Official Title: A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab in Patients With Neovascular Age-Related Macular Degeneration (LUCERNE)

NCT Number: NCT03823300

Document Date: Protocol Version 3: 06-August-2019

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR–CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FARICIMAB IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (LUCERNE)**
PROTOCOL NUMBER:	GR40844
VERSION NUMBER:	3
EUDRACT NUMBER:	2018-004042-42
IND NUMBER:	119225
TEST PRODUCT:	Faricimab (RO6867461)
MEDICAL MONITOR:	[redacted], *M.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 20 November 2018
DATE AMENDED:	Version 2: 28 February 2019 Version 3: See electronic date stamp below.

Date and Time (UTC)	**Title**	**Approver's Name**
06-Aug-2019 18:43:41	Company Signatory	[redacted]

PROTOCOL AMENDMENT APPROVAL

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol GR40844 Version 2 has been amended for the following reasons:

- The primary Medical Monitor name has been updated to [redacted], M.D. (protocol cover page, acceptance form, Section 5.4.1).
- The criteria for the extension of the drug-dosing interval during the personalized treatment interval (PTI) phase has been changed from a qualitative assessment of the presence of fluid to a quantitative assessment of central subfield thickness (CST) stability (Section 3.1.1.5, Table 2).
- The study-eye inclusion criteria have been amended to include patients with extrafoveal choroidal neovascular membranes (CNV) with a subfoveal component, secondary to neovascular age-related macular degeneration (nAMD; Section 4.1.1.2)
- To ensure appropriate patient representation, the Sponsor may elect to cap the recruitment of patients in certain baseline BCVA strata. If implemented, details of the cap will be described in the Statistical Analysis Plan (Section 4.1, Section 4.1.1.2, Section 6.1).
- Reporting of medication errors and associated adverse event in Section 5.4.4 has been updated and moved to Section 5.3.5.12. Medication errors will no longer be reported expeditiously (within 24 hours), unless they cause a serious adverse event or adverse event of special interest (Section 5.3.5.12).

In addition, the following clarifications have been made:

- Section 3.1.1.1: This section, Screening, has been updated to improve readability and to clarify the process for combined screening and Day 1 visits.
- Section 3.1.2: Clarification on handling missed visits has been added.
- [redacted]
- Section 4.1.2.3: Clarification was added that the study ocular-exclusion criteria for the fellow eye pertains to both the screening and Day 1 visits.
- Section 4.4.2: Clarification of the permitted therapies for fellow eye anti-VEGF treatment has been made.
- Section 4.2.2.2: Clarification of the minimum experience required for a non-retinal specialist to be approved as an unmasked treatment administrator has been made; it also clarifies that the unmasked physician assistant may prepare the eye for IVT administration.
- Section 4.5.5: The section has been updated to advise sites that ultra-wide field photography is not permitted.
- Section 4.5.7: Clarification has been made that leftover samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

- Section 4.5.7.1: The section has been modified to improve content flow and readability.
- As applicable throughout the protocol, the term "free" was added before VEGF-A and Ang-2 to more accurately describe what the assays are measuring and to be consistent with the other sections of the protocol.
- Section 4.5.9.6: Language has been added to clarify that, after withdrawal of consent for participation in the Research Biosample Repository (RBR), remaining RBR samples will be destroyed or will no longer be linked to the patient. Details regarding instruction for patient withdrawal of consent to the testing of his or her RBR samples after closure of the site has been added.
- Appendix 1, Schedule of Activities (SoA): Clarification was added in the footnotes of the SoA that, if taken sequentially, indocyanine green angiography (ICGA) should be performed after all other imaging has been performed, but that if the site's standard of practice is to perform ICGA in parallel with fundus fluorescein angiography (FFA), this is also acceptable.

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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 NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (LUCERNE)**
PROTOCOL NUMBER:	GR40844
VERSION NUMBER:	3
EUDRACT NUMBER:	2018-004042-42
IND NUMBER:	119225
TEST PRODUCT:	Faricimab (RO6867461)
MEDICAL MONITOR:	[redacted], *M.D.*
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 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 NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (LUCERNE)**
PROTOCOL NUMBER:	GR40844
VERSION NUMBER:	3
EUDRACT NUMBER:	2018-004042-42
IND NUMBER:	119225
TEST PRODUCT:	Faricimab (RO6867461)
PHASE:	Phase III
INDICATION:	Neovascular age-related macular degeneration
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, durability, and pharmacokinetics of the 6-mg dose of faricimab administered at up to 16-week intervals compared with aflibercept monotherapy every 8 weeks (Q8W) in patients with choroidal neovascularization (CNV) secondary to age-related macular generation (AMD), also known as neovascular AMD (nAMD). Specific objectives and corresponding endpoints for the study are outlined in the following table.

In this protocol, study drug refers to faricimab or aflibercept and study treatment refers to faricimab, aflibercept, or the sham procedure.

Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of IVT injections of the 6-mg dose of faricimab on BCVA outcomes compared with aflibercept	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) based on an average at Weeks 40, 44, and 48
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of faricimab on additional BCVA outcomes	• Change from baseline in BCVA over time • Proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, or ≥ 0 letters in BCVA from baseline over time • Proportion of patients avoiding loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline over time • Proportion of patients with BCVA Snellen equivalent of 20/40 or better over time • Proportion of patients gaining ≥ 15 letters or achieving BCVA of $\geq$ 84 letters over time • Proportion of patients with BCVA Snellen equivalent of 20/200 or worse over time
• To evaluate the frequency of study drug administration	• Proportion of patients on a Q8W, Q12W, and Q16W treatment interval at Weeks 48, 60, and 112 • Number of study drug injections received through Weeks 48, 60, and 112
• To evaluate the efficacy of faricimab on anatomic outcome measures using OCT	• Change from baseline in CST based on an average at Weeks 40, 44, and 48 • Change from baseline in CST 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 intraretinal and subretinal fluid over time • Proportion of patients with absence of intraretinal cysts over time • Proportion of patients with absence of pigment epithelial detachment over time
• To evaluate the efficacy of faricimab on anatomic outcome measures using FFA	• Change from baseline in total area of CNV lesion at Week 48 and Week 112 • Change from baseline in total area of CNV leakage at Week 48 and Week 112

Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the ocular and non-ocular safety and tolerability of faricimab	• Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events
Exploratory Efficacy Objectives	**Corresponding Endpoint**
• To evaluate the efficacy of faricimab on patient-reported vision-related functioning and quality of life using the NEI VFQ-25	• Change from baseline in NEI VFQ-25 composite score over time
Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the systemic pharmacokinetics of faricimab	• Plasma concentration of faricimab over time
Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to faricimab • To evaluate potential effects of ADAs	• Presence of ADAs during the study relative to the presence of ADAs at baseline • Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives	**Corresponding Endpoints**
• To evaluate potential relationships between selected covariates and exposure to faricimab	• Relationship between selected covariates and plasma or aqueous humor (optional) concentration or PK parameters for faricimab
• To evaluate the drug concentration (exposure)-effect relationship for free VEGF-A and *free* Ang-2 • To characterize the aqueous humor (optional) and vitreous (optional) pharmacokinetics of faricimab	• Relationship between pharmacokinetics of faricimab and concentration of free VEGF-A and *free* Ang-2 in aqueous humor (optional), plasma, and/or vitreous (optional) over time • Aqueous humor (optional) and vitreous (optional) concentration of faricimab over time
• To explore concentration-effect relationship for visual acuity and other endpoints (e.g., anatomical markers)	• Pharmacokinetics of faricimab and the change in BCVA or other endpoints (e.g., anatomical markers) over time

Objectives and Corresponding Endpoints (cont.)

Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives (cont.)	Corresponding Endpoints
• 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	• Concentration of biomarkers of angiogenesis and inflammation in aqueous humor (optional) at baseline and over time and their correlation with PK and/or primary and secondary endpoints at baseline and over time • Relationship between efficacy, safety, PK, immunogenicity, [redacted] • Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., frequency of study drug administration) over time • Relationship between anatomic measures and visual acuity • Relationship between LLD and/or low-luminance BCVA and BCVA or other endpoints (e.g., anatomical markers) at baseline, Week 48, and Week 112

ADA=anti-drug antibody; Ang-2=angiopoietin-2; BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; CST=central subfield thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; FFA=fundus fluorescein angiography; IVT=intravitreal; LLD=low-luminance deficit; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT=optical coherence tomography; PK=pharmacokinetic; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; VEGF-A=vascular endothelial growth factor–A.

Note: Additional exploratory efficacy objectives may be evaluated using color fundus photographs, OCT, FFA, optional OCT-angiography, and optional indocyanine green angiography and will be detailed in the Statistical Analysis Plan.

Study Design

Description of Study

This is a Phase III, multicenter, randomized, active comparator–controlled, double-masked, parallel-group, 112-week study to investigate the efficacy, safety, durability, and pharmacokinetics of faricimab administered at up to 16-week intervals to treatment-naive patients with nAMD.

Overview of Study Design

Approximately 640 patients will be enrolled globally and randomized in a 1:1 ratio to one of two treatment arms:

- Arm A (faricimab up to every 16 weeks [Q16W]) (n=320): Patients randomized to Arm A will receive 6 mg of intravitreal (IVT) faricimab every 4 weeks (Q4W) up to Week 12 (4 injections). At Week 20, a protocol-defined assessment of disease activity requires patients in Arm A with active disease to be treated at that visit and to continue with a Q8W dosing regimen of faricimab. A second protocol-defined assessment of disease activity at Week 24 requires patients in Arm A with active disease (excluding those with active disease at Week 20 and therefore receiving a Q8W dosing regimen of faricimab) to be treated at

that visit and to continue with an every 12-week (Q12W) dosing regimen of faricimab. Patients receiving faricimab who do not have active disease according to the protocol-defined criteria at Week 20 and Week 24 will be treated with a Q16W dosing regimen of faricimab. Patients will continue receiving faricimab on a fixed regimen every 8, 12, or 16 weeks until Week 60 according to the disease activity assessments made at Weeks 20 and 24.

From Week 60 (when all patients in Arm A are scheduled to receive faricimab) onward, all patients in Arm A will be treated according to a personalized treatment interval (PTI) dosing regimen (up to Week 108).

- Arm B (comparator arm) (Q8W) (n = 320): Patients randomized to Arm B will receive 2 mg of IVT aflibercept Q4W up to Week 8 (3 injections), followed by 2 mg of IVT aflibercept Q8W up to Week 108.

Patients in both treatment arms will complete scheduled study visits Q4W for the entire study duration (112 weeks). A sham procedure will be administered to patients in both treatment arms at study visits with no study treatment administration to maintain masking among treatment arms.

Only one eye will be assigned as the study eye. If both eyes are considered eligible (per the inclusion and exclusion criteria), the eye with the worse best-corrected visual acuity (BCVA), as assessed at screening, will be selected as the study eye (unless based on medical reasons, 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.

The study will consist of a screening period of up to 28 days (Days −28 to −1) in length and an approximately 108-week treatment period, followed by the final study visit at Week 112 (at least 28 days after the last study treatment administration). A unique screening number will be assigned to each screened patient through an interactive voice or web-based response system (IxRS).

Screening

Informed consent must be administered and signed by each patient 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.

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 on the same day or* within 2 business days.

During screening, a patient's eligibility will be assessed, including a central reading center review of color fundus photographs (CFPs), optical coherence tomography (OCT), and fundus fluorescein angiography (FFA), to ensure that CNV secondary to AMD meets the ocular criteria for the study.

After screening and *pre-treatment* Day 1 assessments have been completed, eligible patients will have a randomization identification number assigned to them through the IxRS and will be randomized in a 1:1 ratio in order that approximately 320 patients are randomized to each of the two treatment arms. Randomization will be stratified by baseline best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score as assessed on Day 1 (≥ 74 letters, 73–55 letters, and ≤ 54 letters), low-luminance deficit (LLD; < 33 letters and ≥ 33 letters), and region (United States and Canada, Asia, and the rest of the world).

Randomization and Visit Schedule

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

Note: 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 *administration*:

urine pregnancy test (if appropriate), slitlamp examination, indirect ophthalmoscopy, and pre-treatment IOP measurements (recorded on the Day 1 eCRF and dated accordingly).

Randomized patients will have the first study treatment administered by the unmasked investigator on Day 1, followed by the safety assessments (finger counting test and post-dose IOP measurement). Afterward, all study patients will have a safety assessment visit on Day 7 ($\pm$3 days) evaluated by the masked investigator. At subsequent scheduled visits, patients will have safety assessments evaluated by the masked investigator prior to receiving study treatment (for additional details about masking). Study treatment administration and study-related assessments will occur Q4W (starting on Day 1), as outlined in the schedule of activities). The sham procedure will be delivered to patients in all arms throughout the study as applicable.

At Weeks 20 and 24, a protocol-defined assessment of disease activity performed for all patients in the study requires patients with active disease receiving faricimab (Arm A) to be treated with an 8 weekly or 12 weekly dosing regimen, respectively, until Week 60. Patients receiving faricimab who do not have active disease according to the protocol-defined criteria will be treated with a 16 weekly dosing regimen until Week 60.

From Week 60 (when all patients in Arm A are scheduled to receive faricimab) to Week 108, patients in Arm A will be treated according to a PTI dosing regimen (Q8W, Q12W, or Q16W). At study drug dosing visits treatment intervals may be maintained or adjusted (i.e., increased by 4 weeks, or decreased by 4 or 8 weeks), based on OCT, BCVA, and clinical assessment.

Patients in Arm B will receive aflibercept Q4W up to Week 8, followed by Q8W up to Week 108.

Patients will receive the assigned therapy up to and including Week 108 and return for a final visit at Week 112. After the final visit, adverse events should be followed. Assessments performed in case of an unscheduled safety visit(s) are at the discretion of the investigator.

Patients who prematurely discontinue 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 40, 44, 48, 60, and 112 visits.

Patients who wish to discontinue from the study prior to completion but have not withdrawn consent will be asked to return for an early termination visit after a minimum of 28 days have elapsed following their last study treatment for monitoring of adverse events and early termination visit assessments.

<u>Weeks 20 and 24 Disease Activity Criteria</u>

Determination of active disease at Weeks 20 and 24 will be made if any of the following criteria are met:

- Increase $>$50 μm in central subfield thickness (CST) compared with the average CST value over the previous two scheduled visits (Weeks 12 and 16 for the Week 20 assessment and Weeks 16 and 20 for the Week 24 assessment)

  Or

- Increase $\geq$75 μm in CST compared with the lowest CST value recorded at either of the previous two scheduled visits

  Or

- Decrease $\geq$5 letters in BCVA compared with average BCVA value over the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)

  Or

- Decrease $\geq$10 letters in BCVA compared with the highest BCVA value recorded at either of the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)

  Or

- Presence of new macular hemorrhage (as determined by the investigator), owing to nAMD activity

Additional considerations at Week 24: If there is significant nAMD disease activity at Week 24 that does not meet the criteria above, but which in the opinion of the investigator would otherwise warrant treatment, following Sponsor notification through the IxRS, patients

randomized to Arm A will receive 6 mg of faricimab at Week 24 and will continue to receive repeated 12 weekly treatments. Patients randomized to Arm A who meet the disease activity criteria at Week 20 will remain on their Q8W dosing schedule and will not receive treatment at Week 24. Patients randomized to Arm B will remain on their Q8W dosing schedule and will receive aflibercept at Week 24.

Personalized Treatment Interval Disease Activity Criteria

Starting at Week 60, when all patients in Arm A are scheduled to receive faricimab, the study drug dosing interval for patients in Arm A will be extended, reduced, or maintained based on assessments made at study drug dosing visits. Study drug dosing interval decisions during the PTI regimen phase for Arm A are automatically calculated by the IxRS based on the algorithm described in the following table. The decision will be made based on data from visits at which patients received study drug. Patients will receive a sham procedure at study visits when they are not receiving treatment with faricimab.

Personalized Treatment Interval Algorithm

Dosing Interval	Criteria
Interval extended by 4 weeks (to a maximum of Q16W)	• *Stable CST[a] compared with the average of the last 2 study drug dosing visits,* and no increase ≥ 50 μm in CST *(*compared with the lowest on-study drug dosing visit measurement*)* **and** • No decrease ≥ 5 letters in BCVA [b] compared with the average from the last two study drug dosing visits, and no decrease ≥10 letters in BCVA [b] compared with the highest on-study drug dosing visit measurement **and** • No new macular hemorrhage [c]
Interval reduced (to a minimum Q8W) If one of the criteria is met, the interval will be reduced by 4 weeks. If two or more criteria are met or one criterion includes new macular hemorrhage, the interval will be reduced to an 8-week interval. [d]	• Increase ≥ 50 μm in CST compared with the average from the last two study drug dosing visits or ≥ 75 μm compared with the lowest on-study drug dosing visit measurement **or** • Decrease ≥ 5 letters in BCVA [b] compared with average of last two study drug dosing visits or decrease ≥ 10 letters in BCVA [b] compared with the highest on-study drug dosing visit measurement **or** • New macular hemorrhage [c]
Interval maintained	If extension or reduction criteria have not been met

BCVA = best-corrected visual acuity; CST = central subfield thickness; nAMD = neovascular age-related macular degeneration; Q8W = every 8 weeks; Q16W = every 16 weeks.

[a] *Where stability is defined as a change of CST of less than 30 μm.*

[b] Change in BCVA should be attributable to nAMD disease activity (as determined by investigator).

[c] Refers to macular hemorrhage owing to nAMD activity (as determined by investigator).

[d] Patients whose treatment interval is reduced by 8 weeks from Q16W to Q8W will not be allowed to return to a Q16W interval during the study.

[redacted]

[redacted]

Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will monitor safety and study conduct on an ongoing basis throughout the study. 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 adjustable as required) to evaluate unmasked ocular and non-ocular safety events, with emphasis on the evaluation of the rate of ocular inflammation, increased IOP, endophthalmitis, arterial thromboembolic events, and clinically significant decreases in BCVA, which will be prepared for the committee by an independent Data Coordinating Center. The iDMC may recommend stopping the study early for safety reasons.

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.

Number of Patients

Approximately 640 patients will be enrolled at approximately 200 sites globally.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

General Inclusion Criteria

Patients must meet the following general criteria for study entry:

- Signed Informed Consent

  Additionally, at U.S. sites, patients must provide Health Insurance Portability and Accountability Act authorization, and in other countries, as applicable according to national laws.
- Age $\geq$ 50 years on Day 1
- Ability to comply with the study protocol, in the investigator's judgment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive measures that result in failure rate $<$ 1% per year during the treatment period and for at least 3 months after the final dose of study treatment

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of acceptable contraceptive methods include bilateral tubal ligation, male sterilization; hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices; and copper intrauterine devices.

  Contraception methods that do not result in a failure rate of $<$ 1% per year such as male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide are not acceptable.

  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 acceptable methods of contraception.

- [redacted]

Ocular Inclusion Criteria for Study Eye

Patients must meet the following ocular criteria for study entry:

- Treatment-naive CNV secondary to AMD (nAMD)
- Subfoveal CNV or juxtafoveal/*extrafoveal* CNV with a subfoveal component related to the CNV activity *identified* by FFA or OCT (*where CNV activity is defined as showing evidence of* subretinal fluid, subretinal hyper-reflective material *or* leakage)
- CNV lesion of any type (i.e., predominantly classic, minimally classic, or occult [including polypoidal choroidal vasculopathy and retinal angiomatous proliferation]) that exhibits **all** of the following characteristics:
  - A total lesion size (including blood, atrophy, fibrosis, and neovascularization) of $\leq$9 disc areas on FFA
  - A CNV component area of $\geq$ 50% of the total lesion size on FFA
  - Active CNV confirmed on FFA (evidence of leakage)
  - CNV exudation confirmed on OCT (presence of fluid)
- BCVA of 78 to 24 letters, inclusive (20/32 to 20/320 approximate Snellen equivalent), using the ETDRS protocol and assessed at the initial testing distance of 4 meters on Day 1
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

Exclusion Criteria

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

General Exclusion Criteria

Patients who meet any of the following general exclusion 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 $\leq$ 6 and a stable prostate-specific antigen for $>$ 12 months
- Requirement for continuous use of any *prohibited* medications and treatments
- 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
- Uncontrolled blood pressure, defined as systolic blood pressure $>$ 180 mmHg and/or diastolic blood pressure $>$ 100 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
- Pregnancy or breastfeeding, or intention 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 treatment. 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 by a patient 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:

- CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis
- Any history of macular pathology unrelated to AMD affecting vision or contributing to the presence of intraretinal or subretinal fluid
- Presence at screening of central serous chorioretinopathy
- Retinal pigment epithelial tear involving the macula on Day 1
- On FFA/CFP:
  - Subretinal hemorrhage of $>$ 50% of the total lesion area and/or that involves the fovea
  - Fibrosis or atrophy of $>$ 50% of the total lesion area and/or that involves the fovea
- Any concurrent intraocular condition (e.g., amblyopia, aphakia, retinal detachment, cataract, diabetic retinopathy or maculopathy, or epiretinal membrane with traction) that, in the opinion of the investigator, could either reduce the potential for visual improvement or require medical or surgical intervention during the study
- Current vitreous hemorrhage on Day 1
- Uncontrolled glaucoma
- Spherical equivalent of refractive error demonstrating more than 8 diopters of myopia

  For patients who have undergone prior refractive or cataract surgery, the preoperative refractive error should not have exceeded –8 diopters of myopia.
- Any prior or concomitant treatment for CNV or vitreomacular-interface abnormalities, including, but not restricted to, IVT treatment (e.g., anti-vascular endothelial growth factor [VEGF], steroids, tissue plasminogen activator, ocriplasmin, C_3F_8, air), periocular pharmacological intervention, argon laser photocoagulation, verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or ocular surgical intervention
- 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, glaucoma surgery, corneal transplant, or radiotherapy)
- 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 exclusion criterion for the fellow eye (non-study eye) *at both the screening and Day 1 visits* will be excluded from study entry:

- Non-functioning non–study eye, defined as either:
  - BCVA of hand motion or worse
  - No physical presence of non-study eye (i.e., monocular)

Exclusion Criteria for Both Eyes

Patients who meet the following exclusion criteria for either eye 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 ocular inflammation or suspected or active ocular or periocular infection in either eye on Day 1

End of Study

The study consists of two enrollment phases: the global enrollment phase, during which patients will be recruited globally, [redacted]

The end of this study is defined as the date when the last patient, last visit occurs, [redacted] The end of the study is expected to occur approximately 112 weeks after the last patient is randomized.

Length of Study

The total length *of the study* [redacted] from screening of the first patient to the end of the *study* is expected to be approximately 48 months.

Investigational Medicinal Products

Test Products (Investigational Drugs)

Intravitreal Faricimab

Patients randomized to Arm A will receive 6 mg of IVT faricimab Q4W up to Week 12 (4 injections). At Week 20, protocol-defined assessment of disease activity requires patients in Arm A with active disease to be treated with a Q8W dosing regimen of 6 mg of faricimab (i.e., injections at Weeks 20, 28, 36, 44, 52, and 60).

A second protocol-defined assessment of disease activity at Week 24 requires patients in Arm A with active disease, excluding those with active disease at Week 20 and therefore receiving a Q8W dosing regimen of 6 mg of IVT faricimab) to be treated with a Q12W dosing regimen of 6 mg of IVT faricimab (i.e., injections at Weeks 24, 36, 48, and 60).

Patients receiving faricimab who do not have active disease according to the protocol-defined criteria at Week 20 or Week 24 will be treated with 6 mg of IVT faricimab Q16W (i.e., injections at Weeks 28, 44, and 60).

From Week 60 (when all patients in Arm A are scheduled to receive study drug) to Week 108, patients in Arm A will be treated according to a PTI dosing regimen (between Q8W and Q16W). At study drug dosing visits, treatment intervals may be maintained or adjusted (i.e., increased by 4 weeks or decreased by 4 or 8 weeks), based on OCT, BCVA, and clinical assessment. Patients will therefore receive between 10 and 16 injections over the study treatment period (Day 1 to Week 108).

Comparator

Intravitreal Aflibercept (Active Comparator) Injections

For patients randomized to the active comparator (Arm B), a 2-mg dose of aflibercept will be administered intravitreally Q8W after 3 consecutive monthly doses during the 108-week treatment period. Patients will receive 15 IVT injections of aflibercept during the 108-week treatment period. This will consist of three initiating injections (2 mg of aflibercept Q4W to Week 8), followed by 12 maintenance injections (2 mg of aflibercept Q8W at Weeks 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96, and 104).

Non-Investigational Medicinal Products

Sham Procedure

Both treatment arms (faricimab up to Q16W and aflibercept Q8W) will maintain Q4W study visits for the duration of the study. To preserve masking of the randomized treatment arm, patients will have the sham procedure performed at study treatment visits when they are not treated with either faricimab or aflibercept as applicable per their treatment arm schedule.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is the change from baseline in BCVA averaged over Weeks 40, 44, and 48. The BCVA outcome measure is based on the ETDRS visual acuity chart assessed at a starting distance of 4 meters.

The primary comparison will be to test non-inferiority of faricimab compared with aflibercept in the intent-to-treat (ITT) population. Additional analysis based on the per-protocol population will also be conducted.

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: $\mu^{\text{faricimab}} - \mu^{\text{aflibercept}} \leq -4$ letters and the alternative hypothesis, H_a: $\mu^{\text{faricimab}} - \mu^{\text{aflibercept}} > -4$ letters, will be tested, for which $\mu^{\text{faricimab}}$ and $\mu^{\text{aflibercept}}$ are the expected change from baseline in BCVA averaged over Weeks 40, 44, and 48 for the faricimab up to Q16W arm and the active comparator (aflibercept Q8W), respectively.

The change from baseline averaged over Weeks 40, 44, and 48 will be compared between the faricimab up to Q16W arm and the aflibercept Q8W arm using a mixed model for repeated measures (MMRM). The model will include the change from baseline at Weeks 4–48 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. Comparisons between the two treatment arms will be made using a composite contrast over Weeks 40, 44, and 48. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a heterogeneous compound symmetry or an AR(1) covariance structure may be fitted.

Missing data will be implicitly imputed by the MMRM model, assuming a missing at random missing data mechanism (i.e., the probability that missing data are dependent on other observed variables but not on the missing data). Data for patients who receive prohibited therapy will be censored at the timing of use of prohibited therapy. Data for patients who discontinue from study drug and do not receive prohibited therapy after discontinuation of study drug will be included in the analysis.

Additional details about the planned analyses, as well as supplementary and sensitivity analyses using other imputation methods for missing data, analysis using the trimmed mean approach for patients who receive prohibited therapy or discontinue study drug due to lack of efficacy or adverse events, analyses of the per-protocol population, and subgroup analyses to assess the robustness of the primary endpoint results will be provided in the Statistical Analysis Plan.

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 640 patients.

Patients will be randomized in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B). The primary comparison will be between the active comparator (aflibercept Q8W) and the faricimab up to Q16W arm.

A sample size of approximately 320 patients in each arm will provide greater than 90% power to show non-inferiority of faricimab to aflibercept in the change in BCVA averaged over Weeks 40, 44, and 48 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 two treatment arms
- Standard deviation (SD) of 14 letters for the change from baseline in BCVA averaged over Weeks 40, 44, and 48
- Two-sample *t*-test
- 2.5% one-sided type I error rate
- 10% dropout rate

To ensure appropriate patient representation, the Sponsor may elect to cap the recruitment of patients in certain baseline BCVA strata. If implemented, details of the cap will be described in the Statistical Analysis Plan.

The sample size may be adjusted as appropriate based on a masked assessment of the pooled SD of the change in BCVA from baseline. The assessment will be performed by the Sponsor at a specified timepoint prior to completing enrollment. Details on the masked sample size re-estimation conducted, as well as actions and decisions taken regarding changes in sample size, will be documented in the Statistical Analysis Plan. The Sponsor will remain masked. Other factors external to the study may also trigger a decision to modify the sample size.

[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AMD	age-related macular degeneration
Ang-2	angiopoietin-2 (protein)
Anti-VEGF	*anti-vascular endothelial growth factor*
BCVA	best-corrected visual acuity
CATT	Comparison of Age-Related Macular Degeneration Treatment Trials (Research Group)
[redacted]	[redacted]
CFP	color fundus photograph
CMH	Cochran-Mantel-Haenszel (test)
CNV	choroidal neovascularization
CRC	*central reading center*
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
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICGA	indocyanine green angiography
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
[redacted]	[redacted]
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intent to treat
IVT	intravitreal
IxRS	interactive voice or web-based response system
LLD	low-luminance deficit
LPLV	last patient, last visit

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (cont.)

Abbreviation	Definition
MMRM	mixed model for repeated measures
nAMD	neovascular age-related macular degeneration
NEI VFQ-25	National Eye Institute Visual Function Questionnaire-25
OCT	optical coherence tomography
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
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SS-OCT	swept-source optical coherence tomography
Tie2	TEK receptor tyrosine kinase-2
ULN	upper limit of normal
UWP	ultra-wide photography
VA	visual acuity
VEGF (-A)	vascular endothelial growth factor (–A)
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

Neovascular age-related macular degeneration (nAMD) (also known as choroidal neovascularization [CNV] secondary to age-related macular degeneration [AMD] or wet AMD) is a form of advanced AMD that causes rapid and severe visual loss and remains a leading cause of visual impairment in the elderly (Bourne et al. 2013; Wong et al. 2014). Several biochemical and biological processes, such as angiogenesis, inflammation, and oxidative stress, are known to play a role in the pathogenesis of nAMD, which is characterized by the abnormal proliferation of choroidal capillaries that penetrate Bruch's membrane and migrate to or through the retinal pigment epithelium. CNV leaks fluid, lipids, and blood into the outer retina causing severe, irreversible loss of central vision if left untreated.

Prior to anti–vascular endothelial growth factor (anti-VEGF) agents, laser photocoagulation therapy and photodynamic therapy with verteporfin were the standard of care and were shown to stabilize vision. Although such treatments remain a therapeutic option for selected patients, the treatment of nAMD has been markedly improved by the introduction of biological molecules that target an important factor in pathological angiogenesis, *vascular endothelial growth factor (-A) (*VEGF-A*)* (Brown et al. 2006; Rosenfeld et al. 2006; Heier et al. 2012). The impressive benefit of anti-VEGF therapies and their ability to restore vision has been widely recognized since the first approval of Lucentis® (ranibizumab) in 2006 (American Academy of Ophthalmology 2015).

A key challenge with currently available anti-VEGF treatments is the requirement for frequent and long-term administration to maintain vision gains (Heier et al. 2012; the Comparison of Age-Related Macular Degeneration Treatment Trials [CATT] Research Group 2016). Real-world data suggest that many patients with nAMD do not receive treatment at the optimal frequency, and this under-treatment in clinical practice is associated with lower visual acuity (VA) gains compared with those observed in controlled clinical trials (Cohen et al. 2013; Finger et al. 2013; Holz et al. 2015; Rao et al. 2018). Under-treatment of nAMD in clinical practice reflects the burden of frequent therapy on patients, caregivers, and the healthcare system (Gohil et al. 2015; Prenner et al. 2015; Varano et al. 2015; CATT Research Group et al. 2016; Vukicevic et al. 2016).

1.2 BACKGROUND ON FARICIMAB

Faricimab is a novel humanized bispecific IgG1 monoclonal antibody that selectively binds to VEGF-A and angiopoietin-2 (Ang-2). The VEGF binding component binds to all isoforms of VEGF-A with high affinity, and the Ang-2 binding component binds to Ang-2, also with high affinity.

VEGF-A is a signal protein produced by cells that stimulates angiogenesis. Uncontrolled VEGF-A expression results in growth of new blood vessels (choroidal neovascular membranes), which fail to mature and show a number of abnormalities, including tortuosity and reduced number of pericytes. These structural defects in the choroidal neovascular membranes can result in fragility, hyperpermeability, and a propensity for exudation and bleeding, all of which are key features of pathological neovascularization and can lead to photoreceptor damage and vision impairment. VEGF has also been shown to have a direct effect on vessel hyperpermeability (Fantin et al. 2017), and hence in nAMD, suppression of VEGF reduces leakage from vessels, allowing for some normalization of structure and restoration of function.

Ang-1 and Ang-2 are of key importance in the homeostasis of the vascular compartment, functioning as ligands of the *TEK receptor tyrosine kinase-2 (*Tie2*)* receptor tyrosine kinase that is expressed on endothelial cells (Davis et al. 1996; Maisonpierre et al. 1997; Fiedler et al. 2003). Ang-1 is a Tie2 receptor agonist and acts as a homeostatic factor that stabilizes the mature vasculature by promoting recruitment of pericytes and smooth muscle cells to the vessel wall. In contrast, Ang-2 is a context-dependent antagonist of Tie2 and acts as a vascular destabilization factor by blocking Ang-1–dependent Tie2 activation, which leads to dissociation of pericytes from existing vessels, thus increasing vessel plasticity, rendering vasculature amendable to endothelial barrier breakdown, and sprouting of new vessels (Yancopolous et al. 2000; Augustin et al. 2009). Ang-2 levels can be upregulated by other pro-angiogenic factors, including VEGF-A, and were shown to be increased during angiogenic stress triggered by hypoxia or hyperglycemia (Bhadari et al. 2006; Fiedler et al. 2006; Benest et al. 2013). Ang-2 may also cause angiogenesis and vascular endothelial destabilization in a Tie2-independent manner by means of β1-integrin activation (Kienast et al. *2015*; Hakanpaa et al. 2015). In addition, Ang-2 functions as a pro-inflammatory cytokine (Fiedler et al. 2006; Benest et al. 2013). Given that upregulation of Ang-2 is associated with the release of inflammatory cytokines, adhesion of leukocytes to endothelial cells, and migration of leukocytes into the retina, its inhibition may also have additional anti-inflammatory benefits (Fiedler et al. 2006; Benest et al. 2013).

Nonclinical studies have shown that VEGF-A and Ang-2 act in concert to regulate the vasculature and to increase retinal endothelial cell permeability in vitro. Simultaneous inhibition of VEGF-A and Ang-2 with the bispecific monoclonal antibody faricimab led to a greater reduction in the leakiness and severity of CNV lesions in a laser-induced CNV model in non-human primates compared with the molar equivalent of anti–VEGF-A

(ranibizumab) or anti–Ang-2 alone. Earlier experiments using a mouse model of spontaneous CNV showed that dual inhibition of VEGF-A and Ang-2 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 VEGF-A and Ang-2 were shown to be upregulated in patients with nAMD, diabetic retinopathy *(DR)*, and retinal vein occlusion (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, VEGF-A and Ang-2, may further normalize the pathological ocular vasculature compared with anti-VEGF therapy alone. Data from the completed Phase II studies (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 nAMD.

Faricimab has been studied for the treatment of nAMD and diabetic macular edema (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). Two global Phase III studies in DME are ongoing (GR40349 [YOSEMITE] and GR40398 [RHINE]).

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

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

As a result of the chronic, progressive nature of nAMD, frequent injections (e.g., monthly or bimonthly injections) of currently available therapies are usually required over extended periods. In the pivotal ranibizumab nAMD studies ANCHOR and MARINA, eyes treated with 0.5 mg of ranibizumab every 4 weeks (Q4W) demonstrated a mean change from baseline in best-corrected visual acuity (BCVA) of +11.3 and +7.2 letters, respectively, at 12 months, and +10.7 and +6.6 letters, respectively, at 24 months (Rosenfeld et al. 2006; Brown et al. 2009).

However, these findings contrast with data from the real world. In routine clinical practice, frequent office visits place a significant burden on patients, caregivers, their treating physicians, and the healthcare system, and hence there are challenges with compliance with approved dosing recommendations. Real-world data suggest many patients with nAMD are under-treated with current intravitreal (IVT) anti-VEGF therapies, leading to suboptimal outcomes in comparison with data from clinical trials. For example, a retrospective, observational study conducted in Canada, France, Germany, Ireland, Italy, Netherlands, the United Kingdom, and Venezuela found that in 2,227 nAMD patients, the mean number of anti-VEGF injections received was 5.0 and 2.2 injections during the first and second years, respectively, with a mean change in VA score from

baseline of +2.4 and +0.6 letters after 1 and 2 years, respectively (Holz et al. 2015). Likewise, data from the American Academy of Ophthalmology Intelligent Research in Sight registry in the United States of nearly 14,000 patients with nAMD who were treated for at least 1 year with a single anti-VEGF agent showed that a mean of 6.1 injections were administered in the first year of treatment and that the mean change in logMAR (logarithm of the minimum angle of resolution) VA from baseline to Year 1 was +0.05 (2.5 letters on the Early Treatment Diabetic Retinopathy Study [ETDRS] chart) (Rao et al. 2018).

This difference in outcomes between patients treated in the real-world setting and those treated in the controlled environment of a clinical trial demonstrates the clear clinical need for therapies with a more durable effect that would thus require less-frequent dosing that is tailored to individual need (e.g., every 2 to 4 months), while still being able to provide VA outcomes comparable to those observed in the pivotal clinical trials of licensed anti-VEGF monotherapies.

1.3.1 Benefits

A Phase I, open-label, multicenter, single-ascending dose (0.5, 1.5, 3, or 6 mg) and multiple-ascending dose (3 or 6 mg) study (BP28936) designed to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of faricimab administered intravitreally to patients with nAMD has been completed (Chakravarthy et al. 2017). Patients recruited in the Phase I study had already received anti-VEGF treatment (3 or more IVT treatments within the preceding 6 months) with an insufficient response, defined as BCVA ≤20/40 and presence of fluid on optical coherence tomography (OCT). Although the primary focus of this study was the safety and tolerability of faricimab following a single dose and 3 sequential doses of faricimab, administered to patients 4 weeks apart, there were signals of biological activity and vision gains in these hard-to-treat patients. 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.

Study BP29647 (AVENUE) evaluated the safety, efficacy, and pharmacokinetics of 1.5 mg and 6.0 mg of IVT faricimab Q4W or every 8 weeks (Q8W) administered to patients with nAMD who were treatment naive compared with 0.5 mg of ranibizumab Q4W. Although the study did not meet its primary or key secondary endpoints for superiority in the change from baseline in BCVA or OCT in either the 1.5-mg faricimab Q4W or the 6-mg faricimab Q4W treatment arm compared with the 0.5-mg ranibizumab Q4W treatment arm at Week 36, it did show that the 6-mg faricimab Q8W treatment arm (after 4 initial Q4W doses) had similar BCVA results and central subfield thickness (CST) reductions compared with the 6-mg faricimab Q4W treatment arm and the 0.5-mg ranibizumab Q4W treatment arm.

Study CR39521 (STAIRWAY) evaluated the safety, efficacy, and pharmacokinetics of 6 mg of faricimab administered to patients by IVT injection at an extended dosing

interval (every 12 weeks [Q12W] and every 16 weeks [Q16W] administration) compared with 0.5 mg of ranibizumab Q4W in treatment-naive patients with nAMD. The treatment regimens for the two faricimab treatment arms were identical up to Week 24, with both arms receiving 6 mg of faricimab Q4W for the first 4 injections, followed by a 12-week observation period. At Week 24, a protocol-defined disease activity assessment was conducted for all patients. Patients in the Q16W dosing arm with protocol-defined disease activity were treated with Q12W dosing for the remainder of the 52-week study. Patients randomized to the Q16W dosing arm who had no protocol-defined disease activity at Week 24 continued to receive Q16W dosing throughout the remainder of the study. In the combined 6-mg faricimab treatment arms (Q12W and Q16W), 36 of 55 patients (65.5%) did not show disease activity according to the pre-specified criteria at Week 24, 12 weeks after their final initiation dose. In the 6-mg faricimab Q16W treatment arm, 19 of 31 patients (61.3%) with no protocol-defined disease activity continued receiving the Q16W regimen, while the remaining 12 patients had their treatment regimen switched to Q12W dosing for the remainder of the study.

Efficacy data demonstrated that patients in the 6-mg faricimab Q12W and Q16W arms maintained the initial gains from baseline in BCVA through to the primary endpoint (Week 40) and study completion (Week 52), comparable to the 0.5-mg ranibizumab Q4W arm. Likewise, the proportions of patients gaining at least 3 lines of VA from baseline and maintaining VA (not losing $\geq$ 15 letters) at Week 52 are comparable across the 6-mg faricimab and 0.5-mg ranibizumab arms. VA outcome data are supported by anatomical outcomes; the reductions in CST from baseline observed in the 6-mg faricimab treatment arms (Q12W and Q16W) are comparable with those in the 0.5-mg ranibizumab Q4W arm, as are the reductions in CNV lesion size on fundus fluorescein angiography (FFA).

The combined evidence from the Phase II studies BP29647 and CR39521 indicates that 6 mg of faricimab administered to patients with nAMD at various treatment intervals delivers similar efficacy compared with 0.5 mg of ranibizumab Q4W, but importantly, has the potential to be given at substantially less-frequent treatment intervals (up to Q16W). As discussed in the scientific rationale (Section 2.2) of the Investigator's Brochure, the proposed hypothesis is that simultaneous neutralization of both VEGF-A and Ang-2 may provide a more sustained anti-leakage effect, allowing for less-frequent dosing compared with anti-VEGF monotherapy in the treatment of nAMD. A less-frequent treatment administration schedule tailored to individual need (e.g., every 2 to 4 months) that could provide VA outcomes comparable to those of more frequently administered anti-VEGF monotherapy (e.g., every 1 to 2 months) would represent an important and meaningful advance relative to currently available therapies.

Refer to the Faricimab (RO6867461) Investigator's Brochure for additional details about nonclinical and clinical Phase I and Phase II studies.

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 nAMD.

In Phase I and II clinical studies, more than 400 patients have been exposed to at least one dose of faricimab.

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 faricimab has an acceptable tolerability and safety profile, with no new or unexpected safety signals. The ocular and non-ocular safety findings for faricimab observed in the Phase II studies were generally consistent with the safety profile findings reported in patients with nAMD or DME who received intravitreally administered approved anti-VEGF products.

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 combined evidence from the Phase II studies BP29647 and CR39521 indicates that the 6-mg dose of faricimab can be administered to patients with nAMD at various treatment intervals (Q4W, Q8W, Q12W, and Q16W) to deliver similar efficacy compared with 0.5 mg of ranibizumab Q4W, and importantly, has the potential to be given at substantially less-frequent treatment intervals (up to Q16W), while still achieving comparable visual (BCVA) and anatomic (OCT) outcomes. Based on the totality of evidence from the Phase I and Phase II studies, and taking into account evidence from the murine and non-human primate preclinical and toxicology models, it is anticipated that the additional anti–Ang-2 mechanism of action of the faricimab molecule will not negatively impact the safety profile compared with IVT anti-VEGF monotherapy, while less-frequent dosing may offer a more favorable benefit–risk profile.

Taken together, data from nonclinical, Phase I and Phase II studies, as well as the clear unmet need for less-frequent dosing in nAMD, support the positive benefit–risk assessment for the initiation of this Phase III study to assess the efficacy, safety, durability, and pharmacokinetics of faricimab administered up to Q16W to patients with nAMD.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, durability, and pharmacokinetics of the 6-mg dose of faricimab administered at up to 16-week intervals compared with aflibercept monotherapy Q8W in patients with CNV secondary to AMD, also known as nAMD. Specific objectives and corresponding endpoints for the study are outlined in Table 1. An overview of the proposed statistical analyses is described in Section 6.

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 for further details).

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of IVT injections of the 6-mg dose of faricimab on BCVA outcomes compared with aflibercept	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) based on an average at Weeks 40, 44, and 48
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of faricimab on additional BCVA outcomes	• Change from baseline in BCVA over time • Proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, or ≥ 0 letters in BCVA from baseline over time • Proportion of patients avoiding loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline over time • Proportion of patients with BCVA Snellen equivalent of 20/40 or better over time • Proportion of patients gaining ≥ 15 letters or achieving BCVA of $\geq$ 84 letters over time • Proportion of patients with BCVA Snellen equivalent of 20/200 or worse over time
• To evaluate the frequency of study drug administration	• Proportion of patients on a Q8W, Q12W, and Q16W treatment interval at Weeks 48, 60, and 112 • Number of study drug injections received through Weeks 48, 60, and 112
• To evaluate the efficacy of faricimab on anatomic outcome measures using OCT	• Change from baseline in CST based on an average at Weeks 40, 44, and 48 • Change from baseline in CST 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 intraretinal and subretinal fluid over time • Proportion of patients with absence of intraretinal cysts over time • Proportion of patients with absence of pigment epithelial detachment over time
• To evaluate the efficacy of faricimab on anatomic outcome measures using FFA	• Change from baseline in total area of CNV lesion at Week 48 and Week 112 • Change from baseline in total area of leakage at Week 48 and Week 112

Table 1 Objectives and Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the ocular and non-ocular safety and tolerability of faricimab	• Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events
Exploratory Efficacy Objectives	**Corresponding Endpoint**
• To evaluate the efficacy of faricimab on patient-reported vision-related functioning and quality of life using the NEI VFQ-25	• Change from baseline in NEI VFQ-25 composite score over time
Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the systemic pharmacokinetics of faricimab	• Plasma concentration of faricimab over time
Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to faricimab • To evaluate potential effects of ADAs	• Presence of ADAs during the study relative to the presence of ADAs at baseline • Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives	**Corresponding Endpoints**
• To evaluate potential relationships between selected covariates and exposure to faricimab	• Relationship between selected covariates and plasma or aqueous humor (optional) concentration or PK parameters for faricimab
• To evaluate the drug concentration (exposure)-effect relationship for free VEGF-A and *free* Ang-2 • To characterize the aqueous humor (optional) and vitreous (optional) pharmacokinetics of faricimab	• Relationship between pharmacokinetics of faricimab and concentration of free VEGF-A and *free* Ang-2 in aqueous humor (optional), plasma, and/or vitreous (optional) over time • Aqueous humor (optional) and vitreous (optional) concentration of faricimab over time
• To explore concentration-effect relationship for visual acuity and other endpoints (e.g., anatomical markers)	• Pharmacokinetics of faricimab and the change in BCVA or other endpoints (e.g., anatomical markers) over time

Table 1 Objectives and Endpoints (cont.)

Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives (cont.)	Corresponding Endpoints
• 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	• Concentration of biomarkers of angiogenesis and inflammation in aqueous humor (optional) at baseline and over time and their correlation with PK and/or primary and secondary endpoints at baseline and over time • Relationship between efficacy, safety, PK, immunogenicity, [redacted] • Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., frequency of study drug administration) over time • Relationship between anatomic measures and visual acuity • Relationship between LLD and/or low-luminance BCVA and BCVA or other endpoints (e.g., anatomical markers) at baseline, Week 48, and Week 112

ADA=anti-drug antibody; Ang-2=angiopoietin-2; BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; CST=central subfield thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; FFA=fundus fluorescein angiography; IVT=intravitreal; LLD=low-luminance deficit; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT=optical coherence tomography; PK=pharmacokinetic; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; VEGF-A=vascular endothelial growth factor–A.

Note: Additional exploratory efficacy objectives may be evaluated using color fundus photographs, OCT, FFA, optional OCT-angiography, and optional indocyanine green angiography and will be detailed in the Statistical Analysis Plan.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, multicenter, randomized, active comparator–controlled, double-masked, parallel-group, 112-week study to investigate the efficacy, safety, durability, and pharmacokinetics of faricimab administered at up to 16-week intervals to treatment-naive patients with nAMD.

3.1.1 Overview of Study Design

Approximately 640 patients will be enrolled globally and randomized in a 1:1 ratio to one of two treatment arms:

- Arm A (faricimab up to Q16W) (n=320): Patients randomized to Arm A will receive 6 mg of IVT faricimab Q4W up to Week 12 (4 injections). At Week 20, a

protocol-defined assessment of disease activity requires patients in Arm A with active disease (for the criteria, refer to Section 3.1.1.4) to be treated at that visit and to continue with a Q8W dosing regimen of faricimab. A second protocol-defined assessment of disease activity at Week 24 requires patients in Arm A with active disease (excluding those with active disease at Week 20 and therefore receiving a Q8W dosing regimen of faricimab) to be treated at that visit and to continue with a Q12W dosing regimen of faricimab. Patients receiving faricimab who do not have active disease according to the protocol-defined criteria at Week 20 and Week 24 will be treated with a Q16W dosing regimen of faricimab. Patients will continue receiving faricimab on a fixed regimen every 8, 12, or 16 weeks until Week 60 according to the disease activity assessments made at Weeks 20 and 24.

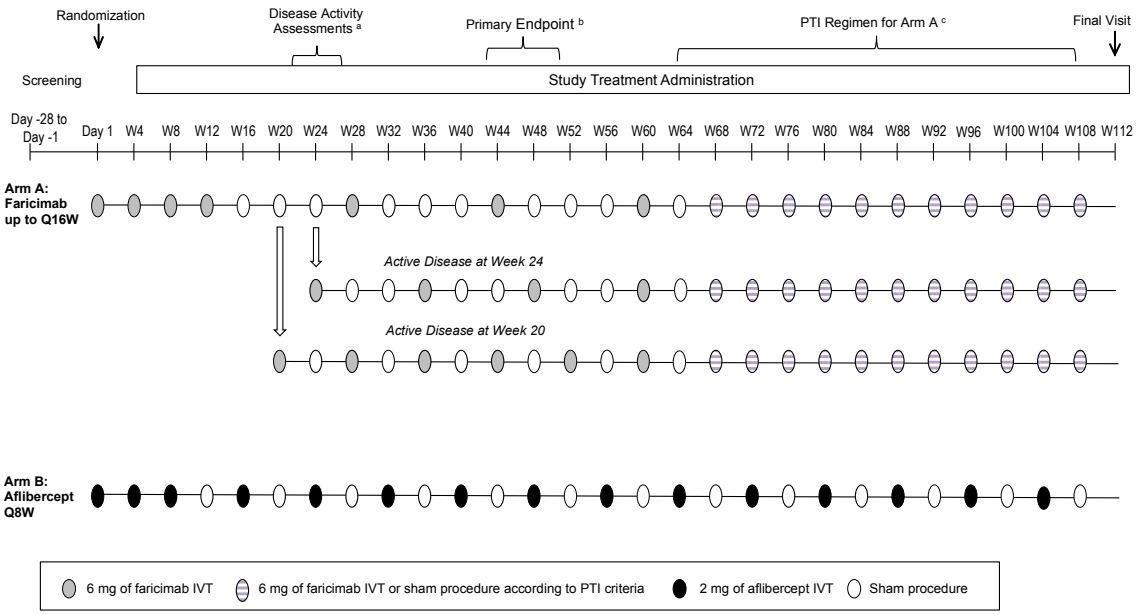
From Week 60 (when all patients in Arm A are scheduled to receive faricimab) onward, all patients in Arm A will be treated according to a personalized treatment interval (PTI) dosing regimen (see Table 2 for the PTI dosing criteria) up to Week 108.

- Arm B (comparator arm) (Q8W) (n = 320): Patients randomized to Arm B will receive 2 mg of IVT aflibercept Q4W up to Week 8 (3 injections), followed by 2 mg of IVT aflibercept Q8W up to Week 108.

Patients in both treatment arms will complete scheduled study visits Q4W for the entire study duration (112 weeks). A sham procedure will be administered to patients in both treatment arms at study visits with no study treatment administration to maintain masking among treatment arms (see Section 4.3.1.1.3).

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

Figure 1 Study Schema



BCVA=best-corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; IVT=intravitreal; PTI = personalized treatment interval; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; W=Week.

[a] At Weeks 20 and 24, patients will undergo a disease activity assessment. Patients with anatomic or functional signs of disease activity at these timepoints will receive Q8W or Q12W dosing, respectively, rather than Q16W dosing.

[b] The primary endpoint is the change from baseline in BCVA (as assessed on the ETDRS chart at a starting distance of 4 meters) based on an average at Weeks 40, 44, and 48.

[c] From Week 60 (when all patients in Arm A are scheduled to receive faricimab) onward, patients in Arm A will be treated according to a PTI dosing regimen (between Q8W and Q16W).

Only one eye will be assigned as the study eye. If both eyes are considered eligible (per the inclusion and exclusion criteria), the eye with the worse BCVA, as assessed at screening, will be selected as the study eye (unless based on medical reasons, 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 masking details).

The study will consist of a screening period of up to 28 days (Days −28 to −1) in length and an approximately 108-week treatment period, followed by the final study visit at Week 112 (at least 28 days after the last study treatment administration). A unique

screening number will be assigned to each screened patient through an interactive voice or web-based response system (IxRS).

3.1.1.1 Screening

Informed consent must be administered and signed by each patient 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).

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

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 on the same day or* within 2 business days.

During screening, a patient's eligibility will be assessed, including a central reading center review of color fundus photographs (CFPs), OCT, and FFA, to ensure that CNV secondary to AMD meets the ocular criteria for the study.

When screening and Day 1 visits are completed as a combined visit, the assessments listed for both visits (see the schedule of activities in Appendix 1) should be conducted only once. Prior discussion with, and approval from, the central reading center is required prior to this combined visit, so as to enable an expedited evaluation of CFP, OCT and FFA images to provide 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 study treatment administration: urine pregnancy test (if appropriate), slitlamp examination, indirect ophthalmoscopy, and pre-treatment intraocular pressure (IOP) measurements (recorded on the Day 1 electronic Case Report Form [eCRF] and dated accordingly).

After screening and *pre-treatment* Day 1 assessments have been completed, eligible patients will have a randomization identification number assigned to them through the IxRS and will be randomized in a 1:1 ratio in order that approximately 320 patients are randomized to each of the two treatment arms. Randomization will be stratified by baseline BCVA ETDRS letter score as assessed on Day 1 ($\geq$74 letters, 73–55 letters, and $\leq$54 letters), low-luminance deficit (LLD; $<$33 letters and $\geq$33 letters; adapted from Frenkel et al. 2016), and region (United States and Canada, Asia, and the rest of the world).

3.1.1.2 Screen-Failed Patients

Patients who are not eligible for enrollment (screen failures) may be eligible for re-screening for up to an additional two times during the enrollment period of the study.

At re-screening, a new screening number will be assigned to each patient through the IxRS and all screening visit assessments will be performed. Only 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 are received by the central reading center within 4 weeks before 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, which will be performed through the IxRS (i.e., at the Day 1 visit).

Note: 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 *administration*: *urine pregnancy test (if appropriate),* slitlamp examination, indirect ophthalmoscopy, and pre-treatment IOP measurements (recorded on the Day 1 eCRF and dated accordingly).

Randomized patients will have the first study treatment administered by the unmasked investigator on Day 1, followed by the safety assessments (finger counting test and post-dose IOP measurement). Afterward, all study patients will have a safety assessment visit on Day 7 (±3 days) evaluated by the masked investigator. At subsequent scheduled visits, patients will have safety assessments evaluated by the masked investigator prior to receiving study treatment (for additional details about masking, see Section 4.2.2). Study treatment administration and study-related assessments will occur Q4W (starting on Day 1), as outlined in the schedule of activities (see Appendix 1). The sham procedure will be delivered to patients in all arms throughout the study as applicable (see Section 4.3.1.1.3).

At Weeks 20 and 24, a protocol-defined assessment of disease activity performed for all patients in the study requires patients with active disease (for the criteria, refer to Section 3.1.1.4) receiving faricimab (Arm A) to be treated with an 8 weekly or 12 weekly dosing regimen, respectively, until Week 60. Patients receiving faricimab who do not have active disease according to the protocol-defined criteria will be treated with a 16 weekly dosing regimen until Week 60.

From Week 60 (when all patients in Arm A are scheduled to receive faricimab) to Week 108, patients in Arm A will be treated according to a PTI dosing regimen (Q8W, Q12W, or Q16W). At study drug dosing visits*,* treatment intervals may be maintained or adjusted (i.e., increased by 4 weeks, or decreased by 4 or 8 weeks), based on OCT, BCVA, and clinical assessment (for the criteria, refer to Section 3.1.1.5).

Patients in Arm B will receive aflibercept Q4W up to Week 8, followed by Q8W up to Week 108.

Patients will receive the assigned therapy up to and including Week 108 and return for a final visit at Week 112. After the final visit, adverse events should be followed as outlined in Section 5.6. Assessments performed in case of an unscheduled safety visit(s) (see Appendix 2) are at the discretion of the investigator.

Patients who prematurely discontinue 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 40, 44, 48, 60, and 112 visits.

Patients who wish to discontinue from the study prior to completion but have not withdrawn consent will be asked to return for an early termination visit after a minimum of 28 days have elapsed following their last study treatment for monitoring of adverse events and early termination visit assessments (see Appendix 1).

3.1.1.4 Weeks 20 and 24 Disease Activity Criteria

Determination of active disease at Weeks 20 and 24 will be made if any of the following criteria are met:

- Increase >50 μm in CST compared with the average CST value over the previous two scheduled visits (Weeks 12 and 16 for the Week 20 assessment and Weeks 16 and 20 for the Week 24 assessment)

  Or

- Increase ≥ 75 μm in CST compared with the lowest CST value recorded at either of the previous two scheduled visits

  Or

- Decrease ≥ 5 letters in BCVA compared with average BCVA value over the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)

  Or

- Decrease ≥ 10 letters in BCVA compared with the highest BCVA value recorded at either of the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)

  Or

- Presence of new macular hemorrhage (as determined by the investigator), owing to nAMD activity

Additional considerations at Week 24: If there is significant nAMD disease activity at Week 24 that does not meet the criteria above, but which in the opinion of the investigator would otherwise warrant treatment, following Sponsor notification through the IxRS, patients randomized to Arm A will receive 6 mg of faricimab at Week 24 and will continue to receive repeated 12 weekly treatments. Patients randomized to Arm A who meet the disease activity criteria at Week 20 will remain on their Q8W dosing

schedule and will not receive treatment at Week 24. Patients randomized to Arm B will remain on their Q8W dosing schedule and will receive aflibercept at Week 24.

3.1.1.5 Personalized Treatment Interval Disease Activity Criteria

Starting at Week 60, when all patients in Arm A are scheduled to receive faricimab, the study drug dosing interval for patients in Arm A will be extended, reduced, or maintained based on assessments made at study drug dosing visits. Study drug dosing interval decisions during the PTI regimen phase for Arm A are automatically calculated by the IxRS based on the algorithm described in Table 2. The decision will be made based on data from visits at which patients received study drug. Patients will receive a sham procedure at study visits when they are not receiving treatment with faricimab.

Table 2 Personalized Treatment Interval Algorithm

Dosing Interval	Criteria
Interval extended by 4 weeks (to a maximum of Q16W)	• *Stable CST[a] compared with the average of the last 2 study drug dosing visits,* and no increase ≥ 50 μm in CST *(*compared with the lowest on-study drug dosing visit measurement*)* **and** • No decrease ≥ 5 letters in BCVA[b] compared with the average from the last two study drug dosing visits, and no decrease ≥10 letters in BCVA[b] compared with the highest on-study drug dosing visit measurement **and** • No new macular hemorrhage[c]
Interval reduced (to a minimum Q8W) If one of the criteria is met, the interval will be reduced by 4 weeks. If two or more criteria are met or one criterion includes new macular hemorrhage, the interval will be reduced to an 8-week interval.[d]	• Increase ≥ 50 μm in CST compared with the average from the last two study drug dosing visits or ≥ 75 μm compared with the lowest on-study drug dosing visit measurement **or** • Decrease ≥ 5 letters in BCVA[b] compared with average of last two study drug dosing visits or decrease ≥ 10 letters in BCVA[b] compared with the highest on-study drug dosing visit measurement **or** • New macular hemorrhage[c]
Interval maintained	If extension or reduction criteria have not been met

BCVA = best-corrected visual acuity; CST = central subfield thickness; nAMD = neovascular age-related macular degeneration; Q8W = every 8 weeks; Q16W = every 16 weeks.

[a] *Where stability is defined as a change of CST of less than 30 μm.*

[b] Change in BCVA should be attributable to nAMD disease activity (as determined by investigator).

[c] Refers to macular hemorrhage owing to nAMD activity (as determined by investigator).

[d] Patients whose treatment interval is reduced by 8 weeks from Q16W to Q8W will not be allowed to return to a Q16W interval during the study.

3.1.2 Compliance with Study Visits and Handling of Missed Visits

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

In a masked manner (through the IxRS), missed faricimab and aflibercept administration (not sham) will be made up at the next visit that the patient attends. The study drug dosing schedule will be reset at that visit. *An exception is for patients in Arm A who miss their Week 12 dose. These patients will not have their dose made up at Week 16, in order to maintain the validity of disease activity assessments at Weeks 20 and 24.*

If more than one study visit is missed between Day 1 and Week 28, the investigator and Sponsor may consider discontinuing the patient from study drug. Beyond Week 28, if a patient misses more than two study visits in any 24-week treatment period, the investigator and Sponsor may consider discontinuing the patient from study treatment.

Study drug dosing visits should not occur earlier than after a full 21 days have elapsed after the previous scheduled study treatment visit.

After the Day 1 visit, if a patient misses a study visit when CFPs and FFA (and indocyanine green angiography [ICGA] performed at selected sites with ICGA capabilities) images are obtained, the images must be obtained at the next scheduled visit that the patient attends (see Appendix 1). Other missed study assessments will not be made up.

3.1.2.1 Handling of Missed Visits up to Week 24 in Arm A

If a patient misses the Week 20 visit only, disease activity will be assessed at Week 24 and, depending on disease activity, the patient will be eligible for Q8W dosing or Q16W dosing up to Week 60.

If a patient misses the Week 24 visit only, the disease activity assessment conducted at Week 20 will determine whether dosing is continued Q8W or Q12W thereafter up to Week 60.

If a patient misses one of the two visits prior to a disease activity assessment visit (Week 20 or Week 24), data will be used from the visit that the patient does attend for a disease activity assessment. If a patient misses both visits prior to a disease activity assessment visit (Week 20 or Week 24), or misses both the Week 20 and 24 disease activity assessment visits, the patient will be dosed Q8W up to Week 60.

3.1.2.2 Additional Considerations for the PTI Regimen Phase in Arm A: IxRS Study Drug Dosing Interval Decision

Missed Study Drug Dosing Visit(s)

For the PTI regimen phase, a decision regarding the subsequent study drug dosing interval will be made by IxRS based on CST, BCVA, and clinical assessments completed at the visit when study drug is administered, and any changes in the study drug dosing interval will be based from the last assigned interval prior to the missed study drug dosing visit. For example, if a patient in Arm A was on a Q12W study drug dosing interval prior to missing the study drug dosing visit, then the IxRS decision to

maintain, extend, or reduce the dosing interval will be made on the basis of the previously assigned study drug interval along with CST and BCVA data obtained at the visit when the patient receives study drug. If the data indicate that the patient should maintain the Q12W interval, then he or she will receive study drug 12 weeks after that visit.

Study Drug Interruption at Study Drug Dosing Visit(s)

If a patient's dosing has to be interrupted (e.g., because of an adverse event) at a study drug dosing visit, the IxRS will assign the patient to receive study drug dosing at the earliest subsequent study visit when the patient is permitted to resume study drug dosing. The IxRS will be used to determine the subsequent dosing interval based on the assumption that the patient was previously on a Q8W interval.

Missing CST Value at Study Drug Dosing Visit

If a patient attends a study drug dosing visit, but the CST value is not available for any reason (e.g., OCT machine is not available or is broken), the IxRS will maintain the study drug dosing interval, unless the BCVA or clinical criteria for dose reduction are met, in which case the IxRS will reduce the study drug dosing interval accordingly.

Missing BCVA Value at Study Drug Dosing Visit

If a patient attends a study drug dosing visit, but the BCVA value is not available for any reason, the IxRS will maintain the study drug dosing interval unless the CST or clinical criteria for dose reduction are met, in which case the IxRS will reduce the study drug dosing interval accordingly.

[redacted]

3.1.5 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will monitor safety and study conduct on an ongoing basis throughout the study. 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 adjustable as required) to evaluate unmasked ocular and non-ocular safety events, with emphasis on the evaluation of the rate of ocular inflammation, increased IOP, endophthalmitis, arterial thromboembolic events, and clinically significant decreases in BCVA, 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.

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 will be recruited globally, [redacted]

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, [redacted] The end of the study is expected to occur approximately 112 weeks after the last patient is randomized.

The total length *of the study* [redacted] from screening of the first patient to the end of the *study* is expected to be approximately 48 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 trial design was selected to minimize bias in the evaluation of faricimab as a treatment for patients with nAMD.

To ensure the safety of all patients during the conduct of the study, several safety assessments have been included, for example, regular ophthalmological monitoring and imaging assessments, adverse event monitoring (of ocular and non-ocular events), and protocol-specified 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 as initiating and maintenance doses in treatment Arm A, as outlined in Section 3.1.1.

In the Phase I study (BP28936), the 6-mg dose of faricimab was the highest feasible dose, and single and multiple doses of up to 6 mg were well tolerated. In the Phase II studies, the ocular and non-ocular safety findings for faricimab were consistent with the safety profiles of anti-VEGF products licensed for nAMD and no clinically meaningful imbalances in events were observed for patients receiving the 1.5-mg and 6-mg doses.

The combined evidence from the Phase II studies BP29647 and CR39521 in nAMD indicates that the 6-mg faricimab dose delivers similar efficacy compared with monthly ranibizumab administration but importantly, has the potential to be given at substantially less-frequent treatment intervals (up to Q16W).

In Phase II, longer dosing intervals (Q8W, Q12W, and Q16W) were studied only with the 6-mg dose. The duration of ocular VEGF and Ang-2 suppression is described by a pharmacokinetic/pharmacodynamic (PK/PD) model (Hutton-Smith et al. 2016). The predicted longer duration of target suppression informed the choice to study the 6-mg dose for evaluation of $\geq$8-week intervals in Phase II.

For Phase III, the 6-mg dose has been selected to maximize the potential for a durable treatment effect on the basis of this PK/PD model, given its similar efficacy and comparable safety profile to the 1.5-mg dose.

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

The dosing schedule in Year 1 of this proposed Phase III study is based primarily on clinical data from the Phase II study CR39521 and is designed to allow the assessment of efficacy of the 6-mg faricimab dose administered at intervals of up to 16 weeks, as outlined in Figure 1.

In Study CR39521, following 4 initial monthly doses, Q12W and Q16W intervals of 6 mg of faricimab were explored. In this study, similar BCVA gains were observed in all treatment arms; patients treated with both the Q12W and Q16W regimens maintained initial improvements in vision (mean change in BCVA from baseline at Week 16, 1 month after the last monthly dose) through to the primary endpoint (Week 40) and the end of study (Week 52). Reductions from baseline in CST and CNV leakage in both the Q12W and Q16W treatment arms during extended dosing were comparable with those with monthly ranibizumab administration.

During the study, an assessment of disease activity according to protocol-defined criteria was conducted at Week 24 (12 weeks after 4 initial monthly doses). In the combined 6-mg faricimab treatment arms (Q12W or Q16W), 66% of patients did not show disease activity according to the pre-specified disease activity criteria at Week 24, 12 weeks after their last dose. In the 6-mg faricimab Q16W treatment arm, 61% of patients with no protocol-defined disease activity continued on the Q16W regimen, while the remaining 39% of patients had their dosing interval decreased to Q12W dosing at Week 24 for the remainder of the study. Patient discontinuation because of lack of efficacy or nAMD disease progression, as defined by investigator assessment, in the 6-mg faricimab treatment arms was low (1 of 55 patients had discontinued prior to Week 24 as did 2 of 55 patients beyond Week 24). As discussed above, initial vision gains were maintained with both the Q12W and Q16W regimens.

In addition, PK and PD assessment of aqueous humor samples from a subset of patients in the Phase II studies demonstrated high ocular suppression of VEGF and Ang-2 for 8 weeks or more with faricimab, supporting dosing regimens beyond Q8W.

In summary, data from Study CR39521 suggest that nAMD disease activity should be managed adequately with a faricimab Q12W or a Q16W regimen in the majority of patients with nAMD. The option for Q8W dosing (which was shown to be effective in Study BP29647) is included in the Phase III study design to help ensure that individual treatment needs are met by allowing dosing according to the most appropriate frequency, ranging between Q8W and Q16W.

In this proposed Phase III study, patients in Arm A will be administered the 6-mg faricimab dose Q4W up to Week 12 (4 injections), as outlined in Section 3.1.1. Disease activity assessments at Weeks 20 and 24 will require patients with anatomic or functional signs of disease activity to be treated with faricimab at Q8W or Q12W

treatment intervals, respectively. Patients receiving faricimab who do not have active disease at Week 20 and Week 24 will be treated with faricimab at Q16W intervals.

From Week 60 (when all patients in Arm A are scheduled to receive faricimab) onward, patients in Arm A will be treated according to a PTI dosing regimen (between Q8W and Q16W). Provision of a PTI approach for patients receiving faricimab after Week 60 closely reflects current clinical practice in nAMD and provides patients with the opportunity to either extend, maintain, or reduce treatment frequency according to need, thus minimizing the administration of unnecessary IVT injections while maintaining gains in VA achieved during fixed dosing.

Given the heterogeneity of disease activity in nAMD and the differences in treatment response across patients, the assessment of disease activity at multiple timepoints during the study, with the opportunity to move to a different treatment frequency aims to ensure that individual treatment needs are met. The disease activity criteria at Weeks 20 and 24 are specified in Section 3.1.1.4 and are based on the assessment of disease activity at Week 24 in Study CR39521. At Week 24, before patients can continue on the Q16W interval, the criteria allow the masked physician to make an assessment of whether there is significant nAMD disease activity that requires immediate treatment but does not meet the other specified disease activity criteria. The PTI criteria are specified in Section 3.1.1, Table 2. The disease activity assessment criteria are based on visual and anatomic criteria and aim to extend the treatment interval (to a maximum of every 16 weeks) in patients with inactive disease, while giving those with demonstrable disease activity the chance to have treatment intervals reduced to a minimum of every 8 weeks.

3.3.3 Rationale for Aflibercept Dose and Schedule

The 2-mg aflibercept dose will be administered to patients in treatment Arm B, 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 nAMD product labeling for Eylea® (aflibercept) (see Section 3.3.6).

3.3.4 Rationale for Biomarker Assessments

Several biochemical and biological processes, such as angiogenesis, inflammation, and oxidative stress, are known to play a role in the pathogenesis of AMD (the CATT Research Group 2011; Turpcu et al. 2014). Therefore, protein biomarkers of pathways involved in these processes may be analyzed to improve the understanding of the patients' response to faricimab treatment. The molecular targets of faricimab (VEGF and Ang-2) will be measured in the systemic circulation and, if possible, in aqueous and vitreous humor. Other biomarkers of angiogenesis that may be measured include Ang-1, VEGF receptor, Tie2, placental growth factor, basic fibroblast growth factor, and

platelet-derived growth factor. Furthermore, biomarkers of inflammation and oxidative stress may be measured in plasma and, if possible, in aqueous humor.

3.3.5 Rationale for Optional Aqueous Humor Samples

Aqueous humor may reflect changes in the retina better than blood, given its close proximity and contiguity to the retina. Single (Krohne et al. 2012) and multiple (Campochiaro et al. 2013) aqueous humor samplings have previously been instrumental in the understanding of the relationship 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. 2016) and were safely obtained from a total of 180 patients in faricimab clinical studies. Therefore, optional aqueous humor samples will be collected from consenting patients in regions where optional sampling is approved, with the aim to increase understanding of the ocular pharmacokinetics and pharmacodynamics of faricimab. Analyses derived from these samples will be used to develop better predictive models for determining optimal dosing intervals in different subgroups and to support selection of a dosing regimen for future clinical trials. Furthermore, additional biomarkers may be analyzed in aqueous humor samples to improve the understanding of patients' response to faricimab treatment (see Section 3.3.4).

3.3.6 Rationale for Control Group

This study is an interventional study to evaluate the efficacy of faricimab compared with a standard-of-care anti-VEGF monotherapy for patients with nAMD. Anti-VEGF therapy is a well-established standard of care in patients with nAMD, 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 nAMD and has demonstrated improvement in BCVA in the target population in controlled, randomized clinical studies (Eylea® [aflibercept] U.S. Package Insert, Eylea® [aflibercept] E.U. Summary of Product Characteristics, and Eylea® [aflibercept] Japan Package Insert). Eylea® is a globally approved anti-VEGF therapy with a Q8W maintenance regimen, facilitating a comparison with the longer regimens of faricimab that are being investigated in Arm A.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 640 patients with CNV secondary to AMD (also known as nAMD) will be randomized during the global enrollment phase of this study. *To ensure appropriate patient representation, the Sponsor may elect to cap the recruitment of patients in certain baseline BCVA strata. If implemented, details of the cap will be described in the Statistical Analysis Plan.*

After completion of the global enrollment phase, [redacted]

The protocol allows enrollment of both men and women, provided the following entry criteria are met (see Sections 4.1.1 and 4.1.2).

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

4.1.1.1 General Inclusion Criteria

Patients must meet the following general criteria for study entry:

- Signed Informed Consent

  Additionally, at U.S. sites, patients must provide Health Insurance Portability and Accountability Act (HIPAA) authorization, and in other countries, as applicable according to national laws.

- Age ≥50 years on Day 1
- Ability to comply with the study protocol, in the investigator's judgment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive measures that result in failure rate <1% per year during the treatment period and for at least 3 months after the final dose of study treatment

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of acceptable contraceptive methods include bilateral tubal ligation, male sterilization; hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices; and copper intrauterine devices.

  Contraception methods that do not result in a failure rate of <1% per year such as male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide are not acceptable.

  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 acceptable methods of contraception.

- [redacted]

4.1.1.2 Ocular Inclusion Criteria for Study Eye

Patients must meet the following ocular criteria for study entry:

- Treatment-naive CNV secondary to AMD (nAMD)
- Subfoveal CNV or juxtafoveal*/extrafoveal* CNV with a subfoveal component related to the CNV activity *identified* by FFA or OCT (*where CNV activity is defined as showing evidence of* subretinal fluid, subretinal hyper-reflective material *or* leakage)
- CNV lesion of any type (i.e., predominantly classic, minimally classic, or occult [including polypoidal choroidal vasculopathy and retinal angiomatous proliferation]) that exhibits **all** of the following characteristics:
  - A total lesion size (including blood, atrophy, fibrosis, and neovascularization) of ≤9 disc areas on FFA
  - A CNV component area of ≥ 50% of the total lesion size on FFA
  - Active CNV confirmed on FFA (evidence of leakage)
  - CNV exudation confirmed on OCT (presence of fluid)
- BCVA of 78 to 24 letters, inclusive (20/32 to 20/320 approximate Snellen equivalent), using the ETDRS protocol and assessed at the initial testing distance of 4 meters (see the BCVA manual for additional details) on Day 1
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

4.1.2 Exclusion Criteria

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

4.1.2.1 General Exclusion Criteria

Patients who meet any of the following general exclusion 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 4.4.3, 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
- Uncontrolled blood pressure, defined as systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 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
- Pregnancy or breastfeeding, or intention 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 treatment. 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 by a patient 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:

- CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis
- Any history of macular pathology unrelated to AMD affecting vision or contributing to the presence of intraretinal or subretinal fluid
- Presence at screening of central serous chorioretinopathy
- Retinal pigment epithelial tear involving the macula on Day 1
- On FFA/CFP:
  - Subretinal hemorrhage of $>$50% of the total lesion area and/or that involves the fovea
  - Fibrosis or atrophy of $>$50% of the total lesion area and/or that involves the fovea
- Any concurrent intraocular condition (e.g., amblyopia, aphakia, retinal detachment, cataract, diabetic retinopathy or maculopathy, or epiretinal membrane with traction) that, in the opinion of the investigator, could either reduce the potential for visual improvement or require medical or surgical intervention during the study
- Current vitreous hemorrhage on Day 1
- Uncontrolled glaucoma

- Spherical equivalent of refractive error demonstrating more than 8 diopters of myopia

  For patients who have undergone prior refractive or cataract surgery, the preoperative refractive error should not have exceeded −8 diopters of myopia.
- Any prior or concomitant treatment for CNV or vitreomacular-interface abnormalities, including, but not restricted to, IVT treatment (e.g., anti-VEGF, steroids, tissue plasminogen activator, ocriplasmin, C_3F_8, air), periocular pharmacological intervention, argon laser photocoagulation, verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or ocular surgical intervention
- 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, glaucoma surgery, corneal transplant, or radiotherapy)
- 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 exclusion criterion for the fellow eye (non-study eye) *at both the screening and Day 1 visits* will be excluded from study entry:

- Non-functioning non–study eye, defined as either:
  - BCVA of hand motion or worse
  - No physical presence of non-study eye (i.e., monocular)

4.1.2.4 Exclusion Criteria for Both Eyes

Patients who meet the following exclusion criteria for either eye 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 ocular inflammation or suspected or active ocular or periocular infection 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 central reading center will evaluate CFPs, FFA, and 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 arms

(faricimab up to Q16W or aflibercept Q8W). 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 (the Day 1 visit).

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

- Baseline BCVA ETDRS letter score ($\geq$74 letters, 73–55 letters, and $\leq$54 letters)
- LLD ($<$33 letters, and $\geq$33 letters) (adapted from Frenkel et al. 2016)
- 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.

LLD may contribute to variability of BCVA outcomes in patients with AMD treated with anti-VEGF therapy. Data from the Harbor study have shown that LLD at baseline is inversely proportional to the change from baseline in BCVA in nAMD patients treated with ranibizumab (Frenkel et al. 2016).

Enrollment may be closed or temporarily paused by region or country to ensure sufficiently balanced recruitment of patients globally.

4.2.2 Masking

This is a double-masked study. There must be a minimum of two investigators per site to fulfill the masking requirements of this study, and a masked and unmasked investigator are required to be present at each scheduled study visit.

4.2.2.1 Masked Roles

Principal Investigator

The Principal Investigator who will be a retina specialist (or the equivalent in ex-U.S. countries) must be in a masked role as he or she has to oversee the whole trial conduct at his or her site and must be masked to patients' treatment assignment. In addition, the Principal Investigator can assume any other masked role for which he or she qualifies except for tasks performed by the BCVA examiner.

Assessor Physician

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

Study Coordinator(s)

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

BCVA Examiner

The BCVA examiner will be masked to both the assigned treatment arm and the location (right vs. left) of the study eye. The BCVA examiner will have no access to patients' medical charts or the VA scores from a patient's previous visits and may have access only to a patient's refraction data from previous visits. The BCVA examiner is not allowed to perform any other task involving direct patient care.

Phlebotomist

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

4.2.2.2 Unmasked Roles

Treatment Administrator

At least one investigator will be designated as the treatment administrator and will be unmasked to the patients' treatment assignment. The treatment administrator 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 the equivalent in ex-U.S. countries)* may be permitted to perform the role of the treatment administrator following Sponsor approval.

The treatment administrator(s) performing the study treatment administration (faricimab, aflibercept, or sham) will also perform the post-treatment administration vision testing (finger counting and, if applicable, hand movement and/or light perception tests) and will treat adverse events that occur during or shortly after the study treatment administration. The person in this role, however, will not evaluate the causality of adverse events, which is the responsibility of the masked assessor physician(s). The treatment administrator will also perform post-treatment IOP measurements, as well as optional aqueous humor sample collection.

In addition, the qualifying treatment administrator can assist with and perform the screening and Day 1 visit assessments. The treatment administrator must not be involved in any other aspect of the study and must not divulge treatment assignment to anyone.

Unmasked Assistant(s) and Pharmacist

If desired, sites may have designated qualified unmasked assistant(s) who can, for example, assemble study treatment supplies, prepare the 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 assistant(s) can be assigned to measure post-dose IOP. If the site uses a pharmacy, then the unmasked role is also assigned to the pharmacist who can perform study drug–related tasks as applicable per the Delegation of Authority Log. In addition, qualifying unmasked assistant(s) 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 *Sponsor*.

Please note that if the site is using a pharmacist(s), they are not included in the overall site unmasked headcount described above. Thus, pharmacists may be in an unmasked role in addition to the above unmasked site staff.

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

4.2.2.3 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 a designated unmasked role perform any unmasked activities, 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 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. If the assessor physician is unavailable, then any clinic physician present, including the physician in the treatment administrator role, should see the patient.

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

Central reading center 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 this 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 Data Access Charter to audit the implementation of the randomization scheme and the treatment 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 either 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.

4.2.2.7 Patient Masking

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

4.2.3 Unmasking

4.2.3.1 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 investigator will be able to break the treatment code by contacting the IxRS. The 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.

4.2.3.2 Single-Patient Non-Emergency Unmasking

If the investigator wants 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 investigator should document and provide an explanation for any non-emergency unmasking. The investigator will be able to break the treatment code by contacting the IxRS.

4.2.3.3 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 investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the 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 (test product).

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

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Faricimab, Aflibercept, and Sham

4.3.1.1.1 Faricimab Formulation

Faricimab will be supplied by the Sponsor as a sterile liquid for IVT injection in single-use glass vials.

4.3.1.1.2 Aflibercept (Active Comparator) Formulation

Aflibercept will be supplied by the Sponsor as a sterile liquid for IVT injection in single-use glass vials.

4.3.1.1.3 Sham Formulation

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.

4.3.1.1.4 Faricimab, Aflibercept, and Sham Packaging and Handling

Faricimab, aflibercept, and sham packaging will be overseen by Roche's Clinical Trial Supplies Department and bear labels with the identification required by local law, the protocol number, drug identification, and its concentration.

The packaging and labeling of faricimab, aflibercept, and sham will be in accordance with Roche standards and local regulations.

Faricimab, aflibercept, and sham must be stored according to the details on the product label and the information provided in the pharmacy manual.

For more detailed information on the formulation and handling of faricimab, aflibercept, and sham, see the pharmacy manual.

Upon arrival of the masked investigational products at the site, site personnel should check individual carton boxes for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the unmasked monitor upon discovery. Any product under investigation for integrity or

temperature excursion should be quarantined by the IxRS, pending final assessment by the Sponsor.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

4.3.2.1 Dosage

4.3.2.1.1 Intravitreal Faricimab Injections

Patients randomized to Arm A will receive 6 mg of IVT faricimab Q4W up to Week 12 (4 injections). At Week 20, protocol-defined assessment of disease activity requires patients in Arm A with active disease (for the criteria, refer to Section 3.1.1.4) to be treated with a Q8W dosing regimen of 6 mg of faricimab (i.e., injections at Weeks 20, 28, 36, 44, 52, and 60).

A second protocol-defined assessment of disease activity at Week 24 requires patients in Arm A with active disease (see Section 3.1.1.4, excluding those with active disease at Week 20 and therefore receiving a Q8W dosing regimen of 6 mg of IVT faricimab) to be treated with a Q12W dosing regimen of 6 mg of IVT faricimab (i.e., injections at Weeks 24, 36, 48, and 60).

Patients receiving faricimab who do not have active disease according to the protocol-defined criteria (see Section 3.1.1.4) at Week 20 or Week 24 will be treated with 6 mg of IVT faricimab Q16W (i.e., injections at Weeks 28, 44, and 60).

From Week 60 (when all patients in Arm A are scheduled to receive study drug) to Week 108, patients in Arm A will be treated according to a PTI dosing regimen (between Q8W and Q16W). At study drug dosing visits, treatment intervals may be maintained or adjusted (i.e., increased by 4 weeks or decreased by 4 or 8 weeks), based on OCT, BCVA, and clinical assessment (for the criteria, refer to Section 3.1.1.5). Patients will therefore receive between 10 and 16 injections over the study treatment period (Day 1 to Week 108).

See the study schema in Figure 1.

4.3.2.1.2 Intravitreal Aflibercept (Active Comparator) Injections

For patients randomized to the active comparator (Arm B), a 2-mg dose of aflibercept will be administered intravitreally Q8W after 3 consecutive monthly doses during the 108-week treatment period (see Figure 1). Patients will receive 15 IVT injections of aflibercept during the 108-week treatment period. This will consist of three initiating injections (2 mg of aflibercept Q4W to Week 8), followed by 12 maintenance injections (2 mg of aflibercept Q8W at Weeks 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96, and 104).

4.3.2.1.3 Sham Procedure

Both treatment arms (faricimab up to Q16W and aflibercept Q8W) will maintain Q4W study visits for the duration of the study. To preserve masking of the randomized

treatment arm, patients will have the sham procedure performed at study treatment visits when they are not treated with either faricimab or aflibercept as applicable per their treatment arm schedule (see Figure 1).

4.3.2.2 Administration

4.3.2.2.1 Faricimab or Aflibercept Intravitreal Injections or Sham Procedure

See the pharmacy manual for the pre-treatment procedures, the administration of faricimab, aflibercept, or sham and the post-treatment procedures for all treated patients.

4.3.2.2.2 Study Treatment Preparation

The pharmacist responsible for dispensing the study drug or designated unmasked site personnel will prepare the correct study drug (faricimab, aflibercept, or sham) as assigned through the 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 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 or aflibercept vials, as well as administration material must not be reused.

4.3.2.3 Compliance

Any medication error, including drug overdose, should be noted on the Adverse Event eCRF, even if it did not result in any adverse event (see Adverse Event eCRF completion guidance and *Section 5.3.5.12*).

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Table 3 and Section 5.1.4.1.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (faricimab, sham, and aflibercept) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm shipment condition and content. Any damaged shipments will be replaced.

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 Inventory Log.

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 would not 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 nAMD
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for nAMD
- 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 prescription drugs or 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 preceding the Day 1 visit and through the conclusion of the patient's study

participation or early termination visit. Patients required to use therapy that is prohibited (see *Section 4.4.3*) will not be eligible for the study.

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

At the discretion of the investigator, patients may continue to receive medications and standard treatments administered for other conditions, with the exceptions listed in Section 4.4.3.

Of note, the following are some common therapies that are permitted:

- Onset of ocular hypertension or glaucoma in the study eye during a patient's study participation should be treated as clinically indicated.
- Onset of cataract or posterior capsular opacification in either eye during a patient's study participation may be treated as clinically indicated. Dose interruption criteria (see Section 5.1.4.1, Table 3) may apply with cataract surgery.
- Short-term use of topical corticosteroids after cataract surgery, yttrium-aluminum garnet laser capsulotomy, or peripheral iridotomy is permitted.
- Patients who require anti-VEGF treatment for their fellow eye should continue or initiate treatment according to instructions in Section 4.4.2.

4.4.2 Fellow (Non–Study) Eye Treatment with Anti-VEGF Therapy

At the discretion of the masked physician, randomized patients may have their fellow (non-study) eye treated with anti-VEGF therapy *licensed for ocular use* if they are diagnosed with an ocular condition for which the selected anti-VEGF therapy is approved *by* the country *regulatory agency*. Consult with the region-specific anti-VEGF prescribing information for the recommended dose and frequency of treatment. *The* Sponsor will cover the cost of the *approved licensed ocular anti-VEGF* therapy in accordance with local regulations. *Note: Avastin® (bevacizumab) is not licensed for ocular use in any country; therefore, its use is prohibited.*

Note: If (per the masked investigator's judgment) treatment with anti-VEGF therapy 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.

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

4.4.3 Prohibited Therapy

At the discretion of the investigator, patients may continue to receive medications and standard treatments administered for other conditions. However, 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 the study eye
- IVT, periocular (subtenon), steroid implants (i.e., Ozurdex®, Illuvien®), or chronic topical (ocular) corticosteroids in the study eye
- Concurrent use of any macular photocoagulation or photodynamic therapy with verteporfin in the study eye
- Other experimental therapies (except those comprising vitamins and minerals)

Note: Patients who discontinue study treatment should be strongly encouraged to continue their study participation and undergo as many scheduled visits as possible, with emphasis on the Weeks 44, 48, 52, and 112 visits.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. Written informed consent will be obtained prior to initiation of any study procedures. The screening evaluation will be performed within 28 days preceding the Day 1 visit (the day of the first study treatment).

Note: Some patients may require an extended screening period as a result of repeated evaluation of images or other issues. Upon agreement with the Medical Monitor, the screening period may be extended for up to 5 business days for such cases.

All assessments for a scheduled visit are to be performed on the same day, except those performed during the screening period (see Section 5.1.4.1, Table 3).

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 or re-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 and Day 1 visit evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization at the Day 1 visit. The investigator will maintain a screening log to record details about all patients screened and to confirm eligibility. Reasons for screening failure have to be documented in patients' source documents.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, chronic and ongoing conditions (e.g., trauma, cancer, cardiovascular, cerebrovascular, and ophthalmic history), 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 a patient within 7 days prior to initiation of study treatment (the Day 1 visit) *and up to 28 days after the last drug dosing visit* will 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 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.

Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

In addition, a patient’s height and weight will be recorded.

4.5.4 Vital Signs

Vital signs will include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure. Vital signs will be taken with the patient in a seated position after resting for 5 minutes.

4.5.5 Ocular Assessments

Ocular assessments include the following and will be performed *on both eyes, unless otherwise indicated,* at specified timepoints according to the schedule of activities in Appendix 1:

- BCVA assessed on an ETDRS chart at a starting distance of 4 meters (performed prior to dilating eyes; see Appendix 4)
- Low-luminance BCVA, as assessed on the ETDRS chart at a starting distance of 4 meters (performed prior to dilating eyes; see Appendix 5)
- Pre-treatment IOP measurement of both eyes (performed prior to dilating eyes)
- Slitlamp examination (for grading scales for anterior and vitreous cells, see Appendix 3)
- 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 by the unmasked treatment administrator
- *Post-treatment* IOP measurement *only* in the study eye *after* 30 (±15) minutes *of study treatment administration* by qualified personnel assigned to the unmasked role

  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, the patient will remain in the clinic and will be managed in accordance with the treatment administrator'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 central reading center(s) will provide sites with the central reading center(s) 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 reading center(s) as specified in the central reading center manual. All ocular images results will be obtained by trained site personnel at the study sites and forwarded to the central reading center(s) for independent analysis and/or storage (see Appendix 6, Appendix 7, and Appendix 8).

Note: After randomization, if a patient misses a study visit when *CFP, FFA, or ICGA (if applicable)* ocular images are scheduled (see Appendix 1), the images should be obtained at the next scheduled visit the patient attends.

Ocular images include the following:

- CFP of both eyes *(please note that ultra-wide photography [UWP)] is not permitted)*

- FFA of both eyes (performed after laboratory samples are obtained*; please note that UWP is not permitted*)
- SD-OCT or swept-source OCT (SS-OCT) images of both eyes

  Certain SS-OCT machines may be acceptable; *consult* the central reading center.
- Optional OCT-angiography (OCT-A) of both eyes at sites with agreed OCT-A capabilities
- Optional ICGA of both eyes at selected sites with agreed ICGA capabilities (performed after laboratory samples are obtained) *and after all other imaging has been performed. However, if a site's standard of practice is to perform ICGA in parallel with FFA, this is also acceptable. Please refer to the central reading center manual.*

Additional details on obtaining these images are included in the central reading center manual.

4.5.6 Concurrent Ocular Procedures

Any ocular procedures performed on either eye during the study (starting on Day 1, post-study treatment) 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 eye treatment and FFA assessments (if applicable). Fasting is not required prior to specimen collection. The specimens will be forwarded to the central laboratory. The central laboratory will either perform the analysis or forward samples to the Sponsor or its designee for analysis and/or storage. Instructions for obtaining, processing, storing, and shipping of all specimens are provided in the laboratory manual. Laboratory supply kits will be provided to the sites by the central laboratory. See Appendix 1 for sample collection timepoints and the laboratory manual for biological sample collection and shipping instructions. Except as noted (see Appendix 9), all samples obtained during screening from patients who are not randomized will be discarded.

The following assessments will be performed:

- Hematology: hemoglobin, hematocrit, quantitative platelet count, RBC counts, WBC counts, and differentials, including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, ALP, AST, ALT, and uric acid
- Urinalysis: specific gravity, pH, blood, protein, ketones, glucose, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal)

- Coagulation: activated partial thromboplastin time and prothrombin time
- Pregnancy test

  All women of childbearing potential (including those who have had tubal ligation) will have a urine pregnancy test at screening and prior to each study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. If the serum pregnancy test is positive, do not administer study treatment.
- Plasma samples for measurement of anti-drug (faricimab) antibodies (ADAs)
- Plasma samples to measure faricimab or aflibercept concentration (mandatory and optional samples from patients who consent to aqueous humor sampling)
- Plasma samples for analysis of systemic free VEGF-A, free Ang-2, and additional biomarkers (PD sample) (mandatory and optional samples from patients who consent to aqueous humor sampling)

Drug concentration, free VEGF-A, and free Ang-2 will be determined in plasma using a validated immunoassay method. ADAs will be detected in plasma using a validated bridging ELISA.

Unless the patient gives specific consent for his or her leftover plasma samples to be stored for optional exploratory research (see Section 4.5.9.1), the samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed. The hematology, serum chemistry, urinalysis, coagulation, and serum and urine pregnancy test *samples* will be destroyed after their analysis during the study.

4.5.7.1 Optional Aqueous Humor *and Optional Plasma* Samples

Collection and submission of optional aqueous humor *and optional plasma* samples is contingent upon the 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 4.5.7.1) will not be applicable at that site.

For patients who consent to provide aqueous humor sampling, the aqueous humor sample should be collected just prior to study treatment by a qualified unmasked treatment administrator, using an aseptic procedure and sterile field and according to local guidelines (see Appendix 9 *and the laboratory manual for further details on sample collection, storage, and transfer*). Samples should be frozen according to the instructions provided to sites. All efforts should be made to obtain a baseline aqueous humor sample on Day 1 (pre-dose). 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.

Aqueous humor samples will be analyzed for faricimab or aflibercept, *free* VEGF-A, and *free* Ang-2 concentrations. Remaining samples will be analyzed for additional

biomarkers, including those involved in angiogenesis [redacted] and inflammation [redacted] 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.

At Day 7, sites will collect optional PK plasma samples for measurement of faricimab or aflibercept concentrations and optional PD plasma sample for analysis of systemic free VEGF-A and free Ang-2 (see Appendix 1 and the laboratory manual for PK/PD samples collection, storage, and transfer).

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.9.5), biological samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

4.5.7.2 Optional Unscheduled Collection of Vitreous Samples

Elective vitrectomy for vitreous sample collection is not allowed in the study eye during a patient's study participation; however, if the surgery is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye (see Appendix 9 for further details). *Associated PK plasma samples will be collected to measure faricimab or aflibercept concentrations. 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 VEGF-A and free Ang-2 concentrations, as well as additional biomarkers, including those involved in angiogenesis* [redacted] *and inflammation* [redacted] *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.*

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.9.5), biological samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

4.5.8 Patient-Reported Outcomes

Patient-reported outcomes (PROs) will be assessed using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25; see Appendix 10). 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 one item on general health. In this study, an additional six 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.

The NEI VFQ-25 will be interviewer administered by the masked site staff (except for the VA examiner) prior to any other visit assessments being performed. Interviews will be conducted in the local language of the patient using linguistically validated translations. Patients may be excluded from completing the NEI VFQ-25 if a translation is not available in their spoken language.

4.5.9 Optional Samples for Research Biosample Repository

4.5.9.1 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 specimens 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.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- 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

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection, and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB or 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 4.5.9) will not be applicable at that site. The RBR portion of the Informed Consent Form has to be agreed to and signed by the consenting patient before these samples can be collected and/or mandatory residual samples used.

4.5.9.3 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 response to faricimab, to improve the understanding of the biology of VEGF-A and Ang-2, or to better understand the targets or diseases (nAMD):

- Whole blood sample for DNA
- Residual aqueous humor sample
- Residual vitreous sample
- Residual plasma PD sample
- Residual PK sample
- Residual ADA sample

The whole blood sample for DNA may be sent to one or more laboratories for analysis via whole genome sequencing (WGS), next-generation sequencing, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides 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.

Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. For all samples, the dates of consent and specimen collection should be recorded on the associated RBR eCRF.

RBR specimens 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).

4.5.9.4 Confidentiality

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

Patient medical information associated with RBR specimens 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 specimens, 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 specimens 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.

4.5.9.5 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 specimens. 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 specimens and data will continue to be used as part of the RBR research.

4.5.9.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens 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 specimens 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 specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, 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 specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from this study.

4.5.9.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice (GCP) 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 specimens 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:

- Occurrence of 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 determines it is in the best interest of the patient
- Pregnancy

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, they should be strongly encouraged to continue their study participation and undergo as many scheduled visits as possible, with emphasis on the Week 40, 44, 48, 60, and 112 visits.

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator and Sponsor has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

- 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.

If a patient discontinues from the study but has not withdrawn informed consent, the site should make every effort to continue to follow-up on serious adverse events, deaths, and adverse events of special interest. In order to avoid loss to follow-up, the investigator should ask the patient at the study start for the contact information of 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 but have not withdrawn consent should return for an early termination visit (see Appendix 1) after a minimum of 28 days have elapsed following the last study treatment.

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 GCP
- 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 pre- and post-treatment antimicrobials, patients will also be asked whether they have self-administered pre- and/or post-treatment antimicrobials.

A finger counting test will be conducted for each patient within 15 minutes following study treatment by the treatment administrator; 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, the patient will remain in the clinic and will be managed in accordance with the treatment administrator's clinical judgment. The adverse event will be recorded on the Adverse Event eCRF as applicable.

Note: 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 4.4.2 for additional details).

Detailed ocular examinations, including indirect ophthalmoscopy and slitlamp examination, will be performed throughout the study. Blood samples for plasma study drug concentrations, antibodies to faricimab, and other biomarker samples (see Section 4.5.7) will be obtained from all patients at selected timepoints. The optional aqueous humor and vitreous samples will be obtained from patients who consent to the procedure and sample collection.

An iDMC will monitor safety and study conduct on an ongoing basis (see Section 3.1.5 for additional details).

Patients who are discontinued from the study prior to completion (Week 112) 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 Section 5.1.4.1, Table 3.

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 the Comparator Aflibercept

Important risks associated with aflibercept IVT injections are infective 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) Summary of Product Characteristics.

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 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 3. 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 or discontinuation should be recorded on the appropriate eCRF and, if applicable, on the Adverse Event eCRF.

Table 3 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 Medical Monitor and investigator.
Intraocular surgery in the study eye	• Interrupt study treatment after intraocular surgery (e.g., cataract surgery) in the 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 or other intraocular, 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 ≥30 letters in BCVA 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 investigator.
Elevated IOP	• Interrupt study treatment if pre-treatment IOP in the study eye is ≥30 mmHg. • Treatment may be permitted when IOP has been lowered to <30 mmHg, either spontaneously or with treatment, as determined by 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 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 infection	• Interrupt study treatment if active or suspected ocular or periocular infections present (e.g., infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis) in either eye or if the patient requires treatment for an active non-ocular infection. • Study treatment may be subsequently permitted after discussion with Medical Monitor.
On-study prohibited medications	• See *Section 4.4.3 for a list of prohibited therapies during the study.*

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 GCP, an adverse event is any untoward medical occurrence in a clinical investigation subject 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 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 Sections 5.3.5.9 and 5.3.5.10 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 according to the Adverse Event Grading Scale; see Section 5.3.3, Table 4); 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 VA score (compared with the last assessment of VA 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 5.2.3 and Appendix 3 for intraocular inflammation grading scales).

All of the above-listed sight-threatening adverse events should 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 investigator who is in the masked role.

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 112. For patients who terminate study treatment and from the study early, all adverse events will be reported up to the early termination visit. For patients who discontinue study treatment early (prior to Week 108 treatment) but continue to participate in the study, adverse events will be reported until their last or final study visit.

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 4 provides guidance for assessing adverse event severity.

Table 4 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: Only the masked investigator will assess all adverse event causality. The following guidance should be taken into consideration (see also Table 5):

- 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 5 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).

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.

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., ALP and bilirubin 5 × the upper limit of normal [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 5.3.5.4 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 5.3.5.1 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3× ULN) in combination with either an elevated total bilirubin (>2× 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× ULN in combination with total bilirubin >2× ULN
- Treatment-emergent ALT or AST >3× 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 5.3.5.2) 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 Worsening of Neovascular Age-Related Macular Degeneration in the Study Eye

Medical occurrences or symptoms of deterioration that are anticipated as part of nAMD in the 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 nAMD 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 of neovascular age-related macular degeneration"). The expedited reporting requirements for associated sight-threatening events (listed in the 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 Adverse Events Associated with an Overdose or Error in Drug Administration

No safety data related to overdosing of faricimab are available. *See Section 5.3.5.12 for additional medication error reporting details.*

5.3.5.12 *Reporting Requirements for Cases of Medication Error and Associated Adverse Events*

Medication Error Definition and Reporting

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

- *Medication error is 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 is 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 a masked manner as described below:*

For medication error enter "Medication Error" on the Adverse Event eCRF as the primary event term and check the "Medication error" box (see eCRF Completion Guidelines for additional details).

For intercepted medication error enter "intercepted Medication Error" on the Adverse Event eCRF as the primary event term and check the "Medication Error" box (see eCRF Completion Guidelines for additional details).

Reporting of Adverse Events Resulting from Special Situation

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 it is 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:

- *Enter the adverse event caused by the medication error as primary adverse event term on Adverse Event eCRF. 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.

5.3.5.13 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)

The investigator must report new significant follow-up information for these events 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 Emergency Medical Contacts

Medical Monitor Contact Information ***for Western Hemisphere*** **(Primary)**

Medical Monitor/*Roche Medical Responsible:* [redacted], *M.D.*

Mobile Telephone No.: [redacted]

Medical Monitor Contact Information

Medical Monitor/Roche Medical Responsible: [redacted], M.D., Ph.D.

Mobile Telephone No.: [redacted]

Medical Monitor Contact Information

Medical Monitor/Roche Medical Responsible: [redacted], M.D., Ph.D.

Mobile Telephone No.: [redacted]

Medical Monitor Contact Information *for Eastern Hemisphere*
Medical Monitor/Roche Medical Responsible: [redacted], *M.B., Ch.B.*
Telephone No.:
Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all 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 112. For patients who terminate from the study treatment and from the study early, all 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 post-study adverse events 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 to immediately inform the investigator if they become pregnant during the study or for at least 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 as a minimum of 28 days after the final dose of study drug for patients who complete study treatment, i.e., the Week 108 visit; for the patients who discontinue study treatment early but continue to participate in the study, the adverse events reporting period is until their last or final study visit whichever is later), if the event is believed to be related to prior administration of study 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 using the following reference documents:

- Faricimab (RO6867461) Investigator's Brochure
- 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 640 patients will be randomized in the global enrollment phase of this study. [redacted]

The primary and the final analyses of this study will include only patients enrolled during the global enrollment phase; [redacted]

The primary analysis will be performed when all patients from the global enrollment phase have either completed the study through Week 48 or have discontinued from the study prior to Week 48, whichever comes later (i.e., timing is defined as the primary analysis after 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. Additional analyses of key efficacy endpoints may be performed between the primary analyses and final analyses to support marketing applications.

Results of the primary analyses, summarized by treatment group, may be reported to the public before completion of the study. However, patients, masked study site personnel, and central reading center 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 112 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 [redacted]. Details of the planned analyses, including any additional analyses needed to support

country-specific or regional marketing applications, will be provided in the Statistical Analysis Plan.

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 640 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 Q8W) and the faricimab up to Q16W arm.

A sample size of approximately 320 patients in each arm will provide greater than 90% power to show non-inferiority of faricimab to aflibercept in the change in BCVA averaged over Weeks 40, 44, and 48 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 two treatment arms
- Standard deviation (SD) of 14 letters for the change from baseline in BCVA averaged over Weeks 40, 44, and 48
- Two-sample *t*-test
- 2.5% one-sided type I error rate
- 10% dropout rate

To ensure appropriate patient representation, the Sponsor may elect to cap the recruitment of patients in certain baseline BCVA strata. If implemented, details of the cap will be described in the Statistical Analysis Plan.

The sample size may be adjusted as appropriate based on a masked assessment of the pooled SD of the change in BCVA from baseline. The assessment will be performed by the Sponsor at a specified timepoint prior to completing enrollment. Details on the masked sample size re-estimation conducted, as well as actions and decisions taken regarding changes in sample size, will be documented in the Statistical Analysis Plan. The Sponsor will remain masked. Other factors external to the study may also trigger a decision to modify the sample size.

[redacted]

6.2 ANALYSIS POPULATIONS

The analysis populations used in this section, such as the ITT population, are based on patients enrolled during the global enrollment phase and [redacted]

6.2.1 Intent-to-Treat Population

The ITT population will comprise 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. 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 comprise all patients who receive at least one injection of active study drug (faricimab or aflibercept). For analyses based on this patient population, patients will be grouped according to the actual treatment received up to Week 48. 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 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 the previous section).

6.2.5 Immunogenicity-Analysis Population

The immunogenicity-analysis population will consist of all patients 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.

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 group 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.

The primary comparison will be between the active comparator (aflibercept Q8W) and the faricimab up to Q16W arm.

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.

6.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in BCVA averaged over Weeks 40, 44, and 48. The BCVA outcome measure is based on the ETDRS VA chart assessed at a starting distance of 4 meters.

The primary comparison will be to test non-inferiority of faricimab compared with aflibercept in the ITT population. Additional analysis based on the per-protocol population will also be conducted.

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: $\mu^{\text{faricimab}} - \mu^{\text{aflibercept}} \leq -4$ letters

and the alternative hypothesis, H_a: $\mu^{\text{faricimab}} - \mu^{\text{aflibercept}} > -4$ letters, will be tested, for which $\mu^{\text{faricimab}}$ and $\mu^{\text{aflibercept}}$ are the expected change from baseline in BCVA averaged over Weeks 40, 44, and 48 for the faricimab up to Q16W arm and the active comparator (aflibercept Q8W), respectively.

The change from baseline averaged over Weeks 40, 44, and 48 will be compared between the faricimab up to Q16W arm and the aflibercept Q8W arm using a MMRM model. The model will include the change from baseline at Weeks 4–48 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. Comparisons between the two treatment arms will be made using a composite contrast over Weeks 40, 44, and 48. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a heterogeneous compound symmetry or an AR(1) covariance structure may be fitted.

Missing data will be implicitly imputed by the MMRM model, assuming a missing at random missing data mechanism (i.e., the probability that missing data are dependent on other observed variables but not on the missing data). Data for patients who receive prohibited therapy will be censored at the timing of use of prohibited therapy. Data for patients who discontinue from study drug and do not receive prohibited therapy after discontinuation of study drug will be included in the analysis.

Additional details about the planned analyses, as well as supplementary and sensitivity analyses using other imputation methods for missing data, analysis using the trimmed mean approach for patients who receive prohibited therapy or discontinue study drug due to lack of efficacy or adverse events, analyses of the per-protocol population, and subgroup analyses to assess the robustness of the primary endpoint results will be provided in the Statistical Analysis Plan.

Non-Inferiority Margin

Non-inferiority hypothesis testing for the primary endpoint of the change from baseline in BCVA averaged over Weeks 40, 44, and 48 will be performed using a 4-letter non-inferiority margin. The non-inferiority margin is based on data from the MARINA ranibizumab pivotal nAMD study and is also supported by both data from the ANCHOR ranibizumab pivotal nAMD study and the VIEW1 and VIEW2 aflibercept pivotal nAMD studies.

The MARINA study compared ranibizumab with sham (placebo) control in 716 patients. At 1 year, in MARINA, patients receiving 0.5 mg of ranibizumab every month gained 6.3 letters from baseline compared with a loss of 11.0 letters for patients in the control arm. The 4-letter non-inferiority margin preserves approximately 70% of the least estimated benefit of ranibizumab over sham control in the MARINA study.

Furthermore, the ANCHOR study compared ranibizumab to verteporfin photodynamic therapy control in 423 patients. At 1 year, in ANCHOR, patients receiving 0.5 mg of ranibizumab every month gained 11.0 letters from baseline compared with a loss of 8.5 letters for patients in the control arm.

The VIEW1 and VIEW2 studies compared different doses and regimens of aflibercept with an active control of 0.5 mg ranibizumab in 2412 patients. VIEW1 was conducted in the United States and Canada, and VIEW2 was conducted in Europe, Latin America, the Middle East, and the Asia-Pacific region. At 1 year, in VIEW1 and VIEW2, patients receiving 0.5 mg of ranibizumab every month gained 8.1 and 9.4 letters from baseline, respectively, and patients receiving 2 mg of aflibercept Q8W gained 7.9 and 9.4 letters from baseline, respectively, demonstrating the clinical equivalence of these treatments.

The non-inferiority margin should be small enough to allow a conclusion that the new treatment is not inferior to the active control to an unacceptable extent on the basis of a combination of clinical judgment and statistical reasoning. From a clinical perspective, the non-inferiority margin should be fewer than 5 letters, given that a loss of 5 letters (one ETDRS line) between treatments would be considered clinically relevant.

6.5.2 Secondary Efficacy Endpoints

For all secondary endpoints measured on a continuous scale, the same analysis method and data handling rules as described in Section 6.5.1 for the primary endpoint will be used.

For binary secondary endpoints, 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). Confidence intervals 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).

Additional details regarding the plan for the secondary endpoint analyses will be provided in the Statistical Analysis Plan.

6.5.3 Exploratory Efficacy Endpoints

Details regarding the exploratory efficacy endpoints will be provided in the Statistical Analysis Plan.

6.6 SAFETY ANALYSES

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

Safety will be assessed through descriptive summary 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 48 data in the safety-evaluable population. In addition, summaries for ongoing safety data (after Week 48 and up to a single specified clinical cutoff date) in the safety-evaluable population will be summarized. At the time of the final analysis, safety summaries will be produced based on cumulative Week 112 data in the safety-evaluable population.

Verbatim descriptions of treatment-emergent adverse events will be mapped to Medical Dictionary for Regulatory Activities (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. Separate summaries will be prepared for non-ocular and ocular adverse events.

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

Additional details regarding the safety analysis plan will be provided in the Statistical Analysis Plan.

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 and aflibercept. 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 to update the current population-PK model. The model may be revised if necessary. 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 VEFG-A, and 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

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 (post-baseline incidence) will be summarized by treatment group. When determining the post-baseline 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 (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-dose samples is greater than the titer of the baseline sample by a scientifically reasonable margin (details to be provided in the Statistical Analysis Plan). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is greater than the titer of the baseline sample by a scientifically reasonable margin such as 4-fold (if 1:2 dilution steps are applied).

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.

Baseline values will be used to evaluate predictive biomarkers in the context of efficacy, PK, safety, and/or immunogenicity endpoints. Descriptive summaries will be presented by treatment and timepoint.

WGS data will be analyzed in the context of this study and may be explored in aggregate with data from other studies to increase researcher's understanding of disease pathobiology and faricimab treatment response, and guide the development of new therapeutic approaches.

[redacted]

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 central reading center 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 on a compact disc 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, PROs, 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 at least 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 Clinical Study Report has been completed for the length of time required by relevant medical 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 GCP and the principles of the Declaration of Helsinki, or the 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 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 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.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. 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. 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. 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 9.6).

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 Roche policy on study data publication (see Section 9.5).

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.

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 study and for 1 year after completion of the study (see the 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 GCP 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 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.

9.4 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 640 patients. Enrollment will occur through an 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.

9.5 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 of the U.S. National Institutes of Health and the European Medicines Agency, 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, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data 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.

9.6 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 48 Assessments

		Visit Day		Visit Week												
	Screening [a]	1 [a]	7	4	8	12	16	20	24	28	32	36	40	44	48	
Day(s) (Visit window)	–28 to –1	N/A	(±3)	28 (±7)	56 (±7)	84 (±7)	112 (±7)	140 (±7)	168 (±7)	196 (±7)	224 (±7)	252 (±7)	280 (±7)	308 (±7)	336 (±7)	ET [b] (≥28)
Informed consent [c]	x															
Sample informed consent [c] for optional aqueous, vitreous, and blood samples	x															
Optional (RBR) residual samples and DNA whole blood sample informed consent [c]	x															
Review of inclusion and exclusion criteria	x	x														
Demographic data	x															
Medical history [d]	x															
Targeted physical examination [e]	x															x
Body weight and height	x															
Vital signs [f]	x	x													x	x
NEI VFQ-25 [g]		x							x						x	x
BCVA [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Low-luminance BCVA		x													x	
Pre-treatment IOP [i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

Table 1 Screening through Week 48 Assessments (cont.)

		Visit Day		Visit Week												
	Screening [a]	1 [a]	7	4	8	12	16	20	24	28	32	36	40	44	48	
Day(s) (Visit window)	–28 to –1	N/A	(±3)	28 (±7)	56 (±7)	84 (±7)	112 (±7)	140 (±7)	168 (±7)	196 (±7)	224 (±7)	252 (±7)	280 (±7)	308 (±7)	336 (±7)	ET [b] (≥28)
Pregnancy test [j]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
*Whole blood sample (*hematology, chemistry panel, coagulation*),* and urinalysis [k]	x														x	
Optional aqueous humor sample [l]		x	x				x	x	x	x						x
Optional vitreous humor sample [m]		If elective vitrectomy is performed [m]														
Optional PK plasma sample (if vitreous humor sample collected) [m]		*If elective vitrectomy is performed and vitreous humor sample collected*														
Optional blood sample for RBR [n]		x														
Mandatory plasma PK sample [o]		x		x			x	x							x	x
Optional PK plasma sample (if aqueous humor sample is collected)			x [p]													
Mandatory plasma PD sample [o]		x		x			x	x							x	x
Optional PD plasma sample (if aqueous humor sample is collected)			x [p]													
Mandatory plasma sample for ADAs [o]		x		x				x							x	x
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

Table 1 Screening through Week 48 Assessments (cont.)

		Visit Day		Visit Week												
	Screening [a]	1 [a]	7	4	8	12	16	20	24	28	32	36	40	44	48	
Day(s) (Visit window)	–28 to –1	N/A	(±3)	28 (±7)	56 (±7)	84 (±7)	112 (±7)	140 (±7)	168 (±7)	196 (±7)	224 (±7)	252 (±7)	280 (±7)	308 (±7)	336 (±7)	ET [b] (≥28)
Indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
OCT [q]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Optional OCT-A [q, r]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
FFA [q]	x														x	x
CFP [q]	x														x	x
Optional ICGA [q, s]	x														x	
Disease activity assessment [t]								x	x							
Administration of study treatment		x		x	x	x	x	x	x	x	x	x	x	x	x	
Finger counting test [u]		x		x	x	x	x	x	x	x	x	x	x	x	x	
Post-treatment IOP [v]		x		x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events [w]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [x]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [y]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; BCVA = best-corrected visual acuity; CFP = color fundus photograph; eCRF = electronic Case Report Form; ET = early termination; FFA = fundus fluorescein angiography; ICGA = indocyanine green angiography; IOP = intraocular pressure; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT = optical coherence tomography; OCT-A = optical coherence tomography–angiography; PD = pharmacodynamic; PK = pharmacokinetic; RBR = Research Biosample Repository; VA = visual acuity.

Appendix 1
Schedule of Activities (cont.)

Table 1 Screening through Week 48 Assessments (cont.)

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 relative to the date of the Day 1 visit (first study treatment). There must be a minimum of 21 days between all study visits occurring from Week 4 through Week 108. 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 4.4.2).

[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. Informed consent must be administered and signed by a patient before any study-specific screening procedure is performed. When screening and randomization are combined and performed on 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: slitlamp examination, indirect ophthalmoscopy, and pre- and post-treatment IOP measurements (recorded on the Day 1 eCRF and dated accordingly). *Verify that the patient has not started any prohibited medication.*

[b] Patients who discontinue from the study early (prior to the final study visit at Week 112) but have not withdrawn consent should return for an ET visit after a minimum of 28 days have elapsed following their last study treatment.

[c] Informed consent must be administered and documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment at the Day 1 visit. The Optional Blood, Aqueous Humor, Vitreous Humor Samples Informed Consent Form as well as Optional (RBR) Informed Consent Form for residual samples and whole blood DNA sample collection can be signed either at the screening or Day 1 visit prior to sample collection.

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

[e] 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. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

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

[g] To be administered by the masked site staff (except for the VA examiner) prior to any other visit assessments being performed on that day.

[h] To be performed prior to other ocular assessments. Perform the assessments prior to dilating the eyes.

[i] 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.

Appendix 1
Schedule of Activities (cont.)

Table 1 Screening through Week 48 Assessments (cont.)

[j] 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, do not administer study treatment. Perform urine pregnancy test before FFA (if applicable).

[k] Hematology includes hemoglobin, hematocrit, quantitative platelet count, RBC counts, WBC counts, and differentials, including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute). Serum chemistry panel includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, ALP, AST, ALT, and uric acid. Coagulation includes activated partial thromboplastin time and prothrombin time. Urinalysis includes specific gravity, pH, blood, protein, ketones, glucose, 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 Pricipal Investigator's discretion.*

[l] 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. Not applicable* for a site that has not been granted approval by a site's Institutional Review Board or Ethics Committee. The sample at ET is not required if there are any safety concerns.

[m] If elective vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. A PK blood sample (for plasma preparation) should also be collected and shipped to the Sponsor. Vitreous humor samples will be analyzed primarily for faricimab concentrations or aflibercept concentrations. The remaining samples may be analyzed for VEGF and Ang-2 concentrations and possibly other biomarkers.

[n] *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).

[o] Obtain prior to FFA (if applicable) and prior to study treatment.

[p] PK and PD samples on Day 7 should be collected only from patients consenting to optional aqueous humor sampling.

[q] *OCT and FFA images obtained at screening will be reviewed by the CRC to determine patient eligibility. At all subsequent visits, please forward imaging outputs from all devices to the CRC. Please see the CRC manual for further details on image requirements.* ***Please remember to forward all OCT images to the CRC as soon as possible. If OCT imaging data is missing due to a missed visit or a problem with the OCT device, please notify the CRC as soon as possible.*** Note: After randomization, if a patient misses a study visit when ocular images are scheduled, the images should be obtained at the next scheduled visit the patient attends.

Appendix 1
Schedule of Activities (cont.)

Table 1 Screening through Week 48 Assessments (cont.)

[r] Optional OCT-A of both eyes to be conducted at sites with agreed OCT-A capability.

[s] Optional ICGA of both eyes performed at sites with agreed ICGA capability. ICGA should be performed after laboratory samples are obtained and, *if images are taken sequentially,* after all other imaging has been performed. *If standard of care at a site, it is acceptable to perform ICGA in parallel with FFA.*

[t] Assessment of disease activity should be conducted per the specified criteria outlined in Section 3.1.1.4.

[u] The finger counting test should be conducted within 15 minutes of study drug or sham administration for the study eye only.

[v] Post-treatment 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 *at* 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 should be used throughout the study period.

[w] 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, all adverse events will be reported until 28 days after the final dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event(s) that are believed to be related to prior administration of study treatment. 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.

[x] All medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment (the Day 1 visit) until 28 days after the final dose of study drug should be recorded.

[y] 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 ET visit.

Appendix 1
Schedule of Activities (cont.)

Table 2 Week 52 through Week 112 Assessments

	Visit Week																
	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	
Day (Visit window)	364 (±7)	392 (±7)	420 (±7)	448 (±7)	476 (±7)	504 (±7)	532 (±7)	560 (±7)	588 (±7)	616 (±7)	644 (±7)	672 (±7)	700 (±7)	728 (±7)	756 (±7)	784 (±7) [a]	ET [b] (≥28)
Targeted physical examination [c]																x	x
Vital signs [d]			x													x	x
NEI VFQ-25 [e]			x													x	x
BCVA [f]	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x
Low-luminance BCVA			x													x	
Pre-treatment IOP [g]	x	x	x	x	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	x	x	x	x
Optional aqueous humor sample [i]				x	x	x	x										x
Optional vitreous humor sample [j]	If elective vitrectomy is performed [j]																
Optional PK plasma sample (if vitreous humor sample is collected) [j]	*If elective vitrectomy is performed and vitreous humor sample collected* [j]																
Plasma PK sample [k]							x									x	x
Plasma PD sample [k]							x									x	x
Plasma sample for ADAs [k]							x									x	x
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

Table 2 Week 52 through Week 112 Assessments (cont.)

	Visit Week																
	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	
Day(s) (Visit window)	364 (±7)	392 (±7)	420 (±7)	448 (±7)	476 (±7)	504 (±7)	532 (±7)	560 (±7)	588 (±7)	616 (±7)	644 (±7)	672 (±7)	700 (±7)	728 (±7)	756 (±7)	784 (±7) [a]	ET [b] (≥28)
Indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
OCT [l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Optional OCT-A [l, m]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
FFA [l]			x													x	x
CFP [l]			x													x	x
Optional ICGA [l, n]			x													x	
Administration of study treatment	x	x	x	x	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	x	x	x	x		
Post-treatment IOP [p]	x	x	x	x	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	x	x	x	x
Concomitant medications [r]	x	x	x	x	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	x	x	x	x

ADA = anti-drug antibody; BCVA = best-corrected visual acuity; CFP = color fundus photograph; eCRF = electronic Case Report Form; ET = early termination; FFA = fundus fluorescein angiography; ICGA = indocyanine green angiography; IOP = intraocular pressure; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT = optical coherence tomography OCT-A = optical coherence tomography–angiography; PD = pharmacodynamic; PK = pharmacokinetic; VA = visual acuity.

Appendix 1
Schedule of Activities (cont.)

Table 2 Week 52 through Week 112 Assessments (cont.)

Notes: There must be a minimum of 21 days between all study visits occurring from Week 4 through Week 108. All assessments should be performed prior to dosing, unless otherwise specified. Standard-of-care treatment for nAMD in the fellow eye may be covered by the Sponsor only as long as the patient remains in the study (for details, refer to Section 4.4.2).

[a] The Week 112 visit must occur ≥28 days and <35 days after the actual date of the Week 108 visit.

[b] Patients who discontinue from the study early but have not withdrawn consent should return for an ET visit 28 days following the last 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. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

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

[e] To be administered by the masked site staff (except for the VA examiner) prior to any other visit assessments being performed on that day.

[f] To be performed prior to other ocular assessments. Perform the assessments prior to dilating the eyes.

[g] The same method should be used throughout the study period. Perform *measurements* prior to dilating the eyes.

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

[i] If a patient consents to collection of optional aqueous humor sample, collect the sample at the indicated timepoints prior to study treatment administration. Not applicable for a site that has not been granted approval by a site's Institutional Review Board or Ethics Committee. The sample at ET is not required if there are any safety concerns.

[j] If elective vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. A PK blood sample (for plasma preparation) should also be collected and shipped to the Sponsor. Vitreous humor samples will be analyzed primarily for faricimab concentrations or aflibercept concentrations. The remaining samples may be analyzed for VEGF and Ang-2 concentrations, and possibly other biomarkers.

Appendix 1
Schedule of Activities (cont.)

Table 2 Week 52 through Week 112 Assessments (cont.)

[k] Obtain prior to FFA (if applicable) and prior to study treatment.

[l] *Please forward imaging outputs from all devices to the CRC. Please see the CRC manual for further details on image requirements.* ***Please remember to forward all OCT images to the CRC as soon as possible, particularly from Week 60 onwards when images need to be read and data submitted to IxRS before the next study visit. If OCT imaging data is missing due to a missed visit or a problem with the OCT device, please notify the CRC as soon as possible so that they may update the IxRS system accordingly.*** Note: If a patient misses a study visit when ocular images are scheduled, the images should be obtained at the next scheduled visit the patient attends.

[m] Optional OCT-A of both eyes to be conducted at sites with agreed OCT-A capability.

[n] Optional ICGA of both eyes performed at sites with agreed ICGA capabilities. ICGA should be performed after laboratory samples are obtained and *if images are taken sequentially,* after all other imaging has been performed. *If standard of care at a site, it is acceptable to perform ICGA in parallel with FFA.*

[o] The finger counting test should be conducted within 15 minutes of study drug or sham administration for the study eye only.

[p] Post-treatment IOP measurement to be conducted in the study eye only within 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 should be used throughout the study period.

[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, all adverse events will be reported until 28 days after the final dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event(s) that are believed to be related to prior administration of study treatment. 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] All medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment (the Day 1 visit) until 28 days after the final dose of study drug should be recorded.

[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 ET visit.

Appendix 2
Unscheduled Safety Assessment Visit

Assessments [a]
Vital signs (blood pressure, respiration rate, pulse, and temperature)
Hematology, serum chemistry panel, and coagulation [b]
Best-corrected visual acuity (assessed at a 4-meter starting distance) [c]
Slitlamp examination
Dilated binocular indirect high-magnification ophthalmoscopy *FFA, ICGA (if applicable), and OCT imaging (if required)*
IOP [d]
Adverse events [e]
Concurrent ocular procedures
Concomitant medications

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] Hematology includes hemoglobin, hematocrit, quantitative platelet count, RBC counts, WBC counts, and differentials, including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute. Serum chemistry panel includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, ALP, AST, ALT, and uric acid. Coagulation includes activated partial thromboplastin time and prothrombin time.

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

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

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

Appendix 3
Grading Scale for Assessment of Anterior Chamber Flare or Cells and Vitreous Cells

Table 1 Grading Scale for Anterior Chamber Flare or Cells

Grade	Description
	Flare
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)
	Cells [a]
Grade	Number of Cells in Field
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.

Appendix 3
Grading Scale for Assessment of Anterior Chamber Flare or Cells and Vitreous Cells (cont.)

Table 2 Grading Scale for Vitreous Cells

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

REFERENCES

Foster CS, Kothari S, Anesi SD, et al. The Ocular and Uveitis Foundation preferred practice patterns of uveitis management. Surv Opthalmol 2016;61:1–17. doi: 10.1016/j.survophthal.2015.07.001. Epub: 9 July 2015.

Appendix 4
Best-Corrected Visual Acuity Testing

SCOPE

The best-corrected visual acuity (BCVA) assessment must be conducted before pupil dilation. BCVA will be measured by trained and certified personnel at the study sites. 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

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 VA examination room also must be certified before any VA examinations are performed.

Appendix 5
Low-Luminance Best-Corrected Visual Acuity Testing

There are the same requirements as the best corrected visual acuity described in Appendix 4; however, low-luminance best-corrected visual acuity will be measured by placing a 2.0-log-unit neutral density filter (Kodak Wratten 2.0 neutral density filter) over the best correction for that eye and having the participant read the normally illuminated Early Treatment Diabetic Retinopathy Study chart.

Appendix 6
Color Fundus Photography

SCOPE

Monoscopic color fundus photographs will be obtained from both eyes by trained personnel at the study sites. Fundus photography will be performed at the intervals specified in the schedule of activities (see Appendix 1). Analysis (if applicable) of fundus photographs will be performed by the central reading center.

EQUIPMENT

See the central reading center manual.

PROCEDURE

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

Appendix 7
Fundus Fluorescein Angiography and Optional Indocyanine Green Angiography

SCOPE

Fundus fluorescein angiography will be performed on both eyes at the study sites by trained personnel who are certified by the central reading center. The fundus fluorescein angiograms will be obtained at the intervals specified in the protocol (see Appendix 1). *FFA image analysis* will be performed by the central reading center.

Indocyanine green angiography (ICGA) will be performed on both eyes at selected sites with agreed ICGA capabilities by trained personnel who are certified by the central reading center. At applicable sites, the indocyanine green angiograms will be obtained at the intervals specified in the protocol (see Appendix 1). Analysis (if applicable) of indocyanine green angiograms will be performed by the central reading center.

EQUIPMENT

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

Film-based angiography is not acceptable.

DIGITAL IMAGING SYSTEMS AND CERTIFICATION

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

PROCEDURES

The central reading center 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. SD-OCT imaging will be performed for each patient at the intervals specified in the protocol (see Appendix 1).

The SD-OCT images of both eyes will be obtained at protocol-specified visits and will be forwarded to the central reading center.

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

EQUIPMENT

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

Note: Certain *swept source* (SS)-OCT machines may be acceptable to use; see the central reading center manual for further details.

PROCEDURES AND CERTIFICATION

The central reading center will provide the study manual and training materials. 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 or aflibercept concentrations (pharmacokinetics), anti-faricimab antibodies, residual 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 4.5.5* 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. The aqueous humor sample collection consists of an anterior chamber paracentesis (removing approximately 0.1 mL of fluid from the anterior chamber of the eye).

The anterior chamber paracentesis will be performed by a qualified unmasked physician by placing a drop of topical anesthetic on the cornea, passing a 30-gauge needle through the limbus into the anterior chamber, and removing 0.1 mL of aqueous fluid.

Samples will be collected with the kit provided by central laboratory and shipped on dry ice as specified in the central laboratory manual as soon as possible after the draw.

For administration of study treatment following the collection of the aqueous humor sample, use of additional anesthesia may be necessary prior to study treatment administration.

OPTIONAL UNSCHEDULED COLLECTION OF VITREOUS HUMOR SAMPLE COLLECTION

Elective vitrectomy is not allowed in the study eye during a patient's study participation. However, if the surgery is medically necessary and the patient consents, a vitreous sample can be collected 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.

Appendix 9
Biological Sample Collection and Shipping Instructions (cont.)

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 concentrations or aflibercept concentrations. The remaining samples may be analyzed for VEGF and Ang-2 concentrations, as well as possibly other biomarkers.

Unless the patient gives specific Research Biosample Repository consent for his or her remaining samples to be stored for optional exploratory research (see Section 4.5.9.5), 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 Function 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.

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Appendix 10
National Eye Institute 25-Item Visual Function Questionnaire (cont.)

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.

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Appendix 10
National Eye Institute 25-Item Visual Function Questionnaire (cont.)

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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Appendix 10
National Eye Institute 25-Item Visual Function Questionnaire (cont.)

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**

Appendix 10
National Eye Institute 25-Item Visual Function Questionnaire (cont.)

9. Because of your eyesight, how much difficulty do you have <u>going down steps, stairs, or curbs in dim light or at night</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**

10. Because of your eyesight, how much difficulty do you have <u>noticing objects off to the side while you are walking along</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**

11. Because of your eyesight, how much difficulty do you have <u>seeing how people react to things</u> 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**

Appendix 10
National Eye Institute 25-Item Visual Function Questionnaire (cont.)

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**

Appendix 10
National Eye Institute 25-Item Visual Function Questionnaire (cont.)

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

Appendix 10
National Eye Institute 25-Item Visual Function Questionnaire (cont.)

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**

Appendix 10
National Eye Institute 25-Item Visual Function Questionnaire (cont.)

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**

Appendix 10
National Eye Institute 25-Item Visual Function Questionnaire (cont.)

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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Appendix 10
National Eye Institute 25-Item Visual Function Questionnaire (cont.)

SUBSCALE: NEAR VISION

A1. Wearing glasses, how much difficulty do you have <u>reading the small print in a telephone book, on a medicine bottle, or on legal forms</u>? 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 <u>figuring out whether bills you receive are accurate</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**

Appendix 10
National Eye Institute 25-Item Visual Function Questionnaire (cont.)

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**

Appendix 10
National Eye Institute 25-Item Visual Function Questionnaire (cont.)

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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