Official Title: A Phase IIIb, Open-Label, Single-Arm Study in Patients With Neovascular Age-Related Macular Degeneration or Diabetic Macular Edema to Evaluate the Safety of the 6-mg Faricimab Prefilled Syringe

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PROTOCOL

PROTOCOL TITLE:	**A PHASE IIIb, OPEN-LABEL, SINGLE-ARM STUDY IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION OR DIABETIC MACULAR EDEMA TO EVALUATE THE SAFETY OF THE 6-MG FARICIMAB PREFILLED SYRINGE**
PROTOCOL NUMBER:	GR43742
VERSION NUMBER:	1
TEST COMPOUND:	Faricimab (RO6867461)
STUDY PHASE:	Phase IIIb
EUDRACT NUMBER:	Not applicable.
IND NUMBER:	119225
NCT NUMBER:	To be determined
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE IIIb, OPEN-LABEL, SINGLE-ARM STUDY IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION OR DIABETIC MACULAR EDEMA TO EVALUATE THE SAFETY OF THE 6-MG FARICIMAB PREFILLED SYRINGE**
PROTOCOL NUMBER:	GR43742
VERSION NUMBER:	1
TEST COMPOUND:	Faricimab (RO6867461)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE: **A PHASE IIIb, OPEN-LABEL, SINGLE-ARM STUDY IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION OR DIABETIC MACULAR EDEMA TO EVALUATE THE SAFETY OF THE 6-MG FARICIMAB PREFILLED SYRINGE**

STUDY RATIONALE

The purpose of the clinical in-use study is to collect observations on the use of the 6-mg faricimab prefiled syringe (PFS) configuration to administer an intravitreal (IVT) injection to patients with either diabetic macular edema (DME) or neovascular age-related macular degeneration (nAMD) in an actual clinical use environment. Observations will be collected during the preparation and administration of a 6-mg faricimab IVT injection using the PFS configuration in accordance with the Instructions for Use (IFU) in the intended use environment. The PFS configuration consists of the faricimab 6-mg PFS together with the co-packed injection filter needle (IFN).

OBJECTIVES AND ENDPOINTS

The primary objective of this study is to collect observations on healthcare providers (HCPs) using a PFS configuration in an actual clinical use environment to prepare and administer a 6-mg faricimab intravitreal injection to patients with either DME or nAMD and as instructed in the IFU.

No patient-related efficacy or safety endpoints are planned for this study. However, in accordance with Good Clinical Practices (GCPs), adverse events (AEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) occurring during the 7-day study reporting period will be summarized.

OVERALL DESIGN

The 6-mg faricimab PFS clinical in-use study is a Phase IIIb, single-arm, open-label multicenter study in patients with nAMD or DME designed to assess the ability of the intended users, HCPs, to follow the IFU to perform an IVT injection using the 6-mg faricimab PFS configuration per the intended use. The study will collect observations related to the use of the PFS configuration.

The study will be conducted in ophthalmology clinical settings. The focus of the usability observation will be on the HCP teams. The HCP team will consist of a retina specialist and any assistants who participate in any stage of the PFS preparation and administration procedure. Approximately three HCP teams will participate in this study to administer a single IVT injection of 6-mg faricimab PFS (120 mg/mL drug concentration) using the PFS configuration for a total of approximately 35 participants.

All patients will be required to have a current diagnosis of nAMD or DME with at least one eye eligible for 6-mg faricimab IVT injection, at the discretion of the retina specialist. Both previously treated and treatment-naive patients will be eligible for enrollment. Only one eye will be selected as the study eye. If both eyes are eligible, the investigator will determine which eye will be selected for study treatment (study eye).

The same retina specialist may act as the Principal Investigator and the HCP using the PFS configuration to administer faricimab. Alternatively, a sub-investigator may perform the duties of the HCP.

DISCLOSURE STATEMENT

This is a single-group device feasibility study that is not masked.

NUMBER OF PARTICIPANTS

Approximately 35 evaluable patients with nAMD or DME will be enrolled in this study.

Note: "Enrolled" means a participant's or their legally acceptable representative's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

STUDY TREATMENT

The investigational medicinal product for this study is 6-mg faricimab PFS.

Patients will receive a single IVT injection of 0.05 mL of the 120-mg/mL faricimab (6-mg dose) formulation delivered via PFS with a co-packaged injection filter needle.

DURATION OF PARTICIPATION

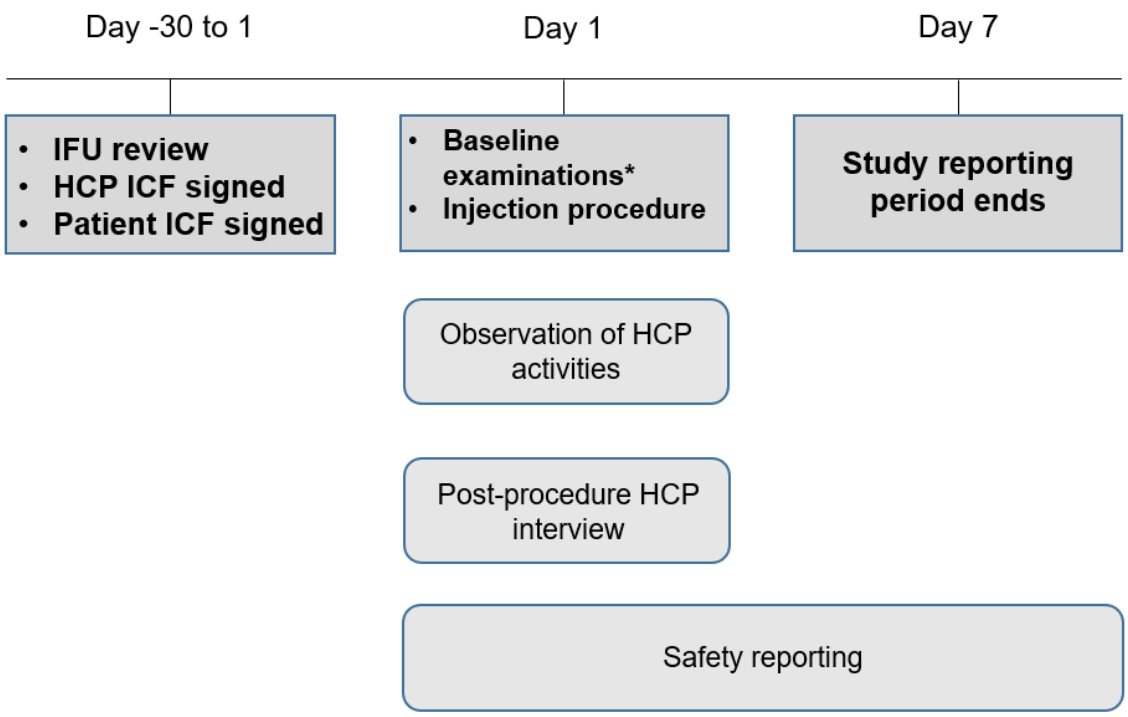
The total duration of study participation for each patient is expected to be approximately 7 days.

INDEPENDENT DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (iDMC) will not be used.

1.2 STUDY SCHEMA

Figure 1 Study Schema



BCVA = best-corrected visual acuity; FPI = first patient in; HCP = health care provider; ICF = Informed Consent Form; IFU = Instructions for Use.

Note: There will be approximately 2–3 HCP teams, with 35 patients in total. Study start corresponds with Day 1 (FPI). Study end is 7 days after the injection in the last patient. The injection procedure (study Day 1 in the schematic) can occur on different calendar days for different HCPs and different patients. HCPs will review the IFU on their own before Day 1 of the study. HCP interviews will be conducted on Day 1.

*Baseline examinations consist of BCVA, slitlamp, and indirect ophthalmoscopy.

1.3 SCHEDULE OF ACTIVITIES

Table 1 Schedule of Activities for Health Care Providers

Health Care Providers				
	Screening	Preparation of Injection Observation	Injection Observation Period	Post-Procedure Interview [a]
Day(s)	−30 to 1	−3 to 1	1	1
Eligibility criteria	x			
IFU review phase		x		
HCP informed consent [b]		x		
Injection procedure and observation of HCP activities			x	
Post-procedure discussion [a]				x

HCP = health care provider; IFU = Instructions for Use.

[a] After each patient procedure, HCPs will be reminded of the complaints procedure (see Appendix 5) to be followed in case any device failures or malfunctions were noted. Further discussion topics may be addressed, if deemed necessary by the human factors observers.

[b] Pre-brief by human factors observers, with HCP informed consent signing (on the morning of Day 1 or afternoon of Day −1).

Table 2 Schedule of Activities for Patients

Patients				
	Screening [a]	Injection Procedure [a]	Safety Telephone Call	Safety Telephone Call
Day(s)	−30 to 1	1	3 (±1)	7 (±1)
Patient informed consent	x			
Review of inclusion and exclusion criteria	x	x		
Demographics	x			
Medical History	x			
Pregnancy test (urine)	x	x		
Baseline examination (BCVA[b], slitlamp exam, indirect ophthalmoscopy)		x		
Injection administration		x		
Study eye predose IOP		x		
Study eye postdose IOP		x		
Finger-counting test [c]		x		
Adverse events		x	x	x
Concomitant medications	x	x	x	x

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; VA = visual acuity.

[a] If screening and injection occur on the same day, assessments listed for both visits should be conducted only once before injection.

[b] BCVA may be measured on any standard VA chart according to local clinical practice. Acceptable charts include ETDRS, Snellen and LogMAR. Refer to Appendix 8 for further details.
Note: in the event that a patient requires an unscheduled safety visit, the same method of VA assessment should be used as the baseline assessment.

[c] Finger counting test will be performed in the study eye within 15 minutes of treatment.

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of the clinical in-use study is to collect observations on the use of the 6-mg faricimab prefiled syringe (PFS) configuration to administer an intravitreal (IVT) injection to patients with either diabetic macular edema (DME) or neovascular age-related macular degeneration (nAMD) in an actual clinical use environment. Observations will be collected during the preparation and administration of a 6-mg faricimab IVT injection using the PFS configuration in accordance with the Instructions for Use (IFU) in the intended use environment.

The PFS configuration consists of the faricimab 6-mg PFS together with the co-packed injection filter needle (IFN).

2.2 BACKGROUND

nAMD 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). Treatment goals are to regain and maintain vision. A key challenge with currently available anti–vascular endothelial growth factor (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). There remains an unmet need for more efficacious and durable treatment.

DME, a complication of diabetic retinopathy (DR), can develop at any stage of the underlying disease of retinal microvasculature (Fong et al. 2004) and is a major cause of vision loss in working-age individuals. Despite advances with the anti-VEGF approach in DME, a significant percentage of patients do not achieve normal vision or have adequate vision required to obtain a driver's license, suggesting that anti-VEGF treatment alone does not address all the pathways underlying DME pathology.

Faricimab is an intravitreously administered, humanized bispecific immunoglobulin G1 (IgG1) antibody that selectively binds to angiopoietin-2 (Ang-2) and VEGF-A. Vitreous concentrations of both Ang-2 and VEGF-A are upregulated in patients with diabetic eye disease, and to a lesser extent, in patients with nAMD. Therefore, selective neutralization of both Ang-2 and VEGF may better stabilize pathological ocular vasculature in addition to further reducing leakage compared with anti-VEGF monotherapy. This may result in further improvement of retinal function and durability of response for patients with DME, DR, and nAMD. As of May 2022, the vial product configuration of faricimab (under the tradename Vabysmo™) has been approved in the United States, United Kingdom, Canada, Japan, Thailand, Switzerland, and the United Arab Emirates for the treatment of nAMD and DME by injection into the eye.

The 6-mg faricimab PFS will contain the same formulation and concentration of the drug as supplied in the faricimab vial that has been used during Phase III clinical development. The vial will be replaced by a siliconized 0.5-mL glass syringe with extended finger flange and coupled plunger rod, with a rubber tip cap closures. The outside surface of the syringe will be sterilized. There is no change in the faricimab solution composition. The 30 G × 1/2-inch injection filter needle with extra thin wall is copackaged- with the PFS. The configuration would provide an alternative to a vial kit and is anticipated to provide a more convenient system for IVT injection.

Detailed information on faricimab is provided in the Faricimab Investigator's Brochure and information about device use in the Instructions for Use.

2.3 BENEFIT–RISK ASSESSMENT

Data from the Phase I (BP28936), Phase II (BP29647 [AVENUE], CR39521 [STAIRWAY], and (BP30099 [BOULEVARD]), and Phase III (GR40349 [YOSEMITE], GR40398 [RHINE], GR40306 [TENAYA], and GR40844 [LUCERNE]) studies provide evidence of efficacy, safety, and tolerability for the use of 6-mg IVT injections of faricimab for patients with nAMD and DME. The safety and efficacy of the 6-mg faricimab PFS configuration is expected to be the same as that for the vial configuration, which has been used during clinical development, as the administration route and technique will remain unchanged.

Refer to Appendix 3 for information on anticipated risks for faricimab and risk mitigation measures, including guidelines for managing adverse events associated with faricimab.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of faricimab may be found in the Investigator's Brochure. An assessment was conducted to determine whether there is any impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment of this study protocol, including, but not limited to, the patient population under study and study treatment being evaluated. Based on that assessment, no impact is anticipated and the existing safety monitoring, management guidelines, and risk-mitigation measures provided in the study protocol are considered adequate.

Taking into account the efficacy data in patients with nAMD and DME, the safety profile of faricimab and that the safety and efficacy of 6-mg faricimab PFS configuration is expected to be the same as that for the vial configuration, the benefit–risk ratio is expected to be acceptable.

3. OBJECTIVES AND ENDPOINTS

The primary objective of this study is to collect observations on healthcare providers (HCPs) using a PFS configuration in an actual clinical use environment to prepare and

administer a 6-mg faricimab intravitreal injection to patients with either DME or nAMD and as instructed in the IFU.

No patient-related efficacy or safety endpoints are planned for this study. However, in accordance with Good Clinical Practices (GCPs), adverse events (AEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) occurring during the 7-day study reporting period will be summarized.

4. STUDY DESIGN

4.1 OVERALL DESIGN

4.1.1 Description of Study

The 6-mg faricimab PFS clinical in-use study is a Phase IIIb, single-arm, open-label, multicenter study in patients with nAMD or DME designed to assess the ability of the intended users, HCPs, to follow the IFU to perform an IVT injection using the 6-mg faricimab PFS configuration per the intended use. The study will collect observations related to the use of the PFS configuration.

The study will be conducted in ophthalmology clinical settings. The focus of the usability observation will be on the HCP teams. The HCP team will consist of a retina specialist and any assistants who participate in any stage of the PFS preparation and administration procedure. Approximately three HCP teams will participate in this study to administer a single IVT injection of 6-mg faricimab PFS (120-mg/mL drug concentration) using the PFS configuration for a total of approximately 35 participants.

All patients will be required to have a current diagnosis of nAMD or DME with at least one eye eligible for 6-mg faricimab IVT injection, at the discretion of the retina specialist. Both previously treated and treatment-naive patients will be eligible for enrollment. Only one eye will be selected as the study eye. If both eyes are eligible, the investigator will determine which eye will be selected for study treatment (study eye).

The same retina specialist may act as the Principal Investigator and the HCP using the PFS configuration to administer faricimab. Alternatively, a sub-investigator may perform the duties of the HCP.

4.1.2 Overview of Study Design and Procedure

A study schema is provided in Section 1.2 (see Figure 1). The schedules of activities are provided in Section 1.3 (see Table 1 and Table 2).

The study will be set up to enable usability (human factors [HF]) observations related to the use of the PFS configuration. This will be performed by the two HF observers who will be present at the study sites to observe each injection procedure. In the 30 days prior to (or including) Day 1, patients will be screened for their eligibility to participate in the trial.

As part of the information package sent in preparation for the study, each clinical study site will be provided with the IFU. Approximately 3 days prior to Day 1, HCPs will be expected to familiarize themselves with the documentation in advance and will be asked to confirm that they have read the IFU by signing an acknowledgement on Day 1. The HF observer and the additional observer will not provide a demonstration or training to HCP participants.

The HF observers will pre-brief the HCPs prior to the HF observations. When the patient is ready, the HF observers will be introduced to the patient in the administration room. The HF observers will be positioned such that they can clearly observe the entire preparation and administration process. The HCP team (i.e., retina specialist alone or retina specialist with assistant/technician, as per local procedure) will be asked to open the folding box only when the HF observers are present and to perform all preparation and administration steps in view of the HF observers. The PFS configuration should be prepared for use immediately prior to the injection, as described in the IFU. The HF observers will remain at a distance specified by the HCPs or facility and will not interrupt or interfere with the procedure. The HF observers will document HCP's performance using an assessment checklist and all administration procedures will be recorded on video to facilitate subsequent HF analysis of observations.

HF observers will ask for good visibility of all activities. To enable assessment of dose setting accuracy, HCPs will be asked to pause briefly during every procedure in order to turn and show the set dose to the observers for a closer look and brief video recording.

Should the HF observers see any HCP actions of potential safety concerns related to safe PFS use, they will not intervene, as it is considered the responsibility of the HCPs to ensure patient safety based on clinical judgement. However, participating HCPs are expected to remain aware of any potential safety concerns (should they arise due to PFS use) and take preventative actions.

Following the completion of each IVT injection, the HF observers will conduct a follow-up interview with the HCPs to discuss observations. No questions will be asked in the presence of patients or other site staff. Interview questions will focus on identifying reasons for observed actions. HCPs will be reminded of the complaints procedure for reporting observations of device failures or malfunctions (Appendix 5).

See Table 1 and Table 2 for the schedules of activities performed by the HCP during the study.

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

Patients with nAMD and DME have been selected for inclusion in this study given that these indications are being investigated in the Phase III program (Studies GR40306 and GR40844 in nAMD, and Studies GR40349 and GR40398 in DME). As of May 2022, the

faricimab (under the tradename Vabysmo™) vial product configuration has been approved in the United States, United Kingdom, Canada, Japan, Thailand, Switzerland, and the United Arab Emirates for the treatment of nAMD and DME by injection into the eye. Licensing applications are currently under health authority review for faricimab in these indications in other countries.

4.2.2 Rationale for Human Factors Observations

The purpose of the usability observations is to observe the use of the PFS configuration in an actual clinical use environment to assess if there are any safety concerns remaining related to the future commercial use of the device components. At the time of the study, the PFS configuration (i.e., its device components) will have gone through full technical development, including design validation to ensure the safety of the PFS and the IFN. However, the PFS configuration will not have received market approval at this time.

4.3 JUSTIFICATION FOR DOSE

The 6-mg dose of faricimab in the PFS has been selected to align with the dose that has been studied in the Phase III program in patients with nAMD (Studies GR40306 and GR40844) and DME (Studies GR40349 and GR40398). The formulation, concentration, and intended injection volume will also remain the same as those used in the Phase III program.

4.4 END OF STUDY DEFINITION

A patient is considered to have completed the study if he or she has completed all phases of the study, including the safety telephone call 7 days after administration of the PFS injection.

The end of this study is defined as the date when approximately 35 patients have received injections, all HCP participants have completed their interviews with the HF observers, and the 7-day (±1 day) reporting period after the PFS injection in the last patient has passed. It is expected that the duration of the investigation (length of study plus enrollment period) will be approximately 1.5 months.

In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

The total duration of study participation for each patient is expected to be approximately 7 days.

5. STUDY POPULATION

Approximately 35 patients with nAMD or DME will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

5.1.1 Inclusion Criteria for Health Care Providers

Criteria necessary for a retina specialist to participate in the clinical in-use study are the following:

- Valid medical license to practice in the United States
- Previous experience performing faricimab IVT injections using the vial and syringe procedure

  Note that only the retina specialist or suitably-qualified retina fellows are allowed to perform the injection.
- Ability to pre-screen and recruit patients with nAMD or DME indicated for faricimab IVT therapy within a reasonable time frame (≤30 days)
- Ability to schedule the required baseline examinations and faricimab PFS injection procedures, and undergo clinical in-use evaluation within a relatively short time frame (≤7 days)

All additional HCPs (i.e., retina specialists nurses, assistants, or technicians) involved in the faricimab PFS preparation or injection procedure will be included in the study observations and the post-procedure interviews. All participating retina specialists and additional HCPs will be asked to sign an informed consent form regarding the observations to be conducted before commencing with injection preparation.

5.1.2 Inclusion Criteria for Patients

Patients are eligible to be included in the study only if all of the following criteria apply:

- Signed Informed Consent Form
- Age ≥18 years at the time of signing Informed Consent Form
- Willing and able to comply with clinic visits and study-related procedures (e.g., video recording during the injection procedure)
- For female patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agree to refrain from donating eggs, as defined below:

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

  A female patient is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian

tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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

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

- Patients who have a confirmed diagnosis of nAMD (any subtype) or DME in one or both eyes by the study site investigator (only one eye will be selected as the study eye, as determined by the retina specialist) with onset at any time prior to study start
- Patients whose study eye is deemed to be indicated for faricimab IVT treatment at the discretion of the retina specialist
- Patients with historical optical coherence tomography (OCT) data available for the study eye within 30 days prior to Day 1.

5.2 EXCLUSION CRITERIA

5.2.1 Exclusion Criteria for Patients

Patients are excluded from the study if any of the following criteria apply:

- Pregnancy or breastfeeding, or intention to become pregnant during the study or within 3 months after the final dose of faricimab

  Female patients of childbearing potential must have a negative urine pregnancy test result during screening and on Day 1.
- Requirement on Day 1 for continuous use of any medications and treatments indicated in Section 6.8.2, Prohibited Therapy
- 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
- Stroke (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab PFS injection, study-related procedure preparations, or any of the anesthetic and antimicrobial preparations used by a participant during the study
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a condition that

contraindicates the use of faricimab or renders the patient at high risk for treatment complications in the opinion of the investigator

- Uncontrolled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg while a patient is at rest)
- Systemic treatment for suspected or active systemic infection on Day 1
- Patients legally blind in the study eye on Day 1 (legal blindness: Best-corrected visual acuity [BCVA] of 20/200 or less).
- History of or any current clinically relevant intraocular inflammation or ocular inflammatory reaction (any grading from trace and greater is excluded), including non-infectious uveitis or infectious uveitis, or sterile inflammatory reaction after previous IVT injections with any agent in either eye
- Suspected or active ocular or periocular infection in either eye on Day 1
- History of or any current indication of excessive bleeding and recurrent hemorrhages, including any prior excessive intraocular or subconjunctival bleeding or hemorrhages after IVT injection or intraocular procedures in either eye
- Uncontrolled glaucoma in the study eye
- Treatment with any IVT injection in the study eye within the 27 days prior to Day 1
- Any invasive intraocular surgery, prior long-acting therapeutic agent, or ocular drug release device implantation (approved or investigational) in the study eye at any time during the 3 months prior to Day 1
- Treatment with panretinal photocoagulation, laser retinopexy or macular (focal, grid, or micropulse) laser in the study eye within one month prior to Day 1

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, patients must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) cannot be re-screened. The investigator will record reasons for screen failure in the screening log (see Section 8).

6. STUDY TREATMENT, OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN, AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study patient according to the study protocol.

The investigational medicinal product (IMP) for this study is 6-mg faricimab PFS.

6.1 STUDY TREATMENTS ADMINISTERED

Table 3 provides a description of the assigned study treatment for this study.

Table 3 Study Treatment Description

	Faricimab 6-mg PFS with IFN
Use	Experimental
Drug form	Solution for injection
Unit dose strength(s)	120 mg/mL
Dosage level(s)	6 mg
Formulation(s)	Refer to the Pharmacy manual and/or Investigator's Brochure
Packaging	0.5 mL single-use PFS
Labeling	Per local requirements
Route of administration	IVT injection
Source	Sponsor

IFN = injection filter needle; IVT = intravitreal, PFS = prefilled syringe.

Participants will receive a single IVT injection of 0.05 mL of the 120-mg/mL faricimab (6-mg dose) formulation delivered by means of a PFS with a co-packaged IFN at the Day 1 visit by a retina specialist. The retina specialist will conduct post-treatment observation according to standard clinical practice. In addition, all participants will be instructed to immediately contact their retina specialist if their eye becomes red, sensitive to light, painful, or develops a change in vision any time after the injection, including after the reporting period ends.

Any overdose or incorrect administration of study drug will be noted on the Adverse Event electronic Case Report Form (eCRF) as a special situation (see Appendix 2). Any adverse events associated with an overdose or incorrect administration of study drug will also be noted on the Adverse Event reporting form by the Investigator (see Appendix 2).

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

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

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMP supplied by the Sponsor by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for the IMP received and that any discrepancies have been reported and resolved before use of the IMP. The IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

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

The IMP will be returned to the Sponsor with the appropriate documentation, as per agreement.

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

Refer to the Instructions for Use and/or the pharmacy manual for information on IMP preparation, storage, handling, and accountability.

Of note, each single-dose PFS will provide a usable amount to deliver a single dose of 6 mg faricimab in a volume of 0.05 mL via IVT injection, using the co-packaged IFN. The PFS and co-packaged IFN utilized in this study are fully representative of the presentation intended for commercialization.

6.3 TREATMENT ASSIGNMENT

This is a non-randomized, open-label study. After eligibility has been established for a patient and written informed consent has been obtained, the study site will obtain the patient's identification number from the Sponsor. All participants will receive 6-mg faricimab with the PFS configuration.

6.4 STUDY TREATMENT COMPLIANCE

When patients are dosed at the site, they will receive study treatment directly from the Investigator or designee, under medical supervision. The date and time of dose administration in the clinic will be recorded in the source documents and on the eCRF. The dose of study treatment and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Appendix 2.

6.5 DOSE MODIFICATION

Modification of the 6-mg faricimab PFS dose is not permitted.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

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

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

- The participant 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 participant
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

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

- The Roche IMP is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant) and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for nAMD or DME
- The Sponsor has reasonable safety concerns regarding the IMP as a treatment for nAMD or DME

- Provision of the Roche IMP is not permitted under the laws and regulations of the participant's country

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

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

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 2.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event, serious adverse event, or laboratory abnormalities for at least 5 weeks.

Doses higher than the recommended dosing regimen have not been studied. Overdosing with greater than recommended injection volume may increase intraocular pressure (IOP). In the event of an overdose, IOP should be monitored and, if deemed necessary by the treating physician, appropriate treatment should be initiated.

6.8 CONCOMITANT THERAPY

Any medication (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 until the conclusion of the patient's study participation must be recorded on the Concomitant Medications eCRF along with the following information:

- Reason for use
- Dates of administration, including start and end dates

The Medical Monitor may be consulted if there are any questions relating to concomitant or prior therapy.

6.8.1 Permitted Therapy

At the discretion of the Investigator, participants may continue to receive medications and standard treatments administered for other conditions, with the exceptions listed in Section 6.8.2.

Of particular note:

- In the event that a patient's fellow eye require treatment for nAMD or DME, treatment is permitted.

- The onset of increased IOP and/or glaucoma in the study eye during a patient's study participation should be treated as clinically indicated.
- The use of topical antimicrobials, anesthesia, and steroids in the study eye and in the fellow eye is permitted at the discretion of the investigator.

6.8.2 Prohibited Therapy

At the discretion of the investigator, patients may continue to receive all medications and standard treatments administered for other conditions. However, after the study drug administration on Day 1 the following medications and treatments are prohibited during study participation:

- Systemic anti-VEGF therapy
- IVT anti-VEGF agents in the study eye
- Planned (non-emergency) ocular or systemic surgical interventions
- Concurrent use of any macular photocoagulation or photodynamic therapy with verteporfin in the study eye
- Other experimental therapies (except those comprising vitamins and minerals)

In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

7. DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1 .

7.1 DISCONTINUATION OF STUDY TREATMENT

Discontinuation of study treatment is not applicable because each patient will receive only one study treatment administration.

7.2 PATIENT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A patient may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

The patient will be permanently discontinued both from the study treatment and from the study at that time.

If a patient withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Patients who withdraw from the study will be replaced.

7.3 PATIENTS LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he or she repeatedly is unable to be contacted by the study site.

The following actions must be taken if a patient fails to be contactable by the study site:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule. If the patient is unable or unwilling to comply with study visits, site personnel should assess reasons the patient is unable or unwilling to participate, and determine if there are ways to support patient participation.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (when possible, three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- In the event that the patient continues to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained from the patients before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. Informed Consent Forms for the HCPs participating in the HF observations will be collected and maintained by the HF observers during their visits at the study sites, and need to be signed before commencing to unpack and prepare the device for use.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a detailed record of all

patients screened to document eligibility or record reasons for screening failure, as applicable.

Medical history and baseline conditions, including clinically significant diseases, surgeries, reproductive status, and smoking history will be recorded at baseline. Any medications (including over-the-counter or prescription medicines, vaccines, vitamins, and/or herbal supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded at baseline. Demographic data, including age, sex, and self-reported race or ethnicity, will also be recorded. At the time of each follow-up, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

HF observations will be conducted by an HF specialist vendor, who will audio- and video-record the observations and will record their observations on prepared paper observation forms in ink (hardcopies). These are original documents and will be handled, maintained, and archived by the HF specialist vendor. Similarly, the original digital recorded interview sessions will be maintained and archived by the HF specialist vendor, as well as the HCP Informed Consent Forms. All information managed by the HF specialists must be traceable to these source documents and source records.

8.1 EFFICACY ASSESSMENTS

No efficacy assessments will be performed during this study.

8.2 SAFETY ASSESSMENTS

8.2.1 Ocular Assessments

IOP will be measured in the study eye predose on Day 1.

Following study treatment, patients will remain at the clinic for approximately 30 minutes.

Finger-counting test followed by hand motion and light perception tests (when necessary) will be performed within approximately 15 minutes post-study treatment in the study eye.

IOP will be measured in the study eye after treatment. If there are no safety concerns following the study treatment, the participant will be allowed to leave the clinic. If the IOP value is of concern to the Investigator, the participant will remain in the clinic and be managed in accordance with the Investigator's clinical judgement. The same device must be used to measure pretreatment IOP and posttreatment IOP.

If applicable, the adverse event and the adverse event treatment (if applicable) will be reported on the appropriate eCRFs.

See Table 2 for the schedule of assessments performed during the study.

If warranted during the study duration (7 days), patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 9).

8.2.2 Pregnancy Testing

The schedule for pregnancy testing for enrolled female patients is outlined in Table 2 of Section 1.3 and will be conducted as outlined in Appendix 6.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 2.

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the patient to discontinue the study (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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 (see Appendix 2). All other medical occurrences deemed significant by the investigator that begin before the start of study treatment but after obtaining informed consent will be recorded on the relevant medical history eCRF, not the Adverse Event eCRF.

All adverse events (ocular and non-ocular) will be reported from the start of treatment until Day 7 after the faricimab PFS injection procedure (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

The 7-day reporting period has been determined based on the expected timing of potential procedure-related events. In addition, all patients will be instructed to immediately contact their retina specialist if their eye becomes red, sensitive to light, painful, or develops a change in vision any time after the injection, including after the reporting period ends.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a patient has been

discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each patient at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the patient is lost to follow-up (as defined in Section 7.3), or the patient withdraws consent. Further information on follow-up procedures is provided in Appendix 2.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

Drug	Document
Faricimab	Faricimab Investigator's Brochure

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.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of faricimab.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 4. 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.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 2.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

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 the investigator becomes aware of the event; see Section A2–5 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 A2–7.6)
- Suspected transmission of an infectious agent by a study treatment, 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 treatment is suspected.

- Sight-threatening adverse events: An adverse event is considered to be sight-threatening and should be reported expeditiously if it meets one or more of the following criteria:
  - It causes a decrease of ≥30 letters in visual acuity (VA) score using Early Treatment Diabetic Retinopathy Study (ETDRS) or greater than 0.6 using LogMAR or more than 6 lines using Snellen (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 A2-7 and Appendix 7 for intraocular inflammation terms and definitions).

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.

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 3 .

8.3.9 Device Product Complaints (Including Failures and Malfunctions)

In this study, 6-mg faricimab single-use PFS with co-packaged injection filter needle is considered a drug-device combination product. The biologic constituent part is

faricimab. The device constituent parts are the prefilled syringe with the extended finger flange and the coupled plunger as well as and the injection filter needle. The investigator must report all medical device complaints (including failures and malfunctions) and any associated adverse events to the Sponsor, as described in Appendix 5 .

8.3.10 Medical Monitors and Emergency Medical Contacts

Contact Information for All Sites

Medical Monitor (Primary): [redacted], M.D., Ph.D.
Mobile Telephone No.: [redacted]

Medical Monitor (Secondary): [redacted], M.D., Ph.D.
Mobile Telephone No.: [redacted]

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

8.4 PHARMACOKINETICS

Pharmacokinetic parameters will not be evaluated in this study.

8.5 PHARMACODYNAMICS

Pharmacodynamic biomarker assessments will not be performed in this study.

8.6 GENETICS

Genetic biomarker assessments will not be performed in this study.

8.7 BIOMARKER ASSESSMENTS

Biomarker assessments will not be performed in this study.

8.8 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed in this study.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health economics and medical resource utilization assessments will not be performed in this study.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

There are no additional assessments and procedures requiring separate consent or performed only at participating sites.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested for this study.

9.2 SAMPLE SIZE DETERMINATION

Because the study aims to assess the safety of 6-mg faricimab PFS and no formal hypothesis testings are planned, there are no formal statistical considerations or analysis plan used to determine sample size. With approximately 12 patients per HCP team and at minimum three teams of HCPs, approximately 35 patients (at minimum 30 patients) with either nAMD or DME will enable evaluation of the safety of the 6-mg faricimab PFS per intended use.

9.3 SAFETY ANALYSES

Descriptive statistics will be used to describe the incidence and severity of ocular and non-ocular adverse event data collected during the study and will also be summarized by the Investigator.

9.4 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study treatment administration and discontinuation from the study, along with the reason for study discontinuation, will be summarized by the Investigator in the final study report. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized.

9.5 INTERIM ANALYSIS

No interim analysis is planned.

9.6 INDEPENDENT DATA MONITORING COMMITTEE

There is no independent Data Monitoring Committee for this study.

10. REFERENCES

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1. REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, patient Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study patients.

The investigator will be responsible for the following:

- 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
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Regulation (E.U.) No. 536/2014 (E.U. sites only), and all other applicable local regulations

A1–2. 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 definition of end of study in Section 4.4).

A1–3. INFORMED CONSENT PROCESS

Health Care Provider Consent

Consent forms will be provided in English and must be signed and dated by the HCP before his or her participation in the study.

Patient Informed Consent

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the patient or his or her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or the patient's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the patient or the patient’s legally authorized representative.

A1–4. DATA PROTECTION

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; the patient's name or any information that would make the patient identifiable will not be transferred.

Patients must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to patients, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Patients must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5. ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring. TEAM Consulting will observe, record, and analyze human factors observations on behalf of the Sponsor.

Approximately 3 sites in the United States will participate to enroll approximately 35 patients. An interactive voice or web-based response system (IxRS) will not be used. Sites will receive logs to manage patient enrollment and study IMP accountability.

Electronic data capture will be used and sites will report and submit data to the Sponsor though this system.

A1–6. DISSEMINATION OF CLINICAL STUDY DATA

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. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

A1–7. DATA QUALITY ASSURANCE

All patient data relating to the study will be recorded on printed forms (if applicable) or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

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

A1–8. SOURCE DOCUMENTS

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered on the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–9. STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of patients by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patients and should ensure appropriate patient therapy and/or followup-.

A1–10. PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site 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.

A1–11. PROTOCOL DEVIATIONS

The integrity and potential deviations of all human factors (HF) aspects of the study, including HF observations, will be documented and explained by the HF observers.

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

Appendix 2
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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A2-1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study patient temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the patient's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

The condition that leads to the procedure is the adverse event.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A2-2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A2-1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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, see Section A2-3.2); 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 electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A2-5 for reporting instructions).

A2-3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND/OR SERIOUS ADVERSE EVENTS

A2-3.1 Adverse Event and Serious Adverse Event Recording

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A2-3.2 Assessment of Severity

The investigator will make an assessment of the severity of each adverse event and serious adverse event during the study and assign it to one of the categories in Table A2-1.

Table A2-1 Adverse Event Severity Grading Scale

Severity	Description
Mild	An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities
Moderate	An event that causes sufficient discomfort and interferes with normal everyday activities
Severe	An event that prevents normal everyday activities An adverse event that is assessed as severe should not be confused with a serious adverse event. Severe is a category utilized for rating the severity of an event, and both adverse events and serious adverse events can be assessed as severe. An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

A2-3.3 Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A2-3.4 Follow-up of Adverse Events and Serious Adverse Events

A2-3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes 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

During the adverse event reporting period (defined in Section 8.3.1), 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.

A2-3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, 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.

A2-4 REPORTING OF SERIOUS ADVERSE EVENTS

A2-4.1 Serious Adverse Event Reporting to The Sponsor via an Electronic Collection Tool

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A2-5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2-5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study patient or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2-5.

A2-4.2 Serious Adverse Event Reporting to The Sponsor via Paper CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2-5.

A2-5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A2-5.1 Events That Occur Prior to Study Treatment Initiation

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

A2-5.2 Events That Occur After Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until Day 7 after injection administration. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware 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 Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur later than Day 7 after injection administration are provided in Section A2-6.

A2-6 REPORTING 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 Day 7 after injection administration), if the event is believed to be related to prior exposure to 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 Adverse Event/Special Situations Form, using the fax number or email address provided to investigators.

A2-7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the patient's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and 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 of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor.

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

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

  The presence of aqueous flare alone will not constitute iritis but should be documented as an anterior chamber flare for adverse event reporting purposes.
- Iridocyclitis: the presence of inflammatory cells in both the aqueous and vitreous
- Vitritis: the presence of active inflammation in the vitreous, demonstrated by the presence of inflammatory cells

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

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

Note: Trace, benign, pigmented cells in the anterior chamber visible on slitlamp examination caused by dilation, and are not red blood cells or white blood cells or the result of any ocular disorder, should not be recorded as an adverse event.

A2-7.1 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.

A2-7.2 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.

A2-7.3 Persistent of 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 the investigator becomes aware that the event became

serious; see Section A2-5 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.

A2-7.4 Abnormal Laboratory Values

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A laboratory value abnormality that is not associated with the underlying disease 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., dose 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 × 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 A2-7.3 for details on recording persistent adverse events).

A2-7.5 Abnormal Vital Sign Values

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease 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., dose 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 (e.g., 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 A2-7.3 for details on recording persistent adverse events).

A2-7.6 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A2-7.4)

and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A2-5).

A2-7.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A2-5).

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 A2-6.

A2-7.8 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").

A2-7.9 Unexpected Worsening of nAMD or DME in the Study Eye

Medical occurrences or symptoms of deterioration that are anticipated as part of nAMD or DME should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. When recording an unanticipated worsening of neovascular age-related macular degeneration (nAMD) or diabetic macular edema (DME) 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"; “accelerated worsening of diabetic macular edema").

A2-7.10 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 A2-2), 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 patient was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - 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

A2-7.11 Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

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

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

Note: Special situations are not in themselves adverse events, but may result in adverse events.

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

or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A2-5). For 6-mg faricimab PFS, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

All special situations associated with 6-mg faricimab PFS, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

Appendix 3
Safety Plan: Management of Identified and Potential Risks

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A3-1 RISKS ASSOCIATED WITH FARICIMAB

Faricimab is currently approved in the United States, United Kingdom, Japan, Thailand, Switzerland, and the United Arab Emirates for the treatment of nAMD and DME by injection into the eye. Clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with faricimab in completed and ongoing studies. The anticipated important safety risks for faricimab are outlined below. Please refer to the Faricimab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of study patients. Following 6-mg faricimab intravitreal (IVT) injection using the PFS configuration, patients will undergo post-treatment observation according to standard clinical practice. Patients will remain at the clinic for approximately 30 minutes after the injection. Intraocular pressure (IOP) will be measured in the study eye at 30 (±15) minutes after treatment. If there are no safety concerns after 30 (±15) minutes following treatment, patients will be allowed to leave the clinic. If any safety concerns or immediate toxicity is noted, the patient will remain at the clinic and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event and treatment of adverse event (if applicable) will be reported on the appropriate electronic Case Report Forms (eCRFs).

All patients will be contacted by study site personnel 3 (±1) days and 7 (±1) days after the injection to elicit reports of any adverse events that may have occurred (e.g., decrease in vision, eye pain, unusual redness, or any other new ocular symptoms) in the study eye. Patients will also be asked whether they have taken the prescribed, self -administered, post-injection antimicrobial treatments (if applicable) for their study eye as directed by the investigator.

If warranted during the 7-day safety follow-up period, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit and will be instructed to contact the investigator at any time should they have any health related concerns. Refer to Appendix 9 for information on assessments required at unscheduled safety visits.

The safety plan for patients in this study consists of monitoring of safety events (including adverse events, serious adverse events, and adverse events of special interest) during the study period. Faricimab drug in the PFS has the same formulation and concentration, and is injected at the same dose, volume, route of administration, and injection procedure as the faricimab supplied in a vial configuration and studied in the Phase III program.

The risks associated with faricimab are published in the Investigator's Brochure. These risks of faricimab include, but are not limited to, intraocular inflammation and increased

IOP. Refer to the current version of the Faricimab Investigator's Brochure for more details on the risks of faricimab.

Appendix 4
Contraceptive and Barrier Guidance

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A4□1. Pregnancies in Female patients
A4□2. Abortions
A4□3. Abnormal Pregnancy Outcomes

A4–1. PREGNANCIES IN FEMALE PATIENTS

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of faricimab. 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 the investigator becomes aware 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 electronic Case Report Form (eCRF). The investigator should 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 or 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A4–2. 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 the investigator becomes aware of the event; see Section A2-5).

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 the investigator becomes aware of the event; see Section A2-5). 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.

A4–3. ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female patient exposed to study treatment 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 the investigator becomes aware of the event; see Section A2-5).

Appendix 5
Reporting Requirements for Device Product Complaints

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A5-1 Reporting Requirements for Device Product Complaints (Including Device Failures and Malfunctions)

In this study, the 6-mg faricimab prefilled syringe (PFS) with co-packaged injection filter needle is considered a drug-device combination product. The investigator must report all device deficiencies related to the PFS and the IFN to the Sponsor in the form of a medical device complaint. A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, and it can include malfunctions, use errors, and inadequate labeling. In reporting a medical device complaint, the investigator should document as much information according to the medical device complaints procedure, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (refer to the Instructions for Use for further details on device use and expected functioning). If the medical device deficiency results in an adverse event to the study patient, the event must be reported on the Adverse Event electronic Case Report Form (eCRF) and submitted through the electronic data system. If the event fulfills seriousness criteria, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as outlined in Section A2-5.

Appendix 6
Clinical Safety Laboratory Tests

The tests detailed in Table A6-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion and exclusion of patients are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A6-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Test
• Pregnancy test All women of childbearing potential will have a urine pregnancy test at screening and Day 1.

Appendix 7
Grading Scale for Assessment of Anterior Chamber Flare or Cells and Vitreous Cell

Anterior Chamber Flare

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

Anterior Chamber Cells

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

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

Vitreous Cells

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

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

Reference:

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

Appendix 8
Refraction and Best-Corrected Visual Acuity Testing

SCOPE

Refraction and best-corrected visual acuity (BCVA) assessment must be conducted before pupil dilation. BCVA data for study eyes should be entered in appropriate eCRF log.

BCVA may be assessed on any standard visual acuity (VA) chart according to local practice. The Early Treatment Diabetic Retinopathy Study (ETDRS) chart is recommended, but Snellen and LogMAR are also acceptable.

Note: the chart used to measure a participant's VA on Day 1 must remain consistent for the duration of the patient's participation in this study.

Appendix 9
Unscheduled Safety Assessment Visit

Assessments[a]
Mandatory assessments:
Best-corrected visual acuity [b, c]
Slitlamp examination
Dilated binocular indirect high-magnification ophthalmoscopy
Intraocular pressure [c]
Adverse events [d]
Assessments at the discretion of the Investigator [e]:
Concurrent ocular procedures
Concomitant medications
Hematology, serum chemistry panel, and coagulation as deemed appropriate by the investigator
Ocular imaging, as necessary

[a] Participants will be instructed to contact the investigator at any time if they have any health related concerns. If warranted, Investigators may ask the participant to return to the clinic for an unscheduled safety assessment visit during the study period. Best-corrected visual acuity (BCVA), slitlamp, intraocular pressure (IOP), and indirect ophthalmoscopy examinations must be conducted at unscheduled safety visits. All other assessments are at the discretion of the investigator. It is recommended to perform ocular assessments on both eyes.

[b] Perform finger -counting test followed by hand motion and light perception tests when necessary. BCVA should assessed at a 4-meter starting distance when using Early Treatment Diabetic Retinopathy Study (ETDRS) chart or equivalent starting distance per local practice guidelines if using Snellen or LogMAR.

[c] The method used for the BCVA and intraocular pressure measurement for a participant must remain consistent throughout the study.

[d] Adverse event causality to be evaluated by an ophthalmologist.

[e] If additional assessments (at the discretion of the Investigator) are performed per standard of care, please add the following information to the adverse event additional case details field: describe the assessments performed (e.g., inflammatory laboratory panel, SD-OCT, etc.) and describe any relevant findings that could help contextualize the adverse event.

Appendix 10
Abbreviations

Abbreviation or Term	Definition
Ang-2	angiopoietin-2
BCVA	best-corrected visual acuity
CATT	Comparison of Age-Related Macular Degeneration Treatment Trials
COVID-19	coronavirus disease 2019
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
HCP	health care provider
HF	human factors
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IFN	injection filter needle
IFU	Instructions for Use
Ig	Immunoglobulin
IMP	investigational medicinal product
IOP	intraocular pressure
IRB	Institutional Review Board
IVT	Intravitreal
nAMD	neovascular age-related macular degeneration
OCT	optical coherence tomography
PFS	prefilled syringe
ULN	upper limit of normal
VA	visual acuity
VEGF	vascular endothelial growth factor

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