W) as outlined in Section 3.1.1. A range of faricimab dosing intervals will be evaluated, as PTI dosing better reflects real-world clinical practice, allowing patients to receive injections individually tailored to maximize vision while minimizing treatment burden. Observational studies of anti-VEGF treatment patterns in patients with RVO demonstrated that visual gains and maintenance of these gains in the real world are worse than outcomes achieved in randomized controlled clinical trials. This is because frequent office monitoring of all patients is often not feasible in the real world, and patients have lower numbers of visits and injections than they need overall. There is an unmet need for more durable treatments and a personalized treatment approach in patients with RVO. Extended treatment intervals are supported by PK/PD data and clinical data in DME.

As described in Section 1.1, while the upstream etiologies are different between DME and macular edema due to RVO, the downstream hypoxia-driven pathways leading to macular edema with subsequent vision loss are similar. Faricimab has a potential for increased durability in RVO based on the dual mechanism of action, with inhibition of both Ang-2 and VEGF. The PK and PD assessments of aqueous humor samples from a subset of patients in BOULEVARD show high suppression of Ang-2 and VEGF for $\geq$8 weeks with faricimab 6 mg, thus supporting the potential for a $\geq$Q8W dosing regimen. Additionally, the PK/PD model characterizing the aqueous humor free-VEGF time course shows a substantial proportion of patients with prolonged aqueous humor free-VEGF suppression for whom a Q12W or Q16W regimen could be sufficient to maintain efficacy. Furthermore, increased durability compared to anti-VEGF monotherapy was shown during the observational phase of the BOULEVARD. On the basis of these data, after achieving the maximum gains from monthly dosing in RVO, extended dosing of intervals up to 16 weeks will be explored.

Therefore, Part 2 of this Phase III study in RVO will investigate PTI dosing with faricimab to demonstrate that vision achieved with monthly dosing (i.e., in Part 1) can be maintained with PTI dosing. It is expected that the PTI regimen will help extend the treatment interval (to a maximum of Q16W) in patients with inactive disease, while giving those with demonstrable disease activity the opportunity to be treated as frequently as Q4W if required.

3.3.3 Rationale for Aflibercept Dose and Schedule

The 2-mg dose of aflibercept will be administered Q4W through Week 20 in patients in Arm B of Part 1, as outlined in Section 3.1.1. The aflibercept dose and schedule used in this study are consistent with global recommended dosing posologies (e.g., in the United States, the European Union, and Japan) for Eylea (aflibercept) RVO product labeling (Eylea E.U. SmPC, Eylea USPI, Eylea Japan local prescribing information).

3.3.4 Rationale for Control Group

Part 1 of this study (up to the primary endpoint at Week 24) is an interventional study to evaluate the efficacy of faricimab compared with standard-of-care anti-VEGF monotherapy for patients with CRVO or HRVO.

Anti-VEGF therapy is a well-established standard of care in patients with RVO, and studies with an inactive comparator (i.e., sham procedure) or macular laser treatment alone are no longer ethically acceptable alternatives given the improvements in visual and anatomical outcomes associated with anti-VEGF treatment.

Aflibercept is an approved anti-VEGF treatment for patients with RVO and has demonstrated improvement in BCVA in the target population in controlled, randomized clinical studies (Eylea E.U. SmPC, Eylea USPI, and Eylea Japan local prescribing information). Eylea is a globally approved anti-VEGF therapy. The most restrictive approved aflibercept dosing regimen on label (USPI) is monthly, facilitating a comparison with monthly faricimab (up to the primary endpoint at Week 24).

In Part 2 of this study, all patients will receive a PTI dosing regimen with faricimab and there will not be a comparator control.

3.3.5 Rationale for Biomarker Assessments

The concentration of free Ang-2 and free VEGF will be measured in plasma to assess the systemic target suppression following intravitreal faricimab injection.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately $750\ patients$ with macular edema due to CRVO or HRVO will be enrolled during the global enrollment phase of this study.

After completion of the global enrollment phase, additional patients may be enrolled at NMPA-recognized Chinese sites in a China extension to ensure a total enrollment that is sufficient to support registration in China.

4.1.1 Inclusion Criteria

4.1.1.1 General Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age $\geq$ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for 3 months after the final dose of study treatment. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For patients enrolled in the extended China enrollment phase at NMPA-recognized sites: current resident of mainland China, Hong Kong, or Taiwan, and of Chinese ancestry

4.1.1.2 Ocular Inclusion Criteria for Study Eye

Patients must also meet the following ocular criteria for study entry:

- Foveal center–involved macular edema due to CRVO or HRVO, diagnosed no longer than 4 months prior to the screening visit and confirmed by CRC based on SD-OCT (or SS-OCT) images

  CRVO or HRVO is defined by retinal hemorrhages, telangiectatic capillary bed, dilated venous system or other biomicroscopic evidence of retinal vein occlusion (RVO; neovascularization, vitreous hemorrhages) in the entire retina (CRVO) or two quadrants of the retina (HRVO)

- BCVA of 73 to 19 letters, inclusive (20/40 to 20/400 approximate Snellen equivalent), as assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters (see the BCVA manual for additional details) on Day 1
- CST ≥325 μm, as measured on Spectralis SD-OCT, or ≥315 μm, as measured on Cirrus SD-OCT or Topcon SD-OCT at screening (SS-OCT acceptable after confirmation with CRC)
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

4.1.2 Exclusion Criteria

4.1.2.1 General Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Any major illness or major surgical procedure within 1 month before screening
- Active cancer within the 12 months prior to Day 1 except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤6 and a stable prostate-specific antigen for >12 months
- Requirement for continuous use of any medications and treatments indicated in Section 4.4.2 (Prohibited Therapy)
- Systemic treatment for suspected or active systemic infection on Day 1

  Ongoing use of prophylactic antibiotic therapy may be acceptable if approved after discussion with the Medical Monitor.

- Any systemic corticosteroid use (e.g., oral or injectable) within 1 month of the screening visit

- Uncontrolled blood pressure, defined as systolic blood pressure $>$ 180 mmHg and/or diastolic blood pressure $>$ 110 mmHg while a patient is at rest on Day 1

  If a patient's initial reading exceeds these values, a second reading may be taken later on the same day or on another day during the screening period. If the patient's blood pressure is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1.
- Stroke (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1
- History of other disease, metabolic dysfunction, physical examination finding, or historical or current clinical laboratory findings giving reasonable suspicion of a condition that contraindicates the use of the investigational drug or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator
- Pregnant or breastfeeding, or intending to become pregnant during the study

  Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to initiation of study drug. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab or aflibercept injections, study- related procedure preparations (including fluorescein), dilating drops, or any of the anesthetic and antimicrobial preparations used during the study
- Participation in an investigational trial that involves treatment with any drug or device (with the exception of vitamins and minerals) within 3 months prior to Day 1

4.1.2.2 Ocular Exclusion Criteria for Study Eye

Patients who meet any of the following ocular exclusion criteria for the study eye will be excluded from study entry:

- History of previous episodes of macular edema due to RVO or persistent macular edema due to RVO diagnosed more than 4 months before screening
- Increase of $\geq$ 10 letters in BCVA ETDRS score between screening and Day 1
- Any current ocular condition which, in the opinion of the investigator, is currently causing or could be expected to contribute to irreversible vision loss due to a cause other than macular edema due to RVO in the study eye (e.g., ischemic maculopathy, Irvine-Gass syndrome, foveal atrophy, foveal fibrosis, pigment abnormalities, dense subfoveal hard exudates, or other non-retinal conditions)
- Current visually significant vitreous hemorrhage on Day 1
- History of retinal detachment or macular hole (Stage 3 or 4)
- Tractional retinal detachment, vitreomacular traction, full thickness macular hole or epiretinal membrane involving the fovea or disrupting the macular architecture in the study eye, as evaluated by the CRC and described in the CRC manual

- Diagnosis of DR moderate non-proliferative or worse, proliferative DR, DME, nAMD, geographic atrophy, myopic choroidal neovascularization as assessed by the investigator
- Active rubeosis, angle neovascularization, neovascular glaucoma
- Aphakia or implantation of anterior chamber intraocular lens
- Any cataract surgery or treatment for complications of cataract surgery with steroids or YAG (yttrium-aluminum-garnet) laser capsulotomy within 3 months prior to Day 1
- Any other intraocular surgery (e.g., pars plana vitrectomy, scleral buckle, glaucoma surgery, corneal transplant, or radiotherapy)
- Any prior or current treatment for macular edema due to RVO, including anti-VEGF IVT for macular edema due to RVO
- Macular laser (focal/grid) in the study eye at any time prior to Day 1
- Panretinal photocoagulation in the study eye within 3 months prior to Day 1 or anticipated within 3 months of study start on Day 1
- Any IVT treatment for any other retinal diseases that can lead to macular edema complication
- Any prior or current treatment for macular edema; macular neovascularization, including DME and nAMD; and vitreomacular-interface abnormalities, including, but not restricted to, IVT treatment with anti-VEGF, steroids, tissue plasminogen activator, ocriplasmin, C3F8, air or periocular injection
- Any prior intervention with verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or vitreo-retinal surgery including *sheathotomy*
- Any prior steroid implant use including dexamethasone intravitreal implant (Ozurdex®) and fluocinolone acetonide intravitreal implant (Iluvien®)
- Prior periocular pharmacological or IVT treatment (including anti-VEGF medication) for other retinal diseases

4.1.2.3 Ocular Exclusion Criteria for Fellow (Non-Study) Eye

Patients who meet the following ocular exclusion criterion for the fellow (non-study) eye at both screening and Day 1 will be excluded from study entry:

- Non-functioning fellow eye, defined as either one of the following:
  - BCVA 20/320 or worse
  - No physical presence of fellow eye (i.e., monocular)

4.1.2.4 Ocular Exclusion Criteria for Both Eyes

Patients who meet any of the following ocular exclusion criteria for both eyes will be excluded from study entry:

- Prior IVT administration of faricimab in either eye
- History of idiopathic or autoimmune-associated uveitis in either eye
- Active periocular, ocular or intraocular inflammation or infection (including suspected) in either eye on Day 1

4.2 METHOD OF TREATMENT ASSIGNMENT AND MASKING

4.2.1 Treatment Assignment

After written informed consent has been obtained, all patients will receive a screening number assigned through the IxRS. A patient must satisfy all eligibility criteria (see Sections 4.1.1 and 4.1.2) prior to randomization through the IxRS. As part of the screening process, the CRC will evaluate CFPs and SD-OCT images to provide an objective, masked assessment of patient eligibility. After all patient eligibility requirements are confirmed, site personnel will contact the IxRS at the Day 1 visit for assignment of a patient identification number (a separate number from the screening number).

Patients will be randomized in a 1:1 ratio to one of two study treatment arms (faricimab Q4W or aflibercept Q4W). After randomization and at each study treatment visit (i.e., including Day 1), the IxRS will assign the appropriate study treatment kit to be used. Patients will be randomized on the same day study treatment is to be initiated (i.e., the Day 1 visit).

Randomization will be stratified by the following baseline factors (Day 1):

- Baseline BCVA ETDRS letter score (≤ 34 letters, 35–54 letters, and $\geq$55 letters)
- Region (United States and Canada, Asia, and the rest of the world)

A stratified permuted-block randomization scheme will be used to obtain approximately a 1:1 ratio among the treatment groups overall and within each of the above strata.

4.2.2 Masking

This is a double-masked study, and only site staff members in unmasked roles, as specified in Section 4.2.2.2, are unmasked in both Part 1 and Part 2. There must be a minimum of two investigators per site to fulfill the masking requirements of this study and both investigators are required to be present at each scheduled study visit.

4.2.2.1 Masked Roles

Principal Investigator

The Principal Investigator will be a retina specialist (or the equivalent in ex-U.S. countries) and must be in a masked role to oversee conduct of the whole trial. The Principal Investigator must be masked to patients' treatment assignment and may assume any other masked role for which he or she qualifies, except for BCVA examiner tasks.

Assessor Physician/Masked Investigator

At least one investigator who is a retina specialist (or the equivalent in ex-U.S. countries) will be designated as the assessor physician/masked investigator. The investigator(s) will be masked to patient treatment assignments and will evaluate all predose assessments, as well as all assessments performed at screening, Day 7, and at the final or early termination visit. The assessor physician/masked investigator will also evaluate the causality of all adverse events reported by the treatment administrator/unmasked investigator. If qualified, this role can take on any other masked role tasks except tasks performed by the BCVA examiner.

Photographer(s) and OCT Technician(s)

If qualified, the photographers and OCT technicians can share any other masked role tasks except tasks performed by the BCVA examiner.

Study Coordinator(s)

If qualified, the study coordinator(s) can share any other masked role tasks except tasks performed by the BCVA examiner.

BCVA Examiner

The BCVA examiner will be masked to both the assigned treatment arm and designation of the study eye. The BCVA examiner may have access only to a patient's refraction data from previous visits. Patients' medical charts and visual acuity scores from patients' previous visits are not accessible to the BCVA examiner. The BCVA examiner is not allowed to perform any other task involving direct patient care.

4.2.2.2 Unmasked Roles

Treatment Administrator/Unmasked Investigator

At least one investigator will be designated as the treatment administrator and will be unmasked to the patients' treatment assignment. The treatment administrator/unmasked investigator will be a retina specialist (or the equivalent in ex-U.S. countries). In addition, ophthalmologists who have completed a minimum of 2 full years of ophthalmology residency (or equivalent in ex-U.S. countries) may be permitted to perform the role of the treatment administrator/unmasked investigator following Sponsor approval.

The treatment administrator/unmasked investigator(s) performing the study treatment administration (faricimab, aflibercept, or sham) will also perform the postdose administration safety assessments (finger-counting, hand-motion and/or light-perception tests [if applicable] and postdose IOP measurement) and will treat adverse events that occur during or shortly after the study treatment administration. Cases of medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.11. The person in this role, however, will not evaluate the causality of adverse events, which is the responsibility of the assessor physician/masked investigator(s). The treatment administrator/unmasked investigator will also perform postdose IOP measurements, as well as optional aqueous humor and vitreous humor sample collection.

In addition, the qualifying treatment administrator/unmasked investigator can assist with and perform the screening and Day 1 visit assessments. The treatment administrator/unmasked investigator must not be involved in any other aspect of the study and must preserve masking of treatment assignment.

Phlebotomist

The phlebotomist's tasks can be performed by any qualified individual in masked or unmasked role, except for BCVA examiner.

Unmasked Assistants and Pharmacist

If desired, sites may have designated qualified unmasked assistants who can, for example, assemble study treatment supplies, prepare sterile field, prepare the patient's study eye for treatment, discard all injection materials (i.e., syringes and needles) immediately following study treatment, and place vials in the kit box. The qualified unmasked assistants can be assigned to measure postdose IOP. If the site uses a pharmacy, the unmasked role is also assigned to the pharmacist who can take on IMP/NIMP-related tasks as applicable per the site delegation log. In addition, qualifying unmasked assistants can assist with and perform the screening and Day 1 visit assessments.

Number of Unmasked Personnel per Site

Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this masked study. There should be no more than six unmasked personnel (e.g., treatment administering physician[s] and assisting technician[s] if applicable) at an investigative site at one time. In certain circumstances, the total number of unmasked personnel might be increased after discussion with and approval by the Medical Monitor. If the site is using a pharmacist, this person may be in an unmasked role in addition to the unmasked staff at the site.

Any other study assisting personnel not listed above will be in the masked roles.

4.2.2.3 Site Delegation Log

All roles for each study staff member should be clearly documented in the site delegation log. The site delegation log must be signed by the Principal Investigator.

4.2.2.4 Role Switching

Once personnel assigned to the designated unmasked role start performing that role, they cannot switch to a masked role during the study. Switching from a masked role to an unmasked role may be possible and must be documented in the site delegation log.

4.2.2.5 Study Backup Staff

Sites are strongly advised to have backup staff for key study roles. In case of an emergency (e.g., an unscheduled safety visit), patients should be seen preferably by the assessor physician/masked investigator. If the assessor physician/masked investigator is unavailable, any clinic physician present, including the physician in the treatment administrator/unmasked investigator role, should attend to the patient.

4.2.2.6 Masking of Vendors, Sponsor's Agents, and Laboratory Personnel

CRC personnel, study vendors, the Sponsor, and its agents will also be masked to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, drug accountability clinical research associates, the images coordinator, iDCC and iDMC members, and an internal unmasking statistician (this person is from the Sponsor's unmasking group and will follow the Sponsor's standard operation procedures to audit the implementation of the randomization scheme and the dosing interval assignment by the IxRS vendor periodically during the conduct of the study; this person will not be involved in other study-related activities).

To maintain the masked design of the study, blood samples, optional aqueous humor samples, and optional vitreous humor samples obtained at the timepoints specified in the schedule of activities (see Appendix 1) will be obtained from consenting patients in any treatment arm. The laboratories responsible for performing sample analyses will be unmasked to patients' treatment assignment to identify appropriate samples to be analyzed. Unmasking for analysis of the relevant biosamples during the conduct of the study will be performed by personnel outside of the study team and according to the Sponsor's internal standard procedures to ensure the integrity of the data. The number of Roche representative(s) and delegates who are unmasked will be kept to the minimum required to address the objective of the biosample analysis.

While PK and immunogenicity samples must be collected from patients assigned to the comparator arm to maintain the masking of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK

and ADA assays will be unmasked to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the comparator arm will not be analyzed for *faricimab* PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all patients. Postbaseline immunogenicity samples from patients assigned to the comparator arm will not be analyzed for ADAs except by request.

4.2.2.7 Patient Masking

Patients will be masked to treatment assignment during the study and until study closeout, or until the Sponsor indicates that the study can be unmasked.

4.2.2.8 Single-Patient Emergency Unmasking

If unmasking is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the masked investigator will be able to break the treatment code by contacting the IxRS. The masked investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

4.2.2.9 Single-Patient Non-Emergency Unmasking

If the masked investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The masked investigator should document and provide an explanation for any non-emergency unmasking. If the Medical Monitor agrees to patient unmasking, the masked investigator will be able to break the treatment code by contacting the IxRS.

4.2.2.10 Single-Patient Unmasking for Health Authority Reporting Requirements

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the masked investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the masked investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain masked to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is faricimab.

Aflibercept is being used as an active comparator in this study in Part 1; therefore, aflibercept is also considered an IMP for this study when administered to the study eye.

The sham is a procedure that mimics an IVT injection to preserve the study masking and involves the blunt end of an empty syringe, without a needle, being pressed against an anaesthetized eye.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Faricimab

Faricimab will be supplied by the Sponsor as a sterile liquid for IVT injection in single-use glass vials. For information on the faricimab formulation, see the pharmacy manual.

4.3.1.2 Aflibercept (Active Comparator)

Aflibercept will be supplied by the Sponsor as a sterile liquid for IVT injection in single-use glass vials. For information on the aflibercept formulation, see the pharmacy manual.

4.3.1.3 Sham

The sham vial is empty and will remain empty throughout the sham treatment. The sham is a procedure that mimics an IVT injection and involves the blunt end of an empty syringe (without a needle) being pressed against the anesthetized eye.

For information on the formulation of the sham vial, see the pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration eCRF. Cases of medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.11.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.4 and Table 1.

4.3.2.1 Faricimab

In Part 1 of the study, patients randomly assigned to Arm A will receive faricimab 6 mg IVT Q4W from Day 1 through Week 20, for a total of 6 injections.

In Part 2 of the study, patients randomly assigned to both Arms A and B will receive faricimab 6 mg IVT administered according to a PTI dosing regimen in intervals between Q4W and Q16W (see the study treatment schema in Figure 1). At faricimab dosing visits, treatment intervals will be maintained or adjusted (i.e., increased by 4 weeks or decreased by 4, 8, or 12 weeks), based on CST and BCVA values (see Section 3.1.4.1). Patients will therefore receive between 3 and 12 injections during the period from Week 24 through Week 68.

All faricimab administrations will be performed at the site. See Appendix 3 for study treatment preparation. Refer to the faricimab pharmacy manual for detailed instructions on drug preparation, storage, administration, and predose and postdose procedures.

4.3.2.2 Aflibercept (Active Comparator)

In Part 1 of the study, patients randomly assigned to Arm B will receive aflibercept 2 mg IVT Q4W from Day 1 through Week 20, for a total of 6 injections.

All aflibercept administrations will be performed at the site. See Appendix 3 for study treatment preparation. Refer to the aflibercept pharmacy manual for detailed instructions on drug preparation, storage, administration, and predose and postdose procedures.

4.3.2.3 Sham Procedure

Both treatment Arms A and B will maintain Q4W study visits for the 72-week study duration. To preserve the masking of faricimab treatment intervals for Week 24 through Week 68, the sham procedure will be administered during study visits at which (according to the PTI dosing regimen) no faricimab treatment is administered (see Figure 1).

See Appendix 3 for study treatment preparation. Refer to the pharmacy manual for detailed instructions on sham preparation, storage, administration, and predose and postdose procedures.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study (faricimab and aflibercept) will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have

been maintained during transit*, either by time monitoring (shipment arrival date and time) or temperature monitoring,* for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the Faricimab Investigator's Brochure or aflibercept local prescribing information for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Faricimab

The Sponsor will offer continued access to Roche IMP (faricimab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP (faricimab) after completing the study if all of the following conditions are met:

- The patient has a sight-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMP (faricimab) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)

- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for CRVO or HRVO
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for CRVO or HRVO
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter preparations or procedures other than protocol-specified procedural medications (e.g., dilating drops or fluorescein dyes, proparacaine, or antimicrobials [if applicable]) used by a patient within 7 days prior to the Day 1 visit and through the conclusion of the patient's study participation or early termination visit.

All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF, except for anti-VEGF therapy in the fellow eye that will be recorded on a separate eCRF. Concomitant ocular procedures performed on either eye during the study should be recorded in the Concurrent Ocular Procedures Log on the eCRF.

4.4.1 Permitted Therapy

Patients who use maintenance therapies should continue their use. Of note, the following are common therapies that are permitted:

- Treatment for onset of ocular hypertension or glaucoma in the study eye during a patient's study participation, as clinically indicated
- Treatment of onset of cataract or posterior capsular opacification in either eye during a patient's study participation, as clinically indicated

  Dose interruption criteria (see Table 1) may apply with cataract surgery
- Short-term use of topical ocular corticosteroids after cataract surgery, yttrium-aluminum garnet capsulotomy, peripheral iridotomy, argon/selective laser trabeculoplasty, or ocular allergic conditions in study eye or fellow eye
- Complete, sector, or local panretinal photocoagulation in the study eye or fellow eye may be allowed if needed for the treatment of ischemic RVO or new peripheral neovascularization after discussion with the Medical Monitor

  These conditions will be recorded as serious adverse events. The patient should remain on study treatment and continue unchanged on the IxRS-assigned interval.

- Vitrectomy may be performed at the discretion of the masked investigator in the event that study eye develops sight-threatening vitreous hemorrhage or retinal detachment

  These conditions will be recorded as serious adverse events and will be recorded as a concomitant procedure. Study treatment should be interrupted and may restart based on the patient's status after consultation with the Medical Monitor. The patient should remain in the study and complete all study visits as planned.

- Fellow (non–study) eye may be treated with anti-VEGF therapy licensed for ocular use, if diagnosed with an ocular condition for which the selected anti-VEGF therapy is approved by the country regulatory agency and at the discretion of the masked investigator

  Consult with the region-specific anti-VEGF prescribing information for the recommended dose and frequency of treatment. The Sponsor will cover the cost of approved licensed ocular anti-VEGF therapy in accordance with local regulations. Note: bevacizumab (Avastin®) is not licensed for ophthalmic use in any country; therefore, it is prohibited from use.

  If (per the masked investigator's judgment) treatment with anti-VEGF is to be given to the fellow (non–study) eye at the same visit as the study eye treatment, all study eye assessments (including study eye study treatment administration) must be completed first. If there are no safety concerns, the site may proceed with the fellow eye treatment administered by the unmasked physician to preserve masking. Individual trays and sterile preparation must be separately prepared for each eye treatment.

  If the fellow eye anti-VEGF treatment is performed outside of the study visit, a qualified investigator, in either masked or unmasked role, can administer the treatment.

At the discretion of the investigator, patients may continue to receive medications and standard treatments administered for other conditions.

4.4.2 Prohibited Therapy

The following medications and treatments are prohibited from use during a patient's study treatment participation. Patients may be discontinued from study treatment and/or the study to receive these therapies:

- Systemic anti-VEGF therapy
- Systemic drugs known to cause macular edema (fingolimod, tamoxifen)
- IVT anti-VEGF agents (other than study-assigned aflibercept or faricimab) in study eye
- IVT, periocular (subtenon), steroid implants (i.e., Ozurdex®, Iluvien®), or chronic topical ocular corticosteroids in study eye
- Treatment with verteporfin (Visudyne®) in study eye

- Administration of micropulse and focal or grid laser in study eye
- Other experimental therapies (except those comprising vitamins and minerals)

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient, and should be performed by site staff as outlined in Section 4.2.2.

All assessments (including the study treatment administration) for a scheduled visit are to be performed on the same day, except those performed during the screening period.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, chronic and ongoing conditions (e.g., trauma, cardiovascular, cerebrovascular, and ophthalmic), surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment (Day 1 visit) will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity is recorded because of the potential contribution of this variable to differences in observed pharmacokinetics, pharmacodynamics, toxicity, and/or response to treatment in retinal microvascular diseases (Zhang and Lai 2018).

4.5.3 Physical Examinations

A targeted physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat. In addition, a patient's height and weight will be recorded. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Ocular Assessments

Ocular assessments will be performed for both eyes, unless otherwise indicated, at specified timepoints according to the schedule of activities in Appendix 1. Assessments include:

- Refraction and BCVA assessed on ETDRS visual acuity chart at a starting test distance of 4 meters (perform prior to dilating eyes; see Appendix 5)
- Predose IOP measurement of both eyes (perform prior to dilating eyes)
- Slitlamp examination (for grading scales for anterior and vitreous cells, see Appendix 4)
- Dilated binocular indirect high-magnification ophthalmoscopy
- Finger-counting test followed by hand-motion and light-perception tests (when necessary) performed within approximately 15 minutes of study treatment in the study eye only
- Postdose IOP measurement only in the study eye taken 30 (±15) minutes after study treatment administration

  If there are no safety concerns after 30 (±15) minutes following study treatment administration, the patient will be permitted to leave the clinic. If the IOP value is of concern to the treatment administrator/unmasked investigator, the patient will remain in the clinic and will be managed in accordance with the treatment administrator/unmasked investigator's clinical judgment. The adverse event will be recorded on the Adverse Event eCRF as applicable.
- The method of IOP measurement used for a patient must remain consistent throughout the study

Ocular Imaging

The CRC(s) will provide sites with the CRC manual and training materials for specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software (where applicable) will be certified and validated by the CRC(s) as specified in the CRC manual. All ocular images results will be obtained by trained site personnel at the study sites and forwarded to the CRC(s) for independent analysis and/or storage (see Appendix 6, Appendix 7, and Appendix 8.

After randomization, if a patient misses a study visit when CFP or FFA ocular images are scheduled (see Appendix 1) or the images are not taken at the scheduled visit (e.g., due to broken equipment), they should be obtained at the next scheduled visit the patient attends.

Ocular images include the following:

- FFA of study eye

  Detailed guidance on the required equipment and image capture is described in the CRC manual. Same field of capture must be used consistently throughout the trial participation (if applicable, perform after blood samples are obtained).

- CFP of study eye

  Detailed guidance on the required equipment and image capture is described in the CRC manual. Same field of capture must be used consistently throughout the trial participation.

- SD-OCT or SS-OCT images of study eye

  Certain SS-OCT machines may be acceptable; consult the CRC.

- Optional OCT-A of study eye at sites with OCT-A capabilities (provided sites approve optional sampling)

For patients diagnosed at screening with bilateral RVO, CFP and OCT images will also be captured of the fellow eye and stored at the CRC.

Additional details on obtaining these images are included in the CRC manual.

4.5.6 Concurrent Ocular Procedures

Any ocular procedures performed on either eye during the study (from Day 1, postdose) will be recorded on the Concurrent Ocular Procedures Log in the eCRF.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

At the scheduled visit, specimens should be obtained prior to study treatment and blood samples must be obtained prior to FFA assessments (if applicable). Fasting is not required prior to specimen collection. Laboratory supply kits will be provided to the sites by the central laboratory. See Appendix 1 for sample collection timepoints and Appendix 9 for biological sample collection and shipping instructions.

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes [absolute], lymphocytes, and other cells)
- Serum chemistry panel: bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN, creatinine, total

protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, and urate

- Urinalysis: pH, specific gravity, glucose, protein, ketones, blood, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal)
- Coagulation: aPTT and PT
- Pregnancy test

  All women of childbearing potential will have a urine pregnancy test at screening and prior to each study treatment. If a urine test is positive, it must be confirmed by a serum pregnancy test.
- Plasma samples for faricimab immunogenicity analysis
- Plasma samples for faricimab PK analysis
- Plasma samples for exploratory research on biomarkers

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Plasma samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Plasma samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Optional aqueous humor and vitreous humor samples and optional plasma samples (if aqueous humor or vitreous humor sample is collected) collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Clinical Outcome Assessments

Patient-reported outcome (PRO) instruments will be completed to assess the treatment benefit of faricimab. In addition, PRO instruments will enable the capture of each patient's direct experience with faricimab.

PRO data will be collected through use of the NEI VFQ-25 (see Appendix 10).

4.5.8.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be interviewer-administered by the masked site staff (except for the BCVA examiner) at the clinic *or over the telephone* at specified timepoints during the study (see schedule of activities in Appendix 1). At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor in pre-printed booklets to enable the instrument to be administered at each specified timepoint. The booklets will be labeled with the timepoint of administration.

PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 10–15 minutes.
- *When onsite at the clinic, site staff* should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should read questions verbatim *and not attempt to interpret or explain questions*.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.8.2 Description of thoClinical Outcome Assessment Instruments

National Eye Institute Visual Function Questionnaire–25

The NEI VFQ-25 captures a patient's perception of vision-related functioning and vision-related quality of life. The core measure includes 25 items that comprise 11 vision-related subscales and 1 item on general health. In this study, an additional six appendix items will be included for the Near Activities and Distance Activities subscales. The composite score and subscale scores range from 0 to 100, with higher scores indicating better vision-related functioning. Subscale scores include general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision.

4.5.9 Optional Aqueous Humor and Plasma Samples (Patients at Participating Sites)

Collection and submission of optional aqueous humor and plasma samples is contingent upon review and approval by the site, each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for sampling, this section of the protocol (Section 4.5.9) will not be applicable at that site.

For patients who consent to provide aqueous humor sampling, the aqueous humor sample should be collected *from the study eye* just prior to study treatment (it is acceptable to collect the sample after FFA assessment) by a qualified treatment administrator/unmasked investigator, using an aseptic procedure and sterile field and according to local guidelines (see Appendix 9 and the central laboratory manual for aqueous humor sample collection, storage, and transfer).

All efforts should be made to obtain a baseline aqueous humor sample on Day 1 (predose). The schedule of activities (see Appendix 1) provides guidance on recommended visits at which aqueous humor samples should be obtained. Patients who are prematurely discontinued from study treatment but who agree to continue to participate in the study should discontinue collection of optional aqueous humor samples and any associated optional plasma samples. However, (unscheduled) sampling may be performed at other or additional planned visits at the discretion of the investigator and in agreement with the participating patient.

Aqueous humor may reflect changes in the retina better than blood, given their close proximity and contiguity to the retina. Aqueous humor samples have previously been demonstrated to be instrumental in improving our understanding of the relationships between ocular pharmacokinetics, VEGF suppression, and duration of clinical efficacy (Muether et al. 2012, 2013, 2014; Fauser et al. 2014; Fauser and Muether 2016; Hutton-Smith et al. 2017). Therefore, to increase our understanding of the ocular pharmacokinetics and pharmacodynamics of faricimab and the relationship to dosing interval, optional aqueous humor samples will be obtained at different timepoints. Aqueous humor will be analyzed for faricimab or aflibercept concentrations as well as

free Ang-2 and free VEGF-A concentrations. Data from these analyses will be used to develop better predictive models for determining optimal PTIs by means of longitudinal target engagement assessments in these surrogate specimens and to support selection of a dosing regimen for future clinical trials.

Remaining samples will be analyzed for additional biomarkers, including those involved in angiogenesis (which may include, but are not limited to, angiopoietin 1 [Ang-1], soluble TEK receptor tyrosine kinase-2 [Tie2], soluble VEGF receptors, and platelet-derived growth factor) and inflammation (which may include, but are not limited to, IL-6, intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion protein 1 (VCAM1), E-selectin, and P-selectin) to identify new therapeutic targets, better understand variability in patient responses to faricimab, and to support patient selection and/or stratification in future clinical trials.

Optional PK and PD plasma samples will be collected according to Appendix 1 for measurement of systemic faricimab or aflibercept concentration, free Ang-2, and free VEGF-A (see the Covance manual for PK/PD samples collection, storage, and transfer).

Faricimab, aflibercept, free Ang-2, and free VEGF-A will be quantified in plasma using validated immunoassay methods. ADAs *against faricimab* will be detected in plasma using a validated bridging ELISA. Based on results of the batch-wise analysis of plasma PD samples, it may be decided not to analyze all samples if no further information gain will be expected.

Samples may be used for exploratory biomarker research as described in Section 4.5.11. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.7 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses).

4.5.10 Optional Unscheduled Collection of Vitreous Humor and Plasma Sample

Vitrectomy may be performed at the discretion of the masked investigator in the event that study eye develops sight-threatening vitreous hemorrhage or retinal detachment (see Section 4.4.1). If the surgery is deemed medically necessary and the patient gives specific consent, a vitreous sample may be obtained from the study eye (see Appendix 9 for further details). Associated PK plasma samples will be collected to measure faricimab or aflibercept concentration. See the laboratory manual for vitreous and PK sample collection, storage, and transfer.

Vitreous humor samples will be analyzed primarily for faricimab or aflibercept concentrations. The remaining samples may be analyzed for free Ang-2 and free VEGF concentrations, as well as additional biomarkers as noted in Section 4.5.9.

Samples may be used for exploratory biomarker research as described in Section 4.5.11. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.7 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to faricimab, diseases, or drug safety:

- Blood sample collected at Day 1 visit
- Leftover aqueous humor, vitreous, and plasma samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.11.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.11.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review,

and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced and will not be allowed to restart study treatment. However, these patients should be strongly encouraged to continue their study participation and undergo as many scheduled visits as possible, with emphasis on the Week 24 and Week 72 visits.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Any medical condition that the investigator determines may jeopardize the patient’s safety if he or she continues in the study
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

In order to avoid loss to follow-up, the investigator should ask the patient at study start for information on a relative or friend who can be contacted in case the patient cannot be reached. However, patients will not be followed for any reason after consent has been withdrawn.

If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

Patients who discontinue from the study early should return for an early termination visit after a minimum of 28 days have elapsed following the last study treatment (see Appendix 1).

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Faricimab is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with faricimab in completed and ongoing studies. Please refer to the Faricimab (RO6867461) Investigator's Brochure for a complete summary of safety information.

5.1.1 Safety Assessments

The schedule of safety assessments to be performed during the study is provided in Appendix 1. After the first study treatment on Day 1, all patients will return for a safety assessment visit on Day 7 (±3 days). Patients will be instructed to contact the site at any time if they have any health-related concerns. If warranted, patients will be asked to

return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 2).

At sites where the masked investigator's decision is for patients to self-administer predose and postdose antimicrobials, patients will also be asked whether they have self-administered predose and/or postdose antimicrobials.

A finger-counting test will be conducted for each patient within 15 minutes postdose by the treatment administrator/unmasked investigator; hand-motion and light-perception tests will be performed when necessary.

Following the study treatment, IOP will be measured in the study eye only at 30 (±15) minutes by qualified personnel assigned to the unmasked role. If there are no safety concerns after 30 (±15) minutes following study treatment, the patient will be permitted to leave the clinic. If the IOP value is of concern to the treatment administrator/unmasked investigator, the patient will remain in the clinic and will be managed in accordance with the treatment administrator/unmasked investigator's clinical judgment. The adverse event will be recorded on the Adverse Event eCRF as applicable.

If an anti-VEGF injection is administered to the non-study (fellow) eye at the same visit as the study eye study treatment (faricimab, aflibercept, or sham), the study eye treatment must be performed first (see Section 4.4.1 for additional details).

An iDMC will monitor safety and study conduct on an ongoing basis (see Section 3.1.6 for additional details).

Patients who are discontinued from the study prior to completion (Week 72) will be asked to return for early termination visit assessments after a minimum of 28 days have elapsed following the last study treatment (see Appendix 1). The visit will include assessment of all adverse events (serious and non-serious; ocular and non-ocular). Serious adverse events will be reported in compliance with GCP guidelines.

Treatment interruption and/or treatment discontinuation for adverse events will be determined using the criteria in Table 1.

5.1.2 Risks Associated with Faricimab

To date, no identified risks for faricimab have been observed.

Based on experience with aflibercept and other anti-VEGF therapies, potential risks of faricimab include intraocular inflammation, the IVT injection-related risks of infectious endophthalmitis, retinal detachment and/or tear, iatrogenic traumatic cataracts, and increased IOP, as well as the potential non-ocular risk of arterial thromboembolic events. An independent Clinical Events Coding Committee will be established to adjudicate

thromboembolic events (myocardial infarcts, strokes, and vascular deaths) reported during the study.

Please see the Faricimab (RO6867461) Investigator's Brochure for more details on the risks of faricimab.

5.1.3 Risks Associated with Aflibercept (Comparator)

Important risks associated with aflibercept IVT injections are conjunctival hemorrhage, eye pain, reduced vision, endophthalmitis, intraocular inflammation, increased intraocular pressure, rhegmatogenous retinal detachment, retinal tear, and iatrogenic traumatic cataract. Important potential risks associated with aflibercept treatment include arterial thromboembolic events and immunogenicity.

For full detail on risks associated with aflibercept, please see the Eylea (aflibercept) E.U. Summary of Product Characteristics.

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 Dose Modification

No dose modifications for faricimab or aflibercept are allowed in this study.

5.1.4.2 Treatment Interruption: Dose Interruption and Treatment Discontinuation Criteria

Study treatment interruption and/or patient discontinuation from the study treatment for adverse events will be determined using the criteria listed in Table 1. If any of these criteria are met, treatment will be interrupted (or discontinued, if applicable) and will not be resumed earlier than the next scheduled study visit. The reason for study treatment interruption/discontinuation should be recorded on the appropriate eCRF and, if applicable, on the Adverse Event eCRF.

Table 1 Dose Interruption and Treatment Discontinuation Criteria

Event	Criteria
Intraocular inflammation	• Interrupt study treatment if intraocular inflammation (iritis, iridocyclitis or vitritis) is ≥ 2+ in the study eye. • Study treatment may be resumed subsequently as determined by the investigator.
Cataract surgery in the study eye	• Interrupt study treatment after cataract surgery in study eye. • Study treatment may be resumed no earlier than 28 days after an uncomplicated cataract surgery and no evidence of post-operational inflammation at that time. For cataract surgery with complications, study treatment may be permitted as determined by Medical Monitor and investigator.
BCVA decrease	• Interrupt study treatment if there is a study treatment–related decrease in BCVA of ≥ 30 letters in the study eye compared with the last assessment of BCVA prior to the most recent treatment. • Study treatment may be permitted subsequently, as determined by the investigator.
Elevated IOP	• Interrupt study treatment if predose IOP in the study eye is ≥ 30 mmHg. • Treatment may be permitted when IOP has been lowered to < 30 mmHg, either spontaneously or by treatment, as determined by the investigator.
Rhegmatogenous retinal break	• Interrupt study treatment if a retinal break is present in the study eye. • Study treatment may be resumed no earlier than 28 days after successful laser retinopexy, as determined by the investigator.
Rhegmatogenous retinal detachment or macular hole	• Interrupt study treatment if rhegmatogenous retinal detachment or Stage 3 or 4 macular hole occurs in the study eye. • Study treatment may be subsequently permitted after discussion with Medical Monitor.
Active or suspected infection	• Interrupt study treatment if active or suspected ocular or periocular infections are present (e.g., infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis) in either eye. • Treatment can also be interrupted in cases where patient currently receives treatment for active systemic infection, per investigator's judgment. • Treatment can be restarted after the event resolves, per investigator judgment.

BCVA = best-corrected visual acuity; IOP = intraocular pressure

Table 1 Dose Interruption and Treatment Discontinuation Criteria (cont.)

Vitrectomy	• Interrupt study treatment if vitrectomy is performed in study eye to treat sight-threatening vitreous hemorrhage or retinal detachment. Study treatment may restart based on the patient's status after consultation with the Medical Monitor.
On-study prohibited medications	• Refer to Section 4.4.2 for additional reasons for potential study treatment discontinuation.

BCVA = best-corrected visual acuity; IOP = intraocular pressure.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject *who has been* administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not *it is* considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)

- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- Sight-threatening adverse events: an adverse event is considered to be sight-threatening and should be reported expeditiously if it meets one or more of the following criteria:
  - It causes a decrease of ≥30 letters in visual acuity score (compared with the last assessment of visual acuity prior to the most recent assessment) lasting more than 1 hour.
  - It requires surgical or medical intervention (i.e., conventional surgery, vitrectomy, vitreous tap, or biopsy with IVT injection of anti-infective treatments, or laser or retinal cryopexy with gas, or a medication) to prevent permanent loss of sight.
  - It is associated with severe intraocular inflammation (i.e., endophthalmitis, 4+anterior chamber cell/flare, or 4+vitritis; see Section 5.3.5 and Appendix 4 for intraocular inflammation grading scales)

All of the above-listed sight-threatening adverse events should also be reported as serious adverse events, listing the underlying cause (if known) of the event as the primary event term

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

For adverse events that occur during or shortly after study treatment, the unmasked investigator may assess the seriousness and severity of the event, but event causality will be assessed by the masked investigator.

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until the final study visit at Week 72. For patients who discontinue study treatment and withdraw prematurely from the study, all adverse events will be reported up to the early termination visit. For patients who discontinue study treatment early (prior to Week 68 treatment) but continue to participate in the study, adverse events will be reported until their last study visit after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 2 provides guidance for assessing adverse event severity.

Table 2 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. Note that only the masked investigator will assess adverse event causality.

The following guidance should be taken into consideration; see also Table 3:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 3 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

For the purposes of reporting events of infection and inflammation, the following are examples of terms and definitions to be used:

- Iritis: the presence of inflammatory cells in the anterior chamber

  The presence of aqueous flare alone will not constitute iritis but should be documented as an anterior chamber flare for adverse event reporting purposes.

- Iridocyclitis: the presence of inflammatory cells in both the aqueous and vitreous
- Vitritis: the presence of active inflammation in the vitreous, demonstrated by the presence of inflammatory cells

  Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, hemorrhage, or other causes.
- Endophthalmitis: diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause

  If possible, a sample for culture should be taken prior to initiating antibiotic treatment for presumed endophthalmitis. Results of bacterial or fungal cultures, treatment given, and final ophthalmologic outcome should also be provided in the details section of the Adverse Event eCRF.

Note: Trace benign, aqueous pigmented cells visible on slitlamp examination that are caused by dilation and are not RBCs or WBCs or the result of any ocular disorder should not be recorded as an adverse event.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.

- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Macular Edema Due to *Central* Retinal Vein Occlusion in the Study Eye

Medical occurrences or symptoms of deterioration that are anticipated as part of *central* retinal vein occlusion (study eye) should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of *central* retinal vein occlusion on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening *central* retinal vein occlusion"). The expedited reporting requirements for associated sight-threatening events (listed in Section 5.2.3) will apply.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Cases of Medication Error and Associated Adverse Events

Medication error, including an error intercepted prior to administration and accidental overdose (hereafter collectively referred to as "special situations"), are defined as follows:

- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with the masked study treatment, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF in masked manner as described below (see eCRF Completion Guidelines for additional details):

- For medication error, enter “Medication Error” on the Adverse Event eCRF as the primary event term and check the “Medication error” box
- For intercepted medication error enter “Intercepted Medication Error” on the Adverse Event eCRF as the primary event term and check the “Medication error” box.

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria (see Section 5.2.2) or *qualifies as* an adverse event of special interest (see Section 5.2.3), the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Adverse events associated with special situations should be recorded as described below for each situation:

- Enter the adverse event caused by the medication error as primary adverse event term. Check the "Medication error" box.

As an example, a special situation that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the medication error and one entry to report the headache. The "Medication error" box would need to be checked for both entries.

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

Contact Information for Western Hemisphere

Medical Monitor/Emergency Medical Contact: [redacted], *M.D., Ph.D. (primary)*

Mobile Telephone No.: [redacted]

Medical Monitor/Emergency Medical Contact: [redacted], M.D., Ph.D. (*secondary*)

Mobile Telephone No.: [redacted]

Medical Monitor/Emergency Medical Contact: [redacted], M.D. (secondary)

Mobile Telephone No.: [redacted]

Contact Information for Europe

Medical Monitor/Emergency Medical Contact: [redacted], M.B.B.S., M.S. (primary)

Mobile Telephone No.: [redacted]

Medical Monitor/Emergency Medical Contact: [redacted], M.B., Ch.B. (secondary)

Mobile Telephone No.: [redacted]

Contact Information for Asia Pacific

Medical Monitor/Emergency Medical Contact: [redacted], *M.D., Ph.D. (primary)*

Mobile Telephone No.: [redacted]

Medical Monitor/Emergency Medical Contact: [redacted], *M.D., Ph.D. (secondary)*

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the final study visit at Week 72. For patients who discontinue study treatment and withdraw prematurely from the study, adverse events will be reported up to the early termination visit. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after Week 72 visit or the early termination visit are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse

events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined in Section 5.3.1), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Faricimab	Faricimab (RO6867461) Investigator's Brochure
Aflibercept	Aflibercept (Eylea®) E.U. Summary of Product Characteristics

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Approximately $750\ patients$ will be randomized in the global enrollment phase of the study. Additional patients may be enrolled in the China extension to ensure a total enrollment sufficient to support registration in China.

The primary analysis of this study will include patients enrolled during the global enrollment phase; data from patients enrolled during the China extension will not be included.

The primary analysis will be performed when all patients from the global enrollment phase have either completed the study through Week 24 or have discontinued from the study prior to Week 24, whichever comes later (i.e., timing is defined as the primary analysis after the LPLV), and all data collected prior to the primary LPLV in the global enrollment phase are in the database and have been cleaned and verified.

Results of the primary analysis, summarized by treatment group, may be reported to the public before completion of the study. However, patients, masked study site personnel, and CRC personnel will remain masked to individual treatment assignment until the study is completed, the database is locked, and the study analyses are final.

The final analysis will be performed when all patients from the global enrollment phase have either completed the study through Week 72 or have discontinued early from the study, all data from the global enrollment phase are in the database, and the database is locked.

Unless otherwise specified, the analyses described in this section are based on patients enrolled during the global enrollment phase (excluding the China extension). Details of the planned analyses, including any additional analyses needed to support country-specific or regional marketing applications, will be provided in the SAP.

6.1 DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on patients enrolled in the global enrollment phase. The global enrollment phase will enroll approximately $750\ patients$.

Patients will be randomized in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B) (refer to Section 3.1.1 for details on dosing regimens). The primary comparison will be between the active comparator (aflibercept Q4W) and the faricimab Q4W arm at Week 24.

A sample size of approximately $375\ patients$ in each arm will provide $>$90% power to show non-inferiority of faricimab to aflibercept in the change in BCVA at Week 24 in the intent-to-treat (ITT) population, using a non-inferiority margin of 4 letters, and under the following assumptions:

- No difference in the mean change from baseline in BCVA between the two treatment arms
- SD of 13 letters for the change from baseline in BCVA at Week 24
- Two-sample $t\text{-}tests$
- 2.5% one-sided type I error rate
- 10% dropout rate

Furthermore, a sample size of approximately $375\ patients$ per arm will provide greater than 80% power to show a 3.5-letter superiority of faricimab over aflibercept in the ITT population, under the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 5%.

Additional patients may be randomized during the China extension to support registration in China.

6.2 ANALYSIS POPULATIONS

The analysis populations described in this section are based on patients enrolled during the global enrollment phase and will not include the China extension unless otherwise specified.

6.2.1 Intent-to-Treat Population

The ITT population will consist of all patients who are randomized in the study. For analyses based on this patient population, patients will be grouped according to the treatment assigned at randomization.

6.2.2 Per-Protocol Population

The per-protocol population is defined as all patients randomized in the study who receive at least one dose of study treatment and who do not have a major protocol violation $that\ impacts\ the\ efficacy\ evaluation$. For analyses based on this patient population, patients will be grouped according to the treatment assigned at randomization.

6.2.3 Safety-Evaluable Population

The safety-evaluable population will consist of all patients who receive at least one injection of active study drug (faricimab or aflibercept) $in\ the\ study\ eye$. For analyses based on this patient population, patients will be grouped according to the actual treatment received up to Week 20. If by error a patient receives a combination of

different active study drugs (faricimab and aflibercept) in the study eye, the patient's treatment group will be as randomized.

6.2.4 Part 2 Efficacy Population

The Part 2 efficacy population will consist of all patients from the ITT population who receive at least one injection of faricimab in Part 2 of the study. For analyses based on this patient population, data will be summarized overall as well as by treatment group assigned in Part 1.

6.2.5 Faricimab-Pooled Safety Population

The faricimab-pooled safety population will consist of all patients from the safety-evaluable population who receive at least one injection of faricimab *in the study eye (i.e., Arm B patients treated with aflibercept who have not received faricimab will be excluded from the faricimab-pooled safety population). ADA will only be assessed in the faricimab-pooled safety population.*

6.2.6 Pharmacokinetic-Evaluable Population

The PK analyses will include safety-evaluable patients with at least one plasma sample, and if sufficient dosing information (dose and dosing time) is available, with patients grouped according to treatment received (as defined in Section 6.2.3).

6.2.7 Immunogenicity Analysis Population

The immunogenicity analysis population will consist of all patients *randomized to faricimab* with at least one plasma sample for ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned at randomization.

6.3 SUMMARIES OF CONDUCT OF STUDY

Summaries of conduct of study will be based on the ITT population.

The number of patients randomized will be tabulated by country, site, and treatment arm. Patient disposition (the number of patients randomized, treated, and completing through the primary endpoint timing, as well as the end of study) will be tabulated by treatment arm. Premature study drug discontinuation and study discontinuation, as well as reasons for discontinuations, will be summarized. Eligibility criteria exceptions and other major protocol deviations will be summarized by treatment arm.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race/ethnicity and region, and baseline disease characteristics (such as baseline BCVA, ocular assessments, and medical history) will be summarized by treatment as assigned for the ITT population using means, SDs, medians, and ranges for continuous variables, and counts and proportions for categorical variables, as appropriate.

Exposure to study drug (number of study drug administrations and duration of treatment) will be summarized by treatment arm for the safety-evaluable population.

6.5 EFFICACY ANALYSES

The primary and secondary efficacy analyses will be based on the ITT population, unless otherwise specified, with patients grouped according to the treatment assigned at randomization. Additional analysis based on the per-protocol population will also be conducted for the primary endpoint.

Unless otherwise noted, analyses of efficacy outcome measures will be stratified by baseline BCVA ETDRS letter score, as assessed on Day 1 (≤ 34 letters, 35–54 letters, and $\geq$ 55 letters), and region (United States and Canada, Asia, and the rest of the world). The stratification factor as recorded in IxRS will be used.

Continuous outcomes will be analyzed using a mixed model for repeated measures (MMRM). Binary secondary endpoints will be analyzed using stratified estimation for binomial proportions. Additional details are provided in Sections 6.5.1 and 6.5.2.

In addition to p-values for statistical tests, the estimates and CIs will be provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment arm and for the difference in means or proportions between the active comparator arm (aflibercept Q4W) and the faricimab Q4W arm. All CIs will be two-sided and at the 95% level.

6.5.1 Primary Efficacy Endpoint

The primary estimand for the study is defined as follows:

- Population: Adult patients with macular edema due to CRVO or HRVO, as defined by the inclusion and exclusion criteria (Sections 4.1.1 and 4.1.2)
- Variable: Change from baseline in BCVA at Week 24

  BCVA is assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters
- Intercurrent events, regardless whether or not a patient has one of the following intercurrent events prior to Week 24
  - Receives any prohibited systemic treatment or prohibited therapy in the study eye (Section 4.4.2)
  - Discontinues study treatment due to adverse events
  - Discontinues study treatment due to lack of efficacy
- Population-level summary: Difference in adjusted mean between the aflibercept Q4W arm and the faricimab Q4W arm

The primary comparison will be between the active comparator (aflibercept Q4W) and faricimab Q4W at Week 24. The following hypothesis will be tested:

- Non-inferiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population (at a 1-sided 0.025 significance level)
- Superiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population (at a 2-sided 0.05 significance level)

The non-inferiority test will be conducted with a non-inferiority margin of 4 letters at a 0.025 one-sided significance level. The null hypothesis (H_0: $\mu^{faricimab} - \mu^{aflibercept} \leq -4$ letters) and the alternative hypothesis (H_a: $\mu^{faricimab} - \mu^{aflibercept} > -4$ letters) will be tested, for which $\mu^{faricimab}$ and $\mu^{aflibercept}$ are the expected change from baseline in BCVA at Week 24 for the faricimab Q4W arm and the active comparator (aflibercept Q4W) arm, respectively.

If the lower bound of a two-sided 95% CI for the difference of two treatments is greater than −4 letters (the NI margin), then the test is considered positive and IVT 6 mg faricimab administered Q4W is considered non-inferior to IVT 2 mg aflibercept administered Q4W. Superiority will be tested only if the non-inferiority test is positive.

The primary analysis will be performed using the mixed-effect model with repeated measures (MMRM) based on all available data up to Week 24. All observed measurements will be included in the analysis regardless whether or not a patient has an intercurrent event. Missing data will be implicitly imputed by the MMRM model, assuming a missing at random mechanism.

The MMRM model will include the change from baseline at Weeks 4−24 as the response variable and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, the continuous baseline value for the response variable (in this case, baseline BCVA), as well as randomization stratification factors as fixed effects. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, a heterogeneous compound symmetry or an AR(1) covariance structure may be fitted.

A per-protocol analysis is planned as a sensitivity analysis for the primary endpoint. The following supplementary analyses will be performed:

- Trimmed mean analysis using an analysis of covariance (ANCOVA) model with adjustment for covariates. The estimand assumes patients have the worst outcome after the following intercurrent events prior to Week 24:
  - Receives any prohibited systemic treatment or prohibited therapy in the study eye (Section 4.4.2)
  - Discontinues study treatment due to adverse events
  - Discontinues study treatment due to lack of efficacy
- Analyses using different handling rules for intercurrent event. Intercurrent events prior to Week 24 are handled as follows:

- Had any prohibited systemic treatment or prohibited therapy in the study eye (Section 4.4.2) not been made available
- Regardless whether a patient discontinues study treatment due to adverse events
- Regardless whether a patient discontinues study treatment due to lack of efficacy as per investigator's clinical judgment

Two analyses will be performed using the same analysis method as the primary endpoint with the exception of data handling methods for intercurrent events and missing data:

- Method 1: Assessments after prohibited treatments will be imputed using the last observation prior to such intercurrent event. Other missing data will be imputed using the last observation carried forward method.
- Method 2: Assessments after prohibited treatment will be excluded. All missing data will be implicitly imputed by the MMRM model, assuming a missing at random mechanism.

Additional details about the planned analyses will be provided in the SAP.

6.5.2 Secondary Efficacy Endpoints

For all secondary endpoints measured on a continuous scale up to Week 24, estimates of each treatment group and difference between the two treatment groups will be provided with 95% CI, using the same analyses methods and data handling rules for intercurrent events and missing data as described in Section 6.5.1 for the primary endpoint.

For binary secondary endpoints up to Week 24, the proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata defined by randomization factors using the Cochran-Mantel-Haenszel weights (Cochran 1954; Mantel and Haenszel 1959). CIs of the proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be calculated using the normal approximation to the weighted proportions (Mehrota and Railkar 2000).

No formal statistical comparisons will be made between the patients randomized to faricimab (Arm A) or aflibercept (Arm B) at the beginning of the study after the Week 24 primary analysis. Maintenance of visual acuity outcomes will be assessed based on descriptive statistics of BCVA change from baseline and change from Week 24 (after the initial monthly doses for each arm). Changes in visual acuity will be assessed based on both continuous and categorical measures of BCVA. Descriptive statistics will be summarized separately for patients randomly assigned to faricimab (Arm A) and aflibercept (Arm B) at the beginning of the study, as well as for pooled patients from the two arms.

Additional details regarding the plan for the secondary endpoint analyses will be provided in the SAP.

6.5.3 Exploratory Efficacy Endpoints

Details regarding analysis of the exploratory efficacy endpoints will be provided in the SAP.

6.6 SAFETY ANALYSES

Safety data will be summarized for the safety-evaluable population up to Week 24 and for the faricimab-pooled *safety* population.

Safety will be assessed through descriptive summaries of ocular and non-ocular adverse events, deaths, and ocular assessments (e.g., IOP). Clinically significant laboratory abnormalities and clinically significant vital sign abnormalities will be reported as adverse events and evaluated as part of the adverse event assessments.

At the time of the primary analysis, safety summaries will be summarized based on the complete Week 24 data in the safety-evaluable population. In addition, summaries for ongoing safety data (after Week 24 and up to a single specified clinical cutoff date) in the faricimab-pooled *safety* population will be summarized. At the time of the final analysis, safety summaries will be produced based on cumulative Week 72 data in the faricimab-pooled *safety* population.

Verbatim descriptions of treatment-emergent adverse events will be mapped to MedDRA thesaurus terms, and the incidence and severity will be summarized by treatment arm. A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug. Adverse events will be tabulated by System Organ Class and *Preferred Term*. In addition, summaries will be generated for serious adverse events, deaths, adverse events leading to discontinuation of study drug, adverse events of special interest, and adverse events judged to be related to study treatment. Non-ocular and ocular adverse events will be summarized. For ocular adverse events, events in the study eye and fellow eye will be summarized separately.

Results of the ocular assessments will be summarized by eye (study vs. fellow) using descriptive summaries. In addition, changes from baseline in predose IOP measurements and changes between predose and postdose IOP measurements will also be summarized.

Additional details regarding the safety analysis plan will be provided in the SAP.

6.7 PHARMACOKINETIC ANALYSES

PK analyses will be performed in the PK-evaluable population.

A non-linear mixed-effects modeling approach (using NONMEM® software [Beal and Sheiner 1998]) will be used to analyze the concentration–time data for faricimab. Population and individual primary PK parameters (i.e., clearances and volumes) will be estimated. The plasma data collected in this study may be pooled with aqueous humor drug concentrations and with data collected in previous studies as appropriate. A covariate modeling approach emphasizing parameter estimation will be implemented for the covariate model development. Potential covariate-parameter relationships will be identified based on mechanistic plausibility and exploratory graphics. Inferences about covariate effects and their clinical relevance will be based on the resulting parameter estimates and measures of estimation precision (asymptotic standard errors). PK parameters, such as area under the concentration–time curve and maximum concentration, will be derived from the individual post-hoc predictions. Additional PK analyses will be conducted as appropriate.

The result of this analysis will be reported in a separate document from the Clinical Study Report.

6.8 PHARMACODYNAMIC ANALYSES

PD analyses will be based on the safety-evaluable population. PD biomarkers and the change from baseline values (absolute or percent change as appropriate) will be summarized by treatment arm and timepoint.

The data collected from this study may be pooled with data from previous studies. The effect of exposure or dosing information on BCVA, aqueous humor free VEGF-A, and free Ang-2 will be explored using a longitudinal model approach. The influence of various baseline covariates on model parameters will be investigated. The PK-PD or dose-PD relationship will be characterized. Additional details about the PK and PD analyses will be provided in the Modeling Analysis Plan. The results will be reported in a separate document from the Clinical Study Report.

6.9 IMMUNOGENICITY ANALYSES

Humoral immunogenicity analyses will be based on the immunogenicity analysis population.

The number and proportion of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining the postbaseline incidence, patients are considered to be ADA-positive if they are ADA-negative or have missing data at baseline but who develop an ADA response following study drug exposure, or if they are ADA-positive at baseline and the titer of one or more postdose samples is greater than the titer of the baseline sample by a scientifically reasonable margin (details to be provided in the SAP). Patients are considered to be ADA-negative if they are ADA-negative or have missing data at baseline and all postbaseline samples are

negative, or if they are ADA-positive at baseline but do not have any postbaseline samples with a titer that is greater than the titer of the baseline sample by a scientifically reasonable margin such as 4-fold.

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported using descriptive statistics.

6.10 BIOMARKER ANALYSES

Biomarker analyses will be based on the safety-evaluable population.

Analyses will be performed, as deemed appropriate, to identify biomarkers that are predictive of response to faricimab, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of faricimab activity, or can increase the knowledge and understanding of disease biology and drug safety. Prognostic biomarker analyses will include all patients for which biomarker assessments were made during randomization ("baseline"). Baseline values will be used to evaluate prognostic biomarkers in the context of efficacy, PK, safety, and/or immunogenicity endpoints. Results will be summarized descriptively.

6.11 CHINA SUBPOPULATION ANALYSES

The China subpopulation will include all patients enrolled at NMPA-recognized sites (i.e., during both the global enrollment phase and the extended China enrollment phase). Details regarding the China subpopulation analysis will be provided in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and CRC reports and images will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent

forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not

participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations

from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 200 sites globally will participate to enroll approximately *750 patients*. Enrollment will occur through IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5.

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Table 1 Screening through Week 24 *(Part 1)* and Early Termination

		Visit Day		Visit Week						ET
	Screening [a]	1[a]	7[b]	4	8	12	16	20	24	Visit [c]
Visit Window (days)	–28 to –1	NA	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥28)
Main informed consent [d]	x									
Optional aqueous, vitreous and plasma sample informed consent	x [d]	x [d]								
Optional collection and/or storage of samples for RBR informed consent	x [d]	x [d]								
Review of inclusion and exclusion criteria	x	x								
Demographics (age, sex, and self-reported race/ethnicity)	x									
Medical and surgical history including tobacco history [e]	x									
Physical examination [f]	x									x
Body weight and height	x									
Vital signs [g]	x	x								x
NEI VFQ-25 [h]		x							x	x
Refraction and BCVA [i]	x	x	x	x	x	x	x	x	x	x
Predose IOP [j]	x	x	x	x	x	x	x	x	x	x
Pregnancy test [k]	x	x		x	x	x	x	x	x	x
Slitlamp examination	x	x	x	x	x	x	x	x	x	x
Indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x
SD-OCT [l] or SS-OCT (if applicable)	x	x	x	x	x	x	x	x	x	x
Optional OCT-A [l, m]		x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

Table 1 Screening through Week 24 *(Part 1)* and Early Termination

		Visit Day		Visit Week						ET
	Screening [a]	1[a]	7[b]	4	8	12	16	20	24	Visit [c]
Visit Window (days)	–28 to –1	NA	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥28)
FFA [l]	(x)	x							x	x
CFP [l]	x								x	x
Hematology [n, o]	x								x	
Chemistry [n, o]	x								x	
Coagulation [n, o]	x								x	
Urinalysis [n, o]	x									
Mandatory plasma PK sample [n]		x		x					x	x
Mandatory plasma PD sample [n]		x							x	x
Mandatory plasma ADA sample [n]		x		x					x	x
Optional aqueous humor sample for biomarkers [p]		x	x	x					x	x
Optional PK plasma sample (if aqueous humor sample is collected) [n, p]			x							
Optional PD plasma sample (if aqueous humor sample is collected) [n, p]			x	x						
Optional vitreous humor sample for biomarkers [q]		Collected if vitrectomy is necessary								
Optional PK plasma sample (if vitreous humor sample is collected) [n, q]		Collect plasma PK sample if vitreous humor sample is collected								
Optional blood sample for RBR [n, r]		x								

Appendix 1
Schedule of Activities (cont.)

Table 1 Screening through Week 24 *(Part 1)* and Early Termination

		Visit Day		Visit Week						ET
	Screening [a]	1[a]	7[b]	4	8	12	16	20	24	Visit [c]
Visit Window (days)	–28 to –1	NA	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥28)
Administration of study treatment		x		x	x	x	x	x	x	
Finger-counting test [s]		x		x	x	x	x	x	x	
Postdose IOP [t]		x		x	x	x	x	x	x	
Adverse events [u]	x	x	x	x	x	x	x	x	x	x
Concomitant medications [v]	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [w]		x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; Ang-2 = angiopoietin-2; BCVA = best-corrected visual acuity; CFP = color fundus photograph; CRC = central reading center; eCRF = electronic Case Report Form; ET = early termination; FFA = fundus fluorescein angiography; IOP = intraocular pressure; IxRS = interactive web-based response system; NEI VFQ-25 = National Eye Institute 25-Item Visual Functioning Questionnaire; OCT-A = optical coherence tomography–angiography; PD = pharmacodynamic; PK = pharmacokinetic; RBR = Research Biosample Repository; SD-OCT = spectral-domain optical coherence tomography; SS-OCT = swept-source optical coherence tomography; UWF = ultrawide field; VA = visual acuity; VEGF-A = vascular endothelial growth factor–A.

Appendix 1
Schedule of Activities (cont.)

Table 1: Screening through Week 24 *(Part 1)* and Early Termination

Notes: All ocular assessments are to be performed on both eyes unless stated otherwise. All assessments are to be performed on the same day, except during screening. All study visits will be scheduled 28 (±7) days relative to the randomization date as registered in IxRS.

There must be a minimum of 21 days between study treatment visits occurring from Day 1 through to Week 68. The final study visit at Week 72 should not occur earlier than 28 days after the final study treatment. All assessments should be performed prior to dosing, unless otherwise specified. Fellow eye anti-VEGF treatment approved by the country regulatory agency for ocular use may be covered by the Sponsor only as long as the patient remains in the study (for details, refer to Section 4.4.1). The fellow eye anti-VEGF treatments after the ET visit or the final study visit (Week 72) will not be covered by the Sponsor.

[a] The screening and Day 1 (randomization) visits may occur as a combined visit if all assessments are completed and evaluated within 2 business days. When screening and randomization are combined and performed in 1 day, assessments listed for both visits should be conducted only once. If the combined visit is conducted within 2 business days, then the following safety assessments will be repeated on the day of patient's randomization and study treatment administration: urine pregnancy test (if applicable), slitlamp examination, indirect ophthalmoscopy, and predose IOP measurements (recorded on the Day 1 eCRF and dated accordingly). Verify that the patient has not started any prohibited medication.

[b] The Day 7 visit should take place 7 days after the Day 1 visit (e.g., if the Day 1 visit takes place on a Wednesday, the Day 7 visit would take place on the following Wednesday).

[c] Patients who discontinue from the study early (prior to the final study visit at Week 72) but have not withdrawn consent should return for an early termination visit after a minimum of 28 days have elapsed following their final study treatment.

[d] Informed consent must be administered and documented before any study-specific screening procedure is performed and may be obtained no more than 28 days before initiation of study treatment at the Day 1 visit. The Informed Consent Forms for optional aqueous humor, vitreous humor, and plasma samples, as well as the Informed Consent Form for optional collection and/or storage of samples for RBR can be signed either at the screening or Day 1 visit prior to sample collection.

[e] Medical history, including clinically significant diseases, chronic and ongoing conditions (e.g., trauma, cardiovascular, cerebrovascular, and ophthalmic), surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history will be recorded at baseline.

[f] A targeted physical examination should include an evaluation of the head, ears, nose and throat. If any abnormalities are noted during the study, the patient may be referred to another doctor.

[g] Vital signs include measurement of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure. Vital signs will be taken while the patient is in a seated position after resting for 5 minutes.

Appendix 1
Schedule of Activities (cont.)

Table 1: Screening through Week 24 *(Part 1)* and Early Termination

[h] To be administered by the masked site staff (except for the BCVA examiner) before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

[i] Perform the assessments prior to dilating the eyes. Both refraction and BCVA will be assessed at every study visit for both eyes, however, only study eye refraction from the Day 1, Week 24 and Week 68 visits will be entered on the refraction-specific eCRF. The BCVA assessment data for both eyes will be entered on the BCVA-specific eCRF for every study visit. The study eye BCVA score at each study treatment visit must be entered in IxRS during the same visit so that the correct study treatment can be assigned for future visits. Prior to entering the study eye BCVA score in IxRS, the study coordinator must recalculate the BCVA score using the BCVA worksheet to verify accurate study eye BCVA score.

[j] The same method should be used throughout the study period. Perform measurements prior to dilating the eyes. At screening and on Day 7, IOP should be performed, although study treatment will not be given.

[k] All women of childbearing potential (including those who had had a tubal ligation) will have a urine pregnancy test performed at screening and prior to each study treatment at subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. If positive, study treatment should not be administered. Perform urine pregnancy test before FFA (if applicable).

[l] The CRC will review SD-OCT (certain SS-OCT equipment may be acceptable; consult CRC) and CFP images obtained at screening for determination of patient eligibility. The investigator will determine unilateral versus bilateral disease status at screening. For patients with bilateral RVO, screening CFP and SD-OCT images of fellow eye *may* be captured and stored at the CRC. No ocular images of the fellow eye will be captured or stored at screening for patients with unilateral RVO. At all subsequent visits, imaging will be performed in the study eye only, except for patients diagnosed at screening with bilateral RVO. For these patients, at subsequent visits CFP and SD-OCT images *may* also be captured in the fellow eye and stored at the CRC. Outputs from all types of imaging assessments will be sent to the relevant CRC. See the CRC manual for details on the required equipment and image-capture guidance for FFA and CFP. The baseline CFP must be completed at screening and sent to the CRC together with the OCT image. The baseline FFA may be obtained either at screening or the Day 1 visit, but it is recommended to obtain it at the Day 1 visit. The FFA images should be obtained after laboratory samples have been collected. Note: After randomization, if a patient misses a study visit when CFP or FFA ocular images are scheduled or these images are not taken at the scheduled visit (e.g., equipment is broken), they must be obtained at the next scheduled visit the patient attends. Please remember to forward OCT images to the CRC immediately after the visit as they need to be evaluated and data submitted to IxRS by the CRC before the next study visit. If the OCT image was missed due to a missed visit or not taken, then notify the CRC immediately so they can inform IxRS that the expected data will not be available.

[m] Optional OCT-A in study eye to be conducted at sites with OCT-A capability and provided sites approve optional OCT-A sampling.

[n] Obtain prior to FFA (if applicable) and prior to study treatment. *Missed mandatory PK, PD, or ADA samples may be obtained at the next scheduled visit the patient attends.*

Appendix 1
Schedule of Activities (cont.)

Table 1: Screening through Week 24 *(Part 1)* and Early Termination

[o] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes [absolute], lymphocytes, and other cells). Serum chemistry panel includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, and urate. Coagulation includes aPTT and PT. Urinalysis includes pH, specific gravity, glucose, protein, ketones, blood, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal). If screening and Day 1 visits are combined, historical laboratory data obtained within 2 months of Day 1 may be used at the Principal Investigator's discretion; samples must still be collected for submission to the central laboratory.

[p] If a patient consents to collection of optional aqueous humor sample, collect the sample *from the study eye* at indicated timepoints prior to study treatment administration. It is permissible to collect aqueous humor sample after FFA was performed at applicable visits. Associated optional PK and PD plasma samples should be collected at scheduled visits only from patients consenting to optional aqueous humor sampling. Not applicable for a site that has not been granted approval by a site's Institutional Review Board or Ethics Committee.

[q] If *a* vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. Associated PK plasma sample should also be collected.

[r] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. If the optional RBR sample is not obtained at the assigned visit (Day 1), the sample may be collected at any subsequent study visit when a blood draw is being performed for other purposes as specified (e.g., PK and ADA sampling, and/or hematology or chemistry).

[s] The finger-counting test should be conducted by the treatment administrator/unmasked investigator within approximately 15 minutes following study treatment administration for the study eye only.

[t] Postdose IOP measurement to be conducted in the study eye only at 30 (±15) minutes by qualified personnel assigned to the unmasked role. If there are no safety concerns after 30 (±15) minutes following the study treatment, the patient will be permitted to leave the clinic. If the IOP value is of concern to the investigator, the patient will remain in the clinic and will be managed in accordance with the investigator's clinical judgment. The adverse event will be recorded on the Adverse Event eCRF as applicable. The same method of measuring IOP should be used throughout the study.

Appendix 1
Schedule of Activities (cont.)

Table 1: Screening through Week 24 *(Part 1)* and Early Termination

[u] After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug (Day 1), all adverse events will be reported until the final study visit, or if applicable, until the early termination visit. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse *events* that are believed to be related to prior study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[v] Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications such as proparacaine, etc.) used by the patient from 7 days prior to initiation of study treatment (Day 1) until the final study visit or early termination visit.

[w] Record all concurrent ocular procedures performed on the study or non-study eye between the Day 1 visit after study treatment and the final study visit or early termination visit.

Appendix 1
Schedule of Activities (cont.)

Table 2 Week 28 through Week 72 *(Part 2)* and Early Termination

	Visit Week												ET Visit [b]
	28	32	36	40	44	48	52	56	60	64	68	72	
Visit Window (days)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥28 and <35) [a]	(≥28)
Physical examination [c]												x	x
Vital signs [d]												x	x
NEI VFQ-25 [e]						x						x	x
Refraction and BCVA [f]	x	x	x	x	x	x	x	x	x	x	x	x	x
Predose IOP [g]	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test [h]	x	x	x	x	x	x	x	x	x	x	x	x	x
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x
Indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [i] or SS-OCT (if applicable)	x	x	x	x	x	x	x	x	x	x	x	x	x
Optional OCT-A [i, j]	x	x	x	x	x	x	x	x	x	x	x	x	x
FFA [i]						x						x	x
CFP [i]						x						x	x
Hematology [k, l]													
Chemistry [k, l]													
Coagulation [k, l]													
Urinalysis [k, l]													
Mandatory plasma PK sample [k]	x						x					x	x
Mandatory plasma PD sample [k]													x
Mandatory plasma ADA sample [k]	x						x					x	x

Appendix 1
Schedule of Activities (cont.)

Table 2 Week 28 through Week 72 *(Part 2)* and Early Termination

	Visit Week												ET Visit [b]
	28	32	36	40	44	48	52	56	60	64	68	72	
Visit Window (days)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥28 and <35) [a]	(≥28)
Optional aqueous humor sample for biomarkers [m]	x		x	x				x					x
Optional PK plasma sample (if aqueous humor sample is collected) [k,m]				x				x					
Optional PD plasma sample (if aqueous humor sample is collected) [k,m]	x		x	x				x					
Optional vitreous humor sample for biomarkers [n]	Can be collected if vitrectomy is necessary												
Optional PK plasma sample (if vitreous humor sample is collected) [k,n]	Collect PK sample if vitreous humor sample is collected												
Administration of study treatment	x	x	x	x	x	x	x	x	x	x	x		
Finger-counting test [o]	x	x	x	x	x	x	x	x	x	x	x		
Postdose IOP [p]	x	x	x	x	x	x	x	x	x	x	x		
Adverse events [q]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [r]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [s]	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; Ang-2 = angiopoietin-2; BCVA = best-corrected visual acuity; CFP = color fundus photograph; CRC = central reading center; eCRF = electronic Case Report Form; ET = early termination; FFA = fundus fluorescein angiography; IOP = intraocular pressure; IxRS = interactive web-based response system; NEI VFQ-25 = National Eye Institute 25-Item Visual Functioning Questionnaire; OCT-A = optical coherence tomography–angiography; PD = pharmacodynamic; PK = pharmacokinetic; RBR = Research Biosample Repository; SD-OCT = spectral-domain optical coherence tomography; SS-OCT = swept-source optical coherence tomography; UWF = ultrawide field; VA = visual acuity; VEGF-A = vascular endothelial growth factor–A.

Appendix 1
Schedule of Activities (cont.)

Table 2 Week 28 through Week 72 *(Part 2)* and Early Termination

Notes: All ocular assessments are to be performed on both eyes unless stated otherwise. All assessments are to be performed on the same day. All study visits will be scheduled 28 (±7) days relative to the randomization date as registered in IxRS.

There must be a minimum of 21 days between study treatment visits occurring from Day 1 through to Week 68. All assessments should be performed prior to dosing, unless otherwise specified. Fellow eye anti-VEGF treatment approved by the country regulatory agency for ocular use may be covered by the Sponsor only as long as the patient remains in the study (for details, refer to Section 4.4.1). The fellow eye anti-VEGF treatments after the ET visit or the final study visit (Week 72) will not be covered by the Sponsor.

[a] The Week 72 visit must occur ≥28 days and <35 days after the actual date of the Week 68 visit.

[b] Patients who discontinue from the study early (prior to the final study visit at Week 72) but have not withdrawn consent should return for an early termination visit after a minimum of 28 days have elapsed following their final study treatment.

[c] A targeted physical examination should include an evaluation of the head, ears, nose, and throat. If any abnormalities are noted during the study, the patient may be referred to another doctor.

[d] Vital signs include measurement of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure. Vital signs will be taken while the patient is in a seated position after resting for 5 minutes.

[e] To be administered by the masked site staff (except for the BCVA examiner) before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

[f] Perform the assessments prior to dilating the eyes. Both refraction and BCVA will be assessed at every study visit for both eyes; however, only study eye refraction from the Day 1, Week 24, and Week 68 visits will be entered on the refraction-specific eCRF. The BCVA assessment data for both eyes will be entered on the BCVA-specific eCRF for every study visit. The study eye BCVA score at each study treatment visit must be entered in IxRS so that the correct study treatment can be assigned for future visits. Prior to entering the study eye BCVA score in IxRS, the study coordinator must recalculate the BCVA score using the BCVA worksheet to verify accurate study eye BCVA score.

[g] The same method should be used throughout the study period. Perform measurements prior to dilating the eyes. At Week 72 and early termination (if applicable) visits, IOP should be performed, although study treatment will not be given.

[h] All women of childbearing potential (including those who had had a tubal ligation) will have a urine pregnancy test performed at screening and prior to each study treatment at subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. If positive, study treatment should not be administered. Perform urine pregnancy test before FFA (if applicable).

Appendix 1
Schedule of Activities (cont.)

Table 2 Week 28 through Week 72 *(Part 2)* and Early Termination

[i] Imaging will be performed in the study eye only, except for patients diagnosed at screening with bilateral RVO. For these patients, CFP and SD-OCT images *may* also be captured in the fellow eye and stored at the CRC. Outputs from all types of imaging assessments will be sent to the relevant CRC. See the CRC manual for details on the required equipment and image-capture guidance for FFA and CFP. Please remember to forward OCT images to the CRC immediately after the visit as they need to be evaluated and data submitted to the IxRS by the CRC before the next study visit. If the OCT image was missed due to a missed visit or not taken, then notify the CRC immediately so they can inform IxRS that the expected data will not be available.

[j] Optional OCT-A in study eye to be conducted at sites with OCT-A capability and provided sites approve optional sampling.

[k] Obtain prior to FFA (if applicable) and prior to study treatment. *Missed mandatory PK, PD, or ADA samples may be obtained at the next scheduled visit the patient attends.*

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes [absolute], lymphocytes, and other cells). Serum chemistry panel includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, and urate. Coagulation includes aPTT and PT. Urinalysis includes pH, specific gravity, glucose, protein, ketones, blood, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal).

[m] If a patient consents to collection of optional aqueous humor sample, collect the sample at indicated timepoints prior to study treatment administration. It is permissible to collect aqueous humor sample after FFA was performed at applicable visits. Associated optional PK and PD plasma samples should be collected at scheduled visits only from patients consenting to optional aqueous humor sampling. Not applicable for a site that has not been granted approval by a site's Institutional Review Board or Ethics Committee.

[n] If *a* vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. Associated PK plasma sample should also be collected.

[o] The finger-counting test should be conducted by the treatment administrator/unmasked investigator within approximately 15 minutes of study treatment administration for the study eye only.

[p] Postdose IOP measurement to be conducted in the study eye only at 30 (±15) minutes by qualified personnel assigned to the unmasked role. If there are no safety concerns after 30 (±15) minutes following the study treatment, the patient will be permitted to leave the clinic. If the IOP value is of concern to the investigator, the patient will remain in the clinic and will be managed in accordance with the investigator's clinical judgment. The adverse event will be recorded on the Adverse Event eCRF as applicable. The same method of measuring IOP should be used throughout the study.

Appendix 1
Schedule of Activities (cont.)

Table 2 Week 28 through Week 72 *(Part 2)* and Early Termination

[q] After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug (Day 1), all adverse events will be reported until the final study visit, or if applicable, until the early *termination* visit. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse *events* that are believed to be related to prior study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[r] Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications such as proparacaine, etc.) used by the patient from 7 days prior to initiation of study treatment (Day 1) until the final visit or early *termination* visit.

[s] Record all concurrent ocular procedures performed on the study or non-study eye between the Day 1 visit after study treatment and the final study visit or early *termination* visit.

Appendix 2
Unscheduled Safety Assessment Visit

Assessments (at the discretion of the investigator) [a]
Vital signs (blood pressure, respiratory rate, pulse rate, and temperature)
Best-corrected visual acuity (assessed at a 4-meter starting distance) [b]
Slitlamp examination
Dilated binocular indirect high-magnification ophthalmoscopy
Intraocular pressure [c]
Adverse events [d]
Concurrent ocular procedures
Concomitant medications
Hematology, serum chemistry panel, and coagulation [e]
Ocular imaging, as necessary

IOP = intraocular pressure.

[a] Patients will be instructed to contact the investigator at any time if they have any health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit. Assessments performed at unscheduled safety visits are at the discretion of the investigator. It is recommended to perform ocular assessments on both eyes.

[b] Perform finger-counting test followed by hand-motion and light-perception tests when necessary.

[c] The method used for the IOP measurement for a patient must remain consistent throughout the study.

[d] Adverse event causality to be evaluated by the masked physician in the assessor role.

[e] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, quantitative platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes [absolute], lymphocytes, and bands). Serum chemistry panel includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, and urate. Coagulation includes aPTT and PT.

Appendix 3
Study Treatment Preparation

The pharmacist responsible for dispensing the study treatment, or designated unmasked site personnel, will prepare the correct study treatment (faricimab, aflibercept, or sham) as assigned through the interactive web-based response system (IxRS).

Detailed stepwise instructions for the preparation of faricimab, aflibercept, or sham for administration, and mandatory materials to be used will be specified by the Sponsor and are detailed in the pharmacy manual.

A specified filter needle must be used for each dose preparation of faricimab or aflibercept according to the instructions provided in the pharmacy manual. All materials to prepare and administer study treatments will be provided or reimbursed by the Sponsor, and no other material than specified should be used.

Vials of faricimab drug product and vials of aflibercept (the active comparator) are for single-use only (one injection preparation per patient per eye). Vials used for one patient must not be used for any other patient. Partially used vials, remaining faricimab drug product or aflibercept vials, as well as administration material must not be *reused*.

Appendix 4
Grading Scale for Assessment of Anterior Chamber Flare or Cells and Vitreous Cell

Anterior Chamber Flare

Grade	Description
0	None
1 +	Faint
2 +	Moderate (iris and lens details clear)
3 +	Marked (iris and lens details hazy)
4 +	Intense (fibrin or plastic aqueous)

Anterior Chamber Cells

Grade	Cells in Field [a]
0	< 1
0.5 +	1–5
1 +	6–15
2 +	16–25
3 +	26–50
4 +	> 50

[a] Field size is a 1-mm slit beam.

Vitreous Cells

Grade	Number of Vitreous Cells
0	No cells
0.5 +	1–10
1 +	11–20
2 +	21–30
3 +	31–100
4 +	> 101 [a]

[a] There is an error in the publication. This should read ≥ 101.

From: The Standardization of Uveitis Nomenclature (SUN) Working Group criteria.

Reference: Foster CS, Kothari S, Anesi SD, et al. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. Surv Ophthalmol 2016;61:1–17.

Appendix 5
Refraction and Best-Corrected Visual Acuity Testing

SCOPE

Best-corrected visual acuity (BCVA) is assessed on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart, at a starting test distance of 4 meters. The refraction BCVA assessment must be conducted before pupil dilation. The refraction and BCVA will be measured by trained and certified personnel at the study sites. Both refraction and BCVA will be assessed at every study visit, however, only study eye refraction on Day 1, Week 24, and Week 68 visits will be entered on the refraction-specific electronic Case Report Form (eCRF). The BCVA assessment data will be entered on the BCVA-specific eCRF for every study visit. The visual acuity (VA) examiner must be masked to each patient's study (treated) eye and treatment arm assignment. VA will be measured at the intervals specified in the protocol (see Appendix 1).

EQUIPMENT

The following are needed to conduct the examination:

- Examination lane of adequate dimensions to allow testing at required distances (4- and 1-meter lanes)
- Standard chair with a firm back
- Set of three Precision Vision™ or Lighthouse distance acuity charts as applicable per country and region (see the BCVA manual for details)
- Retro-Illuminated box
- Study frame
- Study lens set
- Note: for additional details, see the BCVA specification manual.

TRAINING AND CERTIFICATION

A VA specifications document, procedure manual, and training materials will be provided to the investigational sites, and examiner certification will be obtained from a third party vendor. The visual acuity examination room also must be certified before any visual acuity examinations are performed.

ETDRS Reference: Kniestedt C, Stamper RL. Visual acuity and its measurement. Ophthalmol Clin North Am. 2003;16:155–70.

Appendix 6
Color Fundus Photography

SCOPE

Color fundus photographs will be obtained from study eye by trained personnel at the study sites. Please see the central reading center (CRC) manual for details on the required equipment and image-capture guidance.

Fundus photography will be performed at baseline (screening) and at the intervals specified in the schedule of activities (see Appendix 1). Analysis (if applicable) of fundus photographs will be performed by the same CRC that will evaluate fluorescein angiograms.

EQUIPMENT

See the CRC manual.

PROCEDURE

The CRC will provide a study manual and training materials. The fundus photographer and photography equipment will be certified by the CRC before any study images are taken. See the CRC manual for further details.

Appendix 7
Fundus Fluorescein Angiography

SCOPE

Fundus fluorescein angiography (FFA) will be obtained from study eye by trained personnel at the study sites. Please see the central reading center (CRC) manual for details on the required equipment and image-capture guidance. The photographs must be performed by trained personnel who are certified by the CRC and capable of capturing the images at the precise correct times after the fluorescein injection as described in the CRC manual.

The fundus fluorescein angiograms will be obtained at baseline (at screening or on Day 1) and at the intervals specified in the protocol (see Appendix 1). Analysis (if applicable) of fundus fluorescein angiograms will be performed by the CRC.

EQUIPMENT

Digital angiograms must be used while conducting an angiographic evaluation for the study.

Film-based angiography is not acceptable.

UWF (Optos or Zeiss Clarus) is the preferred method for FFA capture. The study sites without Optos or Zeiss Clarus equipment and certification must consult the CRC. Please see the CRC manual for details on the required equipment and image-capture guidance.

DIGITAL IMAGING SYSTEMS AND CERTIFICATION

Digital imaging systems are required. The system and software at the site will be certified by the CRC prior to obtaining any study angiograms. This certification and validation process will ensure that the CRC will be able to correctly calculate the required measurements.

PROCEDURES

The CRC will provide a study manual and training materials. Photographers, systems, and software will be certified prior to obtaining angiograms of patients.

Appendix 8
Spectral-Domain Optical Coherence Tomography

SCOPE

Spectral-domain optical coherence tomography (SD-OCT) will be performed at the study sites by trained personnel who are certified by the central reading center (CRC). SD-OCT imaging will be performed for each patient at the intervals specified in the protocol (see Appendix 1) and will be forwarded to the CRC.

Note: The optional images will be collected at the sites with optical coherence tomography–angiography capabilities and forwarded to the CRC.

EQUIPMENT

Equipment utilized during this study is described in the CRC manual. The ability to transfer images to electronically exportable digital files is required (i.e., no printed SD-OCT images will be sent to the CRC).

Note: Certain swept-source optical coherence tomography (SS-OCT) machines may be acceptable to use; consult the CRC for further details.

PROCEDURES AND CERTIFICATION

The CRC will provide the study manual and training materials. SD-OCT operators, systems, and software will be certified prior to any evaluation of patients.

Appendix 9
Biological Sample Collection and Shipping Instructions

BIOLOGICAL SAMPLES

Biological samples for the assessment of faricimab concentrations (pharmacokinetics), pharmacodynamics, anti-faricimab antibodies, blood DNA sample, laboratory assessment (hematology, serum chemistry, coagulation, and urinalysis), and optional aqueous humor and vitreous samples will be obtained at the timepoints specified in the protocol (see Section 4.5.7 and Appendix 1).

Refer to the central laboratory manual for detailed sample collection, storage, and shipping instructions. All necessary transfer tubes, Vacutainers™, labels, shipping boxes, and forms will be provided by the central laboratory.

OPTIONAL ANTERIOR CHAMBER (AQUEOUS HUMOR) SAMPLE COLLECTION

The study eye optional aqueous humor paracentesis samples will be collected by the unmasked treating physician from patients who consent to the procedure and sample acquisition. An aqueous humor sample will be collected before the patient's study eye treatment at the visits as indicated in Appendix 1. Please refer to the central laboratory manual for additional details regarding sample collection and shipping information.

OPTIONAL UNSCHEDULED COLLECTION OF VITREOUS HUMOR SAMPLE COLLECTION

Vitrectomy may be performed at the discretion of the masked investigator in the event that study eye develops sight-threatening vitreous hemorrhage or retinal detachment (see Section 4.4.1). If the surgery is deemed medically necessary and the patient gives specific consent, a vitreous sample may be obtained from the study eye. Either masked or unmasked investigators can collect the sample. Approximately 0.5 mL of undiluted vitreous humor should be collected using an aseptic procedure and sterile field and according to local guidelines and shipped as specified in the central laboratory manual.

A pharmacokinetic blood sample (for plasma preparation) should also be collected and shipped as specified in the central laboratory manual.

Vitreous humor samples will be analyzed primarily for faricimab or aflibercept concentrations. The remaining samples may be analyzed for free angiopoitin-2 (Ang-2) and free vascular endothelial growth factor (VEGF) concentrations, and possibly other biomarkers.

BIOLOGICAL SAMPLES STORAGE DURATION

The hematology, serum chemistry, urinalysis, coagulation, serum, and urine pregnancy test samples will be destroyed after their analysis during the study.

Unless the patient gives specific Research Biosample Repository consent for his or her remaining samples to be stored for optional exploratory research (see Section 4.5.11), the rest of the biological samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

Appendix 10
National Eye Institute 25-Item Visual Functioning Questionnaire

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

Minor changes to formatting (not affecting the items of the questionnaire) were made.

NEI-VFQ25-IA - United States/English - Mapi.
ID8084 / NEI-VFQ25_IA-with-subscales_TS1.0_eng-USori.doc

Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

NEI-VFQ25-IA - United States/English - Mapi.
ID8084 / NEI-VFQ25_IA-with-subscales_TS1.0_eng-USori.doc

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is*:

(Circle One)

READ CATEGORIES:

Excellent	**1**
Very Good	**2**
Good	**3**
Fair	**4**
Poor	**5**

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

READ CATEGORIES:

Excellent	**1**
Good	**2**
Fair	**3**
Poor	**4**
Very Poor	**5**
Completely Blind	**6**

* **Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0**

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3. How much of the time do you worry about your eyesight?

		(Circle One)
READ CATEGORIES:	**None of the time**	**1**
	A little of the time	**2**
	Some of the time	**3**
	Most of the time	**4**
	All of the time?	**5**

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

		(Circle One)
READ CATEGORIES:	**None**	**1**
	Mild	**2**
	Moderate	**3**
	Severe, or	**4**
	Very severe?	**5**

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

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6. How much difficulty do you have doing work or hobbies that require you to <u>see well up close</u>, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

7. Because of your eyesight, how much difficulty do you have <u>finding something on a crowded shelf</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

8. How much difficulty do you have <u>reading street signs or the names of stores</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

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9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

12. Because of your eyesight, how much difficulty do you have <u>picking out and matching your own clothes</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

13. Because of your eyesight, how much difficulty do you have <u>visiting with people in their homes, at parties, or in restaurants</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

14. Because of your eyesight, how much difficulty do you have <u>going out to see movies, plays, or sports events</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

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15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 *Skip To Q 15c*

No..... 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove..... 1 *Skip To Part 3, Q 17*

Gave up 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight..... 1 *Skip To Part 3, Q 17*

Mainly other reasons..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons..... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4

16. How much difficulty do you have <u>driving at night</u>? Would you say you have:
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight	**5**
Have you stopped doing this for other reasons or are you not interested in doing this	**6**

16a. How much difficulty do you have <u>driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic</u>? Would you say you have:
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight	**5**
Have you stopped doing this for other reasons or are you not interested in doing this	**6**

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

	(Circle One On Each Line)				
READ CATEGORIES:	**All of the time**	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
17. Do you accomplish less than you would like because of your vision?	**1**	**2**	**3**	**4**	**5**
18. Are you limited in how long you can work or do other activities because of your vision?	**1**	**2**	**3**	**4**	**5**
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	**1**	**2**	**3**	**4**	**5**

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For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.....	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me....	1	2	3	4	5
24. I need a lot of help from others because of my eyesight	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight	1	2	3	4	5

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SUBSCALE: NEAR VISION

A1. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A2. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

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A3. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

SUBSCALE: DISTANCE VISION

A4. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A5. Because of your eyesight, how much difficulty do you have <u>taking part in active sports or other outdoor activities that you enjoy</u> (like golf, bowling, jogging, or walking)?
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A6. Because of your eyesight, how much difficulty do you have <u>seeing and enjoying programs on TV</u>?
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

That's the end of the interview. Thank you very much for your time and your help.

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