PROTOCOL

TITLE:	**AN EXPLORATORY, PROSPECTIVE, MULTI-CENTER, OPEN-LABEL, SINGLE-ARM, INTERVENTIONAL, PHASE IIB STUDY TO INVESTIGATE AQUEOUS HUMOR AND MULTIMODAL IMAGING BIOMARKERS IN TREATMENT-NAÏVE PATIENTS WITH DIABETIC MACULAR EDEMA TREATED WITH FARICIMAB (RO6867461) - ALTIMETER STUDY**
PROTOCOL NUMBER:	MR41926
VERSION NUMBER:	*4*
EUDRACT NUMBER:	2020-001174-30
IND NUMBER:	119,225
NCT NUMBER:	NCT04597918
TEST PRODUCT:	Faricimab (RO6867461)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
18-Feb-2022 13:09:00	Company Signatory	[redacted]

PROTOCOL HISTORY

Global Protocol		Associated Country-Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
4	See electronic date stamp on title page.	-	-	-
-	-	E.U. and U.K.	3.1	12 May 2021
-	-	North and South America	3	5 May 2021
-	-	North and South America	2	25 March 2021
1	14 July 2020	-	-	-

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol MR41926, Version 3.1 (E.U. and U.K.) has been amended to add the possibility to increase the sample size up to 100 patients in order to achieve a minimum of 60 patients with analyzable Day 1 (baseline) and Day 112 visit aqueous humor (AH) samples, and to make other minor changes to improve clarity and consistency. The main changes to the protocol, along with a rationale for each change, are summarized below:

- Benefit-risk assessment has been updated to align with the Faricimab Investigator's Brochure, Version 11 and to include recently published data (Section 1.3.2).
- Clarification has been added to the sample size of study population to compensate for those patients that do not have a complete set of analyzable AH samples (Sections 3.1.1, 4.1, and 6.1).
- The responsibilities of the investigator and the role of the Medical Monitor in determining patient eligibility have been clarified (Sections 3.1.1.2, 4.1.2, and 5.1.2.3).
- Clarification added in Section 3.1.1.2 related to the re-screening of screen-failed patients due to the protocol, Versions 1.0 and 2.0 Diabetic Retinopathy Severity Scale (DRSS) criteria.
- Total length of the study has been extended (Section 3.2).
- Language has been added to indicate that systemic corticosteroids also include inhaled corticosteroids from inhalers used regularly for e.g., pulmonary disease, asthma, or seasonal allergy (Section 4.1.2).
- Additional guidance regarding subjects using inhaled corticosteroids occasionally (PRN) has been added (Section 4.1.2).
- Exclusion criterion #29 has been clarified to also exclude some laser procedures that can interfere with AH production.
- Clarification added regarding the assessment of adverse events by the retina specialist (Section 5.3).
- Language has been added to indicate that sites must confirm that appropriate temperature conditions have been maintained during investigational medicinal product (IMP) transit either by time monitoring (shipment arrival date and time) or temperature monitoring (Section 4.3.4).
- Additional guidance regarding the fellow (non-study) eye treatment with anti-vascular endothelial growth factor (VEGF) therapy has been added (Section 4.4.1).
- Section 4.4.2 (prohibited therapy) has been edited to clarify that continuous usage of topical ophthalmic corticosteroids for 100 days or more is considered prohibited therapy, and to add the medications claiming to have an effect on macular pathology to the list of prohibited therapies.

- Language added to include the evaluation of eyes for the targeted physical examination (Section 4.5.3 and Appendix 1).
- Clarification added that the same device must be used to assess the patient's pre-treatment intraocular pressure (IOP) and their post-treatment IOP (Section 4.5.5).
- The risks associated with faricimab have been updated to align with the Faricimab Investigator's Brochure, Version 11 (Section 5.1.1).
- Language has been added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.11).
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- The name of a Roche policy on data sharing has been corrected (Section 9.6).

Protocol MR41926, Version 3.1 (E.U. and U.K.) merges the changes that were implemented in protocol, Versions 2.0 and 3.0. No additional changes have been implemented in protocol, Version 3.1.

The protocol changes from MR41926, Version 2 (North and South America) to Version 3 (North and South America) are summarized below for reference:

- Inclusion criterion 8 (ETDRS DRSS) have been removed (Section 4.1.1)
- Exclusion criterion 22 (ETDRS DRSS) have been modified (Section 4.1.2)
- Clarification that screen failed patients due to only the protocol, Versions 1.0 and 2.0 DRSS criteria that meet all of the inclusion criteria after the protocol amendment v3.0 could be re-screened (Section 3.1.1.2).
- Correction that Adaptive Optics should also be collected for the non-study eye at the Day 140 visit (Appendix 1 and footnote m).

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN EXPLORATORY, PROSPECTIVE, MULTI-CENTER, OPEN-LABEL, SINGLE-ARM, INTERVENTIONAL, PHASE IIB STUDY TO INVESTIGATE AQUEOUS HUMOR AND MULTIMODAL IMAGING BIOMARKERS IN TREATMENT-NAÏVE PATIENTS WITH DIABETIC MACULAR EDEMA TREATED WITH FARICIMAB (RO6867461) - ALTIMETER STUDY**
PROTOCOL NUMBER:	MR41926
VERSION NUMBER:	*4*
EUDRACT NUMBER:	2020-001174-30
IND NUMBER:	119,225
NCT NUMBER:	NCT04597918
TEST PRODUCT:	Faricimab (RO6867461)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**AN EXPLORATORY, PROSPECTIVE, MULTI CENTER, OPEN-LABEL, SINGLE-ARM, INTERVENTIONAL, PHASE IIB STUDY TO INVESTIGATE AQUEOUS HUMOR AND MULTIMODAL IMAGING BIOMARKERS IN TREATMENT-NAÏVE PATIENTS WITH DIABETIC MACULAR EDEMA TREATED WITH FARICIMAB (RO6867461) - ALTIMETER STUDY**
PROTOCOL NUMBER:	MR41926
VERSION NUMBER:	*4*
EUDRACT NUMBER:	2020-001174-30
IND NUMBER:	119,225
NCT NUMBER:	NCT04597918
TEST PRODUCT:	Faricimab (RO6867461)
PHASE:	IIb
INDICATION:	Diabetic macular edema (DME)
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This is an exploratory, prospective, multicenter, open-label, single-arm, interventional, Phase IIb study designed to explore the associations over time between clinical assessments, multimodal imaging assessments, aqueous humor (AH) biomarker patterns, and genetic polymorphisms in patients with DME who are treated with faricimab (RO6867461). The exploratory objective and endpoints for the study are outlined in the following table.

Objectives and Corresponding Endpoints

Exploratory Objective	Exploratory Endpoints

To explore the associations over time between clinical assessments, multimodal imaging assessments, AH biomarker patterns, and genetic polymorphisms	• Proportion of patients with a ≥2-step ETDRS DRSS improvement over time
	• Proportion of patients with a ≥3-step ETDRS DRSS improvement over time
	• Changes from baseline on the ETDRS DRSS over time
	• Changes from baseline in BCVA (as measured on the ETDRS chart) over time
	• Changes from baseline in IRF over time
	• Changes from baseline in SRF over time
	• Changes from baseline in CST over time
	• Changes from baseline in multimodal imaging over time including:
	  • FAZ, ischemic index, ischemic area, and MAs (location and number)
	  • CST, IRF, SRF, HRF, cyst reflectivity, and DRIL in OCT en-face and volumes
	• Changes from baseline in AH biomarker patterns over time including:
	  • Proteins, including but not limited to: cytokines, chemokines, and growth-, angiogenesis-, and complement-related factors, etc.
	  • Metabolites, including but not limited to: lipids, sugars, amino acids, etc.
	• Genetic polymorphisms via standard clinical genotyping
	• Advanced analytics tools (e.g., artificial intelligence-based tools) for the assessment of clinically relevant features

AH=aqueous humor; BCVA=best-corrected visual acuity; CST=central subfield thickness; DRIL=disorganization of retinal inner layers; DRSS=Diabetic Retinopathy Severity Scale; ETDRS=Early Treatment Diabetic Retinopathy Study; FAZ=foveal avascular zone; HRF=hyper-reflective foci; IRF=intraretinal fluid; MA=microaneurysm; OCT=optical coherence tomography; SRF=subretinal fluid.

Study Design

Description of Study

This is an exploratory, prospective, multicenter, open-label, single-arm, interventional, Phase IIb study designed to explore the associations over time between clinical assessments, multimodal imaging assessments, AH biomarker patterns, and genetic polymorphisms in patients with DME who are treated with faricimab (RO6867461). All DME patients enrolled will be treatment-naïve in the study eye. Hypothesis-generating signals will be assessed via associations in visual function, retinal anatomy, and AH protein/metabolite composition. State-of-the-art imaging technologies and new immunoassay platforms will be utilized in this study. Advanced analytics and multivariate analysis will also be used to show the relationships between AH and imaging biomarkers as well as genetic polymorphisms.

- AH taps from the study eye will be collected on Day 1 (baseline) and the Day 112 visit (i.e., prior to injections 1 and 5).
- Multimodal retinal imaging will be applied at the screening visit, Day 1 (baseline), and throughout the study.

Patients will receive 6 doses (one 6 mg faricimab intravitreal [IVT] injection every 28 days [Q4W]) starting at Day 1 and ending on the Day 140 visit. Patients will return for a safety follow up visit (SFV) after ≥28 days and within <35 days following their last study treatment. Patients who discontinue from the study or treatment early (prior to the SFV), but have not withdrawn

consent (and have not been lost to follow-up) should return for an early termination visit (ETV) after ≥28 days have elapsed following their last study treatment (visit should occur within <35 days of the patient's last study treatment).

Data from adaptive optics (AO) instruments will be collected from selected study sites that have the technology available. The purpose of this data collection is to conduct a feasibility test of AO for future studies.

In this study, the ocular inclusion and exclusion criteria for the study eye require an assessment of diabetic retinopathy (DR) severity as assessed on the ETDRS DRSS. If both eyes are considered eligible, the eye with the worse BCVA, as assessed at screening, will be selected for the study eye unless the Investigator deems the other eye to be more appropriate for treatment in the study.

Patients who use concomitant medications should continue their use, unless listed as a prohibited therapy for this study. Patients who receive prohibited therapies may be discontinued from the study treatment and/or the study.

Patients who discontinue the study prematurely will not be replaced and will not be allowed to restart study treatment.

Screening

The Informed Consent Form (ICF) must be administered and signed by a patient before any study-specific screening procedure is performed. Each consented patient must satisfy the eligibility criteria at screening. The screening evaluation will be performed within 28 days preceding the baseline visit (the day of the first study treatment).

Screen-Failed Patients

Screen failures are defined as patients who consent to participate in the clinical study but are subsequently not entered in the study.

The Investigator will maintain a *detailed* record of all patients screened and *will document* eligibility or record reasons for screening failure.

Participants that do not meet one or more of the inclusion criteria are considered screen failure, no re-screening is permitted. However, screen-failed patients (due to only the protocol version 1.0 and 2.0 DRSS criteria) that meet all of the inclusion criteria after the protocol amendment v3.0/v3.1 could be re-screened. *In this situation the following scenarios are to be applied:*

1. *Due to a significant change in the screening criteria being unlikely that features assessed for eligibility change within one month and to reduce patient burden during a pandemic, screening assessments (including ocular imaging) do not have to be repeated at re-screening as long as the re-screening assessment occurs within 28 days after the initial screening.*
2. *If the re-screening assessment is performed more than 28 days after the initial screening visit, all assessments will be re-performed; with the exception of ultra wide field (UWF)-fundus fluorescein angiography (FFA) that does not need to be redone if the previous UWF-FFA was performed within ≤2 months (56 days) of the new screening day.*

In case the central reading center cannot determine Inclusion criteria 7 (DME) and exclusion criteria 22 (ETDRS DRSS) due to poor quality of the retinal images, the image acquisition may be repeated for screening purposes (allowed once) but has to be *in consultation* with the Medical Monitor. Regarding screening number and ICF signature, the below described scenarios should be followed.

Regarding exclusion criteria, a screening may result in 1 of the following 4 scenarios:

1. The patient meets 1 or more of the exclusion criteria that will not change (e.g., any history of idiopathic, infectious, or noninfectious uveitis). Such a patient would be a screen failure and no re-screening is permitted.

2. The patient is eligible, but misses the 28-day window from the screening visit to enrollment on Day 1 due to logistical reasons. Such a patient must be re-screened (all assessments will be performed; exception UWF-FFA does not need to be redone if the previous UWF-FFA was performed within ≤2 months [56 days] of the new screening day), assigned a new screening number through interactive voice or web-based response system (IxRS) (treated as new patient), and re-sign the ICF prior to re-screening.
3. The patient meets 1 or more of the exclusion criteria that may change (time-dependent) and allow(s) for re-screening (e.g., use of any systemic corticosteroids within 1 month prior to Day 1). Such a patient can be re-screened for the criterion/criteria in question within the 28-day screening window and will maintain the same screening number. A full list of applicable criteria is given below. Re-screening is permitted only for the exclusion criteria that include the following statement: "One re-screening for this criterion is permitted."
4. Patient meets 1 or more of the exclusion criteria that may change (time-dependent) and allow(s) for re-screening (e.g., use of any systemic corticosteroids within 1 month prior to Day 1). If such a patient cannot be re-screened for the criterion/criteria in question within the 28-day screening window, a complete new screening is required (all assessments will be performed; exception UWF-FFA does not need to be redone if the previous UWF-FFA was performed within ≤2 months [56 days] of the new screening day), patients will be assigned a new screening number through IxRS (treated as new patient), and patients must re-sign the ICF prior to re-screening. Re-screening is permitted only for the exclusion criteria in that include the following statement: "One re-screening for this criterion is permitted."

A maximum of 1 re-screening per patient (for a total of 2 screenings per patient) will be allowed.

Number of Patients

Approximately 35 global study sites will enroll approximately 80 patients who are treatment-naïve in the study eye. *However, the Sponsor may increase the sample size up to 100 patients, to compensate for those patients who completed the study without having a full set of Day 1 (baseline) and Day 112 visit analyzable AH samples collected. The aim of this increase is to achieve 60 patients with analyzable Day 1 (baseline) and Day 112 visit AH samples. The Sponsor may decide to stop the enrollment as soon as the target of 60 analyzable sets of AH samples is reached.*

Target Population

Inclusion Criteria

Patients must meet all of the following criteria for study entry:

Informed Consent

1. Signed ICF prior to any study-related assessments
   - All patients are able and willing to provide written informed consent and to comply with the study protocol according to International Council for Harmonisation (ICH) and local regulations.
   - Patients are willing to allow AH collection and in the opinion of the Investigator, sampling of >90 µl of AH seems feasible and safe.
2. Ability to comply with the study protocol, in the Investigator's judgment

Age

3. Age ≥18 years at the time of signing the ICF

Type of DME Patients and Disease Characteristics

4. Diagnosis of diabetes mellitus (Type 1 or Type 2), as defined by the World Health Organization (WHO) and/or American Diabetes Association and
   - Current regular use of insulin or other injectable drugs (e.g., dulaglutide and liraglutide) for the treatment of diabetes
     and/or
   - Current regular use of oral anti-hyperglycemic agents for the treatment of diabetes
5. Hemoglobin A_{1c} (HbA_{1c}) ≤10% (historic values up to 2 months before the screening visit will be permissible; otherwise, the study site may collect a sample for analysis at screening)

6. Patients who are IVT treatment-naïve in the study eye (i.e., have not received previous treatment with any anti-vascular endothelial growth factor-A (VEGF-A) IVT or any corticosteroids periocular or IVT in the study eye).

Ocular Inclusion Criteria for Study Eye

7. DME defined as macular thickening by spectral-domain optical coherence tomography (SD-OCT) involving the center of the macula: CST of ≥325 µm with Spectralis® (Heidelberg Engineering, Heidelberg, Germany) at screening. This inclusion criterion is to be assessed by the central reading center (CRC).
8. Decreased VA attributable primarily to DME, with BCVA letter score of 75 to 20 letters (both inclusive) on ETDRS-like charts at the screening visit
9. Clear ocular media and adequate pupillary dilation to allow acquisition of good quality retinal images to confirm diagnosis

Contraception

10. For women of childbearing potential (WOCBP): agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:
    - Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for at least 3 months after the final dose of faricimab.
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the Investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
    - Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    - Contraception methods that do not result in a failure rate of <1% per year such as male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide are not acceptable.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local ICF.

Exclusion Criteria

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

Medical Conditions

1. Currently untreated diabetes mellitus or previously untreated patients who initiated oral or injectable anti-diabetic medication within 3 months prior to Day 1.
2. Any known hypersensitivity to any of the components in the faricimab injection.
3. Any known hypersensitivity to any contrast media (e.g., fluorescein), dilating eye drops, or any of the anesthetics and antimicrobial preparations used by the patient during the study.
4. Any major illness or major surgical procedure within 1 month before the Day 1. One re-screening for this criterion is permitted.
5. History of other diseases, other non-diabetic metabolic dysfunction, physical examination finding, historical or current clinical laboratory finding giving reasonable suspicion of a condition that contraindicates the use of the faricimab or that might affect interpretation of

the results of the study or renders the patient at high-risk for treatment complications, in the opinion of the Investigator.

6. Active cancer within the past 12 months prior to Day 1 except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤6 and a stable prostate-specific antigen for >12 months.
7. Stroke or myocardial infarction within 12 months prior to the Day 1. One re-screening for this criterion is permitted.
8. Any febrile illness within 1 week prior to Day 1. One re-screening for this criterion is permitted.
9. Pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of faricimab.
   - WOCBP must have a negative serum pregnancy test result within 28 days prior to initiation of faricimab and a negative urine pregnancy test at the baseline visit.
10. Uncontrolled blood pressure (BP); defined as systolic > 180 mmHg and/or diastolic > 100 mmHg (while patient at rest). If a patient's initial reading exceeds these values, a second reading may be taken ≥ 30 minutes later on the same day. If the patient's BP is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1. One re-screening for this criterion is permitted.
11. Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis within 6 months prior to Day 1 or anticipated to require hemodialysis or peritoneal dialysis at any time during the study.
12. Any condition resulting in a compromised immune system that is likely to impact the AH inflammatory biomarkers. In case of doubt, the Investigator should consult with the Medical Monitor.

Prior/Concomitant Therapy

13. Patients who are currently enrolled in or have participated in any other clinical study involving an investigational product or device, or in any other type of medical research, within 3 months or 5 half-lives (whichever is longer) prior to Day 1 and up to completion of the current study. One re-screening for this criterion is permitted.
14. Substance abuse occurring within 12 months prior to screening, in the Investigator's judgment.
15. Use of systemic immunomodulatory treatments (e.g., IL-6 inhibitors) within 6 months or 5 half-lives (whichever is longer) prior to Day 1. One re-screening for this criterion is permitted.
16. Use of any systemic corticosteroids *(including inhaled corticosteroids from inhalers used regularly (e.g., pulmonary disease, asthma, or seasonal allergy)* within 1 month prior to Day 1. One re-screening for this criterion is permitted.
    Note: Subjects using inhaled corticosteroids occasionally (PRN); PRN use of inhaled corticosteroids is permitted if a 3-day period of abstinence between corticosteroid inhalation and study visit is respected.
17. Systemic treatment for suspected or active systemic infection.
    Note: Ongoing use of prophylactic antibiotic therapy may be acceptable but has to be *in consultation* with the Medical Monitor.
18. Any prior or concomitant systemic anti-VEGF treatment within 6 months or 5 half-lives (whichever is longer) prior to Day 1. One re-screening for this criterion is permitted.
19. Use of systemic medications known to be toxic to the lens, retina or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, or ethambutol) used during the 6-month period or 5 half-lives (whichever is longer) prior to Day 1 or likely need to be used. One re-screening for this criterion is permitted.
20. Received a blood transfusion within 3 months prior to the screening visit. One re-screening for this criterion is permitted.
21. Received any treatment that leads to immunosuppression within 6 months or 5 half-lives (whichever is longer) prior to Day 1. One re-screening for this criterion is permitted.

Ocular Exclusion Criteria for Study Eye

22. High-risk PDR defined as ETDRS DRSS above 71A. This exclusion criterion is to be assessed by the CRC.
23. Any history of or ongoing rubeosis iridis
24. Any panretinal photocoagulation or macular laser photocoagulation treatment received in the study eye prior to the screening visit or expected to be received between the screening visit and Day 1.
25. Any history of treatment with anti-VEGF or any periocular or IVT corticosteroids in the study eye and no such treatment planned for the time between screening and Day 1
26. Any treatment for dry eye disease in the last month prior to Day 1 (e.g., cyclosporine eye drops, lifitegrast eye drops). Lubricating eye drops and ointments are permitted. One re-screening for this criterion is permitted.
27. Any treatment with anti-inflammatory eye drops (e.g., doxycycline) within 1 month prior to Day 1. One re-screening for this criterion is permitted.
28. Any intraocular surgery (e.g., cataract surgery) within 3 months prior to Day 1 or any planned surgery during the study. One re-screening for this criterion is permitted.
29. Any glaucoma surgery/*laser procedure involving the iris, trabecular meshwork, or ciliary body* prior to the screening visit. *Only iris surgery/laser might be allowed if they occurred more than 6 months prior to Day 1.*
30. History of vitreoretinal surgery/pars plana vitrectomy, corneal transplant, or radiotherapy
31. Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as intraocular pressure [IOP] ≥25 mmHg at the screening visit despite treatment with anti-glaucoma medication)
32. Any active or suspected ocular or periocular infections on Day 1 (i.e., any active infectious or noninfectious conjunctivitis, keratitis, scleritis, or endophthalmitis).
33. Any presence of active intraocular inflammation on Day 1 (i.e., Standardization of Uveitis Nomenclature [SUN] criteria >0 or National Eye Institute [NEI] vitreous haze grading >0) or any history of intraocular inflammation
34. Any history of idiopathic, infectious, or noninfectious uveitis
35. Any current or history of ocular disease other than DME that may confound assessment of the macula or affect central vision (e.g., age-related macular degeneration, retinal vein occlusion, angioid streaks, histoplasmosis, active or inactive cytomegalovirus retinitis, pathological myopia, retinal detachment, macular traction, macular hole, significant cataract, epiretinal membrane) and could either:
    - Require medical or surgical intervention during the study period to prevent or treat visual loss that might result from that condition; or
    - Preclude any visual improvement due to substantial structural damage; or
    - Preclude in the opinion of the investigator acquisition of good quality retinal images to confirm diagnosis.
36. Any current ocular condition or other causes of visual impairment for which, in the opinion of the Investigator, VA loss would not improve from resolution of macular edema (e.g., foveal atrophy, pigment abnormalities, dense sub-foveal hard exudates, and non-retinal condition)

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

37. Patient is currently receiving treatment with brolucizumab or bevacizumab in the non-study eye and is unwilling to switch to a protocol allowed non-study eye treatment during the study
38. Any previous treatment with Iluvien® or Retisert® (fluocinolone acetonide IVT implant) in the non-study eye
39. If patients have been treated with corticosteroids periocular or IVT in the non-study eye in the past, the following washout periods prior to the screening visit would apply:
    - Periocular or IVT corticosteroids:
        - Triamcinolone: 6 months;
        - Ozurdex® (dexamethasone IVT implant): 6 months;
40. Non-functioning non-study eye, defined as either:
    - BCVA of hand motion or worse

- No physical presence of non-study eye (i.e., monocular)
- Legally blind in the patient's relevant jurisdiction

End of Study and Length of Study

The total duration of the study for an individual patient will be approximately up to 203 days (i.e., be approximately 29 weeks) divided as follows:

- Screening period: up to 28 days (i.e., up to 4 weeks)
- Treatment period: 140 days (±7 days) (i.e., approximately 20 weeks)
- Safety follow-up period: 28 days to 35 days (i.e., approximately 4 to 5 weeks)

A patient is considered to have completed the study if he/she has completed the last scheduled procedure shown in the schedule of assessments.

The end of study (EoS) is defined as the date when the last patient completes their last visit (LPLV). The end of the study is expected to occur approximately 168 to 175 days (i.e., 24 to 25 weeks) after the last patient is enrolled. The total length of the study, from the screening visit of the first patient to the EoS, is expected to be approximately *26* months. Alternatively, the Sponsor may decide to terminate the study at any time; in this case, the termination date will be considered the EoS.

Investigational Medicinal Products

The investigational medicinal product (IMP) for this study is faricimab. Faricimab will be supplied by the F. Hoffmann-La Roche Ltd. as a sterile liquid for IVT injection in single-dose glass vials. The packaging and labeling of faricimab will be in accordance with Roche standards and local regulations. The 6-mg dose of faricimab will be administered IVT at the study site to patients Q4W starting at Day 1 and ending on the Day 140 visit.

Statistical Methods

Exploratory Analyses

The objective of this study is to explore the associations over time between clinical assessments, multimodal imaging assessments, AH biomarker patterns, and genetic polymorphisms of treatment-naïve DME patients treated with faricimab on the basis of the endpoints for the study. Scatterplots and correlation coefficients (Pearson or Spearman depending on the data type) will be produced to examine the pairwise associations of variables. As this is an exploratory analysis, the magnitude of the correlations will be examined in conjunction with the plots to assess nature of the relationship (linear or nonlinear) and if it is representative of the relationship or driven by a few outliers. No missing data will be imputed. Data may be subjected to post-hoc analyses as science evolves.

Determination of Sample Size

In this exploratory study, the sample size is based on practical considerations. Approximately 80 patients will be enrolled in the study. With a minimum of 40 patients, there is approximately 80% power to demonstrate that a correlation of 0.4 is statistically significantly different from 0 (alpha=0.05). Sample size was *calculated* to 80 to account (adjust) for exploratory multivariate analyses that may be performed to model clinical outcomes based on multiple AH biomarkers.

The Sponsor may increase the sample size up to 100 patients, to compensate for those patients who completed the study without having a full set of Day 1 (baseline) and Day 112 visit analyzable AH samples collected. The aim of this increase is to achieve 60 patients with analyzable* Day 1 (baseline) and Day 112 visit AH samples. The Sponsor may decide to stop the enrollment as soon as the target of 60 analyzable* sets of AH samples is reached.*

** Analyzable refers to the AH samples with no major deviations that will be analyzed by at least one specialty laboratory.*

Interim Analyses

As this is an open-label study, no formal interim analyses are planned. Exploratory analyses of selected endpoints may be performed during the course of the study (e.g., after all patients have completed the Day 28 visit and the necessary data are available).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AC	anterior chamber
AH	aqueous humor
AMD	age-related macular degeneration
Ang-2	angiopoietin-2
AO	adaptive optics
BCVA	best-corrected visual acuity
BP	blood pressure
CFP	color fundus photographs
COVID-19	coronavirus 2019
CRC	central reading center
CRO	contract research organization
CST	central subfield thickness
CTCAE	Common Terminology Criteria for Adverse Events
DME	diabetic macular edema
DR	diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Scale
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	Electronic data capture
EoS	End of Study
ETDRS	Early Treatment Diabetic Retinopathy Study
ETV	Early termination visit
FDA	Food and Drug Administration
FFA	fundus fluorescein angiography
HbA_{1c}	hemoglobin A_{1c} or glycated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IOP	intraocular pressure
IRB	Institutional Review Board

Abbreviation	Definition
IRF	intraretinal fluid
IVT	intravitreal
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
nAMD	neovascular age-related macular degeneration
NCI	National Cancer Institute
NEI	National Eye Institute
NPDR	non-proliferative diabetic retinopathy
OCT	optical coherence tomography
PD	pharmacodynamic
PDR	proliferative diabetic retinopathy
PK	pharmacokinetic
Q4W	every 28 days
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD-OCT	spectral-domain optical coherence tomography
SD-OCT-A	spectral-domain optical coherence tomography angiography
SFV	safety follow-up visit
SoA	schedule of assessments
SOC	standard of care
SRF	subretinal fluid
SS-OCT	swept-source optical coherence tomography
SS-OCT-A	swept-source optical coherence tomography angiography
SUN	Standardization of Uveitis Nomenclature
ULN	upper limit of normal
UWF	ultra-wide field
UWF-CFP	ultra-wide field color fundus photography
VA	visual acuity
VEGF	vascular endothelial growth factor
WES	whole exome sequencing
WGS	whole genome sequencing
WHO	World Health Organization
WOCBP	women of childbearing potential

1. BACKGROUND

1.1 BACKGROUND ON DIABETIC MACULAR EDEMA AND DIABETIC RETINOPATHY

Diabetic macular edema (DME), a complication of diabetic retinopathy (DR), can develop at any stage of the underlying disease of retinal microvasculature (Fong et al. 2004). DME occurs with increasing frequency as the underlying DR worsens (Henricsson et al. 1999; Johnson 2009) from non-proliferative DR (NPDR) to proliferative DR (PDR). The DME is the most common cause of moderate and severe visual impairment in patients with DR (Ciulla et al. 2003; Davidson et al. 2007; Leasher et al. 2016), and if left untreated can lead to a loss of 10 or more letters in visual acuity (VA) within 2 years in approximately 50% of patients (Ferris and Patz 1984; Ciulla et al. 2003). The DME affects approximately 14% of patients with diabetes and can be found in patients with both Type 1 and Type 2 diabetes (Girach and Lund-Andersen 2007). In 2019, the worldwide population of people with diabetes was approximately 463 million, and it is estimated to grow to 700 million by 2045 (International Diabetes Federation 2019).

With advances in imaging technology, DME is now often diagnosed by optical coherence tomography (OCT) rather than the traditional Early Treatment Diabetic Retinopathy Study (ETDRS) ophthalmoscopy-based criteria. On a molecular level, DME is a result of a vascular endothelial growth factor-A (VEGF-A)-mediated increase in vessel permeability and loss of retinal capillary pericytes, consequent to hypoxia-mediated release of pro-angiogenic, hyperpermeability, and pro-inflammatory mediators (Antonetti et al. 1999). The VEGF also upregulates a homeostatic factor, angiopoietin-2 (Ang-2), which acts as an antagonist of the Tie2 receptor tyrosine kinase on endothelial cells, counteracting vessel stabilization maintained through Ang-1-dependent Tie2 activation. Therefore, Ang-2 acts as a vascular destabilization factor, rendering the vasculature more elastic and amenable to endothelial barrier breakdown and sprouting. The excess of Ang-2 and VEGF in the retinal tissues promotes vessel destabilization, vascular leakage, and neovascularization. Ang-2 is also involved in inflammatory pathways such as lymphocyte recruitment. In summary, both VEGF-A and Ang-2 are recognized as key factors mediating diabetic eye disease pathogenesis (Aiello et al. 1994; Davis et al. 1996; Maisonpierre et al. 1997; Gardner et al. 2002; Joussen et al. 2002; Fiedler et al. 2003).

Although macular laser used to be the standard of care (SOC) for treatment of DME, the development of anti-VEGF pharmacotherapy in the past 10 years has led to dramatic improvements in visual outcomes for patients with DME. Current SOC for DME includes intravitreal (IVT) injection of anti-VEGF treatments such as ranibizumab and aflibercept. Although these are widely recognized as effective treatments, a substantial proportion of patients do not achieve clinically meaningful improvements in VA (Brown et al. 2006; Rosenfeld et al. 2006; Catt 2016). These treatments also require frequent and long-term IVT administration (Catt 2016; Heier 2012), which is a high burden for both patients and

physicians (Catt 2016; Gohil et al. 2015; Prenner et al. 2015; Varano et al. 2015; Vukicevic et al. 2016). Other available approved options for the treatment of DME include periocular or IVT steroids and steroid implants.

Large Phase III trials of anti-VEGF agents in DME demonstrated that after the first year of treatment, the number of injections needed for maintenance of vision gains can be decreased (Diabetic Retinopathy Clinical Research Network et al. 2010; Schmidt-Erfurth et al. 2014; Elman et al. 2015). However, to achieve optimal outcomes in the absence of validated predictive biomarkers of treatment frequency, the standard anti-VEGF approach in DME still relies on frequent monitoring visits and places a substantial burden on patients and healthcare providers. In addition, anti-VEGF monotherapy does not fully address other pathways, including inflammation and pericyte destabilization, that contribute to worsening of diabetic eye disease.

New treatments that target additional pathways and that lead to reduced burden of IVT injections are needed to address high unmet medical need in diabetic eye disease.

1.2 BACKGROUND ON FARICIMAB

Faricimab (also known as RO6867461) is a humanized full-length bispecific IgG1 antibody that selectively neutralizes VEGF-A (hereafter referred to as "VEGF") and Ang-2, the key factors mediating pathophysiology of diabetic eye disease. Faricimab was developed using Roche's CrossMab (monoclonal antibody) technology. The VEGF binding and the Ang-2 binding variable regions of faricimab bind to VEGF and Ang-2 independently and simultaneously with high affinity. The Fc portion of faricimab was engineered for ophthalmic use through inactivation of effector function and elimination of binding to the neonatal receptor that reduces systemic exposure following IVT injection.

The concentrations of both VEGF and Ang-2 in the vitreous were shown to be upregulated in patients with DR (Rangasamy et al. 2011; Park et al. 2014). In vivo pharmacological evaluations in spontaneous and induced mouse and non-human primate models of neovascularization and in models of intraocular inflammation (uveitis) confirmed the improved anti-angiogenic and anti-inflammatory effects of faricimab treatment compared with anti-VEGF monotherapy and anti-Ang-2 monotherapy (Roche Report 1056925; RO6867461 [faricimab] Investigator's Brochure).

Based on the mechanism of action of faricimab through selective neutralization of both VEGF and Ang-2, and based on the pathophysiology of diabetic eye disease, it is hypothesized that faricimab may lead to stabilization of the pathological ocular vasculature and to improve visual and anatomical outcomes in DME and DR compared with anti-VEGF monotherapies or anti-Ang-2 monotherapies.

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

Faricimab has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of DME and neovascular (wet) age-related macular degeneration (nAMD). An initial Marketing Application is currently under review by Health Authorities in other territories.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

This is an exploratory, prospective, multicenter, open-label, single-arm, interventional, Phase IIb study designed to explore the associations over time between clinical assessments, multimodal imaging assessments, aqueous humor (AH) biomarker patterns, and genetic polymorphisms in patients with DME who are treated with faricimab (RO6867461). All DME patients enrolled in the study will be treatment-naïve in the study eye. Hypothesis-generating signals will be assessed via associations in visual function, retinal anatomy, and AH protein/metabolite composition. Relationships between AH biomarkers and disease-relevant genetic polymorphisms will be explored.

1.3.2 Benefit-Risk Assessment

The potential clinical benefit of faricimab injections for patients with DME was demonstrated in the Phase II study (BP30099 [BOULEVARD]). The study met its primary efficacy endpoint, which was the mean change from baseline in best-corrected visual acuity (BCVA) at Week 24 in anti-VEGF treatment–naïve patients treated with faricimab compared with 0.3 mg of ranibizumab.

Study BP30099 (BOULEVARD) enrolled 229 patients with DME. The study was originally designed to enroll anti-VEGF treatment–naïve patients. The protocol was subsequently amended to include an additional cohort of patients (n=61) who were previously treated with anti-VEGF for DME to allow for the exploratory evaluation of the efficacy of faricimab in this population.

Anti-VEGF treatment–naïve patients were randomized equally into three treatment arms: 6 mg of IVT faricimab, 1.5 mg of IVT faricimab, and 0.3 mg of IVT ranibizumab. Patients who were previously treated with anti-VEGF were randomized equally to receive either 6 mg of IVT faricimab or 0.3 mg of IVT ranibizumab. Key demographic and ocular baseline characteristics were generally well balanced. The study consisted of a treatment period (20 weeks in length) and an observational period (up to 16 weeks in length), for a total study duration of up to 36 weeks. Study treatment was administered to patients by IVT injection every 28 days (Q4W) up to the last injection at Week 20, with the primary endpoint assessed at Week 24. The observational period without treatment lasted up to 16 weeks from Week 20 to Week 36. The observation period allowed for exploration of the durability of pharmacodynamic (PD) effects after the last treatment.

The mean BCVA change from baseline in the anti-VEGF treatment–naïve patients treated with 6 mg of faricimab improved steadily over time, with patients experiencing an

average benefit of +3.6 letters (p=0.03; 80% CI: 1.5 to 5.6 letters) over anti-VEGF monotherapy (adjusted for baseline variables) at Week 24 (1 month after the last monthly dose administered at Week 20), which was statistically significant in a mixed-model repeated measures analysis. In this anti-VEGF treatment–naïve population, the mean change in BCVA from baseline in the 6-mg faricimab group and the 1.5-mg faricimab group at Week 24 was 13.9 letters and 11.7 letters, respectively, relative to 10.3 letters in the 0.3-mg ranibizumab group. The proportion of treatment-naïve patients gaining 15 letters or more from baseline over time at Week 24 was 35.3% for the 0.3-mg ranibizumab group relative to 36.0% and 42.5% for the 1.5-mg and 6-mg faricimab groups, respectively. In addition to DME benefit, higher rates of improvement in DR severity from baseline (as assessed on the ETDRS Diabetic Retinopathy Severity Scale [DRSS]) were also observed with faricimab compared with anti-VEGF monotherapy in the anti–VEGF treatment–naïve cohort, with 27.7% and 38.6% of patients (1.5-mg and 6-mg faricimab, respectively) experiencing a ≥2-step improvement from baseline to Week 24 compared with 12.2% in the 0.3-mg ranibizumab treatment cohort.

For the previously anti-VEGF–treated population, the absolute change from baseline was 9.6 letters and 8.3 letters for the 6-mg faricimab group and the anti-VEGF group, respectively. The difference of +1.3 letters was directionally similar to the treatment-naïve cohort but was not statistically significant (p=0.635; 80% CI: −2.3 to 5.0). Additionally, the proportion of patients gaining 15 or more letters from baseline over time at Week 24 was 23.2% and 16.8% for the 6-mg faricimab and anti-VEGF SOC treatment arms, respectively. The anatomical outcomes showed directionally similar benefits for faricimab in this cohort.

Overall, the data from the intent-to-treat study population (both treatment-naïve and previously anti-VEGF–treated patients) suggest consistent benefit and safety profile of faricimab over anti-VEGF monotherapy in the general DME population, with no new safety signals being observed.

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

In summary, the data from Study BP30099 (BOULEVARD) suggested a dose-related benefit favoring the 6-mg dose of faricimab relative to the 1.5-mg dose, as measured by both the efficacy outcomes and duration of effect. Based on these results, the 6-mg dose of faricimab has been chosen for further clinical development in Phase III

studies in patients with DME to explore its benefit-risk compared with SOC IVT anti-VEGF treatment from the following perspectives:

- Potential for superior efficacy outcomes in DME with 6 mg of IVT faricimab compared with SOC IVT
- Potential for prolonged treatment duration while achieving and maintaining comparable efficacy with 6 mg of IVT faricimab compared with SOC IVT

The Phase III clinical development program in DME (YOSEMITE: Study GR40349, and RHINE: Study GR40398) enrolled both patients with DME who were naïve to anti-VEGF therapy in the study eye and patients who were previously treated with anti-VEGF therapy in the study eye to further explore outcomes on DME in both populations. Both studies met their primary endpoint (*Wykoff et al. 2022*).

In the Phase I study (BP28936), single and multiple IVT administrations of faricimab were well tolerated in patients with nAMD up to the highest dose tested, 6 mg. No deaths and no dose-limiting events were reported. The Phase II Study BP30099 (BOULEVARD) in DME also showed an acceptable tolerability and safety profile, with no new or unexpected safety signals. No serious ocular or systemic adverse events considered related to treatment with faricimab were reported. The ocular and systemic safety findings for faricimab observed in the Phase II study were generally consistent with the safety profile reported in patients with DME who receive intravitreally administered anti-VEGF products. Additionally, a similar safety profile to anti-VEGF treatment was observed with faricimab in the nAMD studies (BP29647 [AVENUE] and CR39521 [STAIRWAY]).

As of April 2021, more than 2700 patients have received at least one dose of faricimab in the completed and ongoing clinical studies *for DME/DR, nAMD, and retinal vein occlusion* (RO6867461 [faricimab] Investigator's Brochure). *Overall, the primary analysis of the pivotal Phase III studies (Heier et al. 2022; Wykoff et al. 2022) and final analysis from the supportive Phase II studies showed that faricimab has a comparable safety profile to aflibercept and ranibizumab. To date, the safety data indicate that faricimab was generally well-tolerated, and no new or unexpected safety signals were identified.*

Obtaining AH samples via anterior chamber (AC) paracentesis (i.e., AH tap) is a well-established and safe procedure when performed by an experienced ophthalmologist (Van der Lelij et al. 1997; Kitazawa et al. 2017). This procedure is often used as a diagnostic tool in uveitis (Van der Lelij et al. 1997; Kitazawa et al. 2017; Saxena et al. 2019; Trivedi et al. 2011; Cheung et al. 2004), to lower the intraocular pressure (IOP) associated with IVT injections (Trivedi et al. 2011) or from conditions such as acute angle closure glaucoma (Carnahan and Platt 2002) and central retinal artery occlusion (Chen and Cheema 1994; Atebara et al. 1995). The AH sample has been *collected* for clinical research purposes in multiple studies (Fauser et al. 2014, 2016). In agreement

with these published risk to benefit data, AH samples are collected routinely in Phase I through Phase III ophthalmology clinical studies to monitor drug pharmacokinetics and pharmacodynamics (e.g., target neutralization).

Complications for AH sampling reported in the literature are traumatic injuries of the iris, hyphema, inflammation, infection, and hypotension. The reported complication rates are between 0.01% *and* 0.7% with no long-term sequelae and no effect on VA (Saxena et al. 2019; Trivedi et al. 2011). There is also a small risk of induction of traumatic cataract associated with AC paracentesis (Pleyer and Garweg 2008).

The planned multimodal imaging assessments are considered as part of the current SOC. They are routinely used in the clinic for diagnosis, assessment of the disease course, response to treatment, and for research purposes to better understand the underlying disease pathology. All instruments used will be American National Standards Institute compliant.

Based on the results of the Phase II study (BP30099 [BOULEVARD]), the 6-mg dose of faricimab has the potential for superior efficacy outcomes in DME and the potential for prolonged treatment duration while achieving and maintaining comparable efficacy when compared to SOC IVT. Besides close monitoring and treatment with faricimab, no other direct benefits are foreseen for the patients. However, patients in this study will provide AH biomarker samples and associated data to generate algorithms that could potentially lead to a more personalized treatment option for future patients.

In the setting of the coronavirus 2019 (COVID-19) pandemic, patients with comorbidities including those patients with diabetes are a more vulnerable population. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with diabetes in some retrospective analysis. Susceptibility to infection with diabetes may be argued, but infection once acquired is likely to be more severe and prolonged, determined by a number of factors, including duration of diabetes, the presence of diabetes-related complications, and the level of glycemic control. It is not anticipated that faricimab will increase the risk of infection with SARS-CoV-2. Four Phase 3 clinical trials (2 in DME and 2 in nAMD) with faricimab are ongoing during this pandemic, and to date these studies have not shown any increased risk of developing COVID-19 or of having a worse outcome in patients on faricimab, however this will continue to be monitored.

2. OBJECTIVES AND ENDPOINTS

The exploratory objective and the endpoints are provided in Table 1.

Table 1 Exploratory Objective and Corresponding Endpoints

Exploratory Objective	Exploratory Endpoints

To explore the associations over time between clinical assessments, multimodal imaging assessments, AH biomarker patterns, and genetic polymorphisms	• Proportion of patients with a ≥2-step ETDRS DRSS improvement over time
	• Proportion of patients with a ≥3-step ETDRS DRSS improvement over time
	• Changes from baseline on the ETDRS DRSS over time
	• Changes from baseline in BCVA (as measured on the ETDRS chart) over time
	• Changes from baseline in IRF over time
	• Changes from baseline in SRF over time
	• Changes from baseline in CST over time
	• Changes from baseline in multimodal imaging over time including:
	  • FAZ, ischemic index, ischemic area, and MAs (location and number)
	  • CST, IRF, SRF, HRF, cyst reflectivity, and DRIL in OCT en-face and volumes
	• Changes from baseline in AH biomarker patterns over time including:
	  • Proteins, including but not limited to: cytokines, chemokines, and growth-, angiogenesis-, and complement-related factors, etc.
	  • Metabolites, including but not limited to: lipids, sugars, and amino acids, etc.
	• Genetic polymorphisms via standard clinical genotyping
	• Advanced analytics tools (e.g., artificial intelligence-based tools) for the assessment of clinically relevant features

AH=aqueous humor; BCVA=best-corrected visual acuity; CST=central subfield thickness; DRIL=disorganization of retinal inner layers; DRSS=Diabetic Retinopathy Severity Scale; ETDRS=Early Treatment Diabetic Retinopathy Study; FAZ=foveal avascular zone; HRF=hyper-reflective foci; IRF=intraretinal fluid; MA=microaneurysm; OCT=optical coherence tomography; SRF=subretinal fluid.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is an exploratory, prospective, multicenter, open-label, single-arm, interventional, Phase IIb study designed to explore the associations over time between clinical assessments, multimodal imaging assessments, AH biomarker patterns, and genetic polymorphisms in patients with DME who are treated with faricimab (RO6867461). All DME patients enrolled will be treatment-naïve in the study eye. Hypothesis-generating signals will be assessed via associations in visual function, retinal anatomy, and AH

protein/metabolite composition. State-of-the-art imaging technologies and new immunoassay platforms will be utilized in this study. Advanced analytics and multivariate analysis will also be used to show the relationships between AH and imaging biomarkers as well as genetic polymorphisms.

- AH taps from the study eye will be collected on Day 1 (baseline) and the Day 112 visit (i.e., prior to injections 1 and 5).
- Multimodal retinal imaging will be applied at the screening visit, Day 1 (baseline), and throughout the study (see Appendix 1).

Approximately 35 global study sites will enroll approximately 80 patients who are treatment-naïve in the study eye. *However, the Sponsor may increase the sample size up to 100 patients, to compensate for those patients who completed the study without having a full set of Day 1 (baseline) and Day 112 visit analyzable AH samples collected. The aim of this increase is to achieve 60 patients with analyzable Day 1 (baseline) and Day 112 visit AH samples (see Section 6.1). The Sponsor may decide to stop the enrollment as soon as the target of 60 analyzable sets of AH samples is reached.* Patients will receive 6 doses (one 6 mg faricimab IVT injection Q4W) starting at Day 1 and ending on the Day 140 visit. Patients will return for a safety follow-up visit (SFV) after ≥28 days and within <35 days following their last study treatment. Patients who discontinue from the study or treatment early (prior to the SFV), but have not withdrawn consent (and have not been lost to follow-up) should return for an early termination visit (ETV) after ≥28 days have elapsed following their last study treatment (visit should occur within <35 days of the patient's last study treatment).

Data from adaptive optics (AO) instruments will be collected from selected study sites that have the technology available. The purpose of this data collection is to conduct a feasibility test of AO for future studies.

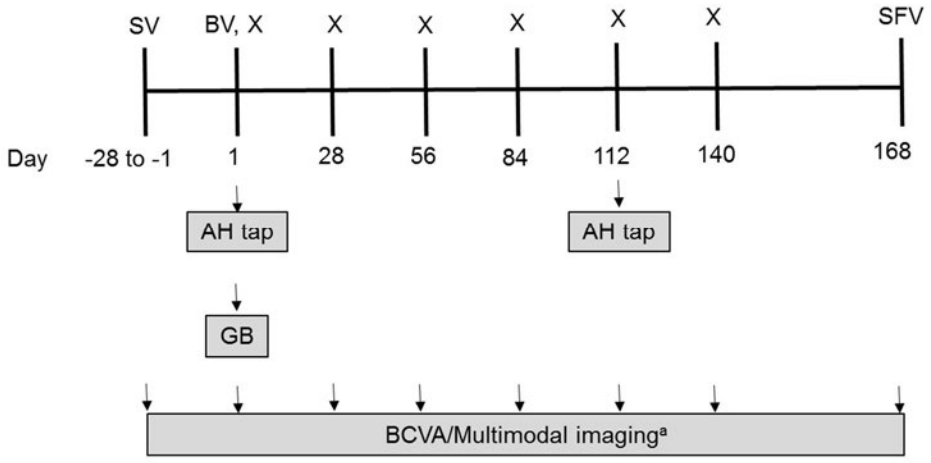
In this study, the ocular inclusion and exclusion criteria (see Section 4.1.1 and Section 4.1.2) for the study eye require an assessment of DR severity as assessed on the ETDRS DRSS (Ip et al. 2012). If both eyes are considered eligible, the eye with the worse BCVA, as assessed at screening, will be selected for the study eye unless the investigator deems the other eye to be more appropriate for treatment in the study.

Patients who use concomitant medications should continue their use, unless listed as a prohibited therapy for this study. Patients who receive prohibited therapies may be discontinued from the study treatment and/or the study.

Patients who discontinue the study prematurely will not be replaced and will not be allowed to restart study treatment.

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

Figure 1 Study Design



AH = aqueous humor; BCVA = best-corrected visual acuity; BV = baseline visit; GB = blood draw for clinical genotyping; IVT = intravitreal; SFV = safety follow-up visit; SV = screening visit; X = 6 mg faricimab (RO6867461) IVT injection.

[a] Multimodal imaging detailed in the Schedule of Assessments (Appendix 1).

3.1.1.1 Screening

The Informed Consent Form (ICF) must be administered and signed by a patient before any study-specific screening procedure is performed. Each consented patient must satisfy the eligibility criteria at screening (see Sections 4.1.1 and 4.1.2). The screening evaluation will be performed within 28 days preceding the baseline visit (the day of the first study treatment; see Appendix 1).

3.1.1.2 Screen-Failed Patients

Screen failures are defined as patients who consent to participate in the clinical study but are subsequently not entered in the study.

The investigator will maintain a *detailed* record of all patients screened and *will document* eligibility or record reasons for screening failure (see Section 4.5.1).

Participants that do not meet one or more of the inclusion criteria are considered screen failure, no re-screening is permitted. However, screen-failed patients (due to only the protocol version 1.0 and 2.0 DRSS criteria) that meet all of the inclusion criteria after the protocol amendment v3.0/v3.1 could be re-screened. *In this situation the following scenarios are to be applied:*

1. *Due to a significant change in the screening criteria being unlikely that features assessed for eligibility change within one month and to reduce patient burden during a pandemic, screening assessments (including ocular imaging) do not have to be repeated at re-screening as long as the re-screening assessment occurs within 28 days after the initial screening.*

2. *If the re-screening assessment is performed more than 28 days after the initial screening visit, all assessments will be re-performed; with the exception of ultra-wide field (UWF)-fundus fluorescein angiography (FFA) that does not need to be redone if the previous UWF-FFA was performed within ≤2 months (56 days) of the new screening day.*

In case the central reading center cannot determine Inclusion criteria 7 (DME) and Exclusion criteria 22 (ETDRS DRSS) (Section 4.1.1) because of the poor quality of the retinal images, the image acquisition may be repeated for screening purposes (allowed once) but has to be *in consultation* with the Medical Monitor. Regarding screening number and ICF signature, the below described scenarios should be followed.

Regarding exclusion criteria, a screening may result in 1 of the following 4 scenarios:

1. The patient meets 1 or more of the exclusion criteria that will not change (e.g., any history of idiopathic, infectious, or noninfectious uveitis). Such a patient would be a screen failure and no re-screening is permitted.
2. The patient is eligible, but misses the 28-day window from the screening visit to enrollment on Day 1 due to logistical reasons. Such a patient must be re-screened (all assessments will be performed; exception UWF-FFA does not need to be redone if the previous UWF-FFA was performed within ≤2 months [56 days] of the new screening day), assigned a new screening number through interactive voice or web-based response system (IxRS) (treated as new patient), and re-sign the ICF prior to re-screening.
3. The patient meets 1 or more of the exclusion criteria that may change (time-dependent) and allow(s) for re-screening (e.g., use of any systemic corticosteroids within 1 month prior to Day 1). Such a patient can be re-screened for the criterion/criteria in question within the 28-day screening window and will maintain the same screening number. A full list of applicable criteria is given below. Re-screening is permitted only for the exclusion criteria in Section 4.1.2 that include the following statement: "One re-screening for this criterion is permitted."
4. Patient meets 1 or more of the exclusion criteria that may change (time-dependent) and allow(s) for re-screening (e.g., use of any systemic corticosteroids within 1 month prior to Day 1). If such a patient cannot be re-screened for the criterion/criteria in question within the 28-day screening window, a complete new screening is required (all assessments will be performed; exception UWF-FFA does not need to be redone if the previous UWF-FFA was performed within ≤2 months [56 days] of the new screening day), patients will be assigned a new screening number through IxRS (treated as new patient), and patients must re-sign the ICF prior to re-screening. Re-screening is permitted only for the exclusion criteria in Section 4.1.2 that include the following statement: "One re-screening for this criterion is permitted."

A maximum of 1 re-screening per patient (for a total of 2 screenings per patient) will be allowed.

3.2 END OF STUDY AND LENGTH OF STUDY

The total duration of the study for an individual patient will be approximately up to 203 days (i.e., be approximately 29 weeks) divided as follows:

- Screening period: up to 28 days (i.e., up to 4 weeks)
- Treatment period: 140 days (±7 days) (i.e., approximately 20 weeks)
- Safety follow-up period: 28 days to 35 days (i.e., approximately 4 to 5 weeks)

A patient is considered to have completed the study if he/she has completed the last scheduled procedure shown in the schedule of assessments (SoA; see Appendix 1).

The end of study (EoS) is defined as the date when the last patient completes their last visit (LPLV). The end of the study is expected to occur approximately 168 to 175 days (i.e., 24 to 25 weeks) after the last patient is enrolled. The total length of the study, from the screening visit of the first patient to the EoS, is expected to be approximately *26* months. Alternatively, the Sponsor may decide to terminate the study at any time; in this case, the termination date will be considered the EoS.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Open-label Study Design

As this exploratory study is not comparative and most variables are objectively assessed, an open-label study design is acceptable.

3.3.2 Rationale for Faricimab Dose and Schedule

Dose

Patients in this study will receive 6-mg doses of faricimab. This dose is based on data from nonclinical in vivo and toxicology models, clinical outcomes from Phase I and Phase II studies, and supported by clinical pharmacokinetic (PK) and PD assessments.

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

The Phase II study (BP30099 [BOULEVARD]) provided evidence of a positive benefit–risk profile for IVT faricimab in patients with DME (n = 229 enrolled). The study compared two doses of IVT faricimab (1.5-mg faricimab and 6-mg faricimab) with 0.3-mg IVT ranibizumab. The effects of 6-mg IVT faricimab on the primary endpoint of the mean change from baseline in BCVA in the anti-VEGF treatment–naïve DME patient subset (n = 168 enrolled) were statistically significant and clinically important compared with 0.3-mg IVT ranibizumab. The mean change in BCVA from baseline in the 6-mg faricimab group and the 1.5-mg faricimab group at Week 24 was 13.9 letters and

11.7 letters, respectively, relative to 10.3 letters in the 0.3-mg ranibizumab group. The proportion of treatment-naïve patients gaining 15 letters or more from baseline over time at Week 24 was 35.3% for the 0.3-mg ranibizumab group relative to 36.0% and 42.5% for the 1.5-mg and 6-mg faricimab groups, respectively. In addition to DME benefit, higher rates of improvement in DR severity from baseline (as assessed on the ETDRS DRSS) were also observed with faricimab compared with anti-VEGF monotherapy in the anti–VEGF treatment–naïve cohort, with 27.7% and 38.6% of patients (1.5-mg and 6-mg faricimab, respectively) experiencing a ≥2-step improvement from baseline to Week 24 compared with 12.2% in the 0.3-mg ranibizumab treatment cohort. Both doses of faricimab, 6 mg and 1.5 mg, were well tolerated and did not result in any new or unexpected safety signals.

In summary, the data from Study BP30099 suggested a dose-related benefit favoring the 6-mg dose of faricimab relative to the 1.5-mg dose, as measured by both the efficacy outcomes and duration of effect. Based on these results, the 6-mg dose has been studied in the 2 ongoing Phase III studies in patients with DME (YOSEMITE: Study GR40349, and RHINE: Study GR40398). The primary endpoint analyses of the studies have been completed, and no new safety signals associated with faricimab treatment have been identified.

Schedule

Patients in this study will receive 6 doses of 6 mg faricimab IVT injection Q4W starting at Day 1 and ending on the Day 140 visit. The dosing schedule is based on the clinical data from the Phase II study (BP30099 [BOULEVARD]) and the PK and PD assessments of AH samples from a subset of patients with DME in the Phase II Study BP30099 (BOULEVARD). The rationale for the initial 6 Q4W doses is based on the continuous BCVA gains seen after each Q4W injection up to Week 24 in the Phase II study (BP30099 [BOULEVARD]).

Furthermore, the dosing schedule in this study aligns with the dosing schedule currently being studied in Arm A (patients randomized to Arm A receive 6 mg IVT faricimab injections Q4W from randomization to Week 20) of the 2 ongoing Phase III studies in patients with DME (YOSEMITE: Study GR40349, and RHINE: Study GR40398).

3.3.3 Rationale for Aqueous Humor Biomarker Assessments

Aqueous humor is considered a reasonable surrogate specimen of the biological activity occurring in the vitreous and the retina, and it may reflect changes in the retina more accurately than blood, as systemically circulating blood is less likely to reflect local biomarker levels whereas the concentration of protein in AH reflects its level in the vitreous and the retina (Funatsu et al. 2005; Noma et al. 2008). The AH samples have been instrumental in understanding the relationship between ocular VEGF suppression and the duration of clinical efficacy (Muether et al. 2012, 2013, 2014; Fauser et al. 2014, 2016; Hutton-Smith et al. 2017). Multiple studies have also demonstrated a relationship between several AH cytokines and anti-VEGF treatment response in DME

(Mastropasqua et al. 2018). Recent studies have highlighted the feasibility of Omics analyses, including proteomics and metabolomics, in human AH and successfully identified differentially regulated pathways in presence of retinal diseases (Yao et al. 2013; Brown et al. 2018). However, no AH biomarkers have been identified so far unambiguously predicting the response to anti-VEGF treatment in DME patients.

In this study, proteomics and metabolomics approaches will be combined to analyze AH biomarker composition at baseline in treatment-naïve patients (i.e., predictive). An additional AH sample will be collected, as described in Appendix 1 (i.e., immediately prior to the fifth IVT faricimab injection), in order to explore the effect of faricimab treatment on AH biomarker composition over time (i.e., prognostic). Thus, comprehensive, patient-specific AH biomarker fingerprints will be generated which will increase the chance of identifying AH biomarkers predictive of response to faricimab.

3.3.4 Rationale for Clinical Genotyping

The DME is a multifactorial disease involving complex pathophysiology and genetic associations. Several common and rare genetic variants have been shown to be associated with DME prevalence, progression, and treatment response (Liu et al. 2017). Therefore, clinical genotyping will be performed on DNA isolated from whole blood samples to evaluate potential associations of common or rare genetic variants with multimodal imaging features, AH biomarkers, and clinical assessments of treatment response.

3.3.5 Rationale for Imaging Biomarker Assessments

In recent years, considerable improvements and novel developments in retinal imaging techniques have significantly improved the resolution of images and visualization of the retina. Utilization of imaging plays an important role for the diagnosis of retinal diseases as well as longitudinal assessment of disease progression and treatment response. Several characteristic features of DME can be visualized by multimodal imaging including neovascularization, retinal thickness, intraretinal fluid (IRF), subretinal fluid (SRF), and integrity of the outer retina. In this study, associations over time between clinical assessments, multimodal imaging assessments, AH biomarker patterns, and genetic polymorphisms will be explored.

Table 2 illustrates a non-exhaustive list of multimodal imaging features that may be assessed in patients with DME.

Table 2 Non-exhaustive List of Multimodal Imaging Features for Diabetic Macular Edema

Fluid	Intraretinal fluid (IRF)
	Subretinal fluid (SRF)
	Cystoid height
	Central retinal thickness
Structural	Hyper-reflective foci (HRF)
	Disorganization of retinal inner layers (DRIL)
	Inner segment/outer segment integrity
	External limiting membrane integrity
	Photoreceptor thickness
	Ganglion cell layer thickness
Vascular	Foveal avascular zone (FAZ)/retinal nonperfusion
	Periphery status (ischemia and proliferation)
	Microaneurysm location, number, and turnover
	Ischemic index
	Ischemic area
	Cyst reflectivity

Table of a non-exhaustive list of multimodal imaging features that may be used for advanced analytics associations with AH biomarkers.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 80 patients will be enrolled in this study. Only one eye will be assigned as the study eye. *However, the Sponsor may increase the sample size up to 100 patients, to compensate for those patients who completed the study without having a full set of Day 1 (baseline) and Day 112 visit analyzable AH samples collected. The aim of this increase is to achieve 60 patients with analyzable Day 1 (baseline) and Day 112 visit AH samples (see Section 6.1). The Sponsor may decide to stop the enrollment as soon as the target of 60 analyzable sets of AH samples is reached.*

Prospective approval of protocol deviations, also known as protocol waivers or exemptions are not permitted.

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

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria for study entry:

Informed Consent

1. Signed ICF prior to any study-related assessments
   - All patients are able and willing to provide written informed consent and to comply with the study protocol according to International Council for Harmonisation (ICH) and local regulations.
   - Patients are willing to allow AH collection and in the opinion of the investigator, sampling of >90 µl of AH seems feasible and safe.
2. Ability to comply with the study protocol, in the investigator's judgment

Age

3. Age ≥ 18 years at the time of signing the ICF

Type of DME Patients and Disease Characteristics

4. Diagnosis of diabetes mellitus (Type 1 or Type 2), as defined by the World Health Organization (WHO) and/or American Diabetes Association and
   - Current regular use of insulin or other injectable drugs (e.g., dulaglutide and liraglutide) for the treatment of diabetes

     and/or
   - Current regular use of oral anti-hyperglycemic agents for the treatment of diabetes
5. Hemoglobin A_{1c} (HbA_{1c}) $\leq 10\%$ (historic values up to 2 months before the screening visit will be permissible; otherwise, the study site may collect a sample for analysis at screening)
6. Patients who are IVT treatment-naïve in the study eye (i.e., have not received previous treatment with any anti-VEGF IVT or any corticosteroids periocular or IVT in the study eye).

Ocular Inclusion Criteria for Study Eye

7. DME defined as macular thickening by spectral-domain optical coherence tomography (SD-OCT) involving the center of the macula: CST of ≥ 325 µm with Spectralis® (Heidelberg Engineering, Heidelberg, Germany) at screening. This inclusion criterion is to be assessed by the central reading center (CRC).
8. Decreased VA attributable primarily to DME, with BCVA letter score of 75 to 20 letters (both inclusive) on ETDRS-like charts at the screening visit
9. Clear ocular media and adequate pupillary dilation to allow acquisition of good quality retinal images to confirm diagnosis

Contraception

10. For women of childbearing potential (WOCBP): agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:
    - Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for at least 3 months after the final dose of faricimab.
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
    - Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    - Contraception methods that do not result in a failure rate of $<1\%$ per year such as male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide are not acceptable.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
      If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local ICF.

4.1.2 Exclusion Criteria

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

Medical Conditions

1. Currently untreated diabetes mellitus or previously untreated patients who initiated oral or injectable anti-diabetic medication within 3 months prior to Day 1.
2. Any known hypersensitivity to any of the components in the faricimab injection.
3. Any known hypersensitivity to any contrast media (e.g., fluorescein), dilating eye drops, or any of the anesthetics and antimicrobial preparations used by the patient during the study.
4. Any major illness or major surgical procedure within 1 month before the Day 1. One re-screening for this criterion is permitted.
5. History of other diseases, other non-diabetic metabolic dysfunction, physical examination finding, historical or current clinical laboratory finding giving reasonable

suspicion of a condition that contraindicates the use of the faricimab or that might affect interpretation of the results of the study or renders the patient at high-risk for treatment complications, in the opinion of the investigator.

6. Active cancer within the past 12 months prior to Day 1 except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤6 and a stable prostate-specific antigen for >12 months.
7. Stroke or myocardial infarction within 12 months prior to the Day 1. One re-screening for this criterion is permitted.
8. Any febrile illness within 1 week prior to Day 1. One re-screening for this criterion is permitted.
9. Pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of faricimab.
    - WOCBP must have a negative serum pregnancy test result within 28 days prior to initiation of faricimab and a negative urine pregnancy test at the baseline visit.
10. Uncontrolled blood pressure (BP); defined as systolic >180 mmHg and/or diastolic >100 mmHg (while patient at rest). If a patient's initial reading exceeds these values, a second reading may be taken ≥30 minutes later on the same day. If the patient's BP is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1. One re-screening for this criterion is permitted.
11. Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis within 6 months prior to Day 1 or anticipated to require hemodialysis or peritoneal dialysis at any time during the study.
12. Any condition resulting in a compromised immune system that is likely to impact the AH inflammatory biomarkers. In case of doubt, the investigator should consult with the Medical Monitor.

Prior/Concomitant Therapy

13. Patients who are currently enrolled in or have participated in any other clinical study involving an investigational product or device, or in any other type of medical research, within 3 months or 5 half-lives (whichever is longer) prior to Day 1 and up to completion of the current study. One re-screening for this criterion is permitted.
14. Substance abuse occurring within 12 months prior to screening, in the investigator's judgment.
15. Use of systemic immunomodulatory treatments (e.g., IL-6 inhibitors) within 6 months or 5 half-lives (whichever is longer) prior to Day 1. One re-screening for this criterion is permitted.
16. Use of any systemic corticosteroids *(including inhaled corticosteroids from inhalers used regularly (e.g., pulmonary disease, asthma, or seasonal allergy)* within 1 month prior to Day 1. One re-screening for this criterion is permitted.

Note: Subjects using inhaled corticosteroids occasionally (PRN); PRN use of inhaled corticosteroids is permitted if a 3-day period of abstinence between corticosteroid inhalation and study visit is respected.

17. Systemic treatment for suspected or active systemic infection.

    Note: Ongoing use of prophylactic antibiotic therapy may be acceptable but has to be *in consultation* with the Medical Monitor.

18. Any prior or concomitant systemic anti-VEGF treatment within 6 months or 5 half-lives (whichever is longer) prior to Day 1. One re-screening for this criterion is permitted.

19. Use of systemic medications known to be toxic to the lens, retina, or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, or ethambutol) used during the 6-month period or 5 half-lives (whichever is longer) prior to Day 1 or likely need to be used. One re-screening for this criterion is permitted.

20. Received a blood transfusion within 3 months prior to the screening visit. One re-screening for this criterion is permitted.

21. Received any treatment that leads to immunosuppression within 6 months or 5 half-lives (whichever is longer) prior to Day 1. One re-screening for this criterion is permitted.

Ocular Exclusion Criteria for Study Eye

22. High-risk PDR defined as ETDRS DRSS above 71A (Ip et al. 2012). This exclusion criterion is to be assessed by the CRC.

23. Any history of or ongoing rubeosis iridis

24. Any panretinal photocoagulation or macular laser photocoagulation treatment received in the study eye prior to the screening visit or expected to be received between the screening visit and Day 1.

25. Any history of treatment with anti-VEGF or any periocular or IVT corticosteroids in the study eye and no such treatment planned for the time between screening and Day 1

26. Any treatment for dry eye disease in the last month prior to Day 1 (e.g., cyclosporine eye drops, lifitegrast eye drops). Lubricating eye drops and ointments are permitted. One re-screening for this criterion is permitted.

27. Any treatment with anti-inflammatory eye drops (e.g., doxycycline) within 1 month prior to Day 1. One re-screening for this criterion is permitted.

28. Any intraocular surgery (e.g., cataract surgery) within 3 months prior to Day 1 or any planned surgery during the study. One re-screening for this criterion is permitted.

29. Any glaucoma surgery/*laser procedure involving the iris, trabecular meshwork, or ciliary body* prior to the screening visit. *Only iris surgery/laser might be allowed if they occurred more than 6 months prior to Day 1.*

30. History of vitreoretinal surgery/pars plana vitrectomy, corneal transplant, or radiotherapy
31. Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as IOP $\geq$25 mmHg at the screening visit despite treatment with anti-glaucoma medication)
32. Any active or suspected ocular or periocular infections on Day 1 (i.e., any active infectious or noninfectious conjunctivitis, keratitis, scleritis, or endophthalmitis).
33. Any presence of active intraocular inflammation on Day 1 (i.e., Standardization of Uveitis Nomenclature [SUN] criteria $>$0 or National Eye Institute [NEI] vitreous haze grading $>$0) or any history of intraocular inflammation
34. Any history of idiopathic, infectious, or noninfectious uveitis
35. Any current or history of ocular disease other than DME that may confound assessment of the macula or affect central vision (e.g., age-related macular degeneration, retinal vein occlusion, angioid streaks, histoplasmosis, active or inactive cytomegalovirus retinitis, pathological myopia, retinal detachment, macular traction, macular hole, significant cataract, epiretinal membrane) and could either:
    - Require medical or surgical intervention during the study period to prevent or treat visual loss that might result from that condition; or
    - Preclude any visual improvement due to substantial structural damage; or
    - Preclude, in the opinion of the investigator, acquisition of good quality retinal images to confirm diagnosis.
36. Any current ocular condition or other causes of visual impairment for which, in the opinion of the investigator, VA loss would not improve from resolution of macular edema (e.g., foveal atrophy, pigment abnormalities, dense sub-foveal hard exudates, and non-retinal condition)

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

37. Patient is currently receiving treatment with brolucizumab or bevacizumab in the non-study eye and is unwilling to switch to a protocol allowed non-study eye treatment during the study
38. Any previous treatment with Iluvien® or Retisert® (fluocinolone acetonide IVT implant) in the non-study eye
39. If patients have been treated with corticosteroids periocular or IVT in the non-study eye in the past, the following washout periods prior to the screening visit would apply:
    - Periocular or IVT corticosteroids:
        - Triamcinolone: 6 months;
        - Ozurdex® (dexamethasone IVT implant): 6 months;
40. Non-functioning non-study eye, defined as either:
    - BCVA of hand motion or worse

- No physical presence of non-study eye (i.e., monocular)
- Legally blind in the patient's relevant jurisdiction

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an exploratory, non-randomized, open-label study. After initial written informed consent has been obtained, all patients will receive a unique screening number assigned through an IxRS. After all the screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number through IxRS.

Patients who do not meet the criteria for participation in this study (screen failures) may qualify for 1 re-screening opportunity (for a total of 2 screenings per patient; see Section 3.1.1.2 for further details).

No more than 50% of patients enrolled will have mild or moderate PDR (defined as ETDRS DRSS 60 through 65C [Ip et al. 2012]).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

4.3.1 Study Treatment Formulation and Packaging

Faricimab will be supplied by the F. Hoffmann-La Roche Ltd. as a sterile liquid for IVT injection in single-dose glass vials. The packaging and labeling of faricimab will be in accordance with Roche standards and local regulations. For more detailed information on the formulation and handling of faricimab, see the pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The 6-mg dose of faricimab will be administered IVT at the study site to patients Q4W starting at Day 1 and ending on the Day 140 visit (see the treatment regimen in Section 3.1 and the study treatment schema in Figure 1).

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

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.2 and Section 4.6.1.

The pharmacist responsible for dispensing the study treatment or designated site personnel will prepare the study treatment. The treatment administrator will be a retina specialist (or the equivalent in non-U.S. countries). In addition, ophthalmologists who have completed ≥2 full years of ophthalmology residency (or the equivalent in

non-U.S. countries) may be permitted to perform the role of treatment administrator following Sponsor approval.

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

Vials of faricimab drug product are for a single-dose only (one injection preparation per patient per eye). Vials used for one patient must not be used for any other patient. Partially used vials, remaining faricimab drug product, as well as administration material must not be reused.

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

4.3.3 Continued Access to Faricimab

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

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

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

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

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

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

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

** Macular Edema can cause severe vision loss and even blindness. As such it is considered a severe medical condition.*

4.3.4 Investigational Medicinal Product Handling and Accountability

The 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 disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site must follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMP supplied by the Sponsor to confirm the shipment condition and content. Any damaged shipments will be replaced. The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit*, either by time monitoring (shipment arrival date and time) or temperature monitoring,* for all IMP received and that any discrepancies have been reported and resolved before use of the IMP. All 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 can receive IMP, and only authorized staff can supply or administer IMP.

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

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

Refer to the pharmacy manual for information on IMP handling, including preparation and storage, and accountability.

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any prescription drugs or over-the-counter preparations or procedures other than protocol-specified procedural medications (e.g., dilating drops or fluorescein dyes, proparacaine, or antimicrobials [if applicable]) used by a patient within 7 days preceding the baseline visit and through the conclusion of the patient's study participation or ETV. Patients required to use therapy that is prohibited (see Section 4.4.2) will not be eligible for the study.

All concomitant medications/treatments should be reported to the investigator and recorded on the eCRF along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency).

4.4.1 Permitted Therapy

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

- Onset of ocular hypertension or glaucoma in the study eye during a patient's study participation should be treated as clinically indicated.
- Onset of cataract or posterior capsular opacification in either eye during a patient's study participation may be treated as clinically indicated. Dose interruption criteria (see Section 5.1.2.2, Section 5.1.2.3, and Table 3 may apply if cataract surgery is required.
- Short-term use of topical ocular corticosteroids after cataract surgery, yttrium-aluminum garnet capsulotomy, peripheral iridotomy, argon/selective laser trabeculoplasty, or ocular allergic conditions.

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

At the discretion of the investigator, the patient's fellow eye (non-study eye) may be treated with anti-VEGF therapy licensed for ocular use if they are diagnosed with an ocular condition for which the selected anti-VEGF therapy (except brolucizumab) is approved by the country regulatory agency (SOC). Should the fellow eye require treatment during the study, the Sponsor will cover the cost of the approved licensed ocular anti-VEGF therapy (except brolucizumab *and Susvimo ™*) in accordance with local regulations*, until faricimab is made available in that region, after which the Sponsor will support fellow-eye treatment with faricimab* as long as the patient remains in the study. *Any exceptions for ongoing reimbursement of other anti-VEGF therapies must be approved by the Sponsor.*

Fellow eye treatment reimbursement will cease if the patient is discontinued from faricimab study treatment. Fellow eye treatment reimbursement will cease once the patient has completed the trial.

Study eye treatment and fellow eye treatment with anti-VEGF agents may be done at the same study visit; however, the study eye should receive study treatment per protocol

prior to anti-VEGF treatment in the fellow eye. *Note: Bevacizumab is not licensed for ophthalmic use in any country; therefore, it is prohibited to be used.*

If (per the investigator's judgment) treatment with anti-VEGF is to be given to the fellow eye (non–study eye) at the same visit as the study eye treatment, study eye assessments (including study eye study treatment administration) must be completed first. If there are no safety concerns, the site may proceed with the fellow eye treatment administered by a qualified physician.

Individual trays and sterile preparation must be separately prepared for each eye treatment.

4.4.2 Prohibited Therapy

At the discretion of the Investigator, patients may continue to receive medications and standard treatments administered for other conditions. However, the following medications and treatments are prohibited from use during a patient's study treatment participation. Patients may be discontinued from study treatment and/or the study to receive these therapies:

- Systemic anti-VEGF therapy
- Systemic immunomodulatory treatments
- Systemic drugs known to cause macular edema (e.g., fingolimod, tamoxifen)
- Systemic drugs known to be toxic to the lens, retina or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, and ethambutol)
- IVT anti-VEGF agents (other than study-assigned faricimab in study eye or the protocol allowed anti-VEGF therapy in the non-study eye) (see Section 4.4.1)
- IVT, periocular (subtenon), steroid implants (i.e., Ozurdex®, Iluvien®, Retisert®), or chronic topical ocular corticosteroids in study eye and the non-study eye *(defined as continuous usage for 100 days or longer).*
- Treatment with Visudyne®
- Administration of MicroPulse® and focal or grid laser in study eye
- Panretinal photocoagulation or macular laser photocoagulation treatment in the study eye
- Receipt of a blood transfusion
- Treatment that leads to immunosuppression
- Other experimental therapies (except those comprising vitamins and minerals), including investigational products and devices, *and therapies that claim to have an effect on macular pathology (e.g., herbal therapies/traditional Chinese medicines with anti-AMD activity or any activity in promoting blood circulation).*

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient. Protocol waivers or exemptions are not allowed.

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

4.5.1 Informed Consent Forms and Screening Log

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

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

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

Medical history, including clinically significant diseases, chronic and ongoing conditions (e.g., trauma, cancer, cardiovascular, cerebrovascular, and ophthalmic comorbidities/history), surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history will be recorded at the screening visit and reconfirmed at baseline visit. In addition, as described in Section 4.3.4, all concomitant treatments/medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by a patient within 7 days preceding the baseline visit and through the conclusion of the patient's study participation or ETV should be reported to the Investigator and recorded on the eCRF.

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

4.5.3 Physical Examinations

A targeted physical examination performed at screening, the SFV, and the ETV should include an evaluation of the head, *eyes,* ears, nose, and throat. If any abnormalities are noted during the study, the patient may be referred to another doctor.

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

4.5.4 Vital Signs

Vital signs will include measurements of temperature, heart rate, and systolic and diastolic BP. Vital signs will be taken with the patient in a seated position after resting for 5 minutes. Record abnormalities observed at the screening visit on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Ocular Assessments

Ocular assessments include the following and will be performed for the study eye and the non-study eye (when indicated) at specified timepoints according to the schedule of activities in Appendix 1:

- Refraction and BCVA assessed on ETDRS chart at a starting distance of 4 meters (perform prior to dilating eyes; see Appendix 4).
- IOP at the screening visit and IOP at the SFV or ETV (perform prior to dilating eyes)
- Pretreatment IOP of the study eye and, if applicable, the non-study eye (fellow eye) (perform prior to dilating eyes)
- Slit lamp examination (for grading scales for AC flares, AC cells, and vitreous cells, see Appendix 3)
- Dilated binocular indirect high-magnification ophthalmoscopy
- Finger-counting test followed by hand motion and light perception tests (when necessary) performed within approximately 15 minutes of post-study treatment in the study eye and, if applicable, in the non-study eye (fellow) eye.
- At study treatment visits, post-treatment IOP measurement in the study eye and, if applicable, in the non-study eye (fellow eye) should be performed 30 (±15) minutes post-treatment (thus also after the AH tap [study eye only]) by qualified personnel. If there are no safety concerns after 30 (±15) minutes following the study treatment, the patient will be permitted to leave. If the IOP value is of concern to the investigator, the patient will remain in the clinic and will be managed in accordance with the investigator's clinical judgment. The adverse event will be recorded on the adverse event eCRF as applicable the clinic.

The *same device must be* used *to assess the* patient*'s pre-treatment IOP and their post-treatment IOP, and* must remain consistent throughout the study.

Ocular Imaging

The CRC will provide the study sites with the Image Acquisition Guidelines and training materials for specified study ocular images. Before any study images are obtained, site personnel, test images, systems, and software (where applicable) will be certified and validated by the CRC as specified in the Image Acquisition Guidelines. All ocular

images results will be obtained by trained site personnel at the study sites and forwarded to the CRC for independent analysis and/or storage.

Ocular images include the following and will be performed for the study eye and the non-study eye (when indicated) at specified timepoints according to the schedule of activities in Appendix 1:

- Stereo color fundus photographs (CFP) using 7-modified field imaging and ultra-wide field color fundus photography (UWF-CFP) (Appendix 5)
- Fundus fluorescein angiography using the UWF-FFA imaging performed (Appendix 6)
- SD-OCT images (Appendix 7)
- Swept-source optical coherence tomography (SS-OCT) images (if capable) (Appendix 7)
- Swept-source optical coherence tomography angiography (SS-OCT-A) or spectral-domain optical coherence tomography angiography (SD-OCT-A) images (Appendix 7)
- AO (at selected study sites only; if the patient is suitable according to the investigator's judgement) (Appendix 8)

Additional details on obtaining these images are included in the Image Acquisition Guidelines.

Ocular images collected from study patients will be evaluated using advanced analytics tools (e.g., artificial intelligence–based tools) to assess clinically relevant features in order to evaluate the performance of the tools; any results will not be used for treatment decisions in the study.

4.5.6 Concurrent Ocular Procedures

Any ocular procedures performed on either eye during the study (from Day 1, post study treatment until the SFV or the ETV) will be recorded on the eCRF.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Fasting is not required prior to specimen collection. See Appendix 1 for sample collection timepoints and Appendix 9 for biological sample collection and shipping instructions.

Samples for the following laboratory tests will be sent to a study site's local laboratory for analysis:

- A blood sample for the assessment of HbA_{1c} will be obtained during screening in case no historic HbA_{1c} values up to 2 months before the screening visit are available. All patients will be required to have an HbA_{1c} sample collection on Day 1 (baseline), the Day 112 visit, and at the SFV or the ETV. Note: In case an HbA_{1c} assessment occurred at screening (in case no historic HbA_{1c} values up to 2 months

before the screening visit are available), this assessment does not have to be repeated at baseline, as long as the baseline visit occurs within 28 days after the screening.

- Pregnancy tests are required for WOCBP only. A negative serum pregnancy test is required for enrollment (i.e., at the screening visit). If any urine pregnancy test is positive during the treatment period or the safety follow-up period, it must be confirmed by a serum pregnancy test. If the serum pregnancy test is positive during the treatment period, do not administer study treatment. A pregnancy test (serum or urine, as applicable) must always be timed to occur before administration of the fluorescein for the UWF-FFA; a negative test is required before administration of the fluorescein.

The HbA_{1c} samples and the pregnancy tests (serum or urine as indicated) will be destroyed after their analysis during the study.

4.5.7.1 Aqueous Humor Biomarker Assessments

A mandatory study eye AH paracentesis sample (sampling of >90 µL) will be collected just prior to the 6 mg faricimab IVT injection by a qualified treatment administrator (i.e., same retina specialist/ophthalmologists will perform both the faricimab IVT injection and AH sample collection), using an aseptic procedure and sterile field and according to local guidelines (see Appendix 9 and the central lab manual for aqueous samples collection, storage, and transfer). The bulbar tension has to be assessed manually immediately after the AH tap. If the bulbar tension is deemed by the treatment administrator to be too low to be able to perform a safe IVT injection, a re-toning with saline solution should be performed through a paracentesis.

The AH sample will be collected at baseline and at the Day 112 visit (see Appendix 1). The actual date and time of each sample collection, as well as the weight of the collected sample will be recorded. The AH sample must be frozen at -80°C immediately or within ≤ 15 minutes from collection (see the central laboratory manual for details).

A panel of protein biomarkers (which may include VEGF, interleukin-6, interleukin-8, placental growth factor, intercellular adhesion molecule-1, platelet-derived growth factor, Ang-2, and others) will be analyzed in AH samples by multiplex assay technology. In addition to this targeted analysis, and depending on the AH volume collected, the global protein and/or metabolite composition of the AH samples will also be analyzed employing, for example, liquid chromatography–mass spectrometry analyses. The AH analysis strategy may evolve over time based on accumulated results.

The AH samples will be destroyed ≤ 5 years after the final Clinical Study Report has been completed. When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

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

4.5.7.2 Clinical Genotyping Assessments

A mandatory whole blood sample will be collected for clinical genotyping at baseline (see Appendix 1). The DNA isolated from whole blood may be used for, but is not limited to, genotyping of genetic variants associated with DME prevalence and treatment response (e.g., complement factors, ARMS2-HTRA1, VEGF, VEGF receptor 1, pigment epithelium-derived factor, etc.).

Samples collected for clinical genotyping include, but are not limited to, genomic analysis and may be sent to one or more laboratories for analysis of germline or somatic mutations of above mentioned biomarkers via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods.

Genomics is increasingly informing researchers' understanding of disease pathobiology. The WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study and restricted to retinal diseases but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, potentially guiding the development of new targeted agents.

Given the complexity and exploratory nature of these analyses, the data and analyses will not be shared with Investigators or patients unless required by law. Patients will not be identified by name or any other personally identifying information.

For sampling procedures, storage conditions, and shipment instructions, see Appendix 9 and the central laboratory manual.

The whole blood samples will be destroyed ≤ 5 years after the final Clinical Study Report has been completed. When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

An excessive rate of withdrawals (either patients discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of patients should be avoided and efforts should be taken to

motivate patients to comply with all the study-specific procedures as outlined in this protocol.

4.6.1 Study Treatment Discontinuation

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

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

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced and will not be allowed to restart study treatment. However, patients who discontinue from the study treatment early (prior to the SFV) but have not withdrawn consent and have not been lost to follow-up should return for an ETV after $\geq$28 days have elapsed following their last study treatment (visit should occur within $<$35 days of the patient's last study treatment).

4.6.2 Patient Discontinuation from the Study

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

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

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the Investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced. However, patients who discontinue from the study early (prior to the SFV) but have not withdrawn consent and have not been lost to follow-up should return for an ETV after $\geq$28 days have elapsed following their last study treatment (visit should occur within $<$35 days of the patient's last study treatment).

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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 RO6867461 (faricimab) Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. The schedule of safety assessments to be performed during the study is provided in Appendix 1. Patients will be instructed to contact the site at any time if they have any health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 2).

In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation are provided below.

Pandemic Preparedness:

Patients on prior or concomitant treatments/medications for active infection are excluded from study participation. It is not anticipated that faricimab will increase the risk of

infection with SARS-CoV-2, but study treatment may be interrupted for medically significant systemic infection in consultation with the Medical Monitor. During the patient's study visits, sites should follow local/institutional guidelines for COVID-19 management or those of applicable professional societies (e.g., American Academy of Ophthalmology, American Society of Retina Specialists), should SARS-CoV-2 be circulating in the locality during study conduct.

5.1.1 Risks Associated with Faricimab

The anticipated safety risks for faricimab *are outlined below; these risks are either from the drug itself or the injection procedure.*

Anticipated risks of faricimab include intraocular inflammation, the IVT injection-related risks of infectious endophthalmitis, retinal detachment/tear, and *transient* increased IOP. Potential risks *associated with faricimab include* iatrogenic traumatic cataract, *immunogenicity*, as well as the non-ocular risk of arterial thromboembolic events.

Please see the RO6867461 (faricimab) Investigator's Brochure for more details on the *safety information for* faricimab.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications

Dose modifications will not be performed in this study.

5.1.2.2 Treatment Interruption

If any of the dose interruption and treatment discontinuation criteria specified in Table 3 are met, treatment will be interrupted (or discontinued, if applicable) and will not be resumed earlier than the next scheduled study visit. The reason for study treatment interruption/discontinuation should be recorded on the appropriate eCRF and, if applicable, on the adverse event eCRF.

5.1.2.3 Management Guidelines

Study treatment interruption and/or patient discontinuation from the study treatment for adverse events will be determined using the criteria listed in Table 3.

Table 3 Dose Interruption and Treatment Discontinuation Criteria

Event	Criteria
Intraocular inflammation	• Interrupt study treatment if intraocular inflammation (iritis, iridocyclitis, or vitritis) is ≥ 2+ in the study eye. • Study treatment may be resumed subsequently as determined by the investigator.
Cataract surgery in the study eye	• Interrupt study treatment after cataract surgery in study eye. • Study treatment may be resumed no earlier than 28 days after an uncomplicated cataract surgery and no evidence of post-operational inflammation at that time. For cataract surgery with complications, study treatment may be permitted *by the* investigator *following consultation with the* Medical Monitor.
BCVA decrease	• Interrupt study treatment if there is a study treatment–related decrease in BCVA of ≥ 30 letters in the study eye compared with the last assessment of BCVA prior to the most recent treatment. • Study treatment may be permitted subsequently, as determined by the investigator.
Elevated IOP	• Interrupt study treatment if pretreatment IOP in the study eye is ≥ 30 mmHg. • Treatment may be permitted when IOP has been lowered to < 30 mmHg, either spontaneously or by treatment, as determined by the investigator.
Rhegmatogenous retinal break	• Interrupt study treatment if a retinal break is present in the study eye. • Study treatment may be resumed no earlier than 28 days after successful laser retinopexy, as determined by the investigator.
Rhegmatogenous retinal detachment or macular hole	• Interrupt study treatment if rhegmatogenous retinal detachment or Stage 3 or 4 macular hole occurs in the study eye. • Study treatment may be subsequently permitted *by the investigator following consultation* with *the* Medical Monitor.
Active or suspected infection	• Interrupt study treatment if active or suspected ocular or periocular infections are present (e.g., infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis) in either eye or if the patient requires treatment for an active systemic infection. Study treatment may be interrupted for other medically significant systemic infection in consultation with Medical Monitor.
On-study prohibited medications	• Refer to Section 4.4.2 for additional reasons for potential study treatment discontinuation.

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital

signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.8 and 5.3.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

- Is a significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., within ≤24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

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

Adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., within ≤24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Sight-threatening adverse events: an adverse event is considered to be sight-threatening and should be reported expeditiously if it meets one or more of the following criteria:

  It causes a decrease of ≥30 letters in VA score (compared with the last assessment of VA prior to the most recent assessment) lasting more than 1 hour.

  It requires surgical or medical intervention (i.e., conventional surgery, vitrectomy, vitreous tap, or biopsy with IVT injection of anti-infective treatments, or laser or retinal cryopexy with gas, or a medication) to prevent permanent loss of sight.

It is associated with severe intraocular inflammation (i.e., endophthalmitis, 4 +AC cell/flare, or 4 +vitritis; see Section 5.3.5 and Appendix 3 for intraocular inflammation grading scales).

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

Please note, throughout the entire study period, the retinal physician is expected to assess adverse events, which includes assigning causality and severity of the event.

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until the SFV ($\geq$28 to $<$35 days from last study treatment). For patients who terminate study treatment and from the study early, all adverse events will be reported up to the ETV. For patients who discontinue study treatment early but continue to participate in the study, adverse events will be reported until their last or final study visit.

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

5.3.2 Eliciting Adverse Event Information

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

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 4 provides guidance for assessing adverse event severity.

Table 4 Adverse Event Severity Grading Scale

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see Table 5):

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

Table 5 Causal Attribution Guidance

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

5.3.5 Procedures for Recording Adverse Events

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

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

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

- Iritis: the presence of inflammatory cells in the AC

  The presence of aqueous flare alone will not constitute iritis but should be documented as an AC 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 AC, implying a suspected underlying infectious cause

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

Note: Trace benign, aqueous pigmented cells visible on slit lamp examination that are 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.

5.3.5.1 Diagnosis Versus Signs and Symptoms

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., within $\leq$24 hours after learning that the event became serious; see Section 5.4.2 for

reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

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

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

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

5.3.5.5 Abnormal Vital Sign Value

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

- Is accompanied by clinical symptoms

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

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

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

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

5.3.5.6 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., within $\leq$24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

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

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

be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

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

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Diabetic Macular Edema or Diabetic Retinopathy in the Study Eye

Medical occurrences or symptoms of deterioration that are anticipated as part of study eye DME or DR should be recorded as an adverse event if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of study eye DME or DR 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 diabetic macular edema"). The expedited reporting requirements for associated sight threatening events (listed in the Section 5.2.3) will apply.

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

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

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

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

  The patient has not experienced an adverse event.

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

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

5.3.5.11 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.

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., within ≤24 hours after learning of the event; see Section 5.4.2). For faricimab, 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.

In addition, all special situations associated with faricimab, 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.

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.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., within $\leq$24 hours after becoming aware of the information). New significant information includes the following:

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board (IRB)/Ethics Committee (EC).

5.4.1 Medical Monitors and Emergency Medical Contacts

Contact Information for Sites in North and South America

Medical Monitor: [redacted], M.D. (Primary)

Telephone No.: [redacted]

Mobile Telephone No.:

Contact Information for Sites in Europe

Medical Monitor: [redacted], M.D. (Primary)

Telephone No.: [redacted]

Mobile Telephone No.:

Alternate Medical Monitor Contact Information for All Sites

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

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special *Situations* Form provided to Investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., within ≤ 24 hours after learning of the event), either by faxing or scanning and emailing the form using the fax number or email address provided to Investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until SFV (≥28 to <35 days from last study treatment). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special *Situations* Form provided to Investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., within ≤24 hours after learning of the event), either by faxing or scanning and emailing the form using the fax number or email address provided to Investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., within ≤24 hours after learning of the pregnancy), either by faxing or scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the Investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., within ≤24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., within ≤24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., within ≤24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The Investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the patient is lost to

follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the Investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (until the SFV [≥28 to <35 days from the last study treatment]), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special *Situations* Form using the fax number or email address provided to Investigators.

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document for IMPs:

- RO6867461 (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 reference document.

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

All exploratory outcomes will be analyzed in the modified intent-to-treat (mITT) population. The mITT population is defined as all patients enrolled in the study that received any amount of study medication. Safety analyses will be performed on the safety-evaluable population, which consists of all patients who receive any amount of study medication. Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

In this exploratory study, the sample size is based on practical considerations. Approximately 80 patients will be enrolled in the study. With a minimum of 40 patients, there is approximately 80% power to demonstrate that a correlation of 0.4 is statistically significantly different from 0 (alpha = 0.05). Sample size was *calculated* to 80 to account (adjust) for exploratory multivariate analyses that may be performed to model clinical outcomes based on multiple AH biomarkers.

The Sponsor may increase the sample size up to 100 patients, to compensate for those patients who completed the study *without having a full set of Day 1 (baseline) and Day 112 visit analyzable* AH samples collected. The aim of this increase is to achieve 60 patients with analyzable* Day 1 (baseline) and Day 112 visit AH samples. The Sponsor may decide to stop the enrollment as soon as the target of 60 analyzable* sets of AH samples is reached.*

** Analyzable refers to the AH samples with no major deviations that will be analyzed by at least one specialty laboratory.*

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics such as age, sex, and race/ethnicity and baseline disease characteristics (such as baseline BCVA, ocular assessments, and medical history) will be summarized using means, SDs, medians, and ranges for continuous variables, and counts and proportions for categorical variables, as appropriate. Exposure to study drug (number of study drug administrations and duration of treatment) will be summarized for the safety-evaluable population.

6.4 EXPLORATORY ANALYSES

The objective of this study is to explore the associations over time between clinical assessments, multimodal imaging assessments, AH biomarker patterns, and genetic polymorphisms of treatment-naïve DME patients treated with faricimab on the basis of the endpoints listed in Table 1. Scatterplots and correlation coefficients (Pearson or Spearman depending on the data type) will be produced to examine the pairwise associations of variables. As this is an exploratory analysis, the magnitude of the correlations will be examined in conjunction with the plots to assess nature of the relationship (linear or nonlinear) and if it is representative of the relationship or driven by a few outliers. No missing data will be imputed. Data may be subjected to post-hoc analyses as science evolves.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all enrolled patients who received at least one dose of study drug.

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

Study treatment exposure (treatment duration and number of study drug administrations) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to the scale provided in Table 4. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

6.6 INTERIM ANALYSES

As this is an open-label study, no formal interim analyses are planned. Exploratory analyses of selected endpoints may be performed during the course of the study (e.g., after all patients have completed the Day 28 visit and the necessary data are available).

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Study sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the study sites, which the study sites will resolve electronically in the EDC system.

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

The Sponsor's sample ICF (and ancillary sample ICF such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate Consent Forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

The Consent Forms must be signed and dated by the patient before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A patient who is re-screened is not required to sign another ICF if the re-screening occurs within 28 days from the previous ICF signature date.

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

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

8.4 CONFIDENTIALITY

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

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

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management and some activities will be outsourced to CROs (e.g., data management and medical monitoring) but the Sponsor will perform oversight of them and the accountability will remain at the Sponsor. Approximately 35 global study sites will participate to enroll approximately 80 patients. *However, the Sponsor may increase the sample size up to 100 patients, to compensate for those patients who completed the study without having a full set of Day 1 (baseline) and Day 112 visit analyzable AH samples collected. The aim of this increase is to achieve 60 patients with analyzable Day 1 (baseline) and Day 112 visit AH samples (see Section 6.1). The Sponsor may decide to stop the enrollment as soon as the target of 60 analyzable sets of AH samples is reached.* Enrollment will occur through an IxRS. Central facilities will be used for certain study assessments throughout the study (e.g., biomarker and CRC), as specified in Section 4.5. If needed as per Appendix 1, accredited local laboratories will be used.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331:1480-7.

Antonetti DA, Lieth E, Barber AJ, et al. Molecular mechanisms of vascular permeability in diabetic retinopathy. Semin Ophthalmol 1999;14:240-8.

Atebara NH, Brown GC, Cater J. Efficacy of anterior chamber paracentesis and Carbogen in treating acute nonarteritic central retinal artery occlusion. Ophthalmology 1995;102(12):2029-34; discussion 2034-5.

Brown CV, Green BD, Thompson RB, den Hollander AI, Lengyel I and on behalf of the EYE-RISK consortium. Metabolomics and Age-Related Macular Degeneration. Metabolites 2018;9(1).

Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355(14):1432-44.

Carnahan MC, Platt LW. Serial paracentesis in the management of acute elevations of intraocular pressure. Ophthalmology 2002;109(9):1604-6.

Chen JC, Cheema D. Repeated anterior chamber paracentesis for the treatment of central retinal artery occlusion. Can J Ophthalmol 1994;29(4):207-9.

Cheung CM, Durrani OM, Murray PI. The safety of anterior chamber paracentesis in patients with uveitis. Br J Ophthalmol 2004;88(4):582-3.

Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening and novel therapies. Diabetes Care 2003;26:2653–64.

Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology 2016;123:1751-61.

Davidson JA, Ciulla TA, McGill JB, et al. How the diabetic eye loses vision. Endocrine 2007;32:107–16.

Davis S, Aldrich TH, Jones PF, et al. Isolation of angiopoietin-1, a ligand for the TIE2 receptor, by secretion-trap expression cloning. Cell 1996;87:1161–9.

Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010:117:1064–77. Epub: 28 April 2010.

Elman MJ, Ayala A, Bressler NM, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. Ophthalmology 2015;122:375–81.

Fauser S, Muether PS. Clinical correlation to differences in ranibizumab and aflibercept vascular endothelial growth factor suppression times. Br J Ophthalmol 2016; 100(11):1494-1498.

Fauser S, Schwabecker V, Muether PS. Suppression of intraocular vascular endothelial growth factor during aflibercept treatment of age-related macular degeneration. Am J Ophthalmol 2014;158(3):532-6.

Ferris FL 3rd, Patz A. Macular edema. A complication of diabetic retinopathy. Surv Ophthamol 1984;28 Suppl:452–61.

Fiedler U, Krissl T, Koidl S, et al. Angiopoietin-1 and angipoietin-2 share the same binding domains in the Tie-2 receptor involving the first Ig like loop and the epidermal growth factor-like repeats. J Biol Chem 2003;278:1721–7.

Fong DS, Aiello LP, Ferris FL 3rd, et al. Diabetic retinopathy. Diabetes Care 2004;27:2540-53.

Funatsu H, Yamashita H, Noma H, et al. Aqueous humor levels of cytokines are related to vitreous levels and progression of diabetic retinopathy in diabetic patients. Graefes Arch Clin Exp Ophthalmol 2005;243(1):3-8.

Gardner TW, Antonetti DA, Barber AJ, et al. Diabetic retinopathy: more than meets the eye. Surv Ophthalmol 2002;47(Suppl 2):S253–62.

Girach A, Lund-Andersen H. Diabetic macular oedema: a clinical overview. Int J Clin Practice 2007;61:88–97.

Gohil R, Crosby-Nwaobi R, Forbes A, Burton B, Hykin P, Sivaprasad S. Caregiver Burden in Patients Receiving Ranibizumab Therapy for Neovascular Age Related Macular Degeneration. PLoS One 2015;10(6):e0129361.

Heier 2012. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012;119(12):2537-48.

Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials [published online ahead of print, 21 Jan 2022]. Lancet. 2022;S0140-6736(22)00010-1. doi:10.1016/S0140-6736(22)00010-1.

Henricsson M, Sellman A, Tyrberg M, Groop L. Progression to proliferative retinopathy and macular oedema requiring treatment. Assessment of the alternative classification of the Wisconsin Study. Acta Ophthalmol Scand 1999;77(2):218-23.

Hutton-Smith LA, Gaffney EA, Byrne HM, Maini PK, Gadkar K, Mazer NA. Ocular Pharmacokinetics of Therapeutic Antibodies Given by Intravitreal Injection: Estimation of Retinal Permeabilities Using a 3-Compartment Semi-Mechanistic Model. Mol Pharm 2017;14(8):2690-2696.

International Diabetes Federation. International Diabetes Federation: Diabetes Atlas, 9th ed. 2019 (cited 11 May 2020). Available from: www.idf.org/diabetesatlas.

Ip MS, Domalpally A, Hopkins JJ, Wong P, Ehrlich JS. Long-term effects of ranibizumab on diabetic retinopathy severity and progression. Arch Ophthalmol 2012;130(9):1145-1152. doi:10.1001/archophthalmol.2012.1043

Johnson MW. Etiology and treatment of macular edema. Am J Ophthalmol 2009;147:11-21.

Joussen AM, Poulaki V, Qin W, et al. Retinal vascular endothelial growth factor induces intercellular adhesion molecule-1 and endothelial nitric oxide synthase expression and initiates early diabetic retinal leukocyte adhesion in vivo. Am J Path 2002;160:501-9.

Kitazawa K, Sotozono C, Koizumi N, Nagata K, Inatomi T, Sasaki H, Kinoshita S. Safety of anterior chamber paracentesis using a 30-gauge needle integrated with a specially designed disposable pipette. Br J Ophthalmol 2017;101(5):548-550.

Leasher JL, Bourne RR, Flaxman SR, et al., Vision Loss Expert Group of the Global Burden of Disease Study. Global estimates on the number of people blind or visually impaired by diabetic retinopathy: a meta-analysis from 1990 to 2010. Diabetes Care 2016;39:1643–9. doi: 10.2337/dc15-2171.

Liu E, Craig JE, Burdon K. Diabetic macular oedema: clinical risk factors and emerging genetic influences. Clin Exp Optom 2017;100(6):569-576.

Maisonpierre PC, Suri C, Jones PF, et al. Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis. Science 1997;277:55-60.

Mastropasqua R, D'Aloisio R, Di Nicola M, Di Martino G, Lamolinara A, Di Antonio L, Tognetto D, Toto L. Relationship between aqueous humor cytokine level changes and retinal vascular changes after intravitreal aflibercept for diabetic macular edema. Sci Rep 2018;8(1).

Muether PS, Droege KM, Fauser S. Vascular endothelial growth factor suppression times in patients with diabetic macular oedema treated with ranibizumab. Br J Ophthalmol 2014;98(2):179-81.

Muether PS, Hermann MM, Dröge K, et al. Long-term stability of vascular endothelial growth factor suppression time under ranibizumab treatment in age-related macular degeneration. Am J Ophthalmol 2013;156:989-93.e2.

Muether PS, Hermann MM, Viebahn U, Kirchhof B, Fauser S. Vascular endothelial growth factor in patients with exudative age-related macular degeneration treated with ranibizumab. Ophthalmology. 2012;119(10):2082-6.

Noma H, Funatsu H, Yamasaki M, et al. Aqueous humour levels of cytokines are correlated to vitreous levels and severity of macular oedema in branch retinal vein occlusion. Eye (Lond) 2008;22(1):42-8.

Park SW, Yun JH, Kim JH, et al. Angiopoietin 2 induces pericyte apoptosis via α3β1 integrin signaling in diabetic retinopathy. Diabetes 2014;63:93057-68.

Pleyer U and Garweg J (2008) Anterior Chamber Tap and Aqueous Humor Analysis. In: Becker M., Davis J. (eds) Surgical Management of Inflammatory Eye Disease. Springer, Berlin, Heidelberg.

Prenner JL, Halperin LS, Rycroft C, Hogue S, Williams Liu Z, Seibert R. Disease Burden in the Treatment of Age-Related Macular Degeneration: Findings from a Time-and-Motion Study. Am J Ophthalmol 2015;160(4):725-31.

Rangasamy S, Srinivasan R, Maestras J, et al. A potential role for angiopoietin 2 in the regulation of blood–retinal barrier in diabetic retinopathy. Invest Ophthamol Vis Sci 2011;52:3784–91. doi: 10.1167/iovs.10-6386.

Roche Report 1056925. Efficacy of RO6867461 in the laser-induced model of choroidal neovascularization in non-human primate. July 2013.

Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355(14):1419-31.

Saxena S, Lai TY, Koizumi H, Farah ME, Ferrara D, Pelayes D, Sato T, Meyer CH, Murray T; International Pharmacokinetic Collaboration. Anterior chamber paracentesis during intravitreal injections in observational trials: effectiveness and safety and effects. Int J Retina Vitreous 2019;5:8.

Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology 2014;121:193-201.

Susvimo ™(ranibizumab injection) U.S. Package Insert, Genentech, Inc. [cited: 11 February 2022]. Available from: https://www.gene.com/download/pdf/susvimo_prescribing.pdf.

Trivedi D, Denniston AK, Murray PI. Safety profile of anterior chamber paracentesis performed at the slit lamp. Clin Exp Ophthal 2011;39(8):725-8.

Van der Lelij A, Rothova A. Diagnostic anterior chamber paracentesis in uveitis: a safe procedure? Br J Ophthalmol 1997;81(11):976-9.

Varano M, Eter N, Winyard S, Wittrup-Jensen KU, Navarro R, Heraghty J. Current barriers to treatment for wet age-related macular degeneration (wAMD): findings from the wAMD patient and caregiver survey. Clin Ophthalmol 2015;9:2243-50.

Vukicevic M, Heraghty J, Cummins R, Gopinath B, Mitchell P. Caregiver perceptions about the impact of caring for patients with wet age-related macular degeneration. Eye (Lond) 2016;30(3):413-21.

Wykoff CC, Abreu F, Adamis AP, et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic

macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials [published online ahead of print, 21 Jan 2022]. Lancet. 2022;S0140-6736(22)00018-6. doi:10.1016/S0140-6736(22)00018-6.

Yao J, Liu X, Yang Q, et al. Proteomic analysis of the aqueous humor in patients with wet age-related macular degeneration. Proteomics Clin Appl. 2013;7(7-8):550-60.

Zhang X, Lai TYY. Baseline predictors of visual acuity outcome in patients with wet age-related macular degeneration. Biomed Res Int 2018 Available from: https:doi.org/10.1155/2018/9640131.

Appendix 1
Schedule of Activities

	Screening Period	Treatment Period						Safety Follow-up Period	-
Visit Name	**Screening Visit**	**Baseline Visit**	**-**	**-**	**-**	**-**	**-**	**SFV**	**ETV [a]**
Visit Week	**-4 to -1**	**NA**	**4**	**8**	**12**	**16**	**20**	**24**	**-**
Visit Day	**-**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**-**
Visit Window (days)	**-28 to -1**	**NA**	**± 7**	**± 7**	**±7**	**± 7**	**± 7**	**≥28 to <35 days from last study treatment**	**≥28 to <35 days from last study treatment [a]**
Informed consent [b]	x	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	x	-	-	-	-	-	-	-	-
Medical history [c]	x	x	-	-	-	-	-	-	-
Previous and/or concomitant treatments/medications [d]	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [e]		x	x	x	x	x	x	x	x
Demographics (age, sex, and self-reported race/ethnicity)	x	-	-	-	-	-	-	-	-
Physical examination [f]	x	-	-	-	-	-	-	x	x
Vital signs [g]	x	-	-	-	-	-	-	x	x
Pregnancy test (serum) [h]	x	-	-	-	-	-	-	-	-
Pregnancy test (urine) [h]	-	x	x	x	x	x	x	x	x
HbA_{1c} test [i]	x	x	-	-	-	x	-	x	x
Blood draw for clinical genotyping	-	x	-	-	-	-	-	-	-
Refraction and BCVA assessed on ETDRS chart [j]	x	x	x	x	x	x	x	x	x
UWF-CFP [k]	x	x	x	x	x	x	x	x	x
CFP (7-modified field fundus imaging) [k]	x	x	-	-	-	-	x	-	x
SD-OCT and (if capable) SS-OCT [k, l]	x	x	x	x	x	x	x	x	x
SD-OCT-A or SS-OCT-A [k, l]	x	x	x	x	x	x	x	x	x
UWF-FFA [m]	x	-	-	-	-	-	x	-	x
AO (selected study sites only) [m]	-	x	-	-	-	-	x	-	-

Appendix 1: Schedule of Activities

	Screening Period	Treatment Period						Safety Follow-up Period	-
Visit Name	**Screening Visit**	**Baseline Visit**	**-**	**-**	**-**	**-**	**-**	**SFV**	**ETV [a]**
Visit Week	**-4 to -1**	**NA**	**4**	**8**	**12**	**16**	**20**	**24**	**-**
Visit Day	**-**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**-**
Visit Window (days)	**-28 to -1**	**NA**	**± 7**	**± 7**	**±7**	**± 7**	**± 7**	**≥28 to <35 days from last study treatment**	**≥28 to <35 days from last study treatment [a]**
IOP (screening, pretreatment, and SFV/ETV) [n, o]	x	x	x	x	x	x	x	x	x
AH tap [p]	-	x	-	-	-	x	-	-	-
6 mg faricimab IVT injection [q]	-	x	x	x	x	x	x	-	-
Slit lamp examination [o]	x	x	x	x	x	x	x	x	x
Dilated binocular indirect high-magnification ophthalmoscopy [o]	x	x	x	x	x	x	x	x	x
Finger-counting test [r]		x	x	x	x	x	x	-	-
IOP post-treatment [n, o]	-	x	x	x	x	x	x	-	-
Adverse events [s]	x	x	x	x	x	x	x	x	x

AH = aqueous humor; AO = adaptive optics; BCVA = best-corrected visual acuity; BP = blood pressure; CFP = color fundus photography; eCRF = electronic Case Report Form; ETDRS = Early Treatment Diabetic Retinopathy Study; ETV = early termination visit; HbA_{1c} = hemoglobin A_{1c}; IOP = intraocular pressure; IVT = intravitreal; NA = not applicable; SD-OCT-A = spectral-domain optical coherence tomography angiography; SD-OCT = spectral-domain optical coherence tomography; SFV = safety follow-up visit; SS-OCT = swept-source optical coherence tomography; SS-OCT-A = swept-source optical coherence tomography angiography; UWF-CFP = ultra-wide field color fundus photography; UWF-FFA = ultra-wide field fundus fluorescein angiography; VEGF = vascular endothelial growth factor; WOCBP = women of childbearing potential.

Notes: All ocular assessments are to be performed for the study eye unless noted otherwise. In general, ocular assessments (as noted in the footnotes below) for the non-study eye (fellow eye) are planned only for the screening visit, baseline visit, and at the SFV / ETV to provide a holistic understanding of the patient's DME which can often be bilateral; as faricimab may have systemic effects, these ocular assessments are also collected for safety reasons. Pre and post-treatment clinical safety checks are also required to be performed on the non-study eye whenever any protocol permitted anti-VEGF treatment is administered.

Appendix 1: Schedule of Activities

All assessments are to be performed on the same day, except those at screening. All study visits will be scheduled relative to the date of the Day 1 visit (first study treatment). The SFV (or ETV, as applicable) should not occur earlier than 28 days after the last study treatment. The fellow eye anti-VEGF treatment approved by the country regulatory agency for ocular use may be covered by the Sponsor as long as the patient remains in the study (see Section 4.4.1). The fellow eye anti-VEGF treatments after the ETV or the SFV will not be covered by the Sponsor.

[a] Patients who discontinue the study or treatment early (prior to the SFV) but have not withdrawn consent (and have not been lost to follow-up) should return for an ETV after ≥28 days have elapsed following their last study treatment (visit should occur within <35 days of the patient's last study treatment).

[b] Informed consent must be administered and documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment at the Day 1 visit.

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

[d] Record in the eCRF any previous and/or concomitant treatments/medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment within 7 days preceding the baseline visit and through the conclusion of the patient's study participation or ETV.

[e] Record all concurrent ocular procedures performed on the both the study and non-study eye (fellow eye) between the Day 1 visit after study treatment and the SFV or the ETV.

[f] A targeted physical examination should include an evaluation of the head, *eyes,* ears, nose, and throat. If any abnormalities are noted during the study, the patient may be referred to another doctor. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the adverse event eCRF.

[g] Vital signs include measurement of temperature, heart rate, and systolic and diastolic BP. Vital signs will be taken with the patient in a seated position after resting for 5 minutes.

[h] Required for WOCBP only. A negative serum pregnancy test is required for enrollment (i.e., at the screening visit). If any urine pregnancy test is positive during the treatment period or the safety follow-up period, it must be confirmed by a serum pregnancy test. If the serum pregnancy test is positive during the treatment period, do not administer study treatment. A pregnancy test (serum or urine, as applicable) must always be timed to occur before administration of the fluorescein for the UWF-FFA; a negative test is required before administration of the fluorescein.

[i] Historic values up to 2 months before the screening visit will be permissible; otherwise, the study site may collect a sample for analysis at screening. All patients will be required to have an HbA_{1c} sample collection on Day 1 (baseline), the Day 112 visit, and at the SFV or the ETV. Note: In case an HbA_{1c} assessment is done at screening (no historic HbA_{1c} values), and the baseline visit occurs within 28 days after screening, this assessment does not have to be repeated at baseline.

[j] Both refraction and BCVA must be performed prior to pupil dilation (study eye and non-study eye), the faricimab IVT injection in the study eye and, if applicable, the anti-VEGF treatment in the non-study eye. Screening BCVA (not baseline) used for eligibility. Both refraction and BCVA will be assessed at every study visit (as indicated in the table above) for the study eye, but only at the screening visit, the baseline visit, and the SFV / ETV for the non-study eye (fellow eye).

[k] Performed prior to the faricimab IVT injection (study eye) and, if applicable, the anti-VEGF treatment (non-study eye). All imaging procedures will be performed at every study visit (as indicated in the table above) for the study eye, but only at the screening visit, baseline visit, and the SFV/ETV for the non-study eye (fellow eye).

[l] If the study site has the capability and is certified to perform SS-OCT-A and SD-OCT-A, the study site must perform SS-OCT-A only. If the study site does not have the capability or certification to perform SS-OCT-A, then the study site must perform SD-OCT-A. The study site must always perform SD-OCT. If the study site additionally has the capability and certification to perform SS-OCT, the study site should also perform SS-OCT.

[m] Performed prior to the faricimab IVT injection (study eye) and, if applicable, the anti-VEGF treatment (non-study eye). It will be performed at every study visit (as indicated in the table above) for the study eye and the non-study eye (fellow eye).

[n] The screening IOP, pretreatment IOP, and SFV or ETV IOP of the study eye and, if applicable, the non-study eye (fellow eye) should be performed prior to dilating the eyes. Post-treatment IOP measurement in the study eye and, if applicable, in the non-study eye (fellow eye) should be performed 30 (±15) minutes post-treatment (thus also after the AH tap [study eye only]) by qualified personnel. If there are no safety concerns after 30 (±15) minutes following the study treatment, the patient will be permitted to leave. If the IOP value is of concern to the Investigator, the patient will remain in the clinic and will be managed in accordance with the Investigator's clinical judgment. The adverse event will be recorded on the adverse event eCRF as applicable the clinic.

[o] After AH tap (of the study eye; at the applicable visits) and faricimab IVT injection (in the study eye, at the applicable study visits) and, if applicable, the anti-VEGF treatment (in the non-study eye), a clinical safety check (including IOP measurement, slit lamp examination, and dilated binocular indirect high-magnification ophthalmoscopy) needs to be performed prior to releasing the patient.

[p] Samples are collected from the study eye only. Performed prior to the faricimab IVT injection in the study eye.

[q] May only be performed after the AH tap (study eye only) and if patient is a WOCBP, their pregnancy test (urine) must be negative. Only the study eye will receive the faricimab IVT injection.

[r] The finger-counting test should be conducted within approximately 15 minutes of study treatment administration for the study eye and, if applicable, the non-study eye (fellow eye).

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

Appendix 2
Unscheduled Safety Assessment Visit

Assessments (at the discretion of the Investigator) [a]
Vital signs (temperature, heart rate, and systolic and diastolic BP)
Best-corrected visual acuity (assessed at a 4-meter starting distance) [b]
Slit lamp examination
Dilated binocular indirect high-magnification ophthalmoscopy
IOP [c]
Adverse events [d]
Concurrent ocular procedures
Concomitant medications/treatments
Ocular imaging, as necessary

BP = blood pressure; IOP = intraocular pressure.

Note: Unscheduled safety visits should only be utilized for the assessment of adverse events and are not to be used for standard of care procedures.

[a] Patients will be instructed to contact the investigator at any time if they have any health-related concerns. *Investigators may ask the patient* to return to the clinic for an unscheduled safety assessment visit*, if there are any concerns*. Assessments performed at unscheduled safety visits are at the discretion of the Investigator. It is recommended to perform ocular assessments on both eyes.

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

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

[d] Adverse event causality to be evaluated by the physician.

Appendix 3
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

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

REFERENCE

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

Appendix 4
Refraction and Best-Correct Visual Acuity Testing

SCOPE

The refraction and best-corrected visual acuity (BCVA) assessment must be conducted before pupil dilation (study eye and non-study eye). The refraction and BCVA will be measured by trained and certified personnel at the study sites. Both refraction and BCVA will be assessed at every study visit for the study eye, but only at the screening visit, the baseline visit, and the safety follow-up visit/early termination visit for the non-study eye (fellow eye; see Appendix 1).

EQUIPMENT

The following are needed to conduct the examination:

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

TRAINING AND CERTIFICATION

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

Appendix 5
Color Fundus Photography

SCOPE

Stereo color fundus photographs (CFP) using 7-modified field imaging and ultra-wide field color fundus photography (UWF-CFP; Optos®) will be obtained by trained personnel at the study sites. Color fundus photographs using 7-modified field imaging and UWF-CFP will be performed for the study eye and the non-study eye (when indicated) at specified timepoints according to the schedule of activities in Appendix 1.

Analysis (if applicable) of fundus photographs will be performed by the central reading center (CRC).

EQUIPMENT

See the Image Acquisition Guidelines for equipment details.

PROCEDURE AND CERTIFICATION

The CRC will provide the study sites with the Image Acquisition Guidelines and training materials. The fundus photographer and photography equipment will be certified by the CRC before any study images are taken. See the Image Acquisition Guidelines for further details.

Appendix 6
Ultra-Wide Field Fundus Fluorescein Angiography

SCOPE

Fundus fluorescein angiography using the ultra-wide field (UWF; Optos®) imaging will be performed at the study sites by trained personnel who are certified by the central reading center (CRC). The fundus fluorescein angiograms will be performed for the study eye and the non-study eye (when indicated) at specified timepoints according to the schedule of activities in Appendix 1. Analysis (if applicable) of fundus fluorescein angiograms will be performed by the CRC.

EQUIPMENT

See the Image Acquisition Guidelines for equipment details.

DIGITAL IMAGING SYSTEMS AND CERTIFICATION

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

PROCEDURES AND CERTIFICATION

The CRC will provide the study sites with the Image Acquisition Guidelines and training materials. Photographers, systems, and software will be certified prior to obtaining angiograms of patients.

Appendix 7
Spectral-Domain Optical Coherence Tomography, Swept-Source Optical Coherence Tomography, and Swept-Source Optical Coherence Tomography Angiography/Spectral-Domain Optical Coherence Tomography Angiography

SCOPE

Spectral-domain optical coherence tomography (SD-OCT), swept-source optical coherence tomography (SS-OCT), and swept-source optical coherence tomography angiography (SS-OCT-A)/spectral-domain optical coherence tomography angiography (SD-OCT-A) will be performed at the study sites by trained personnel who are certified by the central reading center (CRC). SD-OCT, SS-OCT, and SS-OCT-A/SD-OCT-A imaging will be performed for the study eye and the non-study eye (when indicated) at specified timepoints according to the schedule of activities in Appendix 1.

If the study site has the capability, and is certified, to perform SS-OCT-A and SD-OCT-A, the study site must perform SS-OCT-A only. If the study site does not have the capability or certification to perform SS-OCT-A, then the study site must perform SD-OCT-A.

The study site must always perform SD-OCT. If the study site additionally has the capability and certification to perform SS-OCT, the study site should also perform SS-OCT.

The SD-OCT, (if available) SS-OCT, SS-OCT-A/SD-OCT-A images will be forwarded to the CRC.

EQUIPMENT

The SD-OCT will be performed with Spectralis® (Heidelberg Engineering, Heidelberg, Germany) (where Spectralis® is not available, refer to the Image Acquisition Guidelines for a description of any acceptable devices, if applicable). See the Image Acquisition Guidelines for further equipment details. The ability to transfer images to electronically exportable digital files is required (i.e., no printed images will be sent to the CRC).

PROCEDURES AND CERTIFICATION

The CRC will provide the study sites with the Image Acquisition Guidelines and training materials. The OCT operators, systems, and software will be certified prior to any evaluation of patients.

Appendix 8
Adaptive Optics (Selected Study Sites Only)

Acceptability of the site's adaptive optics (AO) data collection capabilities will be determined prior to selecting the study sites involved in this optional data collection. The AO will be performed for the study eye and the non-study eye (when indicated), if the patient is suitable according to the investigator's judgement, at specified timepoints according to the schedule of activities in Appendix 1.

Appendix 9
Biological Sample Collection and Shipping Instructions

BIOLOGICAL SAMPLE COLLECTION

Study eye aqueous humor (AH) paracentesis samples will be collected by the treating physician prior to the faricimab IVT injection at baseline and at the Day 112 visit. A panel of protein biomarkers (which may include VEGF, interleukin-6, interleukin-8, placental growth factor, intercellular adhesion molecule-1, platelet-derived growth factor, Ang-2, and others) will be analyzed in AH samples by multiplex assay technology. In addition to this targeted analysis, and depending on the AH volume collected, the global protein and/or metabolite composition of the AH samples will also be analyzed employing, for example, liquid chromatography – mass spectrometry analyses. The AH analysis strategy may evolve over time based on accumulated results.

Blood for genomic analysis will be withdrawn at baseline. The whole blood sample for DNA may be sent to one or more laboratories for analysis via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other genomic analysis methods.

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

BIOLOGICAL SAMPLES STORAGE DURATION

The AH samples and blood samples for genomic analysis will be destroyed ≤ 5 years after the final Clinical Study Report has been completed.