Official Title: A Multicenter, Open-Label Extension Study to Evaluate The Long-Term Safety and Tolerability of Faricimab in Patients with Diabetic Macular Edema

NCT Number: NCT04432831

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PROTOCOL

TITLE:	**A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF FARICIMAB IN PATIENTS WITH DIABETIC MACULAR EDEMA**
PROTOCOL NUMBER:	GR41987
VERSION NUMBER:	*3*
EUDRACT NUMBER:	2020-000402-29
IND NUMBER:	119,225
NCT NUMBER:	To be determined
TEST PRODUCT:	Faricimab (RO6867461)
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
13-Dec-2021 23:23:33	Company Signatory	[redacted]

PROTOCOL HISTORY

Version	Date Final
2	13 May 2020
1	12 February 2020

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol GR41987 has been amended to include a Final End of Study visit, and extend the study to Week 108 for patients who receive their final dose of faricimab at Week 104, 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:

- Section 3.1.3.6 was added to clarify that it is not possible for a site to manually modify the PTI algorithm to adjust the faricimab treatment interval
- Section 3.2 has been updated to reflect the addition of a Final End of Study visit scheduled approximately 4 weeks after receipt of the final study dose of faricimab to enable adequate safety monitoring of patients following the final administration of study drug
- Section 4.1.2 (exclusion criteria) and Appendix 1 have been updated to reconcile the criterion currently described in the ICF relating to pregnancy
- 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 use of kallidinogenase and other medications claiming to have an effect on macular pathology to the list of prohibited therapies.
- Section 5.1.1 has been updated to reflect updated information on risks of faricimab according to the Investigator's Brochure version 11.
- Section 5.4.1 has been updated to reflect the Medical Monitor change for Western Hemisphere.
- Appendix 1 definitions for Year 1 and Year 2 were clarified to explain the specific time window for these annual visits, to avoid sites bringing patients back unnecessarily outside the PTI scheduling time point.

The following minor changes have been made per Roche guidelines:

- Language has been added to indicate that sites can confirm that appropriate temperature conditions have been maintained during IMP transit either by time monitoring (shipment arrival date and time) or temperature monitoring (Section 4.3.3).
- 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).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics.

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PROTOCOL ACCEPTANCE FORM

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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:	**A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF FARICIMAB IN PATIENTS WITH DIABETIC MACULAR EDEMA**
PROTOCOL NUMBER:	GR41987
VERSION NUMBER:	*3*
EUDRACT NUMBER:	2020-000402-29
IND NUMBER:	119,225
NCT NUMBER:	To be determined
TEST PRODUCT:	Faricimab (RO6867461)
PHASE:	III (Long-term extension)
INDICATION:	Diabetic macular edema
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This long-term extension (LTE) study will evaluate the long-term safety, tolerability, and efficacy of intravitreal (IVT) faricimab in patients with diabetic macular edema who have completed either of the Phase III (GR40349 or GR40398) studies. Additional assessments relating to pharmacokinetics, immunogenicity, and biomarkers will be performed. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective

The primary objective is to evaluate the ocular and systemic safety and tolerability of faricimab in all patients who have enrolled in the LTE study, regardless of adherence to treatment or to the protocol, on the basis of the following endpoints:

- Incidence and severity of ocular adverse events
- Incidence and severity of systemic (non-ocular) adverse events.

Exploratory Objective

The exploratory objective of this study is to assess the long-term efficacy of IVT faricimab for the management of diabetic eye disease in all patients participating in the LTE study on the basis of the following endpoints (**Note**: Where mentioned, “over time” refers to the change from the parent study Day 1 and the LTE study Day 1 visit):

- Change in best-corrected visual acuity (BCVA) over time as measured using the Early Treatment Diabetic Retinopathy Study chart at a starting distance of 4 meters
- Change in central subfield thickness (CST) over time as measured by spectral-domain optical coherence tomography
- Proportion of patients with presence of central retina intraretinal fluid, subretinal fluid, and both over time
- Number of faricimab injections received during the LTE study
- The proportion of patients on a every 4 weeks (Q4W), every 8 weeks, every 12 weeks, and every 16 weeks treatment interval during the study

- Proportion of patients with a ≥2- or ≥3-step improvement in their Diabetic Retinopathy Severity Scale (DRSS) score over time
- Proportion of patients with a ≥2- or ≥3-step worsening in their DRSS score over time
- Proportion of patients who develop new proliferative diabetic retinopathy over time
- Change in patient-reported vision-related functioning and quality of life over time as assessed using the National Eye Institute Visual Functioning Questionnaire 25-item Version composite score, the near activity subscale score, the distance activities subscale score, and driving subscale score

Pharmacokinetic Objective

The exploratory pharmacokinetic objective for this study is to assess the pharmacokinetics of faricimab, including in patients who have switched from the Phase III active comparator, as well as explore concentration-effect relationships, on the basis of the following endpoints:

- Plasma concentration of faricimab over time from the start of the LTE study
- The correlation between concentration of aqueous humor faricimab and the change in BCVA and other endpoints (e.g., anatomical markers) over time from the start of the LTE study

Immunogenicity Objective

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

- Presence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study from the start of the LTE study

Exploratory Biomarker Objectives

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

- Relationship between anatomic measures at baseline or during the course of the study and the change in visual acuity or other endpoints (e.g., the frequency of study drug administration) over time from the start of the LTE study

Study Design

Description of Study

This is a multicenter LTE study designed to evaluate the long-term safety and tolerability of faricimab 6 mg administered by IVT injection at a personalized treatment interval (PTI) to patients who enrolled in and completed one of the Phase III studies (GR40349 or GR40398), also referred to as the parent studies. Patients in the parent studies who discontinued from the study or study treatment prior to completion of the 96-week treatment period are not eligible for enrollment in this extension study.

Eligible patients who consent to participate in this study will be enrolled upon completion of the end-of-study visit in the parent study (i.e., Week 100 visit in Studies GR40349 and GR40398). The end of study of the parent study and the enrollment visit for this extension study will occur on the same day. All assessments from the parent study end-of-study visit must be completed prior to the LTE study enrollment visit assessments. If the end-of-study visit of the parent study and enrollment visit for this extension study cannot be completed on the same day, the investigator must contact the Sponsor for further discussion prior to scheduling the extension study enrollment visit.

Approximately 1800 patients are expected to participate in this extension study after completion of the parent studies, and will follow a single faricimab 6 mg PTI regimen. In this extension study, the study eye will be the same as that randomized in the parent studies, GR40349 and GR40398.

Eligible patients who choose to enroll into the LTE study will have monthly, masked, study visits for the first 4 months of the study (Day 1 through to Week 16). During the masked period, patients and physicians will only be masked to the faricimab treatment interval. Note: The BCVA examiner will remain masked for the duration of the LTE study.

Following the masked period, the study will follow an open-label design in which patients will only be required to attend study visits at which faricimab is to be administered, at intervals determined according to the PTI algorithm. However, the treatment arm to which patients were assigned in the parent Phase III study will not be disclosed until the final Phase III analysis (Year 2) is reported.

An interactive web-based response system will be used to calculate a patient's PTI interval, using the patient's BCVA and optical coherence tomography CST values obtained at dosing visits.

Number of Patients

Approximately 1800 patients are expected to participate in this extension study after completion of the parent studies.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Previous enrollment in and completion of Study GR40349 (YOSEMITE) or GR40398 (RHINE), without study or study drug discontinuation.
- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 3 months after the final dose of study treatment

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

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

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. If a patient is usually not sexually active but becomes active, they, with their partner, must comply with the contraceptive requirements of the study.

Exclusion Criteria

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within $3\ months$ after the final IVT injection of faricimab

  Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to initiation of study treatment. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

- Presence of other ocular diseases that give reasonable suspicion of a disease or condition that contraindicates the use of faricimab, that might affect interpretation of the results of the study or that renders the patient at high risk for treatment complications
- Presence of other diseases, metabolic dysfunction, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of faricimab and that might affect interpretation of the results of the study or that renders the patient at high risk of treatment complications
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab injections, study treatment procedure, dilating drops, or any of the anesthetic and antimicrobial preparations used by a patient during the study
- Requirement for continuous use of any medications or treatments indicated as prohibited therapy

End of Study

The end of this study is defined as the date when the last patient, last visit occurs.

Length of Study

The end of study is expected to occur approximately 10*8* weeks after the last patient is enrolled.

Investigational Medicinal Products

Faricimab

The investigational medicinal product for this study is faricimab. Faricimab 6 mg will be administered intravitreally to patients at a PTI for the duration of the LTE study.

Sham

To preserve the masking of the Phase III treatment arm assignment, patients enrolling in the LTE study will attend Q4W visits for the first 4 months of the study and will have the sham procedure performed at these visits when they are not treated with faricimab.

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

Statistical Methods

Primary Analysis

Safety analyses will be based on the safety-evaluable population. Safety will be assessed through descriptive summary of ocular and non-ocular adverse events, deaths, and ocular assessments (e.g., intraocular pressure [IOP]).

Verbatim descriptions of treatment-emergent adverse events will be mapped to MedDRA thesaurus terms, and the incidence and severity will be summarized.
A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first day (Day 1) of this LTE study. Only adverse events captured in this LTE study will be included for summaries.

Adverse events will be tabulated by System Organ Class and preferred term and presented overall, and by parent study treatment group. Summaries will be generated for serious adverse events, deaths, adverse events leading to discontinuation of study drug, adverse events of special interest, and adverse events judged to be related to study treatment. Separate summaries will be prepared for non-ocular and ocular adverse events.

Results of the ocular assessments will be summarized by timepoint and by eye (study vs. fellow) using descriptive summaries. In addition, changes, from parent study Day 1 and from LTE study Day 1, in pre-dose IOP measurements and changes between pre-dose and post-dose IOP measurements will also be summarized.

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

Determination of Sample Size

No formal sample size calculations will be performed for this LTE study. This study is open to all patients who complete study treatment and the Week 96 visit in one of the parent studies GR40349 (YOSEMITE) or GR40398 (RHINE).

Interim Analyses

No formal interim analysis is planned. Data cuts may be performed at appropriate timepoints for inclusion in the submission with the main studies, for example, to support the safety profile. *An interim analysis may be performed for internal stakeholder data presentations/conference presentations/ publications/market authorization purposes.*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
Ang-2	angiopoietin-2
BCVA	best-corrected visual acuity
CFP	color fundus photograph
CRC	central reading center
CST	central subfield thickness
DME	diabetic macular edema
DR	diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Scale
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FFA	fundus fluorescein angiography
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intent to treat
IVT	intravitreal
IxRS	interactive web-based response system
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire–25
NPDR	non-proliferative diabetic retinopathy
OCT	optical coherence tomography
OCT-A	optical coherence tomography–angiography
PD	pharmacodynamic
PDR	proliferative diabetic retinopathy
PI	Principal Investigator

Abbreviation	Definition
PK	Pharmacokinetic
PRO	patient-reported outcome
PTI	personalized treatment interval
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
Q16W	every 16 weeks
RBR	Research Biosample Repository
SAP	Statistical Analysis Plan
SD-OCT	spectral-domain optical coherence tomography
UWF	ultra-wide field
ULN	upper limit of normal
VA	visual acuity
VEGF(-A)	vascular endothelial growth factor(-A)
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON DIABETIC MACULAR EDEMA

Diabetic macular edema (DME) is a complication of diabetic retinopathy (DR) and 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 from non-proliferative DR (NPDR) to proliferative DR (PDR) (Henricsson et al. 1999; Johnson 2009). DME affects central vision and 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). If left untreated, DME 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). 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). The global prevalence of DME is estimated to be around 7.5%, affecting 21 million individuals (Yau et al. 2012). In 2019, the worldwide population of people living with diabetes was approximately 463 million, and is estimated to grow to 548 million by 2045 (International Diabetes Federation 2019), thus the global burden on DME is expected to increase significantly.

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 pericytes consequent to hypoxia-mediated release of pro-angiogenic, hyperpermeability, and pro-inflammatory mediators (Antonetti et al. 1999). VEGF-A 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-A 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).

Until recently, focal macular laser was the first line of therapy in the treatment of DME, but the development of anti-VEGF biologics in the last 10 years has led to dramatic improvements in visual outcomes for patients with DME (Diabetic Retinopathy Clinical Research Network et al. 2010). Currently available anti-VEGF therapies for DME include ranibizumab and aflibercept. Other available approved options for the treatment of DME include periocular or intravitreal (IVT) steroids and steroid implants.

Despite the significant improvements in both vision and anatomical outcomes achieved with anti-VEGF injections in DME, the current standard-of-care for management requires

patients to undergo frequent clinical examinations and IVT injections. This imposes a significant burden on patients, caregivers, treating physicians, and the healthcare system. Thus, in the real world, the average number of injections received, and the consequent improvements in vision are lower than in clinical trials (Fong et al. 2018, Hodzic-Hadzibegovic et al. 2018, Stefanickova et al. 2018, Ziemssen et al. 2018, Farinha et al. 2019).

Large Phase III trials of anti-VEGF agents in DME demonstrated that after the first year of treatment, fewer injections are needed for maintenance of vision gains (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 biomarkers to predict treatment frequency, the standard anti-VEGF approach in DME still relies on frequent monitoring visits, placing 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 these unmet medical needs in DME.

1.2 BACKGROUND ON FARICIMAB

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

The concentrations of both Ang-2 and VEGF 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.

Based on the novel mechanism of action of faricimab through selective neutralization of both Ang-2 and VEGF, 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 improved visual and anatomical outcomes in DME and DR compared with anti-VEGF monotherapies.

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

1.2.1 Phase III Faricimab Studies: GR40349 (YOSEMITE) and GR40398 (RHINE)

The Sponsor is currently investigating the efficacy and safety of faricimab 6 mg in DME in two identical, global Phase III, randomized, double-masked, active comparator-controlled trials. Approximately 1800 patients have been randomized in a 1:1:1 ratio to one of three treatment arms. The studies include both patients with DME who were naive to anti-VEGF therapy in the study eye and patients who have previously been treated with anti-VEGF therapy in the study eye.

The Phase III study treatment arms are as follows:

- Arm A (administered every 8 weeks [Q8W]) (n=600): Patients randomized to Arm A will have received faricimab 6-mg IVT injections every 4 weeks (Q4W) to Week 20, followed by faricimab 6-mg IVT injections Q8W to Week 96, followed by the final study visit at Week 100.
- Arm B (personalized treatment interval [PTI]) (n=600): Patients randomized to Arm B will have received faricimab 6-mg IVT injections Q4W to at least Week 12, followed by PTI dosing of faricimab 6-mg IVT injections to Week 96, followed by the final study visit at Week 100.
- Arm C (comparator arm; administered Q8W) (n=600): Patients randomized to Arm C will have received aflibercept 2-mg IVT injections Q4W to Week 16, followed by aflibercept 2-mg IVT injections Q8W to Week 96, followed by the final study visit at Week 100.

The aim of the Phase III program is to evaluate the efficacy, safety, and pharmacokinetics of faricimab when administered to patients at Q8W intervals and with a PTI regimen compared with aflibercept (Eylea®) monotherapy in patients with DME. The effect on visual function will be assessed by measuring the change from baseline in best-corrected visual acuity (BCVA). The effect on retinal anatomy will be evaluated by retinal imaging (spectral-domain optical coherence tomography [SD-OCT], color fundus photographs [CFPs], fundus fluorescein angiography [FFA]), and other imaging modalities to assess both DME and DR outcomes. In addition, safety, patient-reported outcomes (PROs), and the pharmacokinetics of faricimab will be assessed.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The Phase II study (BP30099 [BOULEVARD]) provided preliminary evidence of a positive benefit–risk profile for the use of 6-mg IVT injections of faricimab for patients with DME. Further evidence for the efficacy, safety, and tolerability of the drug in this patient group will be generated in the pivotal Phase III studies, GR40349 (YOSEMITE) and GR40398 (RHINE).

The purpose of this extension study is to assess the long-term safety and tolerability of 6 mg faricimab administered intravitreally in patients who complete the Phase III studies and choose to participate in in this extension study. This will also provide opportunity for eligible patients from the aflibercept control treatment arm to receive faricimab. This extension study will add to the evidence base for the benefit-risk profile of long-term faricimab IVT injection treatment in patients with DME.

2. OBJECTIVES AND ENDPOINTS

This long-term extension (LTE) study will evaluate the long-term safety, tolerability, and efficacy of IVT faricimab in patients with DME who have completed either of the Phase III (GR40349 or GR40398) studies. Additional assessments relating to pharmacokinetics, immunogenicity, and biomarkers will be performed. Specific objectives and corresponding endpoints for the study are outlined below. An overview of the proposed statistical analyses is described in Section 6.

2.1 PRIMARY OBJECTIVE

The primary objective is to evaluate the ocular and systemic safety and tolerability of faricimab in all patients who have enrolled in the LTE study, regardless of adherence to treatment or to the protocol, on the basis of the following endpoints:

- Incidence and severity of ocular adverse events
- Incidence and severity of systemic (non-ocular) adverse events.

2.2 EXPLORATORY OBJECTIVE

The exploratory objective of this study is to assess the long-term efficacy of IVT faricimab for the management of diabetic eye disease in all patients participating in the LTE study on the basis of the following endpoints (**Note**: Where mentioned, “over time” refers to the change from the parent study Day 1 and the LTE study Day 1 visit):

- Change in BCVA over time as measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a starting distance of 4 meters
- Change in central subfield thickness (CST) over time as measured by SD-OCT
- Proportion of patients with presence of central retina intraretinal fluid, subretinal fluid, and both over time
- Number of faricimab injections received during the LTE study
- The proportion of patients on a Q4W, Q8W, every 12 weeks (Q12W), and every 16 weeks (Q16W) treatment interval during the study
- Proportion of patients with a $\geq$2- or $\geq$3-step improvement in their Diabetic Retinopathy Severity Scale (DRSS) score over time
- Proportion of patients with a $\geq$2- or $\geq$3-step worsening in their DRSS score over time
- Proportion of patients who develop new PDR over time

- Change in patient-reported vision-related functioning and quality of life over time as assessed using the National Eye Institute Visual Functioning Questionnaire 25-item Version (NEI VFQ-25) composite score, the near activity subscale score, the distance activities subscale score, and driving subscale score

2.3 PHARMACOKINETIC OBJECTIVE

The exploratory pharmacokinetic (PK) objective for this study is to assess the pharmacokinetics of faricimab, including in patients who have switched from the Phase III active comparator, as well as explore concentration-effect relationships, on the basis of the following endpoints:

- Plasma concentration of faricimab over time from the start of the LTE study
- The correlation between concentration of aqueous humor faricimab and the change in BCVA and other endpoints (e.g., anatomical markers) over time from the start of the LTE study

2.4 IMMUNOGENICITY OBJECTIVE

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

- Presence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study from the start of the LTE study

2.5 EXPLORATORY BIOMARKER OBJECTIVES

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

- Relationship between anatomic measures at baseline or during the course of the study and the change in visual acuity or other endpoints (e.g., the frequency of study drug administration) over time from the start of the LTE study

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a multicenter LTE study designed to evaluate the long-term safety and tolerability of faricimab 6 mg administered by IVT injection at a PTI to patients who enrolled in and completed one of the Phase III studies (GR40349 or GR40398), also referred to as the parent studies. Patients in the parent studies who discontinued from the study or study treatment prior to completion of the 96-week treatment period are not eligible for enrollment in this extension study.

Eligible patients who consent to participate in this study will be enrolled upon completion of the end-of-study visit in the parent study (i.e., Week 100 visit in Studies GR40349 and GR40398). Patients will be enrolled into the extension study using an interactive web-based response system (IxRS).

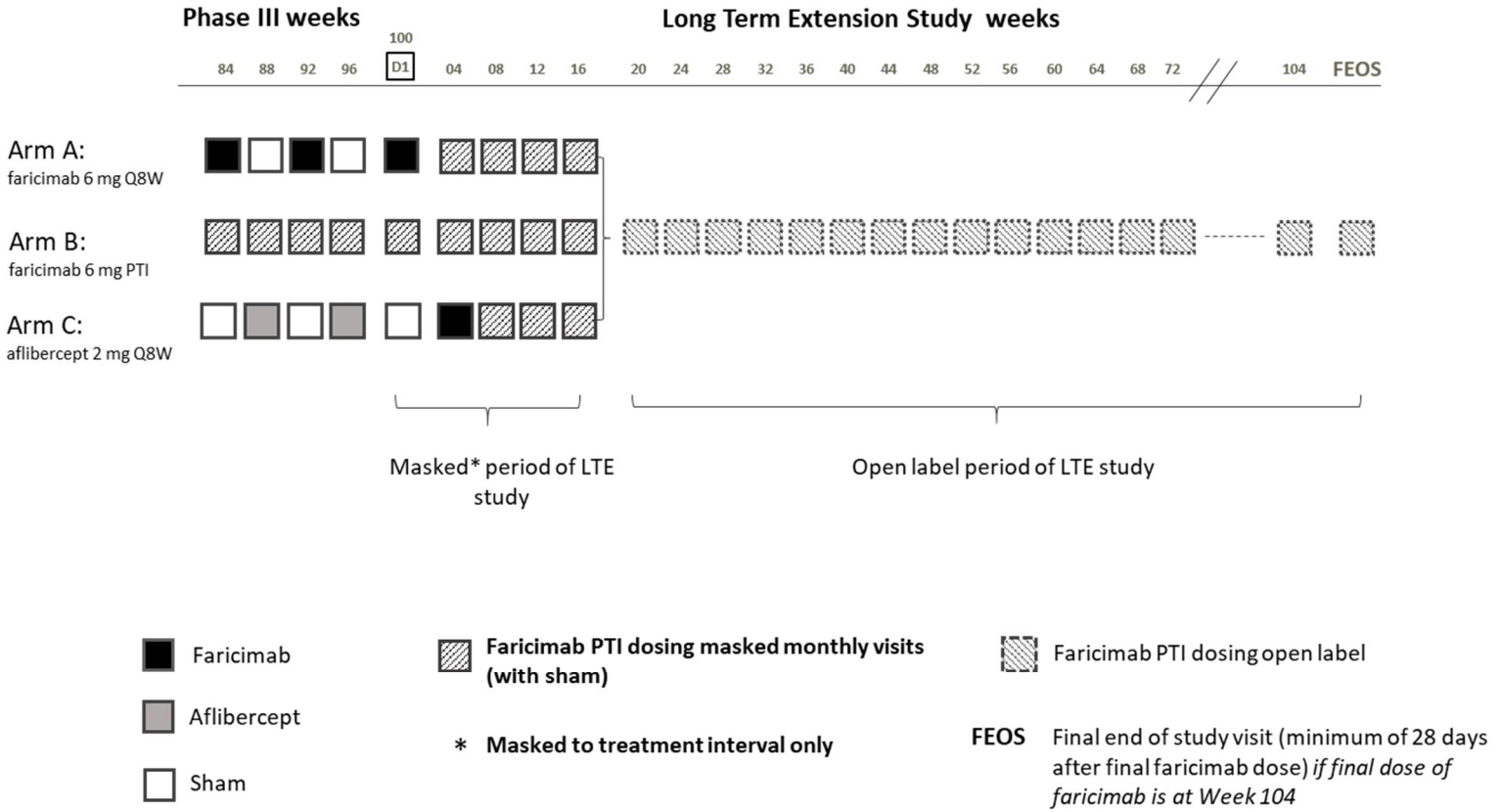
The end of study of the parent study and the enrollment visit for this extension study will occur on the same day. All assessments from the parent study end-of-study visit must be completed prior to the LTE study enrollment visit assessments (refer to the schedule of assessments in Appendix 1). If the end-of-study visit of the parent study and enrollment visit for this extension study cannot be completed on the same day, or within 2 business days, the investigator must contact the Sponsor for further discussion prior to scheduling the extension study enrollment visit.

3.1.1 Overview of Study Design

Approximately 1800 patients are expected to participate in this extension study after completion of the parent studies, and will follow a single faricimab 6 mg PTI regimen. In this extension study, the study eye will be the same as that randomized in the parent studies, GR40349 and GR40398.

Patients will be required to attend study assessment visits at intervals as scheduled by the IxRS system based on the PTI algorithm (see below). Figure 1 outlines the study design, and the schedule of activities is provided in Appendix 1 and Appendix 2.

Figure 1 Study Schema



LTE = long-term extension; PTI = personalized treatment interval; Q8W = every 8 weeks.

In the LTE study, all patients will move from the Phase III parent study arm to a faricimab PTI arm. Refer to Sections 3.1.1.1 and 3.1.1.2 for study design details.

Informed consent must be administered and signed by a patient before any study-specific procedures are performed for this LTE study. Each consented patient must satisfy the eligibility criteria at the Day 1 visit (see Sections 4.1.1 and 4.1.2).

3.1.1.1 LTE Visit Schedule during the Masked Period

Eligible patients who choose to enroll into the LTE study will have monthly, masked, study visits for the first 4 months of the study (Day 1 through to Week 16; see Figure 1). During the masked period, patients and physicians will only be masked to the faricimab treatment interval. **Note:** The BCVA examiner will remain masked for the duration of the LTE study (refer to Section 4.2.1.1 for further details).

Refer to Section 4.2.1 for further masking details.

3.1.1.2 LTE Visit Schedule following Masked Period

Following the masked period, the study will follow an open-label design in which patients will only be required to attend study visits at which faricimab is to be administered, at intervals determined according to the PTI algorithm. However, the treatment arm to which patients were assigned in the parent Phase III study will not be disclosed until the final Phase III analysis (Year 2) is reported.

An IxRS system will be used to calculate a patient's PTI interval, using the patient's BCVA and optical coherence tomography CST values obtained at dosing visits.

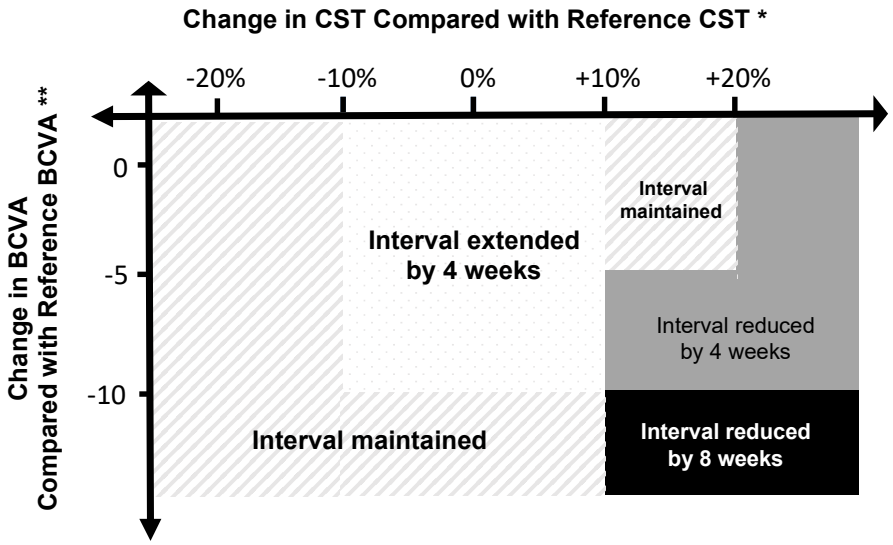
3.1.2 Faricimab Dosing Schedule

Faricimab dosing visits are visits when a patient is assigned to receive faricimab. The dosing interval decisions in the LTE study are automatically calculated by IxRS based on the algorithm described in this section.

3.1.2.1 Faricimab Personalized Treatment Interval

The PTI algorithm is the same as that used in the Phase III studies and uses anatomical (i.e., CST) and functional (i.e., BCVA) data obtained at dosing visits to determine the next interval for faricimab dosing. Faricimab dosing intervals can be adjusted in 4-week increments to a maximum of Q16W and a minimum of Q4W. The PTI algorithm is based on the relative change of the CST and absolute change in BCVA compared with the reference CST and BCVA, respectively (see Figure 2).

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



BCVA = best-corrected visual acuity; CST = central subfield thickness; IxRS = interactive voice or web-based response system; SD-OCT = spectral-domain optical coherence tomography.

* Reference CST: the CST value when the initial CST threshold criteria (CST < 325 μm for Spectralis SD-OCT, or <315 μm for Cirrus SD-OCT or Topcon SD-OCT) are met. The reference CST is adjusted if CST decreases by > 10% from the previous reference CST for two consecutive drug-dosing visits and the values obtained are within 30 μm. The CST value obtained at the latter visit will serve as the new reference CST, starting immediately at that visit. CST values from the parent study will be used as appropriate in the reference CST calculations.

** Reference BCVA: the mean of the three best BCVA values obtained at any prior drug-dosing visit, which will include parent study data.

The study drug dosing interval will be adjusted based on comparisons made to reference CST and reference BCVA data captured in the parent study. The algorithm used by IxRS for interval decision-making is based on the relative change of the CST and BCVA compared with the reference CST and reference BCVA as follows (see Figure 2):

Interval extended by 4 weeks

- If the CST value is increased or decreased by ≤ 10% **without** an associated ≥ 10-letter BCVA decrease

Interval maintained

- If the CST is decreased by > 10% **or**
- CST value is increased or decreased by ≤ 10% **with** an associated ≥ 10-letter BCVA decrease **or**
- CST value is increased between > 10% and ≤ 20% **without** an associated ≥ 5-letter BCVA decrease

Interval reduced by 4 weeks

- If the CST value is increased between $>10\%$ and $\leq 20\%$ **with** an associated ≥ 5- to <10-letter BCVA decrease **or**
- CST value is increased by $>20\%$ **without** an associated ≥ 10-letter BCVA decrease

Interval reduced by 8 weeks

- If the CST value is increased by $>10\%$ **with** an associated ≥ 10-letter BCVA decrease

3.1.2.2 Faricimab Dosing Intervals—Phase III to LTE

As described in Section 1.2, the parent Phase III studies (GR40349 or GR40398) include patients randomized in a 1:1:1 fashion to one of three regimens: a fixed interval faricimab dosing regimen (Arm A: faricimab Q8W), faricimab administered according to a PTI (Arm B: faricimab PTI), and a fixed interval comparator arm (Arm C: aflibercept Q8W). In contrast, the LTE will have only one treatment regimen, faricimab PTI.

Upon enrolling in the LTE study:

- Patients previously randomized to Arm A (faricimab Q8W), who have had their last dose of faricimab at Week 92 of the parent study (see Figure 1), will have a faricimab dose on Day 1 of the LTE study and will then be eligible to have their subsequent faricimab dosing interval extended, reduced, or maintained based on the PTI algorithm.

  Patients from this arm who (e.g., because of dose holds/missed visits in the parent study) received a faricimab dose at Week 96 in the parent study, will not receive a faricimab dose on Day 1 of the LTE study. Instead, these patients will be dosed 8 weeks after the final dose in the parent study (i.e., at Week 4 of the LTE study) and will then be eligible to have their subsequent dosing interval extended, reduced, or maintained on the basis of the PTI algorithm.
- Patients previously randomized to Arm B (faricimab PTI) will remain on their previously calculated faricimab interval at entry to the LTE study.
- Patients previously randomized to Arm C (aflibercept Q8W) who have had their last dose of aflibercept at Week 96 of the parent study (see Figure 1) will have a dose of faricimab at Week 4 of the LTE study, and will then be eligible to have their subsequent faricimab dosing interval extended, reduced, or maintained based on the PTI algorithm.

  Patients in this arm who (e.g., because of dose holds/missed visits in the parent study) received their last aflibercept dose at Week 92 of the parent study will have a faricimab dose on Day 1 of the LTE study. These patients will then be eligible to have their subsequent dosing interval extended, reduced, or maintained based on the PTI algorithm.

Note: During the masked period of the LTE study (from Day 1 through to Week 16; see Section 3.1.1.1), as patients roll in from the parent studies, patients will receive sham injections at study visits at which they are not scheduled to receive faricimab. See Section 4.2 for further details regarding the masked period.

3.1.3 Additional Considerations for PTI IxRS Study Drug–Dosing Interval Decision

Sites will report missed visits and treatment interruption visits to the IxRS.

3.1.3.1 Missed Faricimab Dosing Visits

In view of the potentially extended treatment intervals during the open-label period in the LTE study, sites must follow up on any missed study visits and reschedule patients to attend the clinic as soon as possible—ideally no later than **2 weeks from the scheduled visit date.**

If a dosing visit is missed during the open-label period, the IxRS will assign the patient to receive faricimab at the next visit the patient can attend, and the subsequent PTI will be based on the interval the patient was on prior to the missed visit, using the CST and BCVA data captured at the dosing visit.

3.1.3.2 Treatment Interruption

If a patient's dosing has to be interrupted (e.g., because of an adverse event), the IxRS will assign the patient to receive faricimab at the earliest visit when the patient is permitted to resume faricimab dosing, which should be no sooner than 28 days of the treatment interruption date. Refer to Section 5.1.2.1 for details regarding the criteria for treatment interruption and resuming of treatment.

For treatment interruption periods lasting longer than 28 days, the patient should be monitored at appropriate intervals as judged by the investigator.

Once treatment is resumed, the IxRS will determine the next dosing interval based on a Q8W interval unless the patient was treated on a Q4W interval prior to dose interruption. In that case, the patient will be evaluated on the basis of the Q4W interval.

3.1.3.3 Missing CST Value at LTE Study Visit

If a patient attends an LTE study visit when faricimab is scheduled to be administered, but the CST value is not available for any reason, the IxRS will assign the patient to receive faricimab as scheduled at that visit and maintain the previous faricimab dosing interval. However, if at that visit the patient shows a concurrent $\geq$10-letter decrease relative to the reference BCVA, the IxRS will reduce the faricimab dosing interval by 4 weeks.

3.1.3.4 Missing BCVA Value at LTE Study Visit

If a patient attends an LTE study visit when faricimab is scheduled to be administered, but the BCVA value is not available for any reason, the IxRS will assign the patient to receive faricimab as scheduled at that visit and base the next faricimab dosing interval on the CST value only.

3.1.3.5 Timely Reporting of BCVA and OCT data to eCRF, CRC, and IxRS

For the duration of the LTE study, a central reading center (CRC) will be used to read the optical coherence tomography (OCT) images obtained from patients participating in the study. The CRC will inform the IxRS of the patients' CST value, which is used to determine the patients' next faricimab treatment interval.

As such, from the start of the LTE study, the following procedures **must** be followed:

- OCT images obtained at each LTE study visit must be forwarded to the CRC **as soon as possible** (ideally within 24 hours) to allow for evaluation and transfer of CST data to IxRS for a timely calculation of the patient's next LTE study visit schedule.
- The CRC should be notified **as soon as possible** (ideally within 24 hours) if there are no OCT images available at a scheduled LTE study visit, to allow the CRC to inform IxRS accordingly.

Note: Failure to follow these procedures for OCT reporting will result in a delay to patient notification of subsequent dosing visit timeframe.

In addition, sites must enter the following information in the electronic Case Report Form (eCRF) and/or IxRS, as appropriate:

- The BCVA total score obtained at the current LTE visit

  Note: BCVA data obtained at each study visit should be entered in the eCRF **as soon as possible** (ideally within 24 hours) to allow data to be reconciled against that entered in IxRS.
- Study treatment interruption information (if applicable)
- Missed LTE study visits (if applicable)

3.1.3.6 *Modifications to the PTI Algorithm*

The IxRS PTI algorithm cannot be modified by the investigator, and faricimab will be dispensed according to the PTI dispensing schedule. If a patient is deemed to have DME that requires immediate treatment, the patient will need to be withdrawn from faricimab study treatment and treated with standard care.

If a patient discontinues from faricimab study treatment, they should, where possible, attend at least their Year 1 and Year 2 visits, if not already completed. No other study visits will be required. Please note that the Sponsor will not reimburse for the standard of care treatment in the study eye, and fellow eye reimbursement (if applicable) will cease once a patient has been discontinued from faricimab study treatment.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs. The end of study is expected to occur approximately 10*8* weeks after the last patient is enrolled.

In view of the PTI study design, the Year 2 visit will occur at the earliest scheduled study visit between Week 96 and Week 104. The IxRS Next Study Visit Notification email will indicate if the visit is within the Year 2 study visit window.

Depending on the PTI schedule, it is possible that patients who complete their Year 2 visit may also continue to receive faricimab up to and including Week 104. Once the site has submitted OCT images to the Reading Center, and the CST value has been added to IxRS, the IxRS system will issue a confirmation email if that was final treatment visit. Upon confirmation of the final study treatment via IxRS, patients are expected to attend an end of study visit between 28–35 days after their final study treatment visit date.

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

3.3 RATIONALE FOR STUDY DESIGN

A single arm, open-label trial design is appropriate to meet the objectives of this LTE study assessing the long-term safety and tolerability of faricimab for eligible patients who originally participated in a Phase III multicenter, randomized, comparator-controlled, double-masked study of faricimab in patients with DME.

3.3.1 Rationale for Faricimab Dose and Schedule

The 6-mg dose of faricimab at a PTI schedule will be administered to patients eligible to participate in the extension study as outlined in Section 3.1.1.

Dose

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

The first-in-human study (BP28936) evaluated the safety and tolerability of single and multiple administration of faricimab to 24 patients with neovascular age-related macular degeneration, 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 and 6-mg) 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–naive DME patient subset (n = 168 enrolled) were statistically significant and clinically important compared with 0.3-mg IVT ranibizumab. The efficacy of faricimab was supported by additional secondary BCVA and anatomical DME and DR outcomes in the overall Phase II population and demonstrated a consistent advantage over anti-VEGF monotherapy with ranibizumab across both dose levels. Both doses of faricimab, 6 mg and 1.5 mg, were well tolerated and did not result in any new or unexpected safety signals.

The 6-mg faricimab dose was chosen for further clinical development in Phase III studies in patients with DME. Refer to the Faricimab (RO6867461) Investigator's Brochure for details on efficacy and safety results for the above-mentioned nonclinical and clinical studies.

Schedule

The dosing schedule in the LTE study will continue with a PTI regimen. The mechanism of action of faricimab is through neutralization of Ang-2 and VEGF. Ocular pharmacokinetics and pharmacodynamics have been investigated in Phase I and II studies of faricimab. Aqueous humor free-Ang-2 and free-VEGF concentrations were measured to support the assessments of the primary mode of action and the clinical durability potential of faricimab. Overall, the 6-mg faricimab dose at a Q8W interval suppressed aqueous humor free-VEGF levels for 8 weeks post-dose, supporting at least a Q8W dosing regimen for faricimab at 6 mg with respect to ocular VEGF suppression. A high suppression of free-Ang-2 levels was also observed, lasting for at least 6–8 weeks post-dose of faricimab.

Both the efficacy outcomes from the Phase II study (BP30099) and the variability in individual Ang-2 and VEGF suppression times in the PK/PD aqueous humor assessments indicated a heterogeneous response to treatment and support a flexible dosing regimen with intervals ranging from Q4W to Q16W.

In Study BP30099, the time to disease reactivation (defined as either a 50-μm increase in CST or time to a 5-letter worsening in BCVA) following six Q4W doses demonstrated that, whilst some patients with DME might require more frequent dosing, most patients with DME may need less intensive treatment and may need as little as Q12W or Q16W dosing. Additionally, the PK/PD model characterizing the aqueous humor free-VEGF time course showed that there was a substantial proportion of patients with high suppression of VEGF, for whom a Q12W or Q16W regimen could be sufficient to maintain efficacy. As a result, the Phase III design includes a treatment arm assessing 6-mg IVT faricimab administered in accordance to a PTI regimen.

Real world evidence suggests that the improvements in visual acuity achieved in the clinical trial setting with anti-VEFG monotherapy are not always replicated in clinical practice, potentially due to the reduced frequency of injections administered in clinical

practice (Blinder et al. 2017; Hodzic-Hadzibegovic et al. 2018; Stefanickova et al. 2018; Ziemssen et al. 2018). The PTI regimen aims to optimize efficacy while reducing the IVT injection treatment burden in patients with DME, which in turn may increase patient compliance and reduce the burden to patients, their caregivers, and the healthcare system.

Adopting a personalized treatment approach in the LTE study will provide long-term evidence regarding whether the efficacy outcomes in the pivotal Phase III trials can be maintained over a longer follow-up period.

3.3.2 Rationale for Patient Population

This LTE study will enroll patients with DME who have completed the parent Phase III study (GR40349 or GR40398), and who have not discontinued study treatment.

The rationale for not including patients who were discontinued from treatment is to avoid enrolling patients who may have experienced adverse events or who may not benefit from continued dosing with faricimab, and for whom the risks of treating with further IVT injections outweigh any benefits that may be gained from continued dosing.

3.3.3 Rationale for Optional Biomarker Assessments

Aqueous humor may reflect changes in the retina better than blood, given its close proximity and contiguity to the retina. Aqueous humor samplings have previously been demonstrated to be instrumental in improving our understanding of the relationships between ocular pharmacokinetics, VEGF suppression, and duration of clinical efficacy (Muether et al. 2012, 2013, 2014; Fauser et al. 2014; Fauser and Muether 2016; Hutton-Smith et al. 2017). Therefore, to increase our understanding of the ocular pharmacokinetics and pharmacodynamics of faricimab and the relationship to dosing interval, optional aqueous humor samples will be obtained at different timepoints from patients who provide additional optional consent to participate in regions where optional sampling is approved. Aqueous humor and vitreous humor samples will be measured for free VEGF and free Ang-2, and data from these analyses will be used to develop better predictive models for determining optimal PTIs by means of longitudinal target engagement assessments in these surrogate specimens.

Moreover, other biochemical entities involved in inflammation (e.g., intracellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin among others) and angiogenic growth factors such as angiopoietin 1 may be analyzed in these specimens in an exploratory analysis. These analyses are intended to investigate the role of biochemical and biological processes, such as angiogenesis, inflammation, and oxidative stress in the pathogenesis of DME and in the response to faricimab treatment. Given that these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

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

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 1800 patients are expected to participate in this LTE study after completion of the parent studies, and will be enrolled into a single 6-mg faricimab dose PTI arm. In this extension study, the study eye will be the same as that randomized in the parent studies, GR40349 and GR40398.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Previous enrollment in and completion of Study GR40349 (YOSEMITE) or GR40398 (RHINE), without study or study drug discontinuation.
- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 3 months after the final dose of study treatment

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

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

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. If a patient is usually not sexually active but becomes active, they, with their partner, must comply with the contraceptive requirements of the study.

4.1.2 Exclusion Criteria

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within $3\ months$ after the final IVT injection of faricimab

  Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to initiation of study treatment. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Presence of other ocular diseases that give reasonable suspicion of a disease or condition that contraindicates the use of faricimab, that might affect interpretation of the results of the study or that renders the patient at high risk for treatment complications
- Presence of other diseases, metabolic dysfunction, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of faricimab and that might affect interpretation of the results of the study or that renders the patient at high risk of treatment complications
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab injections, study treatment procedure, dilating drops, or any of the anesthetic and antimicrobial preparations used by a patient during the study
- Requirement for continuous use of any medications or treatments indicated as prohibited therapy (see Section 4.4.2)

4.2 METHOD OF TREATMENT ASSIGNMENT AND MASKING

This is a non-randomized study. After initial written informed consent has been obtained, all procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's study number and treatment assignment from the IxRS.

As outlined in Section 3.1, there will be a masked period in the early phase of the LTE study. Masked site staff and patients will be informed that the patient will receive faricimab 6 mg IVT injections, and that they will be masked to the faricimab treatment interval only. During the masked period, patients will be advised that at masked study visits they will either receive faricimab or sham injection. After the Week 16 treatment procedure, the study will follow an open-label design and patients will only be required to attend study visits at which they are scheduled to receive faricimab.

Please note, as detailed in Section 4.2.1.1, throughout the entire study period, the retinal physician is expected to assess adverse events, which includes assigning causality and severity of the event.

4.2.1 Masking Requirements during the Masked Period of LTE Study

To fulfil the masking requirements, LTE study assessments will be performed by an investigator masked to the patients' faricimab treatment interval, whilst treatment

administration will be undertaken by an unmasked treatment administrator. The sham procedure is designed to mimic the injection procedure to ensure that patients also remain masked to their treatment during the masked period of the LTE study.

4.2.1.1 Masked Roles during the Masked Period of the LTE Study

Principal Investigator

The Principal Investigator (PI) for the LTE study may be the same individual as in the parent Phase III study and should be a retina specialist (or the equivalent in ex-U.S. countries). For the masked period of the LTE study, the PI must be masked to the treatment interval of the patient. During the masked period of the LTE study, the PI can assume any other masked role as described in this section, with the exception of being a VA examiner.

Assessor Physician

Sites are permitted to have at least one additional investigator designated as a masked assessor physician, who will be an ophthalmologist with an expertise in the retinal subspecialty. The masked assessor physician must also be masked to treatment interval of the patient and will evaluate all pre-treatment assessments. The masked assessor physician will also evaluate the causality of all adverse events reported by the treatment administrator physician. If qualified, this role can take on any other masked role tasks with the exception of being a VA examiner.

Photographer(s) and OCT Technician(s)

If qualified, the photographer(s) and OCT technician(s) can share any other masked role tasks except tasks performed by the BCVA examiner.

Study Coordinator(s)

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

BCVA Examiner

For the duration of the LTE study, to minimise bias, the VA examiner will be masked to the study eye (right vs. left) and must not have access to the medical charts of patients or the BCVA scores from a patient's previous visits. The VA examiner may have access to a patient's refraction data from previous visits. The VA examiner is not allowed to perform any other task involving direct or indirect patient care.

Phlebotomist

Any qualified masked or unmasked individual, with the exception of those in the BCVA examiner role, can perform the tasks of the phlebotomist.

4.2.1.2 Unmasked Roles

Treatment Administrator

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

Following treatment administration, the treatment administrator must also perform the post-treatment administration vision testing (finger-counting/hand movement/light perception tests), perform post-treatment intraocular pressure (IOP) testing, and treat adverse events that occur during or shortly after the study treatment administration. During the masked period of the LTE study, the person in this role should not evaluate the causality of adverse events; this is the responsibility of the masked assessor physician. The treatment administrator will also undertake optional aqueous humor sample collection.

During the masked period of the LTE study, the treatment administrator must not be involved in any other aspect of the study and must not divulge treatment assignment to anyone.

Unmasked Assistant and Pharmacist

If desired, sites may have designated qualified unmasked assistant(s) who can assist with tasks such as assembly of study treatment supplies, preparation of sterile field, preparation of the patient's study eye for treatment, disposal of all injection materials (i.e., syringes and needles) immediately following study treatment, and placing used vial in the kit box. The qualified unmasked assistant(s) may measure post-dose IOP. If the site uses a pharmacy, then the unmasked role is also assigned to the pharmacist who can take on investigational medicinal product (IMP)-related tasks as applicable per delegation of authority log.

Any other study assisting personnel not listed above must be in the masked roles during the masked period of the LTE study.

4.2.1.3 Delegation Log

All roles for each study staff member should be clearly documented in the Site Delegation Log. The Site Delegation Log must be signed by the PI.

4.2.1.4 Role Switching

During the masked period of the LTE study, once personnel assigned to a designated unmasked role start performing that role, the personnel cannot switch to a masked role. However, personnel switching from a masked role to an unmasked role may be possible and must be documented in the Delegation Log.

4.2.1.5 Study Backup Staff

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

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The IMP for this study is faricimab.

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

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Faricimab Formulation

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

See Section 3.1.1 for further details regarding the masked period in the LTE study.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

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

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

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.

4.3.2.1 Faricimab Administration

Faricimab 6 mg will be administered intravitreally to patients at a PTI for the duration of the LTE study (see Figure 1).

Refer to the pharmacy manual for the pre-treatment procedures, the administration of faricimab, or sham (when appropriate; refer to Section 3.1.1), and the post-treatment procedures for all LTE patients.

The pharmacist responsible for dispensing the study treatment, or designated unmasked site personnel, will prepare the correct study treatment (faricimab or sham, when appropriate) as assigned through the IxRS.

The Sponsor has specified the mandatory materials required and detailed stepwise instructions for the preparation of study treatment administration (or sham, when appropriate) in the Pharmacy Manual.

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 single-use only (one injection preparation per patient per eye). Vials used for one patient must not be used for any other patient. Partially used vials, remaining faricimab drug product and administration material must not be reused.

4.3.2.2 Sham Administration

As discussed in Section 3.1.1, to preserve the masking of the Phase III treatment arm assignment, patients enrolling in the LTE study will attend Q4W visits for the first 4 months of the study and will have the sham procedure performed at these visits when they are not treated with faricimab.

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

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

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

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

4.3.4 Continued Access to Faricimab

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

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

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

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

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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment for the duration of the LTE study. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF, except for anti-VEGF therapy in the fellow eye that should be recorded on a separate Fellow Eye anti-VEGF Administration eCRF. Concomitant ocular procedures performed on either eye during the study should be recorded in the Concurrent Ocular Procedures eCRF.

4.4.1 Permitted Therapy

Patients who use maintenance therapies 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 5.1.2.1 and Table 1) may apply with cataract surgery.
- Short-term use of topical ocular corticosteroids after cataract surgery, yttrium-aluminum garnet capsulotomy, peripheral iridotomy, argon/selective laser trabeculoplasty, or for ocular allergic conditions
- Panretinal photocoagulation may be allowed for the treatment of DR after discussion with the Medical Monitor

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

At the discretion of the PI, patients enrolled in the LTE study may have their fellow (non-study) eye treated with anti-VEGF therapy. Consult with the region-specific anti-VEGF prescribing information for the recommended dose and frequency of treatment. The Sponsor will cover the cost of an approved anti-VEGF therapy licensed for ocular use, in accordance with local regulations, until faricimab is made available in that region, after which the Sponsor will support fellow-eye treatment with faricimab. *Any exceptions for ongoing reimbursement of other anti-VEGF therapies must be approved by the Sponsor. Avastin use is not prohibited in the fellow eye; however, the Sponsor cannot cover the cost of anti-VEGF therapies not licensed for ocular use.*

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.

If treatment with anti-VEGF is to be given to the fellow (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 the unmasked physician to preserve masking during the masked period of the LTE study).

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

Note: If anti-VEGF treatment of the fellow eye is required outside of the study visit schedule, then any qualified physician can administer this 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 during the LTE study. If necessary, patients may be discontinued from faricimab treatment and/or the LTE study to receive these therapies:

- Systemic anti-VEGF therapy
- Systemic drugs known to cause macular edema (fingolimod, tamoxifen)
- IVT anti-VEGF agents (other than faricimab) in study eye
- IVT, periocular (subtenon), steroid implants (i.e., Ozurdex®, Iluvien®), or chronic topical ocular corticosteroids in study eye *(defined as continuous usage for 100 days or longer).*
- Treatment with Visudyne® in study eye
- Administration of micropulse and focal or grid laser in study eye
- Other experimental therapies (except those comprising vitamins and minerals) *and therapies that claim to have an effect on macular pathology (e.g., kallidinogenase).*

Patients who discontinue faricimab due to receipt of prohibited therapy should be encouraged to attend LTE annual visits (Year 1 and Year 2) visits, as outlined in the schedule of activities (see Appendix 1).

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.

4.5.1 Informed Consent Forms

Written informed consent for participation in the study must be obtained before performing any LTE study-related procedures (i.e., treatment administration and related procedures). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history and demographic data were collected in the parent studies and will not be obtained again during this extension study.

Concomitant medication information will be obtained at each visit.

4.5.3 Vital Signs

Vital signs will be collected as part of the schedule of assessments for the Week 100 visit of the parent study, and will not be obtained again for this extension study.

4.5.4 Ocular Assessments

Ocular assessments include the following and will be performed on both eyes at specified timepoints in accordance 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 3)
- Pre-treatment IOP measurement of both eyes (perform prior to dilating eyes)
- Slitlamp examination (for grading scales for anterior and vitreous cells, see Appendix 4)
- Dilated binocular indirect high-magnification ophthalmoscopy
- Ocular imaging (see below for further details)
- 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 only by the unmasked treatment administrator (during the masked phase of the study).
- At each visit, post-treatment IOP measurement in the study eye by qualified personnel assigned to the unmasked role (unmasked and masked roles are only relevant up until the open-label period of the study; see Section 3.1.1 for details). If there are no safety concerns following the study treatment, the patient will be permitted to leave the clinic. If the IOP value is of concern to the treatment administrator, the patient will remain in the clinic and will be managed in accordance with the treatment administrator's clinical judgment. The adverse event will be recorded on the Adverse Event eCRF as applicable.

NB: 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 protocol for image acquisition for the LTE study will be the same as that used in the parent Phase III studies. The CRC has previously provided sites with CRC manuals and training materials on image acquisition requirements for specified study ocular images. LTE study images will be obtained by site personnel and imaging systems (including software) that have been certified by the CRC. The method for obtaining CRC certification is detailed in the CRC manual. Photographers/study imaging technicians should obtain CRC certification prior to acquiring any LTE study images.

All ocular images obtained by trained and CRC certified site personnel should be forwarded to the CRC as soon as possible (see Section 3.1.3.5 and Appendix 1, Appendix 5 [CFP], Appendix 6 [FFA], and Appendix 7 [SD-OCT]).

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

Ocular images include the following:

- CFP in both eyes (7- or 4-ETDRS fields; method used for each patient should be consistent with that used in the parent study and remain consistent throughout the duration of the LTE study)
- Optional ultra-wide field (UWF) CFP of both eyes (to be undertaken in patients for whom consent was obtained and images acquired in the parent study)
- FFA of both eyes (preferred method is UWF FFA if sites have capability; sites without UWF should capture 7- or 4-field ETDRS as per the parent study and use the same method consistently throughout their LTE study participation). FFA should be performed after blood samples obtained (if applicable).
- SD-OCT or swept-source OCT images of both eyes (to be undertaken using the same device as that used in the parent study)
- Optional OCT-angiography (OCT-A) of both eyes at sites with OCT-A capabilities and agreement by sites to take these images (to be undertaken using the same device as that used in the parent study)

Refer to the CRC manual for additional details regarding obtaining above images.

4.5.5 Concurrent Ocular Procedures

Any ocular procedures performed on either eye during the study will be recorded on the Concurrent Ocular Procedures Log on the eCRF.

4.5.6 Laboratory and Other Biological Samples

At the scheduled visits (see Appendix 1), all samples must be obtained prior to study treatment, and blood samples must be obtained prior to FFA assessments (as applicable). Fasting is not required prior to specimen collection. Laboratory supply kits will be provided to the sites by the central laboratory. See Appendix 1 for sample collection timepoints and Appendix 8 for biological sample collection and shipping instructions.

The following samples will be sent to the central laboratory or to the Sponsor or a designee for analysis and/or storage:

- Urine pregnancy test prior to each study treatment for women of childbearing potential, including those who have had tubal ligation

  If positive, perform the serum pregnancy test. If the serum pregnancy test is positive, do not administer study treatment.
- Plasma samples for faricimab immunogenicity analysis
- Plasma samples for faricimab PK analysis

Drug concentration, will be determined in plasma using a validated immunoassay method. Anti-drug antibodies (ADAs) will be detected in plasma using a validated bridging ELISA.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.8), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

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

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

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

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

4.5.6.1 Optional Aqueous Humor and Associated Optional Plasma Samples

Collection and submission of optional aqueous humor and optional plasma samples is contingent upon review and approval by the site, each site's Institutional Review Board (IRB) or Ethics Committee (EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for sampling, this section of the protocol (Section 4.5.6.1) will not be applicable at that site.

For patients who consent to provide aqueous humor sampling, the aqueous humor sample should be collected just prior to study treatment (it is acceptable to collect the sample after FFA assessment) by a qualified unmasked treatment administrator, using an aseptic procedure and sterile field and according to local guidelines (see Appendix 8 and the central laboratory manual for aqueous samples collection, storage, and transfer).

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

Aqueous humor samples will be analyzed for faricimab, free VEGF-A, and free Ang-2 concentrations. Data from these analyses will be used to develop better predictive models for determining optimal patient treatment interval(s) and to support selection of a dosing regimen for future clinical trials. Remaining samples will be analyzed for additional biomarkers, including those involved in angiogenesis (which may include, but are not limited to, Ang-1 and platelet-derived growth factor) and inflammation (which may include, but are not limited to, intracellular adhesion molecule 1 and E-selectin), to identify new therapeutic targets, better understand variability in patient responses to faricimab, and to support patient selection and/or stratification in future clinical trials.

Sites will collect optional plasma samples for measurement of faricimab concentration (see Appendix 1 and the Covance manual for sample collection, storage, and transfer).

Faricimab will be quantified in plasma using validated immunoassay methods. Remaining plasma samples may be analysed for additional biomarkers.

Refer to Section 4.5.6 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.6.2 Optional Unscheduled Collection of Vitreous Humor and Associated Optional Plasma Samples

Collection and submission of optional vitreous humor and optional plasma samples is contingent upon review and approval by the site, each site's IRB or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for sampling, this section of the protocol (Section 4.5.6.2) will not be applicable at that site.

Elective vitrectomy for vitreous sample collection is not allowed in the study eye during a patient's study participation; however, if the surgery is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye (see Appendix 8 for further details). Approximately 0.5 mL of undiluted vitreous humor should be collected using an aseptic procedure and sterile field and according to local guidelines. Associated PK plasma samples will be collected to measure faricimab concentration. See the Covance manual for vitreous and PK sample collection, storage, and transfer.

Vitreous humor samples will be analyzed primarily for faricimab concentrations. The remaining samples may be analyzed for free VEGF-A and free Ang-2 concentrations, as well as additional biomarkers, including those involved in angiogenesis (which may include, but are not limited to, Ang-1 and platelet-derived growth factor) and inflammation (which may include, but are not limited to, intracellular adhesion molecule 1 and E-selectin), to identify new therapeutic targets, better understand variability in patient responses to faricimab, and to support patient selection and/or stratification in future clinical trials.

Refer to Section 4.5.6 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.7 Patient-Reported Outcomes

The NEI VFQ-25 will be completed to assess the treatment benefit of faricimab.

4.5.7.1 Data Collection Methods for Patient-Reported Outcome Assessments

The NEI VFQ-25 will be interviewer-administered by masked site staff (when appropriate; see Section 3.1.1), excluding the BCVA examiner, at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1). At the clinic, instruments will be administered before the patient receives any information on disease status and prior to the administration of study treatment, unless otherwise specified.

The NEI VFQ-25, translated into the local language as appropriate, will be provided by the Sponsor to enable instruments to be administered at each specified timepoint.

During clinic visits, the NEI VFQ-25 should be administered by masked site staff as outlined below:

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

4.5.7.2 Description of PRO Instrument

PROs will be assessed using the NEI VFQ-25 (Mangione et al. 2001) (see Appendix 9). The NEI VFQ-25 captures a patient's perception of vision-related functioning and vision-related quality of life. The core measure includes 25 items that comprise 11 vision-related subscales and one item on general health. In this study, an additional six appendix items will be included for the Near Activities and Distance Activities subscales. The composite score and subscale scores range from 0 to 100, with higher scores indicating better vision-related functioning. Subscale scores include General Vision, Ocular Pain, Near Activities, Distance Activities, Social Functioning, Mental Health, Role Difficulties, Dependency, Driving, Color Vision, and Peripheral Vision.

Interviews will be conducted in the local language of the patient using linguistically validated translations. Patients may be excluded from completing the NEI VFQ-25 if a translation is not available in their spoken language.

4.5.8 Optional Samples for Research Biosample Repository

4.5.8.1 Overview of the Research Biosample Repository

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

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

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

4.5.8.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.8) will not be applicable at that site.

4.5.8.3 Sample collection

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

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

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

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

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

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

4.5.8.4 Confidentiality

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

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

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

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

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

4.5.8.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.8.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

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

4.5.8.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue faricimab 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 faricimab treatment
- Investigator or Sponsor determination that faricimab 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 from faricimab treatment but remain in the study for follow up must attend an unscheduled visit 28–35 days after their last faricimab dose, and be encouraged to attend both the Year 1 and Year 2 visits if not already completed.

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

Patients who discontinue from the study prior to the end of study must return to the clinic for a treatment discontinuation visit 28–35 days after the final dose of faricimab 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

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:

- Poor protocol adherence
- Inaccurate or incomplete data recording

- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Faricimab is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with faricimab in completed and ongoing studies. The anticipated important safety risks for faricimab are outlined below. Refer to the Faricimab (RO6867461) 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. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Faricimab

The known side effects associated with faricimab, as well as potential side effects based on human and laboratory studies, are listed below. These risks are either from the drug itself or the injection procedure.

*P*otential risks of faricimab include intraocular inflammation, the intravitreal injection-related risks of infectious endophthalmitis, retinal detachment/tear, iatrogenic traumatic cataracts, and *transient* increased IOP, as well as the non-ocular risk of arterial thromboembolic events. An independent clinical events coding committee will adjudicate thromboembolic events (myocardial infarcts, strokes, and deaths) reported during the study.

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

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Treatment Interruption

Study treatment interruption/patient discontinuation from study treatment for adverse events will be determined using the criteria listed in Table 1. If any of these criteria are met, treatment will be interrupted (or discontinued, if appropriate). The reason for study treatment interruption/discontinuation should be recorded on the appropriate eCRF and, if applicable, on the Adverse Event eCRF.

Table 1 Dose Interruption and Treatment Discontinuation Criteria

Event	Criteria
Intraocular inflammation	• Interrupt faricimab treatment if intraocular inflammation (iritis, iridocyclitis or vitritis) is ≥2+ in the study eye. • Faricimab treatment may be resumed subsequently as determined by the investigator.
Cataract surgery in the study eye	• Interrupt faricimab treatment after cataract surgery in study eye. • Faricimab 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, faricimab treatment may be permitted as determined by Medical Monitor and investigator.
BCVA decrease	• Interrupt faricimab 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. • Faricimab treatment may be permitted subsequently, as determined by the investigator.
Elevated IOP	• Interrupt faricimab treatment if pre-treatment IOP in the study eye is ≥30 mmHg. • Treatment may be permitted when IOP has been lowered to <30 mmHg, either spontaneously or by treatment, as determined by the investigator.
Rhegmatogenous retinal break	• Interrupt faricimab treatment if a retinal break is present in the study eye. • Faricimab 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 faricimab treatment if rhegmatogenous retinal detachment or Stage 3 or 4 macular hole occurs in the study eye. • Faricimab treatment may be subsequently permitted after discussion with Medical Monitor.
Active or suspected infection	• Interrupt faricimab 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.
On-study prohibited medications	• Refer to Section 4.4.2 for additional reasons for potential faricimab 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, measuring protocol-specified vital signs, and performing 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., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

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

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

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Sight-threatening adverse events: an adverse event is considered to be sight-threatening and should be reported expeditiously if it meets one or more of the following criteria:
  - It causes a decrease of $\geq$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; laser or retinal cryopexy with gas; or a medication) to prevent permanent loss of sight.
  - It is associated with severe intraocular inflammation (i.e., endophthalmitis, 4+ anterior chamber cell/flare, or 4+ vitritis; see Section 5.3.5 and Appendix 4 for intraocular inflammation grading scales).

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

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

5.3.1 Adverse Event Reporting Period

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

After initiation of study drug, all adverse events will be reported until the final study visit at Year 2. For patients who terminate study treatment and from the study early, all adverse events will be reported up to the early termination visit. For patients who discontinue study treatment early 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 2 provides guidance for assessing adverse event severity.

Table 2 Adverse Event Severity Grading Scale

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 3).

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

Table 3 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

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

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

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

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

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × 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 Values

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

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

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

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

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

5.3.5.6 Abnormal Liver Function Tests

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

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

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

5.3.5.7 Deaths

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

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

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

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the Day 1 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

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on changes in BCVA and OCT criteria and changes observed in the DRSS. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

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., no more than 24 hours after learning of the event; see Section 5.4.2).

During the Masked Phase (i.e., Day 1–Week 16):

All special situations associated with the masked study treatment, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF in a masked manner as described below:

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

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria (see Section 5.2.2) or it is adverse event of special interest (see Section 5.2.3), the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.3.1). Adverse events associated with special situations should be recorded as described below:

- *Enter the adverse event caused by the medication error as primary adverse event term on Adverse Event eCRF. Check the "Medication Error" box.*

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

During the Open-Label Phase (i.e., Week 20 onwards):

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.

5.3.5.12 Patient-Reported Outcome Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

- Pregnancies (see Section 5.4.3 for details on reporting requirements)

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

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

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

5.4.1 Medical Monitors and Emergency Medical Contacts

Contact Information for Eastern Hemisphere

Medical Monitor/Emergency Medical Contact: [redacted] M.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Contact information for Western Hemisphere

Medical Monitor/Emergency Medical Contact: [redacted] M.D., Ph.D.

Mobile Telephone No.: [redacted]

Contact Information for Western Hemisphere

Medical Monitor/Emergency Medical Contact: [redacted] M.D., Ph.D.

Mobile Telephone No.: [redacted]

Contact Information for Asia-Pacific

Medical Monitor/Emergency Medical Contact: [redacted] M.D., Ph.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk 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 after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the final visit at Year 2. For patients who terminate from the study treatment and the study early all adverse events will be reported up to the early termination visit.

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed *through the Informed Consent Form* to inform the investigator immediately if they become pregnant during the study or within 3 months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF,

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

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

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

5.4.3.3 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (see

definition in Section 5.3.1) if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

Drug	Document
Faricimab	Faricimab Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

No formal sample size calculations will be performed for this LTE study. This study is open to all patients who complete study treatment and the Week 96 visit in one of the parent studies GR40349 (YOSEMITE) or GR40398 (RHINE) (see Sections 4.1.1 and 4.1.2).

6.2 ANALYSIS POPULATIONS

6.2.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population will comprise all eligible patients enrolled into this LTE study. For analyses using the parent study treatment group, patients will be grouped according to the treatment assigned at randomization in the parent study.

6.2.2 Per-Protocol Population

The per-protocol population is defined as all ITT patients who received at least one injection of faricimab and who do not have a major protocol violation. For analyses using the parent study treatment group, patients will be grouped according to the treatment assigned at randomization in the parent study.

6.2.3 Safety-Evaluable Population

The safety-evaluable population will comprise all patients who enroll in the LTE, regardless of whether they received faricimab treatment during the LTE. For analyses based on the parent study treatment groups, patients will be grouped according to the actual treatment received in the parent study up to the Week 96 visit as follows (similar algorithm used in the parent studies):

- If the only active treatment received in the parent study by a patient in the study eye was aflibercept, the patient's parent study treatment group will be aflibercept Q8W.
- If the only active treatment received in the parent study by a patient in the study eye was faricimab, the patient's parent study treatment group will be as randomized if the patient was randomized to one of the faricimab arms.
- If a patient received in the parent study a combination of different active treatments (faricimab and aflibercept) in the study eye, the patient's parent study treatment group will be as randomized.

6.2.4 Pharmacokinetic Population

The PK population will include safety-evaluable patients who have at least one plasma sample, and if sufficient dosing information (dose and dosing time) is available. The parent study treatment group will be defined similar to the safety-evaluable population (see Section 6.2.3).

6.2.5 Immunogenicity Population

The immunogenicity population will consist of all patients with at least one plasma sample for ADA assessment. For analyses using the parent study treatment group, patients will be grouped according to treatment received in the parent study.

6.3 SUMMARIES OF CONDUCT OF STUDY

Summaries of conduct of study will be based on the ITT population and presented overall, and by parent study treatment group. The number and percentage of patients who enroll (including from which parent study), discontinue, or complete the LTE study will be summarized overall, and by country and site. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of the study results.

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized using the ITT population presented overall, and by parent study treatment group. Demographic data (e.g., age, sex, and race/ethnicity) will originate from the parent study. Baseline disease characteristics (e.g., baseline BCVA, ocular assessments) will come from the parent study and the LTE study. Descriptive statistics for continuous data will include number of observations, arithmetic mean, standard deviation, median, minimum, and maximum. Descriptive statistics for categorical data will include frequency and/or percent.

Exposure to study drug (number of treatments and duration of treatment) will be summarized from the parent study and the LTE study presented overall, and by parent treatment group for the safety-evaluable population.

6.5 SAFETY ANALYSES

Safety analyses will be based on the safety-evaluable population. Safety will be assessed through descriptive summary of ocular and non-ocular adverse events, deaths, and ocular assessments (e.g., IOP).

Verbatim descriptions of treatment-emergent adverse events will be mapped to MedDRA thesaurus terms, and the incidence and severity will be summarized. A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first day (Day 1) of this LTE study. Only adverse events captured in this LTE study will be included for summaries.

Adverse events will be tabulated by System Organ Class and preferred term and presented overall, and by parent study treatment group. Summaries will be generated for serious adverse events, deaths, adverse events leading to discontinuation of study drug, adverse events of special interest, and adverse events judged to be related to study treatment. Separate summaries will be prepared for non-ocular and ocular adverse events.

Results of the ocular assessments will be summarized by timepoint and by eye (study vs. fellow) using descriptive summaries. In addition, changes, from parent study Day 1 and from LTE study Day 1, in pre-dose IOP measurements and changes between pre-dose and post-dose IOP measurements will also be summarized.

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

6.6 EXPLORATORY EFFICACY ANALYSES

The exploratory efficacy analyses will be based on the ITT population. Additional analyses based on the per-protocol population will also be conducted for the BCVA score and CST analyses over time.

Summary measures will be as follows:

- For proportions:

  Overall for the whole LTE study cohort

  Difference in proportions between each of the two faricimab arms (Q8W and PTI) and the aflibercept (Q8W) arm

- For continuous variables:

  Overall for the whole LTE study cohort

  Difference in adjusted mean between each of the two faricimab arms (Q8W and PTI) and the aflibercept (Q8W) arm and overall

6.6.1 Intercurrent Events

The following intercurrent events will be taken into consideration if the event occurred until the clinical cutoff date

- Discontinuation of study treatment due to adverse events or lack of efficacy
- Use of prohibited therapy in the study eye

If a patient discontinues from study treatment due to adverse events or lack of efficacy, or receives any prohibited systemic treatment or prohibited therapy in the study eye, a treatment policy estimand approach will be followed where all observed values will be used regardless of the occurrence of intercurrent event.

6.6.2 Endpoints (Variables)

All efficacy endpoints will be assessed over time, and at 1- and 2-year timepoints in the LTE study. Change from baseline will be calculated from Day 1 of the parent study and from the Day 1 of this LTE study.

The following endpoints will be included in the exploratory efficacy analyses:

- Change in BCVA over time as measured using the ETDRS chart at a starting distance of 4 meters
- Change in CST over time as measured by SD-OCT
- Proportion of patients with presence of central retina intraretinal fluid, subretinal fluid, and both over time
- Number of faricimab injections received during the LTE study
- The proportion of patients on a Q4W, Q8W, Q12W, and Q16W treatment interval during the study
- Proportion of patients with a $\geq$2- or $\geq$3-step improvement in their DRSS score over time
- Proportion of patients with a $\geq$2- or $\geq$3-step worsening in their DRSS score over time
- Proportion of patients who develop new PDR over time

- Change in patient-reported vision-related functioning and quality of life over time as assessed using the NEI VFQ-25 composite score, the near activity subscale score, the distance activities subscale score, and driving subscale score

Missing data will be implicitly imputed using a mixed-model repeated measures model, assuming a missing-at-random missing data mechanism (i.e., the probability that missing data are dependent on other observed variables but not on the missing data).

Additional details about the planned analyses, as well as sensitivity analyses using other imputation methods for missing data and sensitivity analyses of the per-protocol population will be provided in the SAP.

6.7 PHARMACOKINETIC ANALYSES

The PK analyses will be performed using the PK population. The analyses will be summarized overall and by parent study treatment group. Plasma concentrations of faricimab will be summarized descriptively.

Concentrations of faricimab from the optional collection of aqueous humor may be reported and/or summarized as appropriate. Additional PK/PD and exposure-response analyses may be conducted as appropriate. Population PK modeling may be performed to characterize inter-individual variability, which may be reported separately from the Clinical Study Report.

6.8 IMMUNOGENICITY ANALYSES

Immunogenicity analyses will be based on the immunogenicity analysis population.

The number and proportion of ADA-positive patients and ADA-negative patients at parent study baseline Day 1 (baseline prevalence 1), LTE baseline Day 1 (baseline prevalence 2), and after LTE enrollment (post-baseline 1 and 2 incidence) will be summarized overall and by parent study treatment group. When determining the post-baseline incidences, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but who develop an ADA response following study drug exposure, or if they are ADA positive at baseline and the titer of one or more post-dose samples is greater than the titer of the baseline sample by a scientifically reasonable margin (details to be provided in the SAP). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is greater than the titer of the baseline sample by a scientifically reasonable margin such as 4-fold.

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

6.9 BIOMARKER ANALYSES

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

Analyses will be performed to identify biomarkers that are predictive of response to faricimab, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of faricimab activity, or can increase the knowledge and understanding of disease biology.

6.10 INTERIM ANALYSIS

No formal interim analysis is planned. Data cuts may be performed at appropriate timepoints for inclusion in the submission with the main studies, for example, to support the safety profile. *An interim analysis may be performed for internal stakeholder data presentations/conference presentations/publications/market authorization purposes.*

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure.

Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the

requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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

8.4 CONFIDENTIALITY

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

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

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

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

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease.
In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (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 end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. 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. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

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

Approximately 550 sites globally participated in the parent studies, and these same sites will enroll approximately 1800 patients. Enrollment will occur through an IxRS.

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

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities

	Day 1 [a]	Week 4	Week 8	Week 12	Week 16	PTI interval	Year 1 [b]	Year 2 [b]	*Final e*nd of study visit [c]	ET Visit [d]
Visit Window (days)		(±7)	(±7)	(±7)	(±7)				28–35 days after last dose	(28–35 days *after last study treatment*)
Main informed consent [e]	x									
Optional aqueous, vitreous and blood sample informed consent [e]	x									
Optional (RBR) residual samples and DNA whole blood sample informed consent [e]	x									
Review of inclusion and exclusion criteria	x									
Vital signs [f]	(x) [g]								*x*	x
NEI VFQ-25 [g]	(x) [g]						x	x		x
Refraction and BCVA assessment [i]	(x) [g]	x	x	x	x	x	x	x	*x*	x
Pre-treatment IOP [j]	(x) [g]	x	x	x	x	x	x	x		x
Urine pregnancy test [k]	(x) [g]	x	x	x	x	x	x	x	x	x
Mandatory plasma PK sample [l]	(x) [g]		x	x			x	x		x
Mandatory plasma ADA sample [l]	(x) [g]		x	x			x	x		x
Optional aqueous humor sample [m]	x	x	x	x	x					
PK plasma sample (only if optional aqueous humor sample is collected) [m]		x			x					
Optional PD plasma sample (if aqueous humor sample is collected) [m]		x	x	x	x					
Optional whole blood sample for DNA [n]	(x)									

Appendix 1: Schedule of Activities

	Day 1 [a]	Week 4	Week 8	Week 12	Week 16	PTI interval	Year 1 [b]	Year 2 [b]	*Final e*nd of study visit [c]	ET Visit [d]
Visit Window (days)		(±7)	(±7)	(±7)	(±7)				28–35 days after last dose	(28–35 days *after last study treatment*)
Optional vitreous humor sample [o]		Can be collected if vitrectomy is necessary.								
PK plasma sample (only if optional vitreous humor sample is collected) [o]		Collect if vitreous humor sample is collected.								
Slit-lamp examination	(x) [g]	x	x	x	x	x	x	x	x	x
Indirect ophthalmoscopy	(x) [g]	x	x	x	x	x	x	x	x	x
SD-OCT [o]	(x) [g]	x	x	x	x	x	x	x	x	x
Optional OCT-A [q]	(x) [g]						x	x		x
FFA [r]	(x) [s]						x	x		x
CFP [r]	(x) [s]				x		x	x		x
Optional UWF CFP [r]	(x) [s]				x		x	x		x
Administration of study treatment [t]	x	x	x	x	x	x	x	x		
Finger-counting test [u]	x	x	x	x	x	x	x	x		
IOP (post-study treatment) [v]	x	x	x	x	x	x	x	x		
Adverse events [w]	x	x	x	x	x	x	x	x	x	x
Concomitant medications [x]	(x) [g]	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [y]	(x) [g]	x	x	x	x	x	x	x	x	x

Appendix 1: Schedule of Activities

ADA = anti-drug antibody; BCVA = best-corrected visual acuity; CFP = color fundus photograph; CRC = central reading center; eCRF = electronic Case Report Form; ET = early termination; FFA = fundus fluorescein angiography; IOP = intraocular pressure; IxRS = interactive voice or web-based response system; LTE = long-term extension; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire–25; OCT-A = optical coherence tomography–angiography; PD = pharmacodynamic; PK = pharmacokinetic; PTI = personalized treatment interval; RBR = Research Biosample Repository; SD-OCT = spectral-domain optical coherence tomography; UWF = ultra-wide field.

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments must be performed on the same day.

[a] The LTE study Day 1 visit and the parent Phase III study Week 100 visit should be on the same day. If this is not possible, the Day 1 LTE visit should be within 2 business days of the Phase III Week 100 visit.

[b] Annual visits are defined as the scheduled PTI visit that is *earliest (between Week 48 and Week 64) relative to 52 weeks (for Year 1)* and *earliest (between Week 96 and Week 104) relative to 104 weeks (for Year 2)* from Day 1. *If, due to the patient's faricimab PTI, there are multiple options for Year 1 or Year 2 visits,* IxRS will advise the site *that* the *earliest* scheduled visit *between Week 48 and Week 64* should be considered the Year 1 *visit and that the earliest scheduled visit between Weeks 96 and 104 should be considered the* Year 2 visit. *If the earliest scheduled visit is missed, then the next visit within the period should be considered the annual visit.*

[c] Patients who *undertake their Year 2 visit at Week 96 or Week 100 but are on a PTI that requires them to return at Week 100 and/or Week 104 should also attend these scheduled study visits and attend their Final End of Study visit 28–35 days after their final dose of study treatment. Further information regarding the Year 2 visit will be provided by the study team.*

[d] *Patients who* discontinue the study prior to the final study visit at Year 2 *and* have not withdrawn consent should return for an ET visit *28–35 days* after *receipt* of the last study treatment.

[e] Informed consent must be administered and documented before any study assessment or procedure is performed and may be obtained more than 28 days before the Day 1 visit. The Optional Blood, Aqueous Humor, Vitreous Humor Samples Informed Consent Form as well as Optional (RBR) Informed Consent Form for residual samples and whole blood DNA sample collection can be signed either at the parent study Week 96 visit or the LTE study Day 1 visit prior to sample collection.

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

[g] Assessment will be collected as part of parent Phase III study Week 100 visit. Assessment ***may*** need to be performed again if the LTE Day 1 visit is conducted on a different day to parent study Week 100 visit; see Section 3.1

[h] To be administered by masked site staff (except for the visual acuity examiner) prior to any other visit assessments being performed on that day. Refer to Section 4.5.7.1 for further details on questionnaire administration.

[i] Refraction and BCVA assessments should be performed prior to pupil dilation. Assessments to be performed on both eyes. Study eye refraction data to be entered in appropriate eCRF log on Day 1, Year 1, and Year 2 only. BCVA data for both eyes to be entered in appropriate eCRF log at each visit. **Study eye BCVA data must be entered in IxRS at each visit as soon as possible—ideally within 24 hours of the study visit.** These data will be required by the IxRS to calculate the next treatment interval, and failure to follow this procedure will result in a delay to the patient receiving notification of the timeframe for their subsequent dosing visit.

[j] Pre-treatment IOP should be measured before pupillary dilation at each study visit, and at the ET visit, if applicable.

[k] Urine pregnancy test should be performed on women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, study treatment should be withheld and a serum pregnancy sample collected and forwarded to the central laboratory for testing. If the serum pregnancy test is positive, study treatment should be withheld.

[l] Samples should be collected prior to study treatment administration, and, if scheduled, FFA. *If samples are missed at a scheduled visit, they may be collected at the next scheduled visit. This does not apply to missed Week 8 samples, as Week 12 is also a sampling visit.*

[m] Only applicable to sites for whom IRB/EC approval has been granted and in patients who have consented to optional sampling. Samples to be collected prior to study treatment administration. If applicable, samples may be collected after FFA. Please collect associated optional plasma PK PD samples at the indicated timepoints if aqueous humor sample is collected. *Missed aqueous humor samples and associated optional plasma samples will not be made up at the next scheduled visit.*

[n] Optional whole blood sample collection **only** in patients for whom optional sample was not collected in the parent study. *If the optional whole blood DNA sample was not collected in the parent study, and is not obtained at Day 1, the sample may be collected at any subsequent study visit when a blood draw is being performed for other purposes as specified (e.g., PK, ADA). This sample collection is not applicable for a site that has not been granted approval by the country regulators or site's Institutional Review Board or Ethics Committee. The DNA samples will be collected from patients who give specific consent to participate in this optional research.*

[o] If vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. An associated PK blood sample should also be collected at this time. Samples to be shipped to the central laboratory as per manual instructions.

[p] Parent study CRC certified equipment to be used. SD-OCT images must be sent to the CRC as soon as possible (ideally within 24 hours), as these need to be read by the CRC who will update IXRS to calculate the next treatment interval. **Failure to follow this procedure will result in a delay to the patient receiving notification of the timeframe for their subsequent dosing visit.**

[q] Parent study CRC certified equipment to be used. Only at sites with OCT-A capabilities.

[r] Parent study CRC certified equipment to be used. FFA should be performed after laboratory samples have been collected. If a patient misses a study visit when FFA or CFP is scheduled, or scheduled images missed (e.g., due to faulty equipment), images must be obtained at the next *scheduled* visit.

[s] Images will be collected as part of parent Phase III study Week 96 visit and do not need to be repeated unless the image was not collected at the parent study Week 96 visit.

[t] During the masked period of the LTE study, patients will receive either faricimab or sham injection. Refer to Sections 3.1, 4.2, and 4.3 for further details.

[u] The finger-counting test should be conducted after treatment administration to the study eye.

[v] Post-treatment IOP to be measured in the study eye post-study treatment administration by qualified personnel assigned to the unmasked role during the masked period. If there are safety concerns, the patient should be managed in accordance with the investigator's clinical judgment. Any adverse events will be recorded on the Adverse Event eCRF.

[w] All adverse events will be reported until the final study visit or until the ET visit (if applicable). 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 (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[x] Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications such as proparacaine, etc.) used by a patient until the conclusion of the patient's study participation or ET visit.

[y] Record all concurrent ocular procedures performed on the study or non–study eye up until the final study visit or ET visit (if applicable).

Appendix 2
Unscheduled Safety Assessment Visit

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

IOP = intraocular pressure.

[a] Patients will be instructed to contact the investigator at any time if they have any health-related concerns. *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 masked physician in the assessor role during the masked period.

Please 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.

Appendix 3
Refraction and Best-Corrected Visual Acuity Testing

SCOPE

The refraction and best-corrected visual acuity (BCVA) assessment must be conducted before pupil dilation. The refraction and BCVA will be measured by trained and certified personnel at the study sites. Both refraction and BCVA will be assessed at every study visit. However, only study eye refraction from Day 1, Year 1, and Year 2 visit will be entered to refraction specific electronic Case Report Form (eCRF). The BCVA assessment data will be entered to BCVA specific eCRF from every study visit. **The visual acuity (VA) examiner must be masked to each patient's study (treated) eye and treatment** interval assignment for the duration of the study. VA will be measured at the intervals specified in the protocol (see Appendix 1).

EQUIPMENT

The following are needed to conduct the examination:

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

Note: for additional details, see the BCVA specification manual.

TRAINING AND CERTIFICATION

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

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

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

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

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

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

From: The Standardization of Uveitis Nomenclature (SUN) Working Group criteria. Reference: Foster CS, Kothari S, Anesi SD, et al. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. Surv Ophthalmol 2016;61:1–17.

Appendix 5
Color Fundus Photography

SCOPE

Stereo color fundus photography (CFP) using 7-modified field or 4-wide field imaging will be performed on both eyes by trained and central reading center (CRC) certified personnel. CFP will be performed at baseline (Day 1) and at the intervals specified in the schedule of activities (see Appendix 1).

Sites that have ultra-wide field (UWF) CFP (e.g., Optos®) capabilities, and have agreed to performing these, will collect additional UWP images of both eyes starting at baseline (Day 1) and at the intervals specified in the schedule of activities (Appendix 1).

EQUIPMENT

See the CRC manual.

PROCEDURES

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

Appendix 6
Fundus Fluorescein Angiography

SCOPE

Fundus fluorescein angiography (FFA) using the preferred ultra-wide field (UWF; Optos®) imaging, if available, or otherwise using 7- or 4-wide field imaging, will be performed on both eyes at the study sites by central reading center (CRC) certified trained personnel. FFA will be obtained at baseline (Day 1) and at the intervals specified in the protocol (see Appendix 1).

EQUIPMENT

Digital angiograms must be acquired for the study.

Film-based angiography is not acceptable.

UWF is the preferred method for FFA. Study sites without UWF equipment and certification must use 7- or 4-wide field FFA capture as described in the CRC manual.

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.

PROCEDURES

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

Appendix 7
Spectral-Domain Optical Coherence Tomography

SCOPE

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

SD-OCT images of both eyes obtained at protocol-specified visits will be forwarded to the CRC.

Note: Optional optical coherence tomography–angiography (OCT-A) images will be collected at the sites with OCT-A capabilities and forwarded to the CRC.

EQUIPMENT

See the CRC manual. Only electronically exportable digital image files will be accepted (i.e., print-outs of SD-OCT images are not acceptable).

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

PROCEDURES AND CERTIFICATION

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

Appendix 8
Biological Sample Collection and Shipping Instructions

BIOLOGICAL SAMPLES

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

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

OPTIONAL ANTERIOR CHAMBER (AQUEOUS HUMOR) SAMPLE COLLECTION

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

OPTIONAL UNSCHEDULED COLLECTION OF VITREOUS HUMOR SAMPLE COLLECTION

Elective vitrectomy is not allowed in the study eye during a patient's study participation. However, if the surgery is medically necessary and the patient consents, a vitreous sample can be collected from the study eye. Either masked or unmasked investigators can collect the sample. Approximately 0.5 mL of undiluted vitreous humor should be collected using an aseptic procedure and sterile field and according to local guidelines and shipped as specified in the central laboratory manual.

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

Vitreous humor samples will be analyzed primarily for faricimab concentrations. The remaining samples may be analyzed for free VEGF and Ang-2 concentrations, and possibly other biomarkers.

BIOLOGICAL SAMPLES STORAGE DURATION

The hematology, serum chemistry, coagulation, serum, and urine pregnancy tests samples will be destroyed no later than the time of completion of the final Clinical Study Report.

Unless the patient gives specific Research Biosample Repository consent for his or her remaining samples to be stored for optional exploratory research (see Section 4.5.8), the rest of the biological samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

Appendix 9
National Eye Institute Visual Functioning Questionnaire–25

PB/IA

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

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

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

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

Instructions:

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

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

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

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Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is*:

	(Circle One)
READ CATEGORIES:	
Excellent	**1**
Very Good	**2**
Good	**3**
Fair	**4**
Poor	**5**

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

	(Circle One)
READ CATEGORIES:	
Excellent	**1**
Good	**2**
Fair	**3**
Poor	**4**
Very Poor	**5**
Completely Blind	**6**

* **Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0**

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3. How much of the time do you worry about your eyesight?

(Circle One)

READ CATEGORIES:

None of the time	**1**
A little of the time	**2**
Some of the time	**3**
Most of the time	**4**
All of the time?	**5**

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

READ CATEGORIES:

None	**1**
Mild	**2**
Moderate	**3**
Severe, or	**4**
Very severe?	**5**

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

6. How much difficulty do you have doing work or hobbies that require you to <u>see well up close</u>, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

7. Because of your eyesight, how much difficulty do you have <u>finding something on a crowded shelf</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

8. How much difficulty do you have <u>reading street signs or the names of stores</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

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9. Because of your eyesight, how much difficulty do you have <u>going down steps, stairs, or curbs in dim light or at night</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

10. Because of your eyesight, how much difficulty do you have <u>noticing objects off to the side while you are walking along</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

11. Because of your eyesight, how much difficulty do you have <u>seeing how people react to things</u> you say?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

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12. Because of your eyesight, how much difficulty do you have <u>picking out and matching your own clothes</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this 6

13. Because of your eyesight, how much difficulty do you have <u>visiting with people in their homes, at parties, or in restaurants</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this 6

14. Because of your eyesight, how much difficulty do you have <u>going out to see movies, plays, or sports events</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this 6

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 *Skip To Q 15c*

No..... 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove..... 1 *Skip To Part 3, Q 17*

Gave up 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight..... 1 *Skip To Part 3, Q 17*

Mainly other reasons..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons..... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all..... 1

A little difficulty..... 2

Moderate difficulty..... 3

Extreme difficulty..... 4

16. How much difficulty do you have <u>driving at night</u>? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight	**5**
Have you stopped doing this for other reasons or are you not interested in doing this	**6**

16a. How much difficulty do you have <u>driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic</u>? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight	**5**
Have you stopped doing this for other reasons or are you not interested in doing this	**6**

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
17. Do you accomplish less than you would like because of your vision?.....	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?.....	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:.....	1	2	3	4	5

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For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.....	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me....	1	2	3	4	5
24. I need a lot of help from others because of my eyesight	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight	1	2	3	4	5

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SUBSCALE: NEAR VISION

A1. Wearing glasses, how much difficulty do you have <u>reading the small print in a telephone book, on a medicine bottle, or on legal forms</u>? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A2. Because of your eyesight, how much difficulty do you have <u>figuring out whether bills you receive are accurate</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A3. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

SUBSCALE: DISTANCE VISION

A4. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A5. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A6. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

That's the end of the interview. Thank you very much for your time and your help.