Official Title: A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab (RO6867461) in Patients With Diabetic Macular Edema (YOSEMITE)

NCT Number: NCT03622580

Document Date: Protocol Version 3: 20-Jun-2019

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR–CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF *FARICIMAB (*RO6867461*)* IN PATIENTS WITH DIABETIC MACULAR EDEMA (YOSEMITE)**
PROTOCOL NUMBER:	GR40349
VERSION NUMBER:	3
EUDRACT NUMBER:	2017-005104-10
IND NUMBER:	119225
TEST PRODUCT:	*Faricimab (*RO6867461*)*
MEDICAL MONITOR:	[redacted], *M.D., Ph.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 4 June 2018
DATES AMENDED:	Version 2: 23 August 2018 Version 3: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
20-Jun-2019 19:29:59	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol GR40349 has been amended primarily for the following reasons:

- RO6867461 received World Health Organization (WHO) status of a recommended International Nonproprietary Name (INN) of "faricimab" and will hereafter be referred to in the text as such. Note that in some figure legends, study titles, and appendices, the name "RO6867461" may still be referenced and should be read as synonymous with faricimab. This is a global change and is not shown in italics.
- The Medical Monitor name has been updated to [redacted], M.D., Ph.D. (protocol cover page, acceptance form, and Section 5.4.1).
- [redacted]
- The study eye ocular exclusion criterion has been modified to include vitreomacular traction (Section 4.1.2.2), [redacted]
- The concurrent ocular conditions exclusion criterion has been modified to include retinal embolus (Section 4.1.2.5).
- A section for risks associated with aflibercept has been added (Section 5.1.3).
- Study treatment interruption due to active or suspected infection has been expanded to include "suspected ocular or periocular infections" (Section 5.1.4.1, Table 2).
- Criteria for study treatment interruption due to intraocular inflammation have been updated such that study treatment may be resumed subsequently as determined by the investigator (Section 5.1.4.1; Table 2).
- Reporting of medication errors and associated adverse event in Section 5.4.4 was updated and moved to Section 5.3.5.12. The medication errors themselves will no longer be reported expeditiously (within 24 hours). However, if they cause a serious adverse event or adverse event of special interest, these will continue to be reported in an expedited manner.
- The expedited reporting of medication errors and overdose has been removed from Section 5.4.
- Language has been updated to indicate that therapeutic or elective abortions are not considered adverse events unless performed because of an underlying maternal or embryofetal toxicity. In such cases, the underlying toxicity should be reported as a serious adverse event. Language has also been added to clarify that all abortions are to be reported on the paper Clinical Trial Pregnancy Reporting Form (Section 5.4.3.2).

In addition, the following changes and/or clarifications have been made:

- The secondary efficacy objective endpoint "change from baseline in CST over time" has been further clarified to include "change from baseline in CST at 1 year" (Section 2, Table 1).
- An exploratory efficacy objective has been added to evaluate the efficacy of faricimab on anatomical outcome measures using SD-OCT to correspond to the already existing endpoints of change from baseline in neurosensory CST and in total macular volume over time (Section 2, Table 1).
- Information for the combined screening/Day 1 visit (Section 3.1.1.1) has been enriched to improve readability; text has also been added to clarify conditions for the screening process.
- Information for the randomization and visit schedule (Section 3.1.1.3) has been enriched to promote understanding of protocol-specific requirements.
- [redacted]
- The inclusion criterion for documented diagnosis of diabetes mellitus now includes examples of other injectable drugs (e.g., dulaglutide and liraglutide) (Section 4.1.1.1).
- An additional example (micropulse laser) has been added to study eye macular laser exclusion criterion (Section 4.1.2.2).
- A description for the sham procedure has been added to Section 4.3 for completeness.
- Additional examples (argon/selective laser trabeculoplasty and ocular allergies) have been included as to when short-term use of topical ocular corticosteroids can be used (Section 4.4.1).
- Details have been added to the descriptions for ocular images (Section 4.5.5).
- It has been clarified that leftover samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed (Section 4.5.7).
- As applicable throughout the protocol, [redacted] to more accurately describe what the assays are measuring and to be consistent with the other sections of the protocol.
- To improve content flow and readability, the optional aqueous and optional plasma samples text has been modified (Section 4.5.7.1).
- Details have been added to provide a better description of potential biomarkers assessments that may be performed for this study (Section 4.5.7.2).
- Language has been added to clarify that, after withdrawal of consent for participation in the Research Biosample Repository (RBR), remaining RBR samples will be destroyed or will no longer be linked to the patient; details regarding instruction for patient withdrawal of consent to the testing of his or her RBR samples after closure of the site has been added (4.5.9.6).

- On-study prohibited medications (already included in Section 4.4.2) are now also listed in Section 5.1.4.1, Table 2 for completeness.
- Bevacizumab (Avastin®) for the fellow eye treatment has been added to Section 4.4.1 to clarify that only anti-VEGFs approved for ophthalmic use by the country regulatory agency are allowed to be administered to the fellow eye.
- To improve content flow and readability, the definition of adverse event reporting period was clarified (Section 5.6).
- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Section 7.5).
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Section 8.1).
- Language has been revised to clarify that data posting will not be limited to two clinical trial registries and to clarify that redacted CSRs are provided only if requirements of Roche's global policy on data sharing have been met (Section 9.5).
- The assessment for the [redacted] has been entered on separate line of schedule of activities (Appendix 1) for clarity.
- For consistency with the body text, study details have been added and clarifications made to the schedule of activities (Appendix 1); in addition, minor formatting changes and corrections have been made.
- Refraction data recording on the eCRF at specific timepoints has been added to Appendix 4.
- Additional details have been added to the descriptions and processes for CFP and fundus fluorescein angiography (FFA) in Appendices 5 and 6, respectively.
- The acronym for "CRC" to describe the central reading center has been introduced throughout the protocol. This is a global change and is not shown in italics.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR–CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF *FARICIMAB (*RO6867461*)* IN PATIENTS WITH DIABETIC MACULAR EDEMA (YOSEMITE)**
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SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR–CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF *FARICIMAB (*RO6867461*)* IN PATIENTS WITH DIABETIC MACULAR EDEMA (YOSEMITE)**
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TEST PRODUCT:	*Faricimab (*RO6867461*)*
PHASE:	Phase III
INDICATION:	Diabetic macular edema
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of faricimab when dosed every 8 weeks (Q8W) and with a personalized treatment interval (PTI) regimen compared with aflibercept (Eylea®) monotherapy in patients with diabetic macular edema (DME). Specific objectives and corresponding endpoints for the study are outlined in the following table.

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

Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of IVT injections of the 6-mg dose of faricimab on BCVA outcomes	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) at 1 year [a]
Key Secondary Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of faricimab on DR severity outcomes	• Proportion of patients with a ≥2-step DRS improvement from baseline on the ETDRS DRSS at Week 52
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of faricimab on additional BCVA outcomes	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) over time • Proportion of patients gaining ≥15, ≥10, ≥5, or ≥0 letters in BCVA from baseline over time • Proportion of patients avoiding a loss of ≥15, ≥10, ≥5, or >0 letters in BCVA from baseline over time • Proportion of patients gaining ≥15 letters or achieving BCVA of ≥84 letters over time • Proportion of patients with BCVA Snellen equivalent of 20/40 or better over time • Proportion of patients with BCVA Snellen equivalent of 20/200 or worse over time
• To evaluate the efficacy of faricimab on additional DR outcomes	• Proportion of patients with a ≥2-step DRS improvement from baseline on the ETDRS DRSS over time • Proportion of patients with a ≥3-step DRS improvement from baseline on the ETDRS DRSS over time • Proportion of patients who develop new PDR over time
• To evaluate faricimab treatment intervals in the PTI arm	• Proportion of patients in the PTI arm on a Q4W, Q8W, Q12W, or Q16W treatment interval at 1 year and 2 years • Treatment intervals in the PTI arm over time

[a] *The definition of 1 year is the average of the Week 48, 52, and 56 visits.*

Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate the efficacy of faricimab on anatomical outcome measures using SD-OCT	• *Change from baseline in CST at 1 year* [a] • Change from baseline in CST over time • Proportion of patients with absence of DME (CST <325 μm for Spectralis SD-OCT, or <315 μm for Cirrus SD-OCT or Topcon SD-OCT) over time • Proportion of patients with absence of intraretinal fluid over time • Proportion of patients with absence of subretinal fluid over time • Proportion of patients with absence of intraretinal fluid and subretinal fluid over time
• To evaluate the efficacy of faricimab on patient-reported vision-related functioning and quality of life using the NEI VFQ-25	• Change from baseline in NEI VFQ-25 composite score over time
Safety Objective	**Corresponding Endpoints**
• To evaluate the ocular and systemic safety and tolerability of faricimab	• Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To further evaluate the efficacy of faricimab on additional DR outcomes	• Proportion of patients with a ≥2-step or ≥3-step DRS worsening from baseline on ETDRS DRSS over time • Proportion of patients who receive vitrectomy or PRP over time during the study
• To further evaluate the efficacy of faricimab on anatomical outcome measures using FFA and/or OCT-A [c]	• Change from baseline in *the macular and the* total *retinal* area [b] of *ischemic* non-perfusion *(capillary loss)* over time • Change from baseline in vascular leakage *in the macula and in the total retinal area* [b] over time • Proportion of patients with resolution of *vascular* leakage *in the macula and in the total retinal area* [b] over time
• *To further evaluate the efficacy of faricimab on anatomical outcome measures using SD-OCT*	• Change from baseline neurosensory CST over time • Change from baseline in total macular volume over time

[a] *The definition of 1 year is the average of the Week 48, 52, and 56 visits.*

[b] *The total retinal area is defined as 7-modified fields or 4-wide fields or ETDRS 7-field mask overlay on ultra-wide field (UWF; Optos®) images in all study patients and as the entire UWF image, including peripheral areas in a subset of patients with Optos FFA.*

[c] *In a subset of patients with OCT-A.*

Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objectives (cont.)	Corresponding Endpoints (cont.)
• To further evaluate the efficacy of faricimab on patient-reported vision-related functioning and quality of life using the NEI VFQ-25	• Change from baseline in the NEI VFQ-25 Near Activities, Distance Activities, and Driving subscales at 1 year [a] • Proportion of patients with a ≥ 4-point improvement from baseline in NEI VFQ-25 composite score *at 1 year* [a]
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the systemic pharmacokinetics of faricimab	• Plasma concentration of faricimab over time
Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to faricimab • To evaluate potential effects of ADAs	• Presence of ADAs during the study relative to the presence of ADAs at baseline • Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives	**Corresponding Endpoints**
• To identify biomarkers that are predictive of response to faricimab, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of faricimab activity, or can increase the knowledge and understanding of disease biology	• Concentration of biomarkers of angiogenesis and inflammation in aqueous humor (optional) at baseline and over time and their correlation with PK and/or primary and secondary endpoints at baseline and over time • Relationship between efficacy, safety, PK, immunogenicity, [redacted] • Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., the frequency of study drug administration) over time • Relationship between anatomic measures and visual acuity

[a] *The definition of 1 year is the average of the Week 48, 52, and 56 visits.*

Objectives and Corresponding Endpoints (cont.)

Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate potential relationships between selected covariates and exposure to faricimab	• Relationship between selected covariates and plasma or aqueous humor (optional) concentration or PK parameters for faricimab
• To characterize the aqueous humor (optional) and vitreous (optional) pharmacokinetics of faricimab	• Aqueous humor (optional) and vitreous (optional) concentration of faricimab over time
• To evaluate the drug concentration [redacted]	• [redacted]
• To explore the concentration–effect relationship for visual acuity and other endpoints (e.g., anatomical markers)	• Pharmacokinetics of faricimab and the change in BCVA or other endpoints (e.g., anatomical markers) over time

ADA=anti-drug antibody; [redacted]
BCVA=best-corrected visual acuity; CST=central subfield thickness; DR=diabetic retinopathy; DRS=diabetic retinopathy severity; DRSS=Diabetic Retinopathy Severity Scale; ETDRS=Early Treatment Diabetic Retinopathy Study; FFA=fundus fluorescein angiography; IVT=intravitreal; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT-A=optical coherence tomography–angiography; PDR=proliferative diabetic retinopathy; PK=pharmacokinetic; PRP=panretinal photocoagulation; PTI=personalized treatment interval; Q4W = every 4 weeks; Q8W=every 8 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks; SD-OCT=spectral-domain optical coherence tomography; [redacted]

Study Design

Description of Study

This is a Phase III, double-masked, multicenter, randomized, active comparator–controlled, parallel-group study, evaluating the efficacy, safety, pharmacokinetics, and optimal treatment frequency of faricimab administered by intravitreal (IVT) injection at 8-week intervals or PTI of approximately 100 weeks' duration (excluding the screening period) to patients with DME.

Overview of Study Design

Approximately 900 patients will be randomized during the global enrollment phase of the study in a 1:1:1 ratio to one of three treatment arms at approximately 240 investigational sites globally. The study will randomize patients with DME who are naive to anti–vascular endothelial growth factor (anti-VEGF) therapy in the study eye and patients who have previously been treated with anti-VEGF therapy in the study eye, provided that the last treatment was at least 3 months prior to the Day 1 visit (the first study treatment). Site investigators will be retina specialists or the equivalent outside of the United States.

The study treatment arms will be as follows:

- Arm A (administered every 8 weeks [Q8W]) (n=300): Patients randomized to Arm A will receive 6-mg IVT faricimab injections every 4 weeks (Q4W) to Week 20, followed by 6-mg IVT faricimab injections Q8W to Week 96, followed by the final study visit at Week 100.
- Arm B (PTI) (n=300): Patients randomized to Arm B will receive 6-mg IVT faricimab injections every 4 weeks (Q4W) to at least Week 12, followed by PTI dosing (see the PTI dosing criteria below) of 6-mg IVT faricimab injections to Week 96, followed by the final study visit at Week 100.

- Arm C (comparator arm) (administered Q8W) (n=300): Patients randomized to Arm C will receive 2-mg IVT aflibercept injections Q4W to Week 16, followed by 2-mg IVT aflibercept injections Q8W to Week 96, followed by the final study visit at Week 100.

Patients in all three treatment arms will complete scheduled study visits Q4W for the entire study duration (100 weeks). A sham procedure will be administered to patients in all three treatment arms at applicable visits to maintain masking among treatment arms.

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

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

The study will consist of a screening period of up to 28 days (Days −28 to −1) in length and an approximately 96-week treatment period, followed by the final study visit at Week 100.
A unique screening number will be assigned to each screened patient through an interactive voice or web-based response system (IxRS).

Screening

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

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

In some countries/regions, the screening and Day 1 (randomization) visits may occur as a combined visit if all assessments are completed and evaluated on the same day or within 2 business days. When screening and the Day 1 visit are completed *as a combined visit,* the assessments listed for both visits should be conducted only once. *The following conditions have to be met for a combined visit to occur:*

- [redacted]
- A historic hemoglobin A1c (HbA_{1c}) value must be available from within 2 months *prior to* Day 1.

If the screening and Day 1 visit are not completed on the same day (but rather within 2 business days), the following safety assessments *must* be repeated on the day of patient's randomization and study treatment administration: *urine pregnancy test (if applicable),* slitlamp examination, indirect ophthalmoscopy, and pre- and post-treatment intraocular pressure (IOP) measurements (recorded on the Day 1 electronic Case Report Form [eCRF] and dated accordingly).

*For all study patients, a*fter screening has been completed, *including all assessments listed for the Day 1 visit,* eligible patients will have a randomization identification number assigned through the IxRS and will be randomized in a 1:1:1 ratio in order that approximately 300 patients are randomized to each of the three treatment arms. Randomization will be stratified by baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score, as assessed on Day 1 (64 letters or better vs. 63 letters or worse), prior IVT anti-VEGF therapy (yes vs. no), and region (United States and Canada, Asia, and the rest of the world).

Screen-Failed Patients

Patients who are not eligible for enrollment (screen failures) may be eligible for re-screening for up to an additional two times during the enrollment period of the study. At re-screening, a new screening number will be assigned to each patient through the IxRS and all screening visit assessments will be performed. At the Day 1 visit, fundus FFA images do not have to be

repeated, provided that the same eye is selected for the study eye at rescreening and acceptable FFA images were taken within 4 weeks before the new Day 1 visit (randomization) date.

Randomization and Visit Schedule

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

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

*R*andomized patients will have *the first* study treatment administered by the unmasked investigator *on Day 1,* followed by the safety assessments (finger-counting test and post-dose IOP measurement). *Afterwards, all study* patients will also have *a* safety assessment *visit on Day 7 (±3 days) evaluated by the masked investigator. At subsequent scheduled visits, patients will have pre-dose safety assessments* evaluated by the masked investigator prior to receiving study treatment. *Study treatment administration and study-related assessments will occur Q4W (starting from Day 1), as outlined in the protocol. The sham procedure will be delivered to patients in all arms throughout the study as applicable.*

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

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

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

Note: After the Day 1 visit, if a patient misses a study visit when ocular *CFP and FFA* images are to be obtained, *or these images are not taken at the scheduled visit (e.g. equipment is broken),* the*y* must be obtained at the next scheduled visit the patient attends.

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

Patients who are prematurely discontinued from study treatment but who agree to continue to participate in the study will be encouraged to undergo as many scheduled visits as possible, with emphasis on completing the Week 48, 52, 56, and 100 visits.

Study treatment visits will be scheduled Q4W (±7 days) relative to the Day 1 visit date.

Patients who *are* discontinu*ing* from the study prior to completion will be asked to return for an early termination visit after a minimum of 28 days have elapsed following their last study treatment for monitoring of adverse events and early termination visit assessments.

Patients who complete study treatment (i.e., the Week 96 visit) will return for the final study visit (Week 100) after a minimum of 28 days have elapsed from their last study treatment for monitoring of adverse events and final study visit assessments.

[redacted]

Treatment Schedule for Patients in the Personalized Treatment Interval Arm (Arm B)

Study drug dosing interval decisions in the PTI arm are automatically calculated by the IxRS based on the algorithm described in this section. Study drug dosing visits are visits when a patient is assigned to receive faricimab.

Study Drug Dosing Interval Determination

Patients randomized to the PTI arm (Arm B) will be treated with faricimab on a Q4W dosing interval until *at least* the patient's Week 12 visit, or *a* later *visit when* CST meets the predefined reference central subfoveal thickness (CST) threshold (CST <325 μm for Spectralis SD-OCT, or <315 μm for Cirrus SD-OCT or Topcon SD-OCT), *as determined by the CRC*. The reference CST *(as defined in the protocol)* is used at study drug dosing visits by the IxRS for *the drug dosing* interval decision-making.

After a patient's initial reference CST is established, their study drug dosing interval will be increased by 4 weeks to an initial Q8W dosing interval by the IxRS. From this point forward, the study drug dosing interval will be extended, reduced, or maintained based on assessments made at study drug dosing visits. See *the protocol* for the algorithm used by the IxRS for interval decision-making, which is based on the relative change of the CST and BCVA compared with reference CST and *reference* BCVA.

Study Drug Dosing Intervals

The IxRS can adjust the study drug dosing interval by 4-week increments to a maximum of every 16 weeks (Q16W) and a minimum of Q4W. *The IxRS algorithm for the study drug treatment interval decision making is based on the relative change of the CST and absolute change in BCVA compared with the reference CST and BCVA, respectively.*

Similar to Arms A and C, patients randomized to the PTI arm (Arm B) will receive a sham procedure at study visits when they are not receiving treatment with faricimab.

Additional Considerations for PTI Arm IxRS Study Drug Dosing Interval Decision

Sites will report missed study *treatment* visits and study *treatment* interruption visits to the IxRS for all patients (Arms A, B, and C) to preserve the masking. The following algorithms are only applicable to patients in the PTI arm (Arm B) and are used by the IxRS to automatically determine study drug *dosing* intervals in the event of the following situations.

Missed Study Drug Dosing Visit(s)

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

Example: If a patient was on *an* every *12-week (*Q12W*)* drug dosing interval prior to missing the study drug dosing visit, then the IxRS decision to maintain, extend, or reduce the dosing interval will be made on the basis of the previously assigned drug interval *(Q12W)* along with CST and BCVA data obtained at the visit when the patient receives study drug. If the data indicate that the patient should maintain the Q12W interval, then he or she will receive study drug 12 weeks after that visit.

Study Drug Interruption at Study Drug Dosing Visit(s)

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

Missing CST Value at Study Drug Dosing Visit

If a patient attends a study drug dosing visit, but the CST value is not available for any reason (e.g., optical coherence tomography [OCT] machine is not available or is broken), the IxRS will assign the patient to receive study drug at that visit. Generally, the IxRS will maintain the previous drug dosing interval. However, in the event of a concurrent ≥10-letter decrease

relative to the reference BCVA at that study drug dosing visit, the IxRS will reduce the study drug dosing interval by 4 weeks.

Missing BCVA Value at Study Drug Dosing Visit

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

Missed Study Drug Treatment Visit(s) for Patients in the Q8W Treatment Arms

If a patient randomized to treatment Arm A (faricimab Q8W) or Arm C (aflibercept Q8W) misses study drug *dosing* visit(s) *after the Q4W initiating doses*, the IxRS will assign the patient to receive faricimab or aflibercept at the next study visit he or she attends. The Q8W drug treatment interval will be automatically reset by *the* IxRS from that visit forward, thus 4 weeks later, at the following study visit, the patient will receive sham.

[redacted]

Independent Data Monitoring Committee

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

The iDMC will meet approximately every 6 months (frequency adjustable if required) to evaluate unmasked ocular and systemic (non-ocular) safety events with an emphasis on the evaluation of the rate of ocular inflammation, increased IOP, endophthalmitis, arterial thromboembolic events, and clinically significant decreases in BCVA, which will be prepared for the committee by an independent Data Coordinating Center (iDCC). The iDMC may recommend stopping the study early for safety reasons.

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

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

Number of Patients

Approximately 900 patients will be randomized during the global enrollment phase of the study.

Target Population

Inclusion Criteria

Patients must meet the following inclusion criteria for study entry.

General Inclusion Criteria

Patients must meet the following general inclusion criteria for study entry:

- Willingness and the ability to provide signed informed consent

  Additionally, at U.S. sites, patients must provide Health Insurance Portability and Accountability Act authorization, and in other countries, as applicable according to national laws.
- Age ≥18 years
- Documented diagnosis of diabetes mellitus (Type 1 or Type 2), as defined by the American Diabetes Association or per WHO criteria and
  - Current regular use of insulin *or other injectable drugs (e.g., dulaglutide and liraglutide)* for the treatment of diabetes

    and/or
  - Current regular use of oral anti-hyperglycemic agents for the treatment of diabetes
- HbA_{1c} of ≤10% within 2 months prior to the Day 1 visit date
- Ability and willingness to undertake all scheduled visits and assessments
- 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 (≥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.

Ocular Inclusion Criteria for Study Eye

Patients must meet the following ocular inclusion criteria for the study eye for entry in the study:

- Macular thickening secondary to DME involving the center of the fovea with CST ≥ 325 μm, as measured on Spectralis SD-OCT, or ≥315 μm, as measured on Cirrus SD-OCT or Topcon SD-OCT at screening
- BCVA of 73 to 25 letters, inclusive (20/40 to 20/320 approximate Snellen equivalent), using the ETDRS protocol at the initial testing distance of 4 meters (see the BCVA manual for additional details) on Day 1
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality CFPs (including ETDRS 7 modified fields or 4 wide-angle fields to permit grading of diabetic retinopathy and assessment of the retina) and other imaging modalities.

Exclusion Criteria

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

General Exclusion Criteria

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

- Currently untreated diabetes mellitus or previously untreated patients who initiated oral *or injectable* anti-diabetic medication within 3 months prior to Day 1
- History of allergy or hypersensitivity to active drug aflibercept and any of its excipients, fluorescein, or any study treatment–related mandatory ingredients (e.g., disinfectants, anesthetics, etc.; see the pharmacy manual for additional details) that is not amenable to treatment
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab or to aflibercept injections, study treatment procedure, dilating drops, or any of the anesthetic and antimicrobial *preparations* used by a patient during the study
- Active cancer within the past 12 months except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤ 6 and a stable prostate-specific antigen for > 12 months
- Systemic treatment for suspected or active systemic infection

  Ongoing use of prophylactic antibiotic therapy may be acceptable but has to be discussed with the Medical Monitor.
- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis or anticipated to require hemodialysis or peritoneal dialysis at any time during the study
- History of other disease, other non-diabetic metabolic dysfunction, physical examination finding, *historical* or *current* clinical laboratory finding giving reasonable suspicion of a condition that contraindicates the use of the faricimab or aflibercept or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator
- Uncontrolled blood pressure (defined as systolic >180 mmHg and/or diastolic >100 mmHg while a patient is at rest)

  If a patient's initial reading exceeds these values, a second reading may be obtained later the same day or on another day during the screening period. If the patient's blood pressure is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1.
- *Stroke (c*erebral vascular accident*)* or myocardial infarction within 6 months prior to Day 1
- Pregnancy or breastfeeding, or intention to become pregnant during the study

  Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to initiation of study treatment. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Participation in an investigational trial that involves treatment with any drug or device (with the exception of vitamins and minerals) within 3 months prior to Day 1
- Administration of systemic pro-angiogenic treatments, such as VEGF-based therapies for the peripheral or coronary ischemia (e.g., limb ischemia or myocardial infarction) within 3 months or 5 half-lives prior to Day 1
- Inability to comply with study or follow-up procedures
- Requirement for continuous use of any medications and treatments indicated in *the protocol (see* Prohibited Therapy*)*

Ocular Exclusion Criteria for Study Eye

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

- High-risk proliferative diabetic retinopathy (PDR) in the study eye, using any of the following established criteria for high-risk PDR:
  - Any vitreous or pre-retinal hemorrhage
  - Neovascularization elsewhere ≥1/2 disc area within an area equivalent to the mydriatic ETDRS 7 fields on clinical examination or on CFPs
  - Neovascularization at disc ≥1/3 disc area on clinical examination
- Tractional retinal detachment, pre-retinal fibrosis, *vitreomacular traction,* or epiretinal membrane involving the fovea or disrupting the macular architecture in the study eye, [redacted]
- Active rubeosis
- Uncontrolled glaucoma
- History of retinal detachment or macular hole (Stage 3 or 4)
- Aphakia or implantation of anterior chamber intraocular lens
- IVT anti-VEGF treatment within 3 months prior to Day 1 (applicable to patients whose study eyes were previously treated with IVT anti-VEGF agents) or any IVT anti-VEGF agents to study eye prior to Day 1 (applicable for patients who are treatment naive)
- Treatment with panretinal photocoagulation (PRP) within 3 months prior to Day 1
- Macular (focal*, grid, or micropulse*) laser within 3 months prior to Day 1
- Any cataract surgery or treatment for complications of cataract surgery with steroids or YAG (yttrium-aluminum-garnet) laser capsulotomy within 3 months prior to Day 1
- Any other intraocular surgery (e.g., corneal transplantation, glaucoma filtration, pars plana vitrectomy, corneal transplant, or radiotherapy)
- Any IVT or periocular (subtenon) corticosteroid treatment within 6 months prior to Day 1
- Any use of medicated intraocular implants, including Ozurdex®, within 6 months of Day 1
- Any use of Iluvien® implants at any time prior to Day 1
- Treatment for other retinal diseases that can lead to macular edema

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

Patients who meet the following exclusion criterion for the fellow eye (non–study eye) will be excluded from study entry:

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

Exclusion Criteria for Both Eyes

Patients who meet the following exclusion criterion for either eye will be excluded from study entry:

- Prior administration of IVT faricimab in either eye
- Any history of idiopathic or immune-mediated uveitis in either eye
- Active ocular inflammation or suspected or active ocular or periocular infection in either eye on Day 1

Concurrent Ocular Conditions Exclusion Criteria

Patients who meet the following exclusion criteria related to concurrent ocular conditions will be excluded from study entry:

- Any current or history of ocular disease other than DME that may confound assessment of the macula or affect central vision in the study eye (e.g., choroidal neovascularization, age-related macular degeneration, retinal vein occlusion, uveitis, angioid streaks, histoplasmosis, active or inactive cytomegalovirus, pathological myopia, retinal detachment, *retinal embolus,* macular traction, macular hole, and other)
- Any current ocular condition which, in the opinion of the investigator, is currently causing or could be expected to contribute to irreversible vision loss due to a cause other than DME in the study eye (e.g., foveal atrophy, foveal fibrosis, pigment abnormalities, dense subfoveal hard exudates, or other non-retinal conditions)

End of Study

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

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, [redacted] The end of the study is expected to occur approximately 100 weeks after the last patient is randomized.

Length of the Study

The total length of the study [redacted] from screening of the first patient to the LPLV for patients from the global enrollment phase is expected to be approximately *38* months.

Investigational Medicinal Products

Test Products (Investigational Drugs)

Intravitreal Faricimab Injections

The 6-mg dose of faricimab will be evaluated in this study and will be administered intravitreally to patients randomized to receive faricimab Q8W or PTI during the 96-week treatment period.

Patients randomized to receive Q8W treatment will be administered 15 IVT injections of faricimab during the 96-week treatment period. Treatment will consist of 6 initial injections (6 mg of faricimab Q4W to Week 20), followed by 9 maintenance injections (6 mg of faricimab Q8W between Week 24 and Week 96).

The number of IVT injections of faricimab administered to patients in the PTI arm will vary *(see protocol for the retreatment criteria)*, but a minimum of 10 IVT injections of faricimab will be administered to patients during the 96-week treatment period. This will consist of minimum of 4 initiating injections (6 mg of faricimab Q4W to Week 12), followed by minimum of 6 maintenance injections (6 mg of faricimab between Week 16 and Week 96).

Comparator

Intravitreal Aflibercept *(Active Comparator)* Injections

A 2-mg dose of aflibercept (Arm C) will be administered intravitreally Q8W to patients randomized to the aflibercept treatment arm during the 96-week treatment period. Patients will receive 15 IVT injections of aflibercept during the 96-week treatment period. Treatment will consist of 5 initiating injections (2 mg of aflibercept Q4W to Week 16), followed by 10 maintenance injections (2 mg of aflibercept Q8W between Week 20 and Week 96).

Sham Procedure

All three treatment arms (faricimab Q8W, faricimab PTI, and aflibercept Q8W) will maintain Q4W study visits for the 100-week study duration. To preserve the randomized treatment arm masking, patients will have the sham procedure performed at study treatment visits when they are not treated with either faricimab or aflibercept as applicable per their treatment arm schedule.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is the change from baseline in BCVA averaged over Weeks 48, 52, and 56. The BCVA outcome measure is based on the ETDRS visual acuity chart assessed at a starting distance of 4 meters.

The primary comparisons will be the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the faricimab arms (Q8W and PTI). Additional analyses based on the per-protocol population will also be conducted.

For the two faricimab arms (Q8W and PTI), the following three hypotheses will be tested for each treatment group separately at an overall significance level of $\alpha = 0.05$ using a graph-based testing procedure to control for the overall type I error rate:

- Non-inferiority of faricimab compared with aflibercept Q8W in the intent-to-treat (ITT) population
- Superiority of faricimab compared with aflibercept Q8W in the treatment-naive population
- Superiority of faricimab compared with aflibercept Q8W in the ITT population

If the tests for one treatment sequence are all positive, then $\alpha/2$ will be propagated to the beginning of the other treatment sequence, which will be tested at a significance level of $\alpha = 0.05$. Of note, non-inferiority will be tested one sided at half of the designated significance level.

The non-inferiority tests for the faricimab Q8W arm and the faricimab PTI arm compared with aflibercept Q8W arm will be conducted with a non-inferiority margin of 4 letters. For each faricimab group (Q8W or PTI) the null hypothesis,
H_0: $\mu^{\text{faricimab}} - \mu^{\text{aflibercept}} \leq -4$ letters, and the alternative hypothesis,
H_a: $\mu^{\text{faricimab}} - \mu^{\text{aflibercept}} > -4$ letters, will be tested, for which $\mu^{\text{faricimab}}$ and $\mu^{\text{aflibercept}}$ are the expected change from baseline in BCVA averaged over Weeks 48, 52, and 56 for the treatment group in question (faricimab Q8W or PTI) and the active comparator (aflibercept Q8W), respectively.

The change from baseline averaged over Weeks 48, 52, and 56 will be compared between each faricimab arm and the aflibercept Q8W arm using a mixed-model repeated measures (MMRM) model. The model will include the change from baseline at Weeks 4–56 as the response variables and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, the continuous baseline value for the response variable (in this case, baseline BCVA), as well as randomization stratification factors as fixed effects. Comparisons between each faricimab arm and the aflibercept Q8W arm will be made using a composite contrast over Weeks 48, 52, and 56. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a heterogeneous compound symmetry or an AR(1) covariance structure may be fitted.

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

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

Determination of Sample Size

Determination of sample size is based on patients enrolled in the global enrollment phase. The global enrollment phase will enroll approximately 900 patients. Patients will be randomized in a 1:1:1 ratio to receive treatment with faricimab Q8W (Arm A), faricimab PTI (Arm B), or aflibercept Q8W (Arm C). The primary comparisons will be the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the faricimab arms (Q8W and PTI).

A sample size of approximately 300 patients in each arm will provide greater than 90% power to show non-inferiority of faricimab to aflibercept (pairwise comparisons between the active comparator and each of the faricimab arms) in the ITT population, using a non-inferiority margin of 4 letters and under the following assumptions:

- Standard deviation (SD) of 11 letters for the change from baseline in BCVA averaged over Week 48, Week 52, and Week 56
- Two-sample *t*-test
- 1.25% one-sided type I error rate
- 10% dropout rate

Assuming 75%–90% of patients recruited will be treatment naive, approximately 225–270 treatment-naive patients will be enrolled per arm. A sample size of 225–270 patients per arm will provide greater than 80% power to show a 3.5-letter superiority of faricimab over aflibercept (pairwise comparisons between the active comparator and each of the faricimab arms) in the treatment-naive population, using the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 2.5%.

Furthermore, a sample size of approximately 300 patients per arm will provide greater than 80% power to show a 3-letter superiority of faricimab over aflibercept (pairwise comparisons between the active comparator and each of the faricimab arms) in the ITT population, under the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 2.5%.

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

[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
Ang-2	angiopoietin-2
ANGPT2	*angiopoietin-2 protein (gene)*
BCVA	best-corrected visual acuity
CFP	color fundus photograph
CI	center involvement
CRC	*central reading center*
CST	central subfield thickness
DME	diabetic macular edema
DR	diabetic retinopathy
DRS	diabetic retinopathy severity
DRSS	Diabetic Retinopathy Severity Scale
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FFA	fundus fluorescein angiography
GCP	Good Clinical Practice
HbA_{1c}	hemoglobin A_{1c}
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IL-1b (-6)	interleukin-1b (-6)
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intent to treat
IVT	intravitreal
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MMRM	mixed-model repeated-measures (model)
nAMD	neovascular age-related macular degeneration
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire–25
NPDR	non-proliferative diabetic retinopathy
OCT-A	optical coherence tomography–angiography
PD	pharmacodynamic
PDR	proliferative diabetic retinopathy
PK	pharmacokinetic
[redacted]	[redacted]
PRO	patient-reported outcome
PRP	panretinal photocoagulation
PTI	personalized treatment interval
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
Q16W	every 16 weeks
RBR	Research Biosample Repository
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SOC	standard of care
SS-OCT	swept-source optical coherence tomography
UWF	*ultra-wide field*
ULN	upper limit of normal
VA	visual acuity
VEGF(-A)	vascular endothelial growth factor(-A)
[redacted]	[redacted]
[redacted]	[redacted]
YAG	yttrium-aluminum-garnet

1. BACKGROUND

1.1 BACKGROUND ON DIABETIC MACULAR EDEMA

Diabetic macular edema (DME), a complication of diabetic retinopathy (DR), can develop at any stage of the underlying disease of retinal microvasculature (Fong et al. 2004). DME occurs with increasing frequency as the underlying DR worsens (Henricsson et al. 1999; Johnson 2009) from non-proliferative DR (NPDR) to proliferative DR (PDR). DME is the most common cause of moderate and severe visual impairment in patients with DR (Ciulla et al. 2003; Davidson et al. 2007; Leasher et al. 2016), and if left untreated can lead to a loss of 10 or more letters in visual acuity (VA) within 2 years in approximately 50% of patients (Ferris and Patz 1984; Ciulla et al. 2003). DME affects approximately 14% of patients with diabetes and can be found in patients with both Type 1 and Type 2 diabetes (Girach and Lund-Andersen 2007). In 2013, the worldwide population of people with diabetes was approximately 382 million, and it is estimated to grow to 592 million by 2035 (International Diabetes Federation 2013).

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

Although macular laser used to be the standard of care (SOC) for treatment of DME, the development of anti-VEGF pharmacotherapy in the past 10 years has led to dramatic improvements in visual outcomes for patients with DME. 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 strong efficacy achieved with anti-VEGF therapies in DME, a significant proportion of patients do not experience clinically meaningful improvements in vision in the real world. Frequent IVT administration is required to achieve, and in some cases, to maintain the observed early benefits of DME treatment over a long period of time.

The current SOC for administration of anti-VEGF injections requires patients to undergo frequent clinical examinations and IVT injections. This imposes a significant burden on patients, caregivers, treating physicians, and the healthcare system.

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

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

1.2 BACKGROUND ON FARICIMAB

Faricimab (also known as RO6867461*)* is a humanized full-length bispecific IgG1 antibody that selectively neutralizes VEGF-A *(hereafter referred to as "VEGF")* and Ang-2, the key factors mediating pathophysiology of diabetic eye disease. Faricimab was developed using Roche's CrossMab (monoclonal antibody) technology. The VEGF binding and the Ang-2 binding variable regions of faricimab bind to VEGF and Ang-2 *independently and* simultaneously with high affinity. The Fc portion of faricimab was engineered for ophthalmic use through inactivation of effector function (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 VEGF and Ang-2 in the vitreous were shown to be upregulated in patients with DR (Rangasamy et al. 2011; Park et al. 2014). In vivo pharmacological evaluations in spontaneous and induced mouse and non-human primate models of neovascularization and in models of intraocular inflammation (uveitis) confirmed the improved anti-angiogenic and anti-inflammatory effects of faricimab treatment compared with anti-VEGF monotherapy.

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

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

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The Phase III program will evaluate the efficacy, safety, and pharmacokinetics of faricimab when administered to patients every 8 weeks (Q8W) and with a personalized treatment interval (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) (i.e., the number of ETDRS letters). 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.

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 and supports further evaluation of faricimab in Phase III DME studies.

Additionally, the efficacy, safety, and treatment frequency of IVT faricimab administration has been assessed in another retinal disease indication, neovascular age-related macular degeneration (nAMD), in one Phase I study (BP28936) and in two Phase II studies (BP29647 [AVENUE] and CR39521 [STAIRWAY]).

Based on the totality of evidence from the Phase II studies, and taking into account evidence from the preclinical models, it is anticipated that the well-established anti-VEGF mechanism of action combined with anti–Ang-2 targeting in the bispecific faricimab molecule will lead to improved efficacy and/or reduced injection burden compared with anti-VEGF monotherapy. This would represent an important advance for patients with DME.

1.3.1 Benefits

The clinical benefit of IVT faricimab injections for patients with DME was demonstrated in the Phase II study BP30099. The study met its primary efficacy endpoint, which was the mean change from baseline in BCVA at Week 24 in anti-VEGF treatment–naive patients treated with faricimab compared with 0.3 mg of ranibizumab.

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

Anti-VEGF treatment–naive patients were randomized equally into three treatment arms: 6 mg of IVT faricimab, 1.5 mg of IVT faricimab, and 0.3 mg of IVT ranibizumab. Patients who were previously treated with anti-VEGF were randomized equally to receive either 6 mg of IVT faricimab or 0.3 mg of IVT ranibizumab. Key demographic and ocular

baseline characteristics were generally well balanced. The study consisted of a treatment period (20 weeks in length) and an observational period (up to 16 weeks in length), for a total study duration of up to 36 weeks. Study treatment was administered to patients by IVT injection at every-4-week (Q4W) intervals up to the last injection at Week 20, with the primary endpoint assessed at Week 24. The observational period without treatment lasted up to 16 weeks from Week 20 to Week 36. The observation period allowed for exploration of the durability of pharmacodynamic (PD) effects after the last treatment.

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

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

Overall, the data from intent-to-treat (ITT) study population (both treatment-naive and previously anti-VEGF–treated patients) suggest consistent benefit of faricimab over anti-VEGF monotherapy in the general DME population.

The outcomes in the off-treatment study observation period provided evidence of prolonged duration of effect with faricimab compared with anti-VEGF monotherapy. Assessment of time to disease reactivation up to 16 weeks after the last dose showed

an improvement in the duration of the effect of faricimab over ranibizumab, as measured by the time to loss of ≥5 ETDRS letters because of DME and an increase ≥50 μm in CST in the treatment-naive patient population in a dose-dependent manner. This improvement in the duration of effect of faricimab over ranibizumab was also seen in the previously treated group and the overall patient group.

In summary, the data from Study BP30099 suggested a dose-related benefit favoring the 6-mg dose of faricimab relative to the 1.5-mg dose, as measured by both the efficacy outcomes and duration of effect. Based on these results, the 6-mg dose of faricimab has been chosen for further clinical development in Phase III studies in patients with DME to explore its benefit compared with SOC IVT anti-VEGF treatment from the following perspectives:

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

The Phase III clinical development program will enroll both patients with DME who are naive to anti-VEGF therapy in the study eye and patients who were previously treated with anti-VEGF therapy in the study eye to further explore outcomes on DME in both populations.

1.3.2 Risks

In the Phase I study (BP28936), single and multiple IVT administrations of faricimab were well tolerated in patients with nAMD up to the highest dose tested, 6 mg. No deaths and no dose-limiting events were reported.

The Phase II study BP30099 in DME also showed an acceptable tolerability and safety profile, with no new or unexpected safety signals. No serious ocular or systemic adverse events considered related to treatment with faricimab were reported. The ocular and systemic safety findings for faricimab observed in the Phase II study were generally consistent with the safety profile reported in patients with DME who receive intravitreally administered anti-VEGF products.

Additionally, the safety of IVT faricimab administration has been assessed in patients with nAMD in two Phase II studies (BP29647 [AVENUE] and CR39521 [STAIRWAY]). A total of 436 patients have been exposed to at least one dose of faricimab to date. No unexpected safety signals have been identified in these studies that would change the anticipated safety profile in the Phase III DME program.

Based on the totality of evidence from the Phase I and Phase II studies, and taking into account evidence from the murine and non-human primate preclinical and toxicology models, it is anticipated that the additional anti–Ang-2 mechanism of action of the

faricimab molecule will not lead to an increase in safety risks compared with IVT anti-VEGF monotherapy.

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

1.3.3 Conclusions

The available Phase I and II efficacy and safety data showed a benefit–risk profile that supports further assessment of the efficacy and safety of 6 mg faricimab across various treatment intervals compared with anti-VEGF IVT monotherapy in a Phase III DME program.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of faricimab when dosed Q8W and with a PTI regimen compared with aflibercept (Eylea®) monotherapy in patients with DME. Specific objectives and corresponding endpoints for the study are outlined in Table 1. An overview of the proposed statistical analyses is described in Section 6.

In this protocol, study drug refers to faricimab or aflibercept (intended for the study eye) and study treatment refers to faricimab, aflibercept, or the sham procedure (see Section 4.3 for further details).

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of IVT injections of the 6-mg dose of faricimab on BCVA outcomes	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) at 1 year [a]
Key Secondary Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of faricimab on DR severity outcomes	• Proportion of patients with a ≥2-step DRS improvement from baseline on the ETDRS DRSS at Week 52
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of faricimab on additional BCVA outcomes	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) over time • Proportion of patients gaining ≥15, ≥10, ≥5, or ≥0 letters in BCVA from baseline over time • Proportion of patients avoiding a loss of ≥15, ≥10, ≥5, or >0 letters in BCVA from baseline over time • Proportion of patients gaining ≥15 letters or achieving BCVA of ≥84 letters over time • Proportion of patients with BCVA Snellen equivalent of 20/40 or better over time • Proportion of patients with BCVA Snellen equivalent of 20/200 or worse over time
• To evaluate the efficacy of faricimab on additional DR outcomes	• Proportion of patients with a ≥2-step DRS improvement from baseline on the ETDRS DRSS over time • Proportion of patients with a ≥3-step DRS improvement from baseline on the ETDRS DRSS over time • Proportion of patients who develop new PDR over time
• To evaluate faricimab treatment intervals in the PTI arm	• Proportion of patients in the PTI arm on a Q4W, Q8W, Q12W, or Q16W treatment interval at 1 year and 2 years • Treatment intervals in the PTI arm over time

[a] *The definition of 1 year is the average of the Week 48, 52, and 56 visits.*

Table 1 Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate the efficacy of faricimab on anatomical outcome measures using SD-OCT	• *Change from baseline in CST at 1 year* [a] • Change from baseline in CST over time • Proportion of patients with absence of DME (CST <325 μm for Spectralis SD-OCT, or <315 μm for Cirrus SD-OCT or Topcon SD-OCT) over time • Proportion of patients with absence of intraretinal fluid over time • Proportion of patients with absence of subretinal fluid over time • Proportion of patients with absence of intraretinal fluid and subretinal fluid over time
• To evaluate the efficacy of faricimab on patient-reported vision-related functioning and quality of life using the NEI VFQ-25	• Change from baseline in NEI VFQ-25 composite score over time
Safety Objective	**Corresponding Endpoints**
• To evaluate the ocular and systemic safety and tolerability of faricimab	• Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To further evaluate the efficacy of faricimab on additional DR outcomes	• Proportion of patients with a ≥2-step or ≥3-step DRS worsening from baseline on ETDRS DRSS over time • Proportion of patients who receive vitrectomy or PRP over time during the study
• To further evaluate the efficacy of faricimab on anatomical outcome measures using FFA and/or OCT-A [c]	• Change from baseline in *the macular and the* total *retinal* area [b] of *ischemic* non-perfusion *(capillary loss)* over time • Change from baseline in vascular leakage *in the macula and in the total retinal area* [b] over time • Proportion of patients with resolution of *vascular* leakage *in the macula and in the total retinal area* [b] over time
• *To further evaluate the efficacy of faricimab on anatomical outcome measures using SD-OCT*	• Change from baseline neurosensory CST over time • Change from baseline in total macular volume over time

[a] *The definition of 1 year is the average of the Week 48, 52, and 56 visits.*

[b] *The total retinal area is defined as 7-modified fields or 4-wide fields or ETDRS 7-field mask overlay on ultra-wide field (UWF; Optos®) images in all study patients and as the entire UWF image, including peripheral areas in a subset of patients with Optos FFA.*

[c] *In a subset of patients with OCT-A.*

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objectives (cont.)	Corresponding Endpoints (cont.)
• To further evaluate the efficacy of faricimab on patient-reported vision-related functioning and quality of life using the NEI VFQ-25	• Change from baseline in the NEI VFQ-25 Near Activities, Distance Activities, and Driving subscales at 1 year [a] • Proportion of patients with a ≥ 4-point improvement from baseline in NEI VFQ-25 composite score *at 1 year* [a]
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the systemic pharmacokinetics of faricimab	• Plasma concentration of faricimab over time
Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to faricimab • To evaluate potential effects of ADAs	• Presence of ADAs during the study relative to the presence of ADAs at baseline • Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives	**Corresponding Endpoints**
• To identify biomarkers that are predictive of response to faricimab, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of faricimab activity, or can increase the knowledge and understanding of disease biology	• Concentration of biomarkers of angiogenesis and inflammation in aqueous humor (optional) at baseline and over time and their correlation with PK and/or primary and secondary endpoints at baseline and over time • Relationship between efficacy, safety, PK, immunogenicity, [redacted] • Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., the frequency of study drug administration) over time • Relationship between anatomic measures and visual acuity

[a] *The definition of 1 year is the average of the Week 48, 52, and 56 visits.*

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate potential relationships between selected covariates and exposure to faricimab	• Relationship between selected covariates and plasma or aqueous humor (optional) concentration or PK parameters for faricimab
• To characterize the aqueous humor (optional) and vitreous (optional) pharmacokinetics of faricimab	• Aqueous humor (optional) and vitreous (optional) concentration of faricimab over time
• To evaluate the drug concentration [redacted]	• [redacted]
• To explore the concentration–effect relationship for visual acuity and other endpoints (e.g., anatomical markers)	• Pharmacokinetics of faricimab and the change in BCVA or other endpoints (e.g., anatomical markers) over time

ADA=anti-drug antibody; [redacted]
BCVA=best-corrected visual acuity; CST=central subfield thickness; DR=diabetic retinopathy; DRS=diabetic retinopathy severity; DRSS=Diabetic Retinopathy Severity Scale; ETDRS=Early Treatment Diabetic Retinopathy Study; FFA=fundus fluorescein angiography; IVT=intravitreal; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT-A=optical coherence tomography–angiography; PDR=proliferative diabetic retinopathy; PK=pharmacokinetic; PRP=panretinal photocoagulation; PTI=personalized treatment interval; Q4W = every 4 weeks; Q8W=every 8 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks; SD-OCT = spectral-domain optical coherence tomography; [redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, double-masked, multicenter, randomized, active comparator–controlled, parallel-group study, evaluating the efficacy, safety, pharmacokinetics, and optimal treatment frequency of faricimab administered by IVT injection at 8-week intervals or PTI of approximately 100 weeks' duration (excluding the screening period) to patients with DME.

3.1.1 Overview of Study Design

Approximately 900 patients will be randomized during the global enrollment phase of the study in a 1:1:1 ratio to one of three treatment arms (see Figure 1) at approximately 240 investigational sites globally. The study will randomize patients with DME who are naive to anti-VEGF therapy in the study eye and patients who have previously been treated with anti-VEGF therapy in the study eye, provided that the last treatment was at least 3 months prior to the Day 1 visit (the first study treatment). Site investigators will be retina specialists or the equivalent outside of the United States (see Section 4.2.2 for additional details).

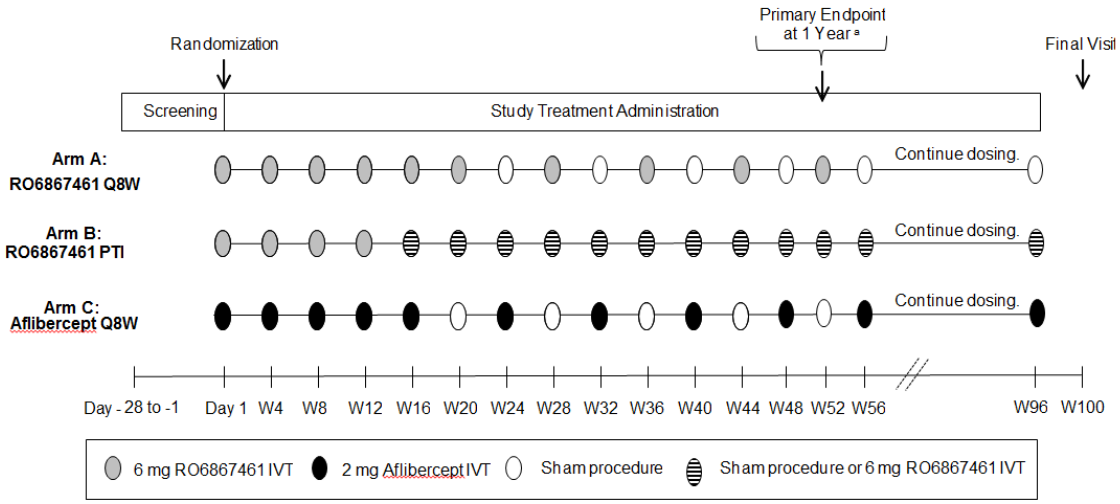
The study treatment arms will be as follows:

- Arm A (administered Q8W) (n=300): Patients randomized to Arm A will receive 6-mg IVT faricimab injections Q4W to Week 20, followed by 6-mg IVT faricimab injections Q8W to Week 96, followed by the final study visit at Week 100.
- Arm B (PTI) (n=300): Patients randomized to Arm B will receive 6-mg IVT faricimab injections Q4W to at least Week 12, followed by PTI dosing (see the PTI dosing criteria below) of 6-mg IVT faricimab injections to Week 96, followed by the final study visit at Week 100.
- Arm C (comparator arm) (administered Q8W) (n=300): Patients randomized to Arm C will receive 2-mg IVT aflibercept injections Q4W to Week 16, followed by 2-mg IVT aflibercept injections Q8W to Week 96, followed by the final study visit at Week 100.

Patients in all three treatment arms will complete scheduled study visits Q4W for the entire study duration (100 weeks). A sham procedure will be administered to patients in all three treatment arms at applicable visits to maintain masking among treatment arms (see Figure 1).

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

Figure 1 Study Treatment Schema



IVT=intravitreal; Q8W=every 8 weeks; PTI=personalized treatment interval (see Section 3.1.2 for additional details); W=week.

[a] The definition of 1 year used for the primary efficacy endpoint— defined as the change from baseline in BCVA, as measured on the ETDRS chart at a starting distance of 4 meters at 1 year—is the average of the Week 48, 52, and 56 visits.

Only one eye will be assigned as the study eye. If both eyes are considered eligible, the eye with the worse BCVA, as assessed at screening, will be selected as the study eye

unless the investigator deems the other eye to be more appropriate for treatment in the study.

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

The study will consist of a screening period of up to 28 days (Days −28 to −1) in length and an approximately 96-week treatment period, followed by the final study visit at Week 100. A unique screening number will be assigned to each screened patient through an interactive voice or web-based response system (IxRS).

3.1.1.1 Screening

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

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

*In some countries/regions, t*he screening and Day 1 (randomization) visits may occur as a combined visit if all assessments are completed and evaluated on the same day or within 2 business days. When screening and the Day 1 visit are completed *as a combined visit,* the assessments listed for both visits (see the schedule of activities in Appendix 1) should be conducted only once. *The following conditions have to be met for a combined visit to occur:*

- [redacted]
- A historic hemoglobin A_{1c} (HbA_{1c}) value must be available from within 2 months prior to Day 1.

If the screening and Day 1 visit are not completed on the same day (but rather within 2 business days), the following safety assessments *must* be repeated on the day of patient's randomization and study treatment administration: *urine pregnancy test (if applicable),* slitlamp examination, indirect ophthalmoscopy, and pre- and post-treatment intraocular pressure (IOP) measurements (recorded on the Day 1 electronic Case Report Form [eCRF] and dated accordingly).

*For all study patients, a*fter screening has been completed, *including all assessments listed for the Day 1 visit,* eligible patients will have a randomization identification number assigned through the IxRS and will be randomized in a 1:1:1 ratio in order that approximately 300 patients are randomized to each of the three treatment arms. Randomization will be stratified by baseline BCVA ETDRS letter score, as assessed on Day 1 (64 letters or better vs. 63 letters or worse), prior IVT anti-VEGF therapy (yes vs. no), and region (United States and Canada, Asia, and the rest of the world).

3.1.1.2 Screen-Failed Patients

Patients who are not eligible for enrollment (screen failures) may be eligible for re-screening for up to an additional two times during the enrollment period of the study. At re-screening, a new screening number will be assigned to each patient through the IxRS and all screening visit assessments will be performed. At the Day 1 visit, fundus FFA images do not have to be repeated, provided that *the same eye is selected for the study eye at rescreening and* acceptable FFA images *were taken* within 4 weeks before the new Day 1 visit (randomization) date.

3.1.1.3 Randomization and Visit Schedule

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

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

*R*andomized patients will have *the first* study treatment administered by the unmasked investigator *on Day 1,* followed by the safety assessments (finger-counting test and post-dose IOP measurement). *Afterwards, all study* patients will also have *a* safety assessment *visit on Day 7 (±3 days) evaluated by the masked investigator. At subsequent scheduled visits, patients will have pre-dose safety assessments* evaluated by the masked investigator prior to receiving study treatment. *Study treatment administration and study-related assessments will occur Q4W (starting from Day 1), as outlined in the schedule of activities (see Appendix 1). The sham procedure will be delivered to patients in all arms throughout the study as applicable (see* Figure 1*).*

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

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

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

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

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

Patients who are prematurely discontinued from study treatment but who agree to continue to participate in the study will be encouraged to undergo as many scheduled visits as possible, with emphasis on completing the Week 48, 52, 56, and 100 visits.

Study treatment visits will be scheduled Q4W (±7 days) relative to the Day 1 visit date.

Patients who *are* discontinu*ing* from the study prior to completion will be asked to return for an early termination visit after a minimum of 28 days have elapsed following their last study treatment for monitoring of adverse events and early termination visit assessments (see Appendix 1).

Patients who complete study treatment (i.e., the Week 96 visit) will return for the final study visit (Week 100) after a minimum of 28 days have elapsed from their last study treatment for monitoring of adverse events and final study visit assessments (see Appendix 1).

[redacted]

3.1.2 Treatment Schedule for Patients in the Personalized Treatment Interval Arm (Arm B)

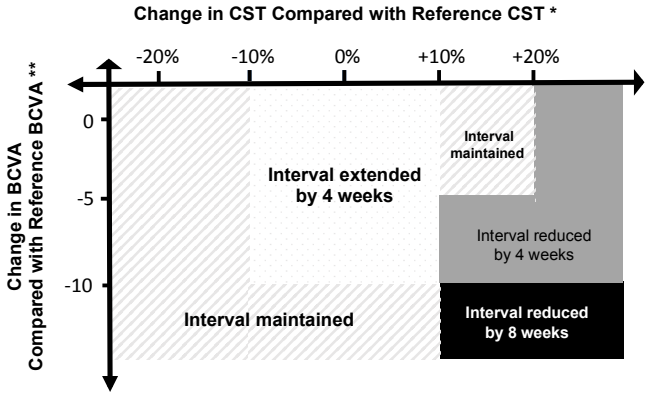
Study drug dosing interval decisions in the PTI arm are automatically calculated by the IxRS based on the algorithm described in this section. Study drug dosing visits are visits when a patient is assigned to receive faricimab.

3.1.2.1 Study Drug Dosing Interval Determination

Patients randomized to the PTI arm (Arm B) will be treated with faricimab on a Q4W dosing interval until *at least* the patient's Week 12 visit, or *a* later *visit when* CST meets the predefined reference CST threshold (CST <325 μm for Spectralis SD-OCT, or <315 μm for Cirrus SD-OCT or Topcon SD-OCT), *as determined by the CRC*. The reference CST *(as defined in Figure 2)* is used at study drug dosing visits by the IxRS for *the drug dosing* interval decision-making.

After a patient's initial reference CST is established, their study drug dosing interval will be increased by 4 weeks to an initial Q8W dosing interval by the IxRS. From this point forward, the study drug dosing interval will be extended, reduced, or maintained based on assessments made at study drug dosing visits. Figure 2 outlines the algorithm used by the IxRS for interval decision-making, which is based on the relative change of the CST and BCVA compared with reference CST and *reference* BCVA.

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



All comparisons are made relative to the reference CST* and reference BCVA**. The IxRS will determine the study drug dosing interval based on CST and BCVA data obtained from the study drug dosing visits.

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 $\leq 10\%$ **with** an associated $\geq$10-letter BCVA decrease **or**
- CST value is increased between $>10\%$ and $\leq 20\%$ **without** an associated $\geq$5-letter BCVA decrease

Interval reduced by 4 weeks:

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

Interval reduced by 8 weeks:

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

* Reference *central subfield* thickness (CST): the CST value when the initial CST threshold criteria are met. Reference CST is adjusted if CST decreases by $>10\%$ from the previous reference CST for two consecutive study 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*.

** Reference best-corrected visual acuity (BCVA): the mean of the three best BCVA scores obtained at any prior study drug dosing visit.

3.1.2.2 Study Drug Dosing Intervals

The IxRS can adjust the study drug dosing interval by 4-week increments to a maximum of every 16 weeks (Q16W) and a minimum of Q4W. *The IxRS algorithm for the study drug treatment interval decision making is based on the relative change of the CST and absolute change in BCVA compared with the reference CST and BCVA, respectively.*

Similar to Arms A and C, patients randomized to the PTI arm (Arm B) will receive a sham procedure at study visits when they are not receiving treatment with faricimab.

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

Sites will report missed study *treatment* visits and study *treatment* interruption visits to the IxRS for all patients (Arms A, B, and C) to preserve the masking. The following algorithms are only applicable to patients in the PTI arm (Arm B) and are used by the IxRS to automatically determine study drug *dosing* intervals in the event of the following situations.

3.1.3.1 Missed Study Drug Dosing Visit(s)

If a patient misses a study drug dosing visit, the IxRS will assign the patient to receive study drug dosing at the next scheduled study visit the patient attends. A decision regarding the subsequent study drug dosing interval will be made by IxRS based on CST and BCVA assessments completed at the visit when study drug is administered,

and any changes in the drug dosing interval will be based from the last assigned interval prior to the missed drug dosing visit.

Example: If a patient was on an every 12-week (Q12W) drug dosing interval prior to missing the study drug dosing visit, then the IxRS decision to maintain, extend, or reduce the dosing interval will be made on the basis of the previously assigned drug interval (Q12W) along with CST and BCVA data obtained at the visit when the patient receives study drug. If the data indicate that the patient should maintain the Q12W interval, then he or she will receive study drug 12 weeks after that visit.

3.1.3.2 Study Drug Interruption at Study Drug Dosing Visit(s)

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

3.1.3.3 Missing CST Value at Study Drug Dosing Visit

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

3.1.3.4 Missing BCVA Value at Study Drug Dosing Visit

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

3.1.4 Missed Study Drug Treatment Visit(s) for Patients in the Q8W Treatment Arms

If a patient randomized to treatment Arm A (faricimab Q8W) or Arm C (aflibercept Q8W) misses study drug dosing visit(s) after the Q4W initiating doses, the IxRS will assign the patient to receive faricimab or aflibercept at the next study visit he or she attends. The Q8W drug treatment interval will be automatically reset by the IxRS from that visit forward, thus 4 weeks later, at the following study visit, the patient will receive sham.

3.1.6 Independent Data Monitoring Committee

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

The iDMC will meet approximately every 6 months (frequency adjustable if required) to evaluate unmasked ocular and systemic (non-ocular) safety events with an emphasis on the evaluation of the rate of ocular inflammation, increased IOP, endophthalmitis, arterial thromboembolic events, and clinically significant decreases in BCVA, which will be prepared for the committee by an independent Data Coordinating Center (iDCC). The iDMC may recommend stopping the study early for safety reasons.

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

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

3.2 END OF STUDY AND LENGTH OF STUDY

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

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, [redacted] The end of the study is expected to occur approximately 100 weeks after the last patient is randomized.

The total length of the study [redacted] from screening of the first patient to the LPLV for patients from the global enrollment phase is expected to be approximately *38* months.

3.3 RATIONALE FOR STUDY DESIGN

A multicenter, double-masked, randomized, comparator-controlled trial design was selected to minimize bias in the evaluation of faricimab as a treatment for patients with DME.

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

Optional aqueous humor samples will be collected from consenting patients in regions where optional sampling is approved, with the aim to further understand the ocular pharmacokinetics of faricimab as well as to assess biomarkers (see Section 3.3.4). Single (Krohne et al. 2012) and multiple (Campochiaro et al. 2013) aqueous humor samplings have previously been instrumental in the understanding of ocular pharmacokinetics and VEGF suppression (Muether et al. 2012, 2013, 2014; Fauser et al. 2014; Fauser and Muether 2016; Hutton-Smith et al. 2017) and were safely applied in faricimab clinical studies in a total of 180 patients.

3.3.1 Rationale for Treatment Arms Dose and Schedule

3.3.1.1 Rationale for Faricimab Dose and Schedule

The 6-mg dose of faricimab will be administered to patients as initiating and maintenance doses in treatment Arm A and Arm B, as outlined in Section 3.1.1.

Dose

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

The first-in-human study (BP28936) evaluated the safety and tolerability of single and multiple administration of faricimab to 24 patients with nAMD, at doses ranging from 0.5

mg to 6 mg. The selection of these doses was based on nonclinical findings and absolute IVT doses administered in toxicology studies. The 6-mg dose of faricimab was the highest feasible dose of faricimab, and single and multiple doses of up to 6 mg were well tolerated.

The Phase II study (BP30099 [BOULEVARD]) provided evidence of a positive benefit–risk profile for IVT faricimab in patients with DME (n=229 enrolled). The study compared two doses of IVT faricimab (1.5-mg faricimab and 6-mg faricimab) with 0.3-mg IVT ranibizumab. The effects of 6-mg IVT faricimab on the primary endpoint of the mean change from baseline in BCVA in the anti-VEGF treatment–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.

As a result, the 6-mg faricimab dose has been chosen for further clinical development in Phase III studies in patients with DME. Refer to the RO6867461 *(faricimab)* Investigator's Brochure for details on efficacy and safety results for the above-mentioned nonclinical and clinical studies.

Schedule

The dosing schedule in the Phase III study is designed to allow the assessment of both efficacy and the optimal treatment frequency of the 6-mg IVT faricimab dose. The dosing schedule is based on the clinical data from the Phase II study (BP30099 [BOULEVARD]) and the PK and PD assessments of aqueous humor samples from a subset of patients with DME in the Phase II study BP30099.

The mechanism of action of faricimab is through neutralization of VEGF and Ang-2. PK and PD assessments of aqueous humor samples from a subset of patients in Study BP30099 demonstrated high suppression of VEGF and Ang-2 for 8 weeks or more with faricimab, fully supporting the Q8W dosing regimen with a potential to further extend the intervals between injections.

An initiating phase with six IVT injections of 6-mg faricimab Q4W was selected for Arm A (faricimab Q8W). The rationale for the initial six Q4W doses is based on the continuous BCVA gains seen after each Q4W injection up to Week 24 in the Phase II study (BP30099). The maintenance dosing phase for patients in Arm A (faricimab Q8W) will consist of 6 mg of IVT faricimab administered to patients Q8W. The rationale for Q8W maintenance phase dosing is based on the evidence of the durability of the 6-mg faricimab dose in the 16-week observation period of the Phase II study (after the last dose at Week 20 until the end of observation period at Week 36), and on the VEGF and Ang-2 target neutralization in the aqueous humor in a subset of patients. An additional

rationale for the Q8W maintenance dosing schedule for patients in Arm A is that it matches the U.S., Japan, and E.U. approved interval for the active comparator Arm C (aflibercept Q8W) in the Phase III design.

Both the efficacy outcomes from the Phase II study and the variability in individual VEGF and Ang-2 suppression times in the PK/PD aqueous humor assessments indicated a heterogeneous response to treatment and supported a flexible dosing regimen with intervals from Q4W to Q16W. The Phase II study (BP30099) time to disease re-activation data (time to a 50-μm increase in CST or time to a 5-letter worsening in BCVA) following six Q4W doses demonstrated that although some patients with DME may 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 structural model of PK/PD model characterizing the aqueous humor free VEGF time course showed that there was a substantial proportion of patients with high aqueous humor free VEGF suppression for whom a Q12W or Q16W regimen could be sufficient to maintain efficacy.

As a result, the Phase III design will assess 6-mg IVT faricimab administered at PTIs to patients in Arm B. The PTI regimen aims to achieve maximum efficacy while reducing the IVT injection treatment burden in patients with DME.

3.3.1.2 Rationale for Aflibercept Dose and Schedule

The 2-mg aflibercept doses will be administered to patients in treatment Arm C, as outlined in Section 3.1.1. The aflibercept dose and schedule used in this study are consistent with global recommended dosing posologies (e.g., in the United States, European Union, and Japan) DME product labeling for Eylea (aflibercept) (see Section 3.3.3).

3.3.2 Rationale for Patient Population

This study will be conducted in patients with decreased vision due to DME who meet all of the eligibility criteria for this protocol (for the inclusion and exclusion criteria, see Sections 4.1.1 and 4.1.2, respectively).

Patients who are both naive to anti-VEGF therapy in the study eye and those who have previously been treated with anti-VEGF therapy in the study eye will be randomized. Inclusion of previously anti-VEGF–treated patients in the study will enable exploratory evaluation of the impact of previous IVT anti-VEGF treatment on the efficacy of faricimab. The target for participation of previously anti-VEGF–treated patients will be capped at a minimum 10% and a maximum 25% of enrollment. The rationale for capping the number of previously anti-VEGF–treated patients is based on the heterogeneous nature of this population with potentially a history of long-standing DME and irreversible retinal damage that may limit the possibility of detecting additional VA improvements.

3.3.3 Rationale for Control Group

This study is an interventional study, aiming to evaluate the efficacy of faricimab compared with a SOC anti-VEGF therapy, aflibercept, for patients with DME. Anti-VEGF therapy is a well-established SOC in patients with DME, and studies with an inactive comparator or macular laser treatment alone are no longer ethically acceptable alternatives given the improvements in visual and anatomical outcomes associated with anti-VEGF treatment.

Aflibercept is an approved anti-VEGF treatment in patients with DME and has demonstrated improvement of BCVA in the target population in controlled, randomized clinical studies (Eylea® [aflibercept] U.S. Package Insert, Eylea® [aflibercept] E.U. Summary of Product Characteristics, and Eylea® [aflibercept] Japan Package Insert). Eylea is the only globally approved anti-VEGF therapy with a Q8W maintenance regimen, facilitating a comparison with the Q8W maintenance regimen of faricimab in treatment Arm A.

3.3.4 Rationale for Pharmacodynamic and Biomarker Assessments

PD parameters comprise the primary target engagement markers [redacted]

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 Muethe 2016; Hutton-Smith et al. 2017). Therefore, to increase our understanding of the ocular pharmacokinetics and pharmacodynamics of faricimab and its relationship to PTIs, optional aqueous humor samples will be obtained from patients who provide additional optional consent to participate. Aqueous humor and vitreous humor samples will be measured at different timepoints for patients who consent in regions where optional sampling is approved. 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 such as cytokines [redacted] may be analyzed in these specimens in an exploratory analysis. The analysis of these entities aims at the investigation of the role of biochemical and biological processes, such as angiogenesis, inflammation, and oxidative stress in the pathogenesis of DR (Goldberg 2009; Kaul et al. 2010) and DME (Campochiaro 2015) 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 the molecular targets unbound to faricimab [redacted] will be measured in the systemic circulation as part of PD assessments at different timepoints for all patients and at two *additional* timepoints for patients who consent in regions where optional sampling is approved.

4. MATERIALS AND METHODS

4.1 PATIENTS

Patient Selection and Sex Distribution

Approximately 900 patients with DR and macular edema secondary to diabetes mellitus (Type 1 and 2) will be randomized to the study.

The study will recruit patients who are naive to anti-VEGF therapy in the study eye and those who have previously been treated with anti-VEGF therapy in the study eye. Study participation of previously anti-VEGF–treated patients will be capped at a maximum 25% of enrollment.

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

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

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry.

4.1.1.1 General Inclusion Criteria

Patients must meet the following general inclusion criteria for study entry:

- Willingness and the ability to provide signed informed consent

  Additionally, at U.S. sites, patients must provide Health Insurance Portability and Accountability Act (HIPAA) authorization, and in other countries, as applicable according to national laws.
- Age ≥18 years
- Documented diagnosis of diabetes mellitus (Type 1 or Type 2), as defined by the American Diabetes Association or per WHO criteria and
  - Current regular use of insulin *or other injectable drugs (e.g., dulaglutide and liraglutide)* for the treatment of diabetes

    and/or
  - Current regular use of oral anti-hyperglycemic agents for the treatment of diabetes
- HbA_{1c} of ≤10% within 2 months prior to the Day 1 visit date

- Ability and willingness to undertake all scheduled visits and assessments
- 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 (≥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.

4.1.1.2 Ocular Inclusion Criteria for Study Eye

Patients must meet the following ocular inclusion criteria for the study eye for entry in the study:

- Macular thickening secondary to DME involving the center of the fovea with CST ≥325 μm, as measured on Spectralis SD-OCT, or ≥315 μm, as measured on Cirrus SD-OCT or Topcon SD-OCT at screening
- BCVA of 73 to 25 letters, inclusive (20/40 to 20/320 approximate Snellen equivalent), using the ETDRS protocol at the initial testing distance of 4 meters (see the BCVA manual for additional details) on Day 1
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality CFPs (including ETDRS 7 modified fields or 4 wide-angle fields to permit grading of DR and assessment of the retina) and other imaging modalities.

4.1.2 Exclusion Criteria

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

4.1.2.1 General Exclusion Criteria

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

- Currently untreated diabetes mellitus or previously untreated patients who initiated oral *or injectable* anti-diabetic medication within 3 months prior to Day 1

- History of allergy or hypersensitivity to active drug aflibercept and any of its excipients, fluorescein, or any study treatment–related mandatory ingredients (e.g., disinfectants, anesthetics, etc.; see the pharmacy manual for additional details) that is not amenable to treatment
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab or to aflibercept injections, study treatment procedure, dilating drops, or any of the anesthetic and antimicrobial *preparations* used by a patient during the study
- Active cancer within the past 12 months except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤ 6 and a stable prostate-specific antigen for >12 months
- Systemic treatment for suspected or active systemic infection

  Ongoing use of prophylactic antibiotic therapy may be acceptable but has to be discussed with the Medical Monitor.
- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis or anticipated to require hemodialysis or peritoneal dialysis at any time during the study
- History of other disease, other non-diabetic metabolic dysfunction, physical examination finding, *historical* or *current* clinical laboratory finding giving reasonable suspicion of a condition that contraindicates the use of the faricimab or aflibercept or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator
- Uncontrolled blood pressure (defined as systolic >180 mmHg and/or diastolic >100 mmHg while a patient is at rest)

  If a patient's initial reading exceeds these values, a second reading may be obtained later the same day or on another day during the screening period. If the patient's blood pressure is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1.
- *Stroke (c*erebral vascular accident*)* or myocardial infarction within 6 months prior to Day 1
- Pregnancy or breastfeeding, or intention to become pregnant during the study

  Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to initiation of study treatment. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Participation in an investigational trial that involves treatment with any drug or device (with the exception of vitamins and minerals) within 3 months prior to Day 1
- Administration of systemic pro-angiogenic treatments, such as VEGF-based therapies for the peripheral or coronary ischemia (e.g., limb ischemia or myocardial infarction) within 3 months or 5 half-lives prior to Day 1
- Inability to comply with study or follow-up procedures

- Requirement for continuous use of any medications and treatments indicated in Section 4.4.2, Prohibited Therapy

4.1.2.2 Ocular Exclusion Criteria for Study Eye

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

- High-risk PDR in the study eye, using any of the following established criteria for high-risk PDR:
  - Any vitreous or pre-retinal hemorrhage
  - Neovascularization elsewhere ≥1/2 disc area within an area equivalent to the mydriatic ETDRS 7 fields on clinical examination or on CFPs
  - Neovascularization at disc ≥1/3 disc area on clinical examination
- Tractional retinal detachment, pre-retinal fibrosis, *vitreomacular traction,* or epiretinal membrane involving the fovea or disrupting the macular architecture in the study eye*,* [redacted]
- Active rubeosis
- Uncontrolled glaucoma
- History of retinal detachment or macular hole (Stage 3 or 4)
- Aphakia or implantation of anterior chamber intraocular lens
- IVT anti-VEGF treatment within 3 months prior to Day 1 (applicable to patients whose study eyes were previously treated with IVT anti-VEGF agents) or any IVT anti-VEGF agents to study eye prior to Day 1 (applicable for patients who are treatment naive)
- Treatment with panretinal photocoagulation (PRP) within 3 months prior to Day 1
- Macular (focal*,* grid*, or micropulse*) laser within 3 months prior to Day 1
- Any cataract surgery or treatment for complications of cataract surgery with steroids or YAG (yttrium-aluminum-garnet) laser capsulotomy within 3 months prior to Day 1
- Any other intraocular surgery (e.g., corneal transplantation, glaucoma filtration, pars plana vitrectomy, corneal transplant, or radiotherapy)
- Any IVT or periocular (subtenon) corticosteroid treatment within 6 months prior to Day 1
- Any use of medicated intraocular implants, including Ozurdex®, within 6 months of Day 1
- Any use of Iluvien® implants at any time prior to Day 1
- Treatment for other retinal diseases that can lead to macular edema

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

Patients who meet the following exclusion criterion for the fellow eye (non–study eye) will be excluded from study entry:

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

4.1.2.4 Exclusion Criteria for Both Eyes

Patients who meet the following exclusion criterion for either eye will be excluded from study entry:

- Prior administration of IVT faricimab in either eye
- Any history of idiopathic or immune-mediated uveitis in either eye
- Active ocular inflammation or suspected or active ocular or periocular infection in either eye on Day 1

4.1.2.5 Concurrent Ocular Conditions Exclusion Criteria

Patients who meet the following exclusion criteria related to concurrent ocular conditions will be excluded from study entry:

- Any current or history of ocular disease other than DME that may confound assessment of the macula or affect central vision in the study eye (e.g., choroidal neovascularization, age-related macular degeneration, retinal vein occlusion, uveitis, angioid streaks, histoplasmosis, active or inactive cytomegalovirus, pathological myopia, retinal detachment, *retinal embolus,* macular traction, macular hole, and other)
- Any current ocular condition which, in the opinion of the investigator, is currently causing or could be expected to contribute to irreversible vision loss due to a cause other than DME in the study eye (e.g., foveal atrophy, foveal fibrosis, pigment abnormalities, dense subfoveal hard exudates, or other non-retinal conditions)

4.2 METHOD OF TREATMENT ASSIGNMENT AND MASKING

4.2.1 Treatment Assignment

After written informed consent has been obtained, all patients will receive a screening number assigned through the IxRS. A patient must satisfy all eligibility criteria (see Sections 4.1.1 and 4.1.2) prior to randomization through the IxRS. As part of the screening process, the CRC will evaluate CFPs and SD-OCT images to provide an objective, masked assessment of patient eligibility. After all patient eligibility requirements are confirmed, site personnel will contact the IxRS at the Day 1 visit for assignment of a patient identification number (a separate number from the screening number). Patients will be randomized in a 1:1:1 ratio to one of three study treatment arms (faricimab Q8W, faricimab PTI, or aflibercept Q8W). After randomization and at each study treatment visit (i.e., including Day 1), the IxRS will assign the appropriate

study treatment kit to be used. Patients will be randomized on the same day study treatment is to be initiated (the Day 1 visit).

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

- Baseline BCVA ETDRS letter score (≥64 letters vs. <64 letters)
- Prior IVT anti-VEGF treatment (yes vs. no)
- Region (United States and Canada, Asia, and the rest of the world)

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

Patients who are not eligible for enrollment (screen failures) may be eligible for re-screening for up to an additional two times during the enrollment period of the study. At re-screening, a new screening number will be assigned to each patient through the IxRS and all screening visit assessments will be performed. At the Day 1 visit, FFA images do not have to be repeated, provided *the same eye is selected for the study eye at rescreening and* CRC *acceptable* FFA images were *taken* within 4 weeks before the new Day 1 visit (randomization) date.

4.2.2 Masking

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

4.2.2.1 Masked Roles

Principal Investigator

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

Assessor Physician

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

Photographer(s) and OCT Technician(s)

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

Study Coordinator(s)

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

BCVA Examiner

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

Phlebotomist

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

4.2.2.2 Unmasked Roles

Treatment Administrator

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

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

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

Unmasked Assistant(s) and Pharmacist

If desired, sites may have designated qualified unmasked assistant(s) who can, e.g., assemble study treatment supplies, prepare sterile field, *prepare the patient's study*

eye for treatment, discard all injection materials (i.e., syringes and needles) immediately following study treatment, and place vial in the kit box. The qualified unmasked assistant(s) can be assigned to measure post-dose IOP. If the site uses a pharmacy, then the unmasked role is also assigned to the pharmacist who can take on IMP-related tasks as applicable per delegation of authority log. In addition, qualifying unmasked assistant(s) can assist with and perform the screening and Day 1 visit assessments.

Number of Unmasked Personnel per Site

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

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

4.2.2.3 Delegation Log

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

4.2.2.4 Role Switching

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

4.2.2.5 Study Backup Staff

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

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

CRC personnel, study vendors, the Sponsor, and its agents will also be masked to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, drug accountability clinical research associates, the images coordinator, iDCC and iDMC members, and an internal unmasking statistician (this person is from the Sponsor's unmasking group and will follow the Sponsor's standard operation procedures to audit the implementation of the randomization scheme

and the treatment interval assignment by the IxRS vendor periodically during the conduct of the study; this person will not be involved in other study-related activities).

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

4.2.2.7 Patient Masking

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

4.2.3 Unmasking

4.2.3.1 Single-Patient Emergency Unmasking

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

4.2.3.2 Single-Patient Non-Emergency Unmasking

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

4.2.3.3 Single-Patient Unmasking for Health Authority Reporting Requirements

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

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

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

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 the anesthetized eye.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Faricimab, Aflibercept and Sham

4.3.1.1.1 Faricimab Formulation

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

4.3.1.1.2 Aflibercept (Active Comparator) Formulation

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

4.3.1.1.3 Sham Formulation

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

4.3.1.1.4 Faricimab, Aflibercept, and Sham Packaging and Handling

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

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

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

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

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

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

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

4.3.2.1 Dosage

4.3.2.1.1 Intravitreal Faricimab Injections

The 6-mg dose of faricimab will be evaluated in this study and will be administered intravitreally to patients randomized to receive faricimab Q8W or PTI during the 96-week treatment period (see the study treatment schema in Figure 1).

Patients randomized to receive Q8W treatment will be administered 15 IVT injections of faricimab during the 96-week treatment period. Treatment will consist of 6 initial injections (6 mg of faricimab Q4W to Week 20), followed by 9 maintenance injections (6 mg of faricimab Q8W between Week 24 and Week 96).

The number of IVT injections of faricimab administered to patients in the PTI arm will vary (see Section 3.1.2.1 for the retreatment criteria), but a minimum of 10 IVT injections of faricimab will be administered to patients during the 96-week treatment period. This will consist of minimum of 4 initiating injections (6 mg of faricimab Q4W to Week 12), followed by minimum of 6 maintenance injections (6 mg of faricimab between Week 16 and Week 96).

4.3.2.1.2 Intravitreal Aflibercept (Active Comparator) Injections

A 2-mg dose of aflibercept (Arm C) will be administered intravitreally Q8W to patients randomized to the aflibercept treatment arm during the 96-week treatment period (see Figure 1). Patients will receive 15 IVT injections of aflibercept during the 96-week treatment period. Treatment will consist of 5 initiating injections (2 mg of aflibercept Q4W to Week 16), followed by 10 maintenance injections (2 mg of aflibercept Q8W between Week 20 and Week 96).

4.3.2.1.3 Sham Procedure

All three treatment arms (faricimab Q8W, faricimab PTI, and aflibercept Q8W) will maintain Q4W study visits for the 100-week study duration. To preserve the randomized treatment arm masking, patients will have the sham procedure performed at study treatment visits when they are not treated with either faricimab or aflibercept as applicable per their treatment arm schedule (see Figure 1).

4.3.3 Administration

4.3.3.1 Faricimab or Aflibercept Intravitreal Injections or Sham Procedure

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

4.3.4 Study Treatment Preparation

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

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

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

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

4.3.5 Compliance

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

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Table 2 and Section 5.1.4.1.

4.3.6 Investigational Medicinal Product Accountability

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

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

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.7 Continued Access to Faricimab

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

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

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

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

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for 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 prescription drugs or over-the-counter preparations or procedures other than protocol-specified procedural medications (e.g., dilating drops or fluorescein dyes, proparacaine, or antimicrobials [if applicable]) used by a patient within 7 days preceding the Day 1 visit and through the conclusion of the patient's study participation or early termination visit. Patients required to use therapy that is prohibited (see Section 4.4.2) will not be eligible for the study.

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

4.4.1 Permitted Therapy

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 5.1.4.1, Table 2) may apply with cataract surgery
- Short-term use of topical *ocular* corticosteroids after cataract surgery, yttrium-aluminum garnet capsulotomy, peripheral iridotomy*, argon/selective laser trabeculoplasty, or ocular allergic conditions*
- PRP 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 masked physician, randomized patients may have their fellow (non–study) eye treated with anti-VEGF *therapy licensed for ocular use* if they are diagnosed with an ocular condition for which the selected anti-VEGF therapy is approved *by* the country *regulatory agency*. Consult with the region-specific anti-VEGF prescribing information for the recommended dose and frequency of treatment. *The Sponsor will cover the* cost of approved *licensed ocular* anti-VEGF therapy in accordance with local regulations. *Note: Avastin (bevacizumab) is not licensed for ophthalmic use in any country; therefore, it is prohibited to be used.*

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

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

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

4.4.2 Prohibited Therapy

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

- Systemic anti-VEGF therapy
- Systemic drugs known to cause macular edema (fingolimod, tamoxifen)
- IVT anti-VEGF agents (other than study-assigned aflibercept or faricimab) in study eye
- IVT, periocular (subtenon), steroid implants (i.e., Ozurdex®, Iluvien®), or chronic topical ocular corticosteroids in study eye
- Treatment with Visudyne® in study eye
- Administration of micropulse and focal or grid laser in study eye
- Other experimental therapies (except those comprising vitamins and minerals)

Note: patients who discontinue study treatment should be strongly encouraged to continue their study participation and undergo as many scheduled visits as possible, with emphasis on the Weeks 48, 52, 56, and 100 visits.

4.5 STUDY ASSESSMENTS

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

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

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

4.5.1 Informed Consent Forms and Screening Log

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

All screening and Day 1 visit evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization at the Day 1 visit. The

investigator will maintain a screening log to record details about all patients screened and to confirm eligibility. Reasons for screening failure have to be documented in patients' source documents.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, chronic and ongoing conditions (e.g., trauma, cancer, cardiovascular, cerebrovascular, and ophthalmic history), surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 7 days prior to initiation of study treatment (the Day 1 visit) will be recorded.

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

4.5.3 Physical Examinations

A targeted physical examination should include an evaluation of the head, ears, nose and throat. A patient's height and weight will be recorded as well. If any abnormalities are noted during the study, the patient may be referred to another doctor.

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

4.5.4 Vital Signs

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

4.5.5 Ocular Assessments

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

- *Refraction and* BCVA assessed on ETDRS chart at a starting distance of 4 meters (perform prior to dilating eyes; see Appendix 4)
- Pre-treatment IOP measurement of both eyes (perform prior to dilating eyes)
- Slitlamp examination (for grading scales for anterior and vitreous cells, see Appendix 3)
- Dilated binocular indirect high-magnification ophthalmoscopy

- Finger-counting test followed by hand motion and light perception tests (when necessary) performed within *approximately* 15 minutes of post-study treatment in the study eye only by the unmasked treatment administrator.
- At study treatment visits, post-treatment IOP measurement in the study eye only *at* 30 (±15) minutes by qualified personnel assigned to the unmasked role. If there are no safety concerns after 30 (±15) minutes following the study treatment, the patient will be permitted to leave the clinic. If the IOP value is of concern to the treatment administrator, the patient will remain in the clinic and will be managed in accordance with this physician clinical judgment. The adverse event will be recorded on the Adverse Event eCRF as applicable.

The method of IOP measurement used for a patient must remain consistent throughout the study.

Ocular Imaging

The CRC(s) will provide sites with the CRC(s) manual and training materials for specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software (where applicable) will be certified and validated by the CRC(s) as specified in the CRC manual. All ocular images results will be obtained by trained site personnel at the study sites and forwarded to the CRC(s) for independent analysis and/or storage (see Appendix 5, Appendix 6, and Appendix 7).

Note: After randomization, if a patient misses a study visit when ocular *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*y* should be obtained at the next scheduled visit the patient attends.

Ocular images include the following:

- *Mandatory* CFP *(7- or 4-wide fields; perform one of these methods for the patient consistently throughout the trial participation)* of both eyes
- [redacted]
- FFA *(preferred method is UWF (Optos) FFA if sites have capability; the sites without UWF (Optos) FFA to capture 7 or 4-wide fields using the same method consistently throughout the trial participation)* of both eyes (*if applicable,* performed after *blood* samples are obtained)
- SD-OCT or swept-source OCT (SS-OCT) images of both eyes

  Certain SS-OCT machines may be acceptable; *consult* the CRC.
- Optional OCT-angiography (OCT-A) of both eyes at sites with OCT-A capabilities *and agreement by sites to take these images*

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

4.5.6 Concurrent Ocular Procedures

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

4.5.7 Laboratory, Biomarker, and Other Biological Samples

At the scheduled visit, *all samples must be obtained prior to study treatment and blood samples must* be obtained prior to FFA assessments (if applicable). Fasting is not required prior to specimen collection. The specimens will be forwarded to the central laboratory. The central laboratory will either perform the analysis or forward samples to the Sponsor or its designee for analysis and/or storage. Instructions for obtaining, processing, storing, and shipping of all specimens are provided in the laboratory manual. Laboratory supply kits will be provided to the sites by the central laboratory. See Appendix 1 for sample collection timepoints and Appendix 8 for biological sample collection and shipping instructions.

All samples obtained during screening from patients who are not randomized will be discarded.

The following assessments will be performed:

- Hematology: hemoglobin, hematocrit, quantitative platelet count, RBC counts, WBC counts, and differentials, including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, ALP, AST, ALT, and uric acid
- Urinalysis: specific gravity, pH, blood, protein, ketones, glucose, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal)
- Coagulation: activated partial thromboplastin time and prothrombin time
- Urine pregnancy test at screening and 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.
- HbA_{1c}
- Plasma samples for measurement of anti-faricimab antibodies
- Plasma samples to measure faricimab or aflibercept concentration *(PK sample)*
- [redacted]

Unless the patient gives specific consent for his or her leftover plasma samples to be stored for optional exploratory research (see Section 4.5.9.1), the samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

The hematology, serum chemistry, urinalysis, coagulation, serum, urine pregnancy tests, and HbA_{1c} *samples* will be destroyed after their analysis during the study.

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

4.5.7.1 Optional Aqueous Humor *and Optional Plasma* Samples

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

For patients who consent to provide aqueous humor sampling, the aqueous humor sample should be collected just prior to study treatment *(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 lab manual for aqueous samples collection, storage, and transfer*).

All efforts should be made to obtain a baseline aqueous humor sample on Day 1 (pre-dose). The schedule of activities (see Appendix 1) provides guidance on recommended visits at which aqueous humor samples should be obtained. Patients who are prematurely discontinued from study treatment but who agree to continue to participate in the study should discontinue collection of optional aqueous humor samples and any associated optional plasma samples. 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 or aflibercept [redacted] 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 [redacted] and inflammation [redacted] to identify new therapeutic targets, better understand variability in patient responses to faricimab, and to support patient selection and/or stratification in future clinical trials.

At Day 7 and Week 32, sites will collect optional PK plasma samples for measurement of faricimab or aflibercept concentration and optional PD plasma sample for analysis of systemic [redacted] *(see Appendix 1 and the Covance manual for PK/PD samples collection, storage, and transfer).*

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.9.1), biological samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

4.5.7.2 Optional Unscheduled Collection of Vitreous *and Optional PK* Samples

Elective vitrectomy for vitreous sample collection is not allowed in the study eye during a patient's study participation; however, if the surgery is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye (see Appendix 8 for further details). *Associated PK plasma samples will be collected to measure faricimab or aflibercept concentration. See the Covance manual for vitreous and PK sample collection, storage, and transfer.*

Vitreous humor samples will be analyzed primarily for faricimab or aflibercept concentrations. The remaining samples may be analyzed for [redacted] *as well as additional biomarkers, including those involved in angiogenesis* [redacted] *and inflammation* [redacted] *to identify new therapeutic targets, better understand variability in patient responses to faricimab, and to support patient selection and/or stratification in future clinical trials.*

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

4.5.8 Patient-Reported Outcomes

PROs will be assessed using the National Eye Institute Visual Functioning Questionnaire–25 (NEI VFQ-25) (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.

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

4.5.9 Optional Samples for Research Biosample Repository

4.5.9.1 Overview of the Research Biosample Repository

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

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

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.9) will not be applicable at that site. The RBR portion of the Informed Consent Form has to be agreed to and signed by the consenting patient before these samples can be collected and/or mandatory residual samples used.

4.5.9.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to response to faricimab, to improve the understanding of the biology of VEGF-A and Ang-2, or to better understand the targets or diseases (DR and DME):

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

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

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

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

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

4.5.9.4 Confidentiality

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

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

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

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

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

4.5.9.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the

objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

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

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

4.5.9.6 Withdrawal from the Research Biosample Repository

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

global_rcr-withdrawal@roche.com

A patient's withdrawal from Study GR40349 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study GR40349.

4.5.9.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

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

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced and will not be allowed to restart study treatment. However, they should be strongly encouraged to continue their study participation and undergo as many scheduled visits as possible, with emphasis on the Week 48, 52, 56, and 100 visits.

4.6.2 Patient Discontinuation from Study

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

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

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

If a patient discontinues from the study but has not withdrawn informed consent, the site should make every effort to continue to follow-up on serious adverse events, deaths, and adverse events of special interest. In order to avoid loss to follow-up, the investigator should ask the patient at the study start for the contact information of a relative or friend who can be contacted in case the patient cannot be reached. However, patients will not be followed for any reason after consent has been withdrawn. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

Patients who discontinue from the study early but have not withdrawn consent should return for an early termination visit (see Appendix 1) after a minimum of 28 days have elapsed following the last study treatment.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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

5.1.1 Safety Assessments

The schedule of safety assessments to be performed during the study is provided in Appendix 1. After the first study treatment on Day 1, all patients will return for a safety assessment visit on Day 7 (±3 days). Patients will be instructed to contact the site at any time if they have any health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 2).

At sites where the masked investigator's decision is for patients to receive pre- and post-injection antimicrobials, patients will also be asked whether they have taken the prescribed, self-administered, pre- and/or post-injection antimicrobials.

A finger-counting test will be conducted for each patient within *approximately* 15 minutes following study treatment by the treatment administrator; hand motion and light perception tests will be performed when necessary.

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

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

Detailed ocular examinations, including indirect ophthalmoscopy and slitlamp examination, will be performed throughout the study. Blood samples for plasma study drug concentrations, antibodies to faricimab, and other biomarker samples (see Section 4.5.6) will be obtained from all patients at selected timepoints. The optional aqueous humor and vitreous samples will be obtained from patients who consent to the procedure and sample collection.

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

Patients *who* are discontinu*ing* from the study prior to completion (Week 100) will be asked to return for early termination visit assessments after a minimum of 28 days have elapsed following the last study treatment (see Appendix 1). The visit will include assessment of all adverse events (serious and non-serious; ocular and non-ocular). Serious adverse events will be reported in compliance with GCP guidelines.

Treatment interruption and/or treatment discontinuation for adverse events will be determined using the criteria in Section 5.1.4.1, Table 2.

5.1.2 Risks Associated with Faricimab

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

Based on experience with aflibercept and other anti-VEGF therapies, potential risks of faricimab include intraocular inflammation, the intravitreal injection-related risks of infectious endophthalmitis, retinal detachment/tear, iatrogenic traumatic cataracts and increased IOP, as well as the *non-ocular* risk of arterial thromboembolic events. An independent clinical events coding committee will be established to adjudicate thromboembolic events (myocardial infarcts, strokes, and deaths) reported during the study.

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

5.1.3 *Risks Associated with Aflibercept (Comparator)*

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

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

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 Treatment Interruption: Dose Interruption and Treatment Discontinuation Criteria

Study treatment interruption and/or patient discontinuation from the study treatment for adverse events will be determined using the criteria listed in Table 2. If any of these criteria are met, treatment will be interrupted (or discontinued, if applicable) and will not be resumed earlier than the next scheduled study visit. The reason for study treatment interruption/discontinuation should be recorded on the appropriate eCRF and, if applicable, on the Adverse Event eCRF.

Table 2 Dose Interruption and Treatment Discontinuation Criteria

Event	Criteria
Intraocular inflammation	• Interrupt study treatment if intraocular inflammation (iritis, iridocyclitis or vitritis) is ≥2 +in the study eye. • Study treatment may be resumed subsequently as determined by the investigator
Cataract surgery in the study eye	• Interrupt study treatment after cataract surgery in study eye. • Study treatment may be resumed no earlier than 28 days after an uncomplicated cataract surgery and no evidence of post-operational inflammation at that time. For cataract surgery with complications, study treatment may be permitted as determined by Medical Monitor and investigator.
BCVA decrease	• Interrupt study treatment if there is a study treatment–related decrease in BCVA of ≥ 30 letters in the study eye compared with the last assessment of BCVA prior to the most recent treatment. • Study treatment may be permitted subsequently, as determined by the investigator.
Elevated IOP	• Interrupt study treatment if 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 study treatment if a retinal break is present in the study eye. • Study treatment may be resumed no earlier than 28 days after successful laser retinopexy, as determined by the investigator.

Table 2 Dose Interruption and Treatment Discontinuation Criteria (cont.)

Event	Criteria
Rhegmatogenous retinal detachment or macular hole	• Interrupt study treatment if rhegmatogenous retinal detachment or Stage 3 or 4 macular hole occurs *in the study eye.* • Study treatment may be subsequently permitted after discussion with Medical Monitor.
Active *or suspected* infection	• Interrupt study treatment if *active or suspected ocular or periocular infections* are present *(e.g.,* infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis*)* in either eye 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 study treatment discontinuation.*

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.8 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 the Adverse Event Grading Scale; see Section 5.3.3, Table 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 site staff to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

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

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

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Sight-threatening adverse events: an adverse event is considered to be sight-threatening and should be reported expeditiously if it meets one or more of the following criteria:
  - It causes a decrease of ≥ 30 letters in VA score (compared with the last assessment of VA prior to the most recent assessment) lasting more than 1 hour.
  - It requires surgical or medical intervention (i.e., conventional surgery, vitrectomy, vitreous tap, or biopsy with IVT injection of anti-infective treatments, or laser or retinal cryopexy with gas, or a medication) to prevent permanent loss of sight.
  - It is associated with severe intraocular inflammation (i.e., endophthalmitis, 4+ anterior chamber cell/flare, or 4+ vitritis; see Section 5.3.5 and Appendix 3 for intraocular inflammation grading scales).

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until the final study visit at Week 100. For patients who terminate study treatment and from the study early, all adverse events will be reported up to the early termination visit. For patients who discontinue study treatment early (prior to Week 96 treatment) but continue to participate in the study, adverse events will be reported until their last or final study visit.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

Table 3 provides guidance for assessing adverse event severity.

Table 3 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 4). Note: Only the masked investigator will assess all adverse event causality.

- 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 4 Causal Attribution Guidance

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

5.3.5 Procedures for Recording Adverse Events

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

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

For the purposes of reporting events of infection and inflammation, 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, aqueous pigmented cells visible on slitlamp examination that are caused by dilation and are not RBCs or WBCs or the result of any ocular disorder should not be recorded as an adverse event.

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a

descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 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× ULN) in combination with either an elevated total bilirubin (>2× ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1)

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

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

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

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

5.3.5.8 Preexisting Medical Conditions

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

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

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

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

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

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

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

  The patient has not experienced an adverse event

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

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

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

No safety data related to overdosing of faricimab are available.

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

Medication Error Definition and Reporting

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

- *Medication error is accidental deviation in the administration of a drug. In some cases, a medication error may be intercepted prior to administration of the drug.*
- *Accidental overdose is accidental administration of a drug in a quantity that is higher than the assigned dose.*

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

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

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

Reporting of Adverse Events Resulting from Special Situation

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

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

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

5.3.5.13 Patient-Reported Outcome Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results

- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact information for Western Hemisphere

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

Mobile Telephone No.: [redacted]

Medical Monitor Contact Information for Eastern Hemisphere

Medical Monitor/Roche Medical Responsible: [redacted], MB, Ch.B.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events, and adverse events of special interest will be reported until the final study visit at Week 100. 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 to immediately inform the investigator if they become pregnant during the study or *within 3 months* after the last 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. The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- RO6867461 *(faricimab)* Investigator's Brochure
- Aflibercept (Eylea) E.U. Summary of Product Characteristics

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Approximately 900 patients will be randomized in the global enrollment phase of this study. [redacted]

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

The primary analyses will be performed when all patients from the global enrollment phase have either completed the study through Week 56 or have discontinued from the study prior to Week 56, whichever comes later (i.e., timing is defined as the primary analysis after the LPLV), and all data collected prior to the primary LPLV in the global enrollment phase are in the database and have been cleaned and verified.

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

The final analysis will be performed when all patients from the global enrollment phase have either completed the study through Week 100 or have discontinued early from the study, all data from the global enrollment phase are in the database, and the database is locked.

Unless otherwise specified, the analyses described in this section are based on patients enrolled during the global enrollment phase [redacted]. Details of the planned analyses, including any additional analyses needed to support country-specific or regional marketing applications, will be provided in the Statistical Analysis Plan.

6.1 DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on patients enrolled in the global enrollment phase. The global enrollment phase will enroll approximately 900 patients. Patients will be randomized in a 1:1:1 ratio to receive treatment with faricimab Q8W (Arm A), faricimab PTI (Arm B), or aflibercept Q8W (Arm C). The primary comparisons will be the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the faricimab arms (Q8W and PTI).

A sample size of approximately 300 patients in each arm will provide greater than 90% power to show non-inferiority of faricimab to aflibercept (pairwise comparisons between the active comparator and each of the faricimab arms) in the ITT population, using a non-inferiority margin of 4 letters and under the following assumptions:

- Standard deviation (SD) of 11 letters for the change from baseline in BCVA averaged over Week 48, Week 52, and Week 56
- Two-sample *t*-test
- 1.25% one-sided type I error rate
- 10% dropout rate

Assuming 75%–90% of patients recruited will be treatment naive, approximately 225–270 treatment-naive patients will be enrolled per arm. A sample size of 225–270 patients per arm will provide greater than 80% power to show a 3.5-letter superiority of faricimab over aflibercept (pairwise comparisons between the active comparator and each of the faricimab arms) in the treatment-naive population, using the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 2.5%.

Furthermore, a sample size of approximately 300 patients per arm will provide greater than 80% power to show a 3-letter superiority of faricimab over aflibercept (pairwise comparisons between the active comparator and each of the faricimab arms) in the ITT population, under the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 2.5%.

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

[redacted]

6.2 ANALYSIS POPULATIONS

The analysis populations used in this section, such as the ITT population, are based on patients enrolled during the global enrollment phase and will not include the [redacted] unless otherwise specified.

6.2.1 Intent-to-Treat Population

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

6.2.2 Treatment-Naive Population

The treatment-naive population is defined as all patients randomized in the study who have not received any IVT anti-VEGF agents in the study eye prior to Day 1. For analyses based on this patient population, patients will be grouped according to the treatment assigned at randomization.

6.2.3 Per-Protocol Population

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

6.2.4 Safety-Evaluable Population

The safety-evaluable population will comprise all patients who receive at least one injection of active study treatment (faricimab or aflibercept). For analyses based on this patient population, patients will be grouped according to the actual treatment received up to the Week 56 visit as follows.

- If the only active treatment received by a patient in the study eye is aflibercept, the patient's treatment group will be aflibercept Q8W.

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

6.2.5 Pharmacokinetic-Evaluable Population

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

6.2.6 Immunogenicity-Analysis population

The immunogenicity analysis population will consist of all patients with at least one plasma sample for anti-drug antibody assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

6.3 SUMMARIES OF CONDUCT OF STUDY

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

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

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

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

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

6.5 EFFICACY ANALYSES

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

The primary comparisons will be the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the faricimab arms (Q8W and PTI).

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

6.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in BCVA averaged over Weeks 48, 52, and 56. The BCVA outcome measure is based on the ETDRS VA chart assessed at a starting distance of 4 meters.

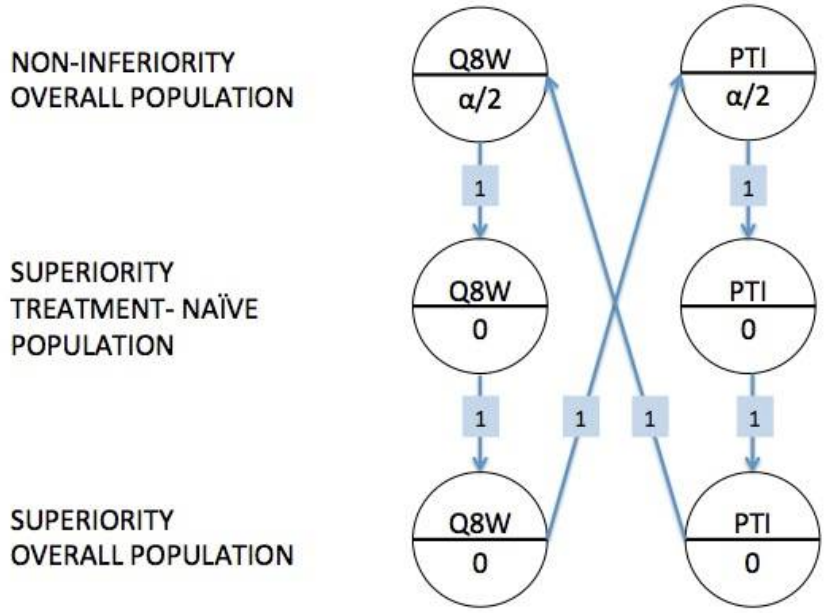
The primary comparisons will be the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the faricimab arms (Q8W and PTI). Additional analyses based on the per-protocol population will also be conducted.

For the two faricimab arms (Q8W and PTI), the following three hypotheses will be tested for each treatment group separately at an overall significance level of $\alpha = 0.05$ using a graph-based testing procedure (Bretz et al. 2009, 2011) to control for the overall type I error rate:

- Non-inferiority of faricimab compared with aflibercept Q8W in the ITT population
- Superiority of faricimab compared with aflibercept Q8W in the treatment-naive population
- Superiority of faricimab compared with aflibercept Q8W in the ITT population

The order in which hypothesis tests for the primary endpoint will be performed is illustrated in Figure 3, with arrows denoting the direction of α-propagation. If the tests for one treatment sequence are all positive, then $\alpha/2$ will be propagated to the beginning of the other treatment sequence, which will be tested at a significance level of $\alpha = 0.05$. Of note, non-inferiority will be tested one sided at half of the designated significance level shown in Figure 3.

Figure 3 Graph-Based Testing Procedure for the Primary Endpoint



PTI = personalized treatment interval; Q8W = every 8 weeks.
Note: $\alpha = 0.05$.

The non-inferiority tests for the faricimab Q8W arm and the faricimab PTI arm compared with aflibercept Q8W arm will be conducted with a non-inferiority margin of 4 letters. For each faricimab group (Q8W or PTI) the null hypothesis,
H_0: $\mu^{faricimab} - \mu^{aflibercept} \leq -4$ letters, and the alternative hypothesis,
H_a: $\mu^{faricimab} - \mu^{aflibercept} > -4$ letters, will be tested, for which $\mu^{faricimab}$ and $\mu^{aflibercept}$ are the expected change from baseline in BCVA averaged over Weeks 48, 52, and 56 for the treatment group in question (faricimab Q8W or PTI) and the active comparator (aflibercept Q8W), respectively.

The change from baseline averaged over Weeks 48, 52, and 56 will be compared between each faricimab arm and the aflibercept Q8W arm using a MMRM model. The model will include the change from baseline at Weeks 4–56 as the response variables and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, the continuous baseline value for the response variable (in this case, baseline BCVA), as well as randomization stratification factors as fixed effects. Comparisons between each faricimab arm and the aflibercept Q8W arm will be made using a composite contrast over Weeks 48, 52, and 56. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a heterogeneous compound symmetry or an AR(1) covariance structure may be fitted.

Missing data will be implicitly imputed using the MMRM model, assuming a missing at random missing data mechanism (i.e., the probability that missing data are dependent

on other observed variables but not on the missing data). Data for patients who receive prohibited therapy will be censored at the timing of use of prohibited therapy. Data for patients who discontinue from study drug and do not receive any prohibited therapy after discontinuation of study drug will be included in the analysis.

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

Non-Inferiority Margin

Non-inferiority hypothesis testing for the primary endpoint of the change from baseline in BCVA averaged over Weeks 48, 52, and 56 will be performed using a 4-letter non-inferiority margin based on the VISTA and VIVID aflibercept pivotal DME studies. These studies compared aflibercept to laser control. The 4-letter non-inferiority margin also preserves approximately 50% of the least estimated benefit of aflibercept over control in both VISTA and VIVID studies individually.

The VISTA study randomized 466 patients in the United States and the VIVID study randomized 406 patients in Europe, Japan, and Australia. At Week 52, in VISTA, patients receiving 2 mg of aflibercept Q8W gained 10.7 letters from baseline compared with 0.2 letters for patients in the control arm. The corresponding results from the VIVID study were a gain of 10.7 letters for aflibercept versus 1.2 letters for the control arm.

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

[redacted]

[redacted]

6.5.2 Secondary Efficacy Endpoints

The key secondary endpoint is the proportion of patients with a ≥2-step improvement in DR severity from baseline on the ETDRS DRSS at Week 52.

[redacted]

Additional secondary endpoints are listed in Section 2, Table 1. For all secondary endpoints measured on a continuous scale, the same analysis method and data handling rules as described in Section 6.5.1 for the primary endpoint will be used. For binary secondary endpoints, the proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata defined by randomization factors using the Cochran-Mantel-Haenszel weights (Cochran 1954; Mantel and Haenszel 1959). CIs of the proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be calculated using the normal approximation to the weighted proportions (Mehrota and Railkar 2000). Superiority will be assessed, as appropriate, using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factors.

[redacted]

All secondary endpoints will be assessed at 1 year and at additional timepoints over time during the study. For the purpose of analysis, the definition of 1 year is the average of the Week 48, 52, and 56 visits.

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

6.5.3 Exploratory Efficacy Endpoints

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

6.6 SAFETY ANALYSES

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

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

At the time of the primary analysis, safety summaries will be summarized based on the complete Week 56 data in the safety-evaluable population. In addition, summaries for ongoing safety data (after Week 56 and up to a single specified clinical cutoff date) in the safety-evaluable population will also be summarized. At the time of the final analysis, safety summaries will be produced based on cumulative Week 100 data in the safety-evaluable population.

Verbatim descriptions of treatment-emergent adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and their incidence and severity will be summarized by treatment arm. A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug. Adverse events will be tabulated by System Organ Class and preferred term. In addition, summaries will be generated for serious adverse events, deaths, adverse events leading to discontinuation of study drug, adverse events of special interest, and adverse events judged to be related to study treatment. Separate summaries will be prepared for systemic (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 baseline in pre-dose IOP measurements and changes between pre-dose and post-dose IOP measurements will also be summarized.

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

6.7 PHARMACOKINETIC ANALYSES

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

A non-linear mixed-effects modeling approach (with NONMEM software [Beal and Sheiner 1998]) will be used to analyze the concentration–time data for faricimab and aflibercept. Population and individual primary PK parameters (i.e., clearances and

volumes) will be estimated. The plasma data collected in this study may be pooled with aqueous humor drug concentrations and with data collected in previous studies as appropriate to update the current population-PK model. The model may be revised if necessary. A covariate modeling approach emphasizing parameter estimation will be implemented for the covariate model development. Potential covariate–parameter relationships will be identified based on mechanistic plausibility and exploratory graphics. Inferences about covariate effects and their clinical relevance will be based on the resulting parameter estimates and measures of estimation precision (asymptotic standard errors). PK parameters such as area under the concentration–time curve and maximum concentration will be derived from the individual post-hoc predictions.

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

6.8 PHARMACODYNAMIC ANALYSES

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

The data collected from this study may be pooled with data from previous studies. The effect of exposure or dosing information on BCVA, aqueous humor [redacted] will be explored using a longitudinal model approach. The influence of various baseline covariates on model parameters will be investigated. The PK–PD or dose–PD relationship will be characterized. Additional PD markers, such as anatomical endpoints, may be included. Additional details about the PK and PD analyses will be provided in the Modeling Analysis Plan. The results will be reported in a separate document from the Clinical Study Report.

6.9 IMMUNOGENICITY ANALYSES

Immunogenicity analyses will be based on the immunogenicity analysis population.

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

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

6.10 BIOMARKER ANALYSES

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

Analyses will be performed 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.

[redacted]

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly on 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 Clinical Study Report has been completed 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 GCP and the principles of the Declaration of Helsinki, or the *applicable* laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC)*, and applicable local, regional, and national laws*.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final

IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

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

Approximately 225 sites globally will participate to enroll approximately 900 patients. Enrollment will occur through an IxRS.

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

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

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both 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*, provided the requirements of Roche's global policy on data sharing have been met*. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities

Screening through Week 52 and Early Termination

		Visit Day		Visit Week													ET
	Screening	1[a]	7	4	8	12	16	20	24	28	32	36	40	44	48	52	Visit[b]
Visit Window (days)	–28 to –1	NA	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥28)
Main informed consent[c]	x																
Optional aqueous, vitreous and blood sample informed consent[c]	x	x															
Optional (RBR) residual samples and DNA whole blood sample informed consent[c]	x	x															
Review of inclusion and exclusion criteria	x	x															
Demographics (age, sex, and self-reported race/ethnicity)	x																
Medical and surgical history including tobacco history[d]	x																
Physical examination[e]	x																x
Body weight and height	x																
Vital signs[f]	x	x															x
NEI VFQ-25[g]		x							x							x	x
Refraction and BCVA[h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pre-treatment IOP[i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test[j, k]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

Screening through Week 52 and Early Termination

		Visit Day		Visit Week													ET
	Screening	1[a]	7	4	8	12	16	20	24	28	32	36	40	44	48	52	Visit[b]
Visit Window (days)	–28 to –1	NA	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥ 28)
Whole blood sample (hematology, coagulation [aPTT and PT], serum chemistry, and urinalysis)[j, l]	x	*x*[l]															
HbA_{1c}[j]	x															x	x
Optional aqueous humor sample *for biomarkers*[m]		x	x				x	x			x						x
Optional PK plasma sample (if aqueous humor sample is collected)[j, m]			*x*								*x*						
Optional PD plasma sample (if aqueous humor sample is collected)[j, m]			*x*								*x*						
Optional vitreous humor sample *for biomarkers*[n]		Can be collected if vitrectomy is necessary															
Optional PK plasma sample (if vitreous humor sample is collected)[j, n]		*Collect PK sample if vitreous humor sample is collected*															
Optional whole blood sample for DNA[j, o]		x															
*Mandatory p*lasma PK sample[j, p]		x		x						x						x	x
*Mandatory p*lasma PD sample[j, p]		x		x						x						x	x

Appendix 1
Schedule of Activities (cont.)

Screening through Week 52 and Early Termination

		Visit Day		Visit Week													ET
	Screening	1[a]	7	4	8	12	16	20	24	28	32	36	40	44	48	52	Visit[b]
Visit Window (days)	–28 to –1	NA	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥ 28)
*Mandatory p*lasma ADA sample [j, p]		x		x						x						x	x
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [q]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Optional OCT-A [q, r]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
FFA [q]	(x) [q]	x					x									x	x
CFP [q]	x						x									x	x
[redacted] [q]	x	(x) [q]					x									x	x
Administration of study treatment [s]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Finger-counting test [t]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	
IOP (post-study treatment) [u]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events [v]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [w]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [x]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA=anti-drug antibody; Ang-2=angiopoietin-2; BCVA=best-corrected visual acuity; CFP=color fundus photograph; *CRC = central reading center;* DME=diabetic macular edema; eCRF=electronic Case Report Form; ET=early termination; FFA=fundus fluorescein angiography; HbA_{1c}=hemoglobin A_{1c}; ICF = Informed Consent Form; IOP=intraocular pressure; NEI VFQ-Q25=National Eye Institute 25-Item Visual Functioning Questionnaire; OCT-A=optical coherence tomography–angiography; PD=pharmacodynamic; PK=pharmacokinetic; RBR=Research Biosample Repository; SD-OCT=spectral-domain optical coherence tomography; SOC=standard of care; [redacted] VA=visual acuity; VEGF-A=vascular endothelial growth factor–A.

Appendix 1
Schedule of Activities (cont.)

Screening through Week 52 and Early Termination

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day, except those at screening. All study visits will be scheduled relative to the date of the Day 1 visit (first study treatment). *For the study visits windows, the sites should utilize patient's study visit calculator posted on DrugDev.*

There must be a minimum of 21 days between study treatment visits occurring from the Day 1 visit through the Week 96 visit. The final study visit at Week 100 should not occur earlier than 28 days after the last study treatment. *The fellow eye anti-VEGF* treatment *approved by the country regulatory agency for ocular use* may be *covered* by the Sponsor as long as the patient remains in the study (see Section 4.4.1). *The fellow eye anti-VEGF* treatments after the ET visit or the final study visit (Week 100) will not be *covered* by the Sponsor.

[a] The screening and Day 1 (randomization) visits may occur as a combined visit if all assessments are completed and evaluated within 2 business days. *The following two conditions must be met for the combined visit to occur: prior communication with the CRC so the screening images are evaluated in expedited manner; and availability of the historical HbA_{1c} data (obtained within 2 months prior to Day 1 visit; it is permissible to use site's own HbA_{1c} analyzer with print-out results). There is no need to wait for Covance sample results.* When screening and randomization are combined and performed in 1 day, assessments listed for both visits should be conducted only once. If the combined visit is conducted within 2 business days, then the following safety assessments will be repeated on the day of patient's randomization and study treatment administration: *urine pregnancy test (if applicable),* slitlamp examination, indirect ophthalmoscopy, and pre-treatment IOP measurements (recorded on the Day 1 eCRF and dated accordingly). *Verify that patient did not start on any prohibited medication.*

[b] Patients who are discontinuing from the study early (prior to the final study visit at Week 100) but have not withdrawn consent should return for an ET visit after a minimum of 28 days have elapsed following their last study treatment.

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

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

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

[f] Vital signs include measurement of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure; at the Day 1 visit, vital signs should be recorded before study treatment. Vital signs will be measured with the patient in a seated position after resting for 5 minutes.

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

Appendix 1
Schedule of Activities (cont.)

Screening through Week 52 and Early Termination

[h] Perform the assessments prior to dilating the eyes. *Both refraction and BCVA will be assessed at every study visit for both eyes. However, only study eye refraction from the Day 1, Week 56 and Week 96 visits will be entered on the refraction-specific eCRF. The BCVA assessment data for both eyes will be entered on the BCVA-specific eCRF from every study visit.* ***The study eye visual acuity score from each study treatment visit must be entered to IxRS after each visit; IxRS needs the data to assign the correct study treatment at future visits.***

[i] Perform the assessments prior to dilating the eyes at screening and at each study visit, and if applicable, at the ET visit.

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

[k] Starting *at screening*, collect and perform the urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, collect the serum pregnancy sample and forward it to the central laboratory for testing. If the serum pregnancy test is positive, do not administer study treatment.

[l] Hematology includes hemoglobin, hematocrit, quantitative platelet count, RBC counts, WBC counts, and differentials, including neutrophils, lymphocytes, bands, eosinophils, basophils, and monocytes (absolute). Serum chemistry panel includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, ALP, AST, ALT, and uric acid. Urinalysis includes specific gravity, pH, blood, protein, ketones, glucose, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal). If the screening and Day 1 (randomization) visits occur as a combined visit, a historic HbA_{1c} value must be available from within 2 months prior to Day 1. *If the screening and Day 1 visits are performed separately, then these samples collections can be done at either visit based on investigator judgment, but historical (obtained within 2 months of Day 1 visit) or current HbA_{1c} results must be available at Day 1 prior to randomization to confirm eligibility.*

[m] If a patient consents to collection of optional aqueous humor sample, collect the sample at indicated timepoints prior to study treatment administration. *It is permissible to collect aqueous humor sample after FFA was performed at applicable visits. Associated optional PK and PD plasma samples have to be collected at the Day 7 and Week 32 visits. See the central lab manual for additional details. Not applicable for a site that has not been granted approval by a site's Institutional Review Board or Ethics Committee.*

[n] If vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. *Associated* PK blood sample (for plasma preparation) should also be collected and shipped to the *central lab*. Vitreous humor *and PK* samples will be analyzed primarily for faricimab concentrations and may also be analyzed for aflibercept concentrations. The remaining samples may be analyzed for [redacted] and possibly other biomarkers.

[o] If the optional whole blood DNA sample is not obtained at the assigned visit (Day 1), the sample may be collected at any subsequent study visit when a blood draw is being performed for other purposes as specified (e.g., PK, 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.

[p] *At specified visits, the mandatory plasma PK, PD, and ADA samples will be collected prior to FFA assessment (if applicable) and prior to study treatment.*

Appendix 1
Schedule of Activities (cont.)

Screening through Week 52 and Early Termination

[q] The CRC will review SD-OCT *(certain SS-OCT equipment may be acceptable; consult CRC) and 7-modified field or 4-wide field* CFP images obtained at screening for determination of patient eligibility. [redacted] outputs from all types of imaging assessments will be sent to the relevant CRC. *The preferred method for FFA collection is UWF (Optos) at sites with capability, and 7 or 4-wide fields at all the other sites.* See the CRC manual for additional details. *The baseline FFA may be obtained either at screening or the Day 1 visit, but it is recommended to obtain it at the Day 1 visit if both eyes appear eligible to become the study eye. The FFA images should be obtained after lab samples have been collected.* **Note:** After randomization, if a patient misses a study visit when *CFP or FFA* ocular images are scheduled *or these images are not taken at the scheduled visit (e.g. equipment is broken)*, the*y must* be obtained at the next scheduled visit the patient attends. ***Please remember to forward OCT images to the CRC immediately after the visit as they need to be evaluated and data submitted to the IxRS by the CRC before the next study visit. If the OCT image was missed due to a missed visit or not taken, then notify the CRC immediately so they can inform IxRS that the expected data will not be available.***

[r] To be conducted at sites with OCT-A capability.

[s] At study treatment visits, randomized patients will receive *faricimab* at some visits and sham at other visits or aflibercept at some visits and sham at other visits. The timing of these treatments will depend on the treatment arm to which they are randomized, which will be masked.

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

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

[v] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment (Day 1), all adverse events will be reported until the final study visit or if applicable until the ET visit. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event 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.

[w] 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 within 7 days preceding Day 1 and through the conclusion of the patient's study participation or ET visit.

[x] Record all concurrent ocular procedures performed on the study or non–study eye between the Day 1 visit after study treatment and the final study visit or ET visit.

Appendix 1
Schedule of Activities (cont.)

Week 56 through Week 100 and Early Termination

	Week Visit												ET Visit [a]
	56	60	64	68	72	76	80	84	88	92	96	100	
Visit Window (days)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥28 and <35)	(≥28)
Physical examination [b]												x	x
Vital signs [c]												x	x
NEI VFQ-25 [d]												x	x
Refraction and BCVA [e]	x	x	x	x	x	x	x	x	x	x	x	x	x
Pre-treatment IOP [f]	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [g, h]	x	x	x	x	x	x	x	x	x	x	x	x	x
Whole blood sample (hematology, coagulation [aPTT and PT], serum chemistry, and urinalysis) [g, i]	x												
HbA_{1c} [g]												x	x
Optional aqueous humor sample *for biomarkers* [j]						x	x	x	x				x

Appendix 1
Schedule of Activities (cont.)

Week 56 through Week 100 and Early Termination

	Week Visit												ET Visit [a]
	56	60	64	68	72	76	80	84	88	92	96	100	
Visit Window (days)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥28 and <35)	(≥28)
Optional vitreous humor sample *for biomarkers* [k]	Can be collected if vitrectomy is necessary.												
Optional PK plasma sample (if vitreous humor sample is collected) [g,k]	*Collect PK sample if vitreous humor sample is collected*												
Mandatory plasma PK sample [g]						*x*						*x*	*x*
*Mandatory p*lasma PD sample [g]						x						x	x
*Mandatory p*lasma ADA sample [g]						x						x	x
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x
Indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [l] *or SS-OCT (if applicable)*	x	x	x	x	x	x	x	x	x	x	x	x	x
Optional OCT-A [l, m]	x	x	x	x	x	x	x	x	x	x	x	x	x
FFA [l]											x		x
CFP [l]											x		x
[redacted] [l]											*x*		*x*
Administration of study treatment [n]	x	x	x	x	x	x	x	x	x	x	x		
Finger-counting test [o]	x	x	x	x	x	x	x	x	x	x	x		
IOP post-treatment [p]	x	x	x	x	x	x	x	x	x	x	x		

Appendix 1
Schedule of Activities (cont.)

Week 56 through Week 100 and Early Termination

	Week Visit												ET Visit [a]
	56	60	64	68	72	76	80	84	88	92	96	100	
Visit Window (days)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥28 and <35)	(≥28)
Adverse events [q]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [r]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [s]	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA=anti-drug antibody; BCVA=best-corrected visual acuity; CFP=color fundus photograph; DME=diabetic macular edema; eCRF=electronic Case Report Form; ET=early termination; FFA=fundus fluorescein angiography; HbA_{1c}=hemoglobin A_{1C}; IOP=intraocular pressure; NEI VFQ-Q25=National Eye Institute 25-Item Visual Functioning Questionnaire; OCT-A=optical coherence tomography–angiography; PD=pharmacodynamic; PK=pharmacokinetic; SD-OCT=spectral-domain optical coherence tomography; SOC=standard of care; [redacted] VA=visual acuity; VEGF-A=vascular endothelial growth factor–A.

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day. All study visits will be scheduled relative to the date of the Day 1 visit (first study treatment). There must be a minimum of 21 days between all study treatment visits occurring at the Day 1 visit through the Week 100 visit.

The fellow eye anti-VEGF treatment *approved by the country regulatory agency for ocular use* may be *covered* by the Sponsor as long as the patient remains in the study (see Section 4.4.1). *The fellow eye anti-VEGF* treatment after the ET visit or the final study visit (Week 100) will not be *covered* by the Sponsor.

[a] Patients who are discontinuing from the study early (prior to the final study visit at Week 100) but have not withdrawn consent should return for an ET visit after a minimum of 28 days have elapsed following the last study treatment.

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

[c] Vital signs include measurement of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure; at the Day 1 visit, vital signs should be recorded before study treatment. Vital signs will be measured with the patient in a seated position after resting for 5 minutes.

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

Appendix 1
Schedule of Activities (cont.)

Week 56 through Week 100 and Early Termination

[e] Perform the assessments prior to dilating the eyes. *Both refraction and BCVA will be assessed at every study visit for both eyes. However, only study eye refraction from the Day 1, Week 56 and Week 96 visits will be entered on the refraction-specific eCRF. The BCVA assessment data for both eyes will be entered on the BCVA-specific eCRF from every study visit.* ***The study eye visual acuity score from each study treatment visit must be entered to IxRS at the visit; IxRS needs the data to assign the correct study treatment at future visits.***

[f] Perform the assessments prior to dilating the eyes *and* prior to study treatment.

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

[h] Starting *at screening*, collect and perform the urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, collect the serum pregnancy sample and forward it to the central laboratory for testing. If the serum pregnancy test is positive, do not administer study treatment.

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

[j] If a patient consents to collection of optional aqueous humor sample, collect the sample at indicated timepoints prior to study treatment administration. *It is acceptable to collect aqueous sample after FFA was performed at applicable visits.* Not applicable for a site that has not been granted approval by a site's Institutional Review Board or Ethics Committee.

[k] If vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. *Associated* PK blood sample (for plasma preparation) should also be collected and shipped to the *central lab*. Vitreous humor *and PK* samples will be analyzed primarily for faricimab concentrations and may also be analyzed for aflibercept concentrations. The remaining samples may be analyzed for [redacted] and possibly other biomarkers.

[l] The outputs from imaging assessments will be sent to the CRC. See the CRC manual for additional details. Note: After randomization, if a patient misses a study visit when ocular *CFP* [redacted] *and FFA* images are scheduled *or these images are not taken at the scheduled visit (e.g. equipment is broken)*, the*y must* be obtained at the next scheduled visit the patient attends. ***Please remember to forward OCT images to the CRC immediately after the visit as they need to be evaluated and data submitted to the IxRS by the CRC before the next study visit. If the OCT image was missed due to a missed visit or not taken, then notify the CRC immediately so they can inform IxRS that the expected data will not be available.***

[m] To be conducted at sites with OCT-A capability.

Appendix 1
Schedule of Activities (cont.)

Week 56 through Week 100 and Early Termination

[n] At study treatment visits, randomized patients will receive study drug at some visits and sham at other visits or aflibercept at some visits and sham at other visits. The timing of these treatments will depend on the treatment arm to which patients are randomized, which will be masked.

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

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

[q] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment (Day 1), all adverse events will be reported until *the patient's last or final study visit or, if applicable, until the ET visit*. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event 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.

[r] Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications such as proparacaine, etc.) used by the patient within 7 days preceding Day 1 and through the conclusion of the patient's study participation or the ET visit.

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

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 [e]
Ocular imaging, as necessary

IOP = intraocular pressure.

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

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

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

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

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

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

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

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

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

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

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

Appendix 4
Refraction and Best-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, Week 56, and Week 96 visit will be entered to Refraction specific 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 arm assignment. VA will be measured at the intervals specified in the protocol (see Appendix 1).

EQUIPMENT

The following are needed to conduct the examination:

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

TRAINING AND CERTIFICATION

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

Appendix 5
Color Fundus Photography

SCOPE

Stereo color fundus photographs *using 7-modified field or 4-wide field imaging* will be obtained from both eyes by trained personnel at the study sites. Fundus photography will be performed *at baseline (screening) and* at the intervals specified in the schedule of activities (see Appendix 1). Analysis (if applicable) of fundus photographs will be performed by the central reading center *(CRC)*.

[redacted]

EQUIPMENT

See the CRC manual.

PROCEDURE

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

Appendix 6
Fundus Fluorescein Angiography

SCOPE

Fundus fluorescein angiography *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 trained personnel who are certified by the central reading center *(CRC)*. The fundus fluorescein angiograms will be obtained at *baseline (at screening or on Day 1) and at* the intervals specified in the protocol (see Appendix 1). Analysis (if applicable) of fundus fluorescein angiograms will be performed by the CRC.

EQUIPMENT

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

Film-based angiography is not acceptable.

UWF (Optos) is the preferred method for fundus fluorescein angiography (FFA) capture. The study sites without Optos 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. This certification and validation process will ensure that the CRC will be able to correctly calculate the required measurements.

PROCEDURES

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

Appendix 7
Spectral-Domain Optical Coherence Tomography

SCOPE

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

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

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

EQUIPMENT

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

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

PROCEDURES AND CERTIFICATION

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

Appendix 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 urinalysis), hemoglobin A_{1c} (HbA_{1c}), 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 treating physician from patients who consent to the procedure and sample acquisition. An aqueous humor sample will be collected before the patient's study eye treatment at the visits as indicated in Appendix 1. Please refer to the central laboratory manual for additional details regarding sample collection and shipping information.

OPTIONAL UNSCHEDULED COLLECTION OF VITREOUS HUMOR SAMPLE COLLECTION

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

Appendix 8
Biological Sample Collection and Shipping Instructions (cont.)

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

Vitreous humor samples will be analyzed primarily for faricimab concentrations and may also be analyzed for aflibercept concentrations. The remaining samples may be analyzed for [redacted] and possibly other biomarkers.

BIOLOGICAL SAMPLES STORAGE DURATION

The hematology, serum chemistry, urinalysis, coagulation, serum, urine pregnancy tests, and HbA_{1c} samples will be destroyed after their analysis during the study.

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

Instructions:

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

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

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

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

(Circle One)

READ CATEGORIES:

Excellent	**1**
Very Good	**2**
Good	**3**
Fair	**4**
Poor	**5**

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

(Circle One)

READ CATEGORIES:

Excellent	**1**
Good	**2**
Fair	**3**
Poor	**4**
Very Poor	**5**
Completely Blind	**6**

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

		(Circle One)
READ CATEGORIES:	**None of the time**	**1**
	A little of the time	**2**
	Some of the time	**3**
	Most of the time	**4**
	All of the time?	**5**

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

		(Circle One)
READ CATEGORIES:	**None**	**1**
	Mild	**2**
	Moderate	**3**
	Severe, or	**4**
	Very severe?	**5**

PART 2 - DIFFICULTY WITH ACTIVITIES

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

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

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

(Circle One)

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

No..... 2

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

(Circle One)

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

Gave up 2

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

(Circle One)

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

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

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

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

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

(Circle One)

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

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

(Circle One)

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

PART 3: RESPONSES TO VISION PROBLEMS

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

(Circle One On Each Line)

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

(Circle One On Each Line)

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

SUBSCALE: NEAR VISION

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

(Circle One)

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

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

(Circle One)

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

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

Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

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

SUBSCALE: DISTANCE VISION

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

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

Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

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

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

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

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

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

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol GR40349 has been amended to include additional prohibited medications (Section 4.4.2) and more detailed examples of contraceptive methods for females of childbearing potential (Section 4.1.1.1) to enhance patient safety and to comply with health authority requests, enabling this protocol to be conducted globally.

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

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR–CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RO6867461 IN PATIENTS WITH DIABETIC MACULAR EDEMA (YOSEMITE)**
PROTOCOL NUMBER:	GR40349
VERSION NUMBER:	1
EUDRACT NUMBER:	2017-005104-10
IND NUMBER:	119225
TEST PRODUCT:	RO6867461
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	04-Jun-2018 21:17:00

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR–CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RO6867461 IN PATIENTS WITH DIABETIC MACULAR EDEMA (YOSEMITE)**
PROTOCOL NUMBER:	GR40349
VERSION NUMBER:	1
EUDRACT NUMBER:	2017-005104-10
IND NUMBER:	119225
TEST PRODUCT:	RO6867461
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR–CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RO6867461 IN PATIENTS WITH DIABETIC MACULAR EDEMA (YOSEMITE)**
PROTOCOL NUMBER:	GR40349
VERSION NUMBER:	1
EUDRACT NUMBER:	2017-005104-10
IND NUMBER:	119225
TEST PRODUCT:	RO6867461
PHASE:	Phase III
INDICATION:	Diabetic macular edema
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of RO6867461 when dosed every 8 weeks (Q8W) and with a personalized treatment interval (PTI) regimen compared with aflibercept (Eylea®) monotherapy in patients with diabetic macular edema (DME). Specific objectives and corresponding endpoints for the study are outlined in the following table.

Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of IVT injections of the 6-mg dose of RO6867461 on BCVA outcomes	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) at 1 year [a]
Key Secondary Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of RO6867461 on DR severity outcomes	• Proportion of patients with a ≥2-step DRS improvement from baseline on the ETDRS DRSS at Week 52
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of RO6867461 on additional BCVA outcomes	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) over time • Proportion of patients gaining ≥15, ≥10, ≥5, or ≥0 letters in BCVA from baseline over time • Proportion of patients avoiding a loss of ≥15, ≥10, ≥5, or >0 letters in BCVA from baseline over time • Proportion of patients gaining ≥15 letters or achieving BCVA of ≥84 letters over time • Proportion of patients with BCVA Snellen equivalent of 20/40 or better over time • Proportion of patients with BCVA Snellen equivalent of 20/200 or worse over time
• To evaluate the efficacy of RO6867461 on additional DR outcomes	• Proportion of patients with a ≥2-step DRS improvement from baseline on the ETDRS DRSS over time • Proportion of patients with a ≥3-step DRS improvement from baseline on the ETDRS DRSS over time • Proportion of patients who develop new PDR over time
• To evaluate RO6867461 treatment intervals in the PTI arm	• Proportion of patients in the PTI arm on a Q4W, Q8W, Q12W, or Q16W treatment interval at 1 year and 2 years • Treatment intervals in the PTI arm over time

Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate the efficacy of RO6867461 on anatomical outcome measures using SD-OCT	• Change from baseline in CST over time • Proportion of patients with absence of DME (CST <325 μm for Spectralis SD-OCT, or <315 μm for Cirrus SD-OCT or Topcon SD-OCT) over time • Proportion of patients with absence of intraretinal fluid over time • Proportion of patients with absence of subretinal fluid over time • Proportion of patients with absence of intraretinal fluid and subretinal fluid over time
• To evaluate the efficacy of RO6867461 on patient-reported vision-related functioning and quality of life using the NEI VFQ-25	• Change from baseline in NEI VFQ-25 composite score over time
Safety Objective	**Corresponding Endpoints**
• To evaluate the ocular and systemic safety and tolerability of RO6867461	• Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To further evaluate the efficacy of RO6867461 on additional DR outcomes	• Proportion of patients with a ≥2-step or ≥3-step DRS worsening from baseline on ETDRS DRSS over time • Proportion of patients who receive vitrectomy or PRP over time during the study
• To further evaluate the efficacy of RO6867461 on anatomical outcome measures using FFA and/or OCT-A	• Change from baseline in total area of macular non-perfusion and macular ischemia over time • Change from baseline in total area of vascular leakage over time • Proportion of patients with resolution of macular leakage over time • Change from baseline CST neurosensory over time (as measured on SD-OCT) • Change from baseline in total macular volume over time (as measured on SD-OCT)

Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objectives (cont.)	Corresponding Endpoints (cont.)
• To further evaluate the efficacy of RO6867461 on patient-reported vision-related functioning and quality of life using the NEI VFQ-25	• Change from baseline in the NEI VFQ-25 Near Activities, Distance Activities, and Driving subscales at 1 year [a] • Proportion of patients with a ≥ 4-point improvement from baseline in NEI VFQ-25 composite score
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the systemic pharmacokinetics of RO6867461	• Plasma concentration of RO6867461 over time
Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to RO6867461 • To evaluate potential effects of ADAs	• Presence of ADAs during the study relative to the presence of ADAs at baseline • Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives	**Corresponding Endpoints**
• To identify biomarkers that are predictive of response to RO6867461, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of RO6867461 activity, or can increase the knowledge and understanding of disease biology	• Concentration of biomarkers of angiogenesis and inflammation in aqueous humor (optional) at baseline and over time and their correlation with PK and/or primary and secondary endpoints at baseline and over time • Relationship between efficacy, safety, PK, immunogenicity, [redacted] • Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., the frequency of study drug administration) over time • Relationship between anatomic measures and visual acuity

Objectives and Corresponding Endpoints (cont.)

Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate potential relationships between selected covariates and exposure to RO6867461	• Relationship between selected covariates and plasma or aqueous humor (optional) concentration or PK parameters for RO6867461
• To characterize the aqueous humor (optional) and vitreous (optional) pharmacokinetics of RO6867461	• Aqueous humor (optional) and vitreous (optional) concentration of RO6867461 over time
• To evaluate the drug concentration [redacted]	• [redacted]
• To explore the concentration–effect relationship for visual acuity and other endpoints (e.g., anatomical markers)	• Pharmacokinetics of RO6867461 and the change in BCVA or other endpoints (e.g., anatomical markers) over time

ADA=anti-drug antibody; [redacted];
BCVA=best-corrected visual acuity; CST=central subfield thickness; DR=diabetic retinopathy; DRS=diabetic retinopathy severity; DRSS=Diabetic Retinopathy Severity Scale; ETDRS=Early Treatment Diabetic Retinopathy Study; FFA=fundus fluorescein angiography; IVT=intravitreal; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT-A=optical coherence tomography–angiography; PDR=proliferative diabetic retinopathy; PK=pharmacokinetic; PRP=panretinal photocoagulation; PTI=personalized treatment interval; Q4W = every 4 weeks; Q8W=every 8 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks; SD-OCT=spectral-domain optical coherence tomography; [redacted]

The definition of 1 year for the primary endpoint is the average of the Week 48, 52, and 56 visits.

Study Design

Description of Study

This is a Phase III, double-masked, multicenter, randomized, active comparator–controlled, parallel-group study, evaluating the efficacy, safety, pharmacokinetics, and optimal treatment frequency of RO6867461 administered by intravitreal (IVT) injection at 8-week intervals or PTI of approximately 100 weeks' duration (excluding the screening period) to patients with DME.

Overview of Study Design

Approximately 900 patients will be randomized during the global enrollment phase of the study in a 1:1:1 ratio to one of three treatment arms at approximately 240 investigational sites globally. The study will randomize patients with DME who are naive to anti–vascular endothelial growth factor (anti-VEGF) therapy in the study eye and patients who have previously been treated with anti-VEGF therapy in the study eye, provided that the last treatment was at least 3 months prior to the Day 1 visit (the first study treatment). Site investigators will be retina specialists or the equivalent outside of the United States.

The study treatment arms will be as follows:

- Arm A (administered every 8 weeks [Q8W]) (n=300): Patients randomized to Arm A will receive 6-mg IVT RO6867461 injections every 4 weeks (Q4W) to Week 20, followed by 6-mg IVT RO6867461 injections Q8W to Week 96, followed by the final study visit at Week 100.
- Arm B (PTI) (n=300): Patients randomized to Arm B will receive 6-mg IVT RO6867461 injections every 4 weeks (Q4W) to at least Week 12, followed by PTI dosing (see the PTI dosing criteria below) of 6-mg IVT RO6867461 injections to Week 96, followed by the final study visit at Week 100.
- Arm C (comparator arm) (administered Q8W) (n=300): Patients randomized to Arm C will receive 2-mg IVT aflibercept injections Q4W to Week 16, followed by 2-mg IVT aflibercept injections Q8W to Week 96, followed by the final study visit at Week 100.

Patients in all three treatment arms will complete scheduled study visits Q4W for the entire study duration (100 weeks). A sham procedure will be administered to patients in all three treatment arms at applicable visits to maintain masking among treatment arms.

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

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

The study will consist of a screening period of up to 28 days (Days −28 to −1) in length and an approximately 96-week treatment period, followed by the final study visit at Week 100.
A unique screening number will be assigned to each screened patient through an interactive voice or web-based response system (IxRS).

Screening

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

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

The screening and Day 1 (randomization) visits may occur as a combined visit if all assessments are completed and evaluated on the same day or within 2 business days. When screening and the Day 1 visit are completed on the same day, the assessments listed for both visits should be conducted only once. A historic hemoglobin A_{1c} (HbA_{1c}) value must be available from within 2 months of Day 1 to enable screening and randomization to occur on the same day. If a historic value is used, receipt of screening laboratory results would not be required prior to randomization. If the screening and Day 1 visit are not completed on the same day (but rather within 2 business days), the following safety assessments will be repeated on the day of patient's randomization and study treatment administration: slitlamp examination, indirect ophthalmoscopy, and pre- and post-treatment intraocular pressure (IOP) measurements (recorded on the Day 1 electronic Case Report Form [eCRF] and dated accordingly).

[redacted]

After screening has been completed, eligible patients will have a randomization identification number assigned through the IxRS and will be randomized in a 1:1:1 ratio in order that approximately 300 patients are randomized to each of the three treatment arms.
Randomization will be stratified by baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score, as assessed on Day 1 (64 letters or better vs. 63 letters or worse), prior

IVT anti-VEGF therapy (yes vs. no), and region (United States and Canada, Asia, and the rest of the world).

Randomization and Visit Schedule

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

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

Starting at the Day 1 visit, randomized patients will have study treatment administered Q4W by the unmasked investigator that will be followed by the safety assessments (finger-counting test and post-dose IOP measurement). After the Day 1 visit, patients will also have safety assessments evaluated by the masked investigator prior to receiving study treatment. Patients will be instructed to contact the study site at any time if they have any health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit.

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

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

Note: After the Day 1 visit, if a patient misses a study visit when ocular images are to be obtained, the images must be obtained at the next scheduled visit the patient attends.

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

For study masking requirements, see Section 4.2.

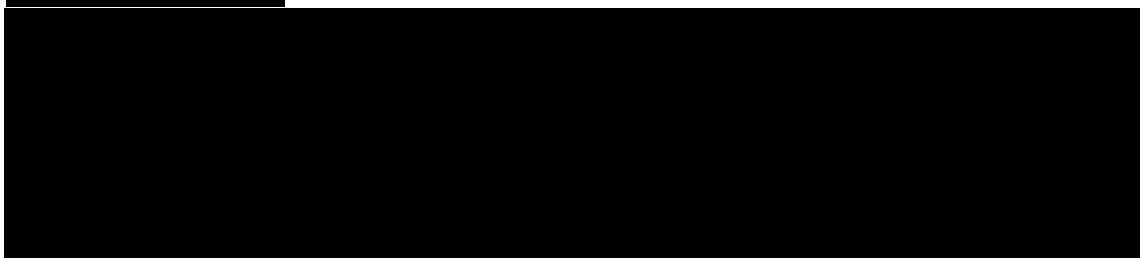
Patients who are prematurely discontinued from study treatment but who agree to continue to participate in the study will be encouraged to undergo as many scheduled visits as possible, with emphasis on completing the Week 48, 52, 56, and 100 visits.

Study treatment visits will be scheduled Q4W (±7 days) relative to the Day 1 visit date.

Patients who discontinue from the study prior to completion will be asked to return for an early termination visit after a minimum of 28 days have elapsed following their last study treatment for monitoring of adverse events and early termination visit assessments.

Patients who complete study treatment (i.e., the Week 96 visit) will return for the final study visit (Week 100) after a minimum of 28 days have elapsed from their last study treatment for monitoring of adverse events and final study visit assessments.

[redacted]



Treatment Schedule for Patients in the Personalized Treatment Interval Arm (Arm B)

Study drug dosing interval decisions in the PTI arm are automatically calculated by the IxRS based on the algorithm described in this section. Study drug dosing visits are visits when a patient is assigned to receive RO6867461.

Study Drug Dosing Interval Determination

Patients randomized to the PTI arm (Arm B) will be treated with RO6867461 on a Q4W dosing interval until the patient's Week 12 visit or later CST meets the predefined reference central subfoveal thickness (CST) threshold (CST <325 μm for Spectralis SD-OCT, or <315 μm for

Cirrus SD-OCT or Topcon SD-OCT). The reference CST is used at study drug dosing visits by the IxRS for interval decision-making.

After a patient's initial reference CST is established, their study drug dosing interval will be increased by 4 weeks to an initial Q8W dosing interval by the IxRS. From this point forward, the study drug dosing interval will be extended, reduced, or maintained based on assessments made at study drug dosing visits. See Section 3.1.2.1, Figure 2, for the algorithm used by the IxRS for interval decision-making, which is based on the relative change of the CST and BCVA compared with reference CST and BCVA.

Study Drug Dosing Intervals

The IxRS can adjust the study drug dosing interval by 4-week increments to a maximum of every 16 weeks (Q16W) and a minimum of Q4W.

Patients whose drug dosing interval is reduced from Q16W to a shorter interval because of disease activity will not be allowed to return to a Q16W interval but may be eligible for Q12W, Q8W, or Q4W interval, depending on disease activity.

Patients whose drug dosing interval is reduced from Q16W to a shorter interval because of study treatment interruption at the study drug dosing visit will be allowed to re-initiate the Q16W interval.

Similar to Arms A and C, patients randomized to the PTI arm (Arm B) will receive a sham procedure at study visits when they are not receiving treatment with RO6867461.

Additional Considerations for PTI Arm IxRS Study Drug Dosing Interval Decision

Sites will report missed study visits (except of Day 7 visit) and study drug interruption visits to the IxRS for all patients (Arms A, B, and C) to preserve the masking. The following algorithms are only applicable to patients in the PTI arm (Arm B) and are used by the IxRS to automatically determine study drug intervals in the event of the following situations.

Missed Study Drug Dosing Visit(s)

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

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

Study Drug Interruption at Study Drug Dosing Visit(s)

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

Missing CST Value at Study Drug Dosing Visit

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

Missing BCVA Value at Study Drug Dosing Visit

If a patient attends a study drug dosing visit, but the BCVA value is not available for any reason (e.g., patient refuses BCVA examination), the IxRS will assign the patient to receive study drug at that visit. The IxRS will base the study drug dosing interval determination on CST only.

Missed Study Drug Treatment Visit(s) for Patients in the Q8W Treatment Arms

If a patient randomized to treatment Arm A (RO6867461 Q8W) or Arm C (aflibercept Q8W) misses study drug treatment visit(s), the IxRS will assign the patient to receive RO6867461 or aflibercept at the next study visit he or she attends. The Q8W drug treatment interval will be automatically reset by IxRS from that visit forward, thus 4 weeks later, at the following study visit, the patient will receive sham.

Timely Reporting of BCVA Scores, CST Values, Missed Study Treatment Visits, or Study Treatment Interruptions for All Study Patients

Starting at the Day 1 visit, patients' BCVA scores in all randomized treatment arms (Arms A, B, and C) from each study treatment visit have to be reported by the sites to the IxRS in a timely manner (ideally, within 24 hours of obtaining them). Similarly, OCT images obtained at each study treatment visit have to be forwarded to the central reading center in a timely manner (ideally, within 24 hours of obtaining them). Sites will report in a timely manner in the IxRS the study treatment visits that patients miss. Sites will report in the IxRS the study treatment interruption(s) in order that the correct study treatment (study drug or sham) can be assigned by the system to a patient for a future study treatment visit.

Independent Data Monitoring Committee

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

The iDMC will meet approximately every 6 months (frequency adjustable if required) to evaluate unmasked ocular and systemic (non-ocular) safety events with an emphasis on the evaluation of the rate of ocular inflammation, increased IOP, endophthalmitis, arterial thromboembolic events, and clinically significant decreases in BCVA, which will be prepared for the committee by an independent Data Coordinating Center (iDCC). The iDMC may recommend stopping the study early for safety reasons.

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

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

Number of Patients

Approximately 900 patients will be randomized during the global enrollment phase of the study.

Target Population

Inclusion Criteria

Patients must meet the following inclusion criteria for study entry.

General Inclusion Criteria

Patients must meet the following general inclusion criteria for study entry:

- Willingness and the ability to provide signed informed consent

  Additionally, at U.S. sites, patients must provide Health Insurance Portability and Accountability Act authorization, and in other countries, as applicable according to national laws.
- Age ≥18 years
- Documented diagnosis of diabetes mellitus (Type 1 or Type 2), as defined by the American Diabetes Association or per WHO criteria and
  - Current regular use of insulin for the treatment of diabetes

    and/or
  - Current regular use of oral anti-hyperglycemic agents for the treatment of diabetes

- HbA_{1c} of ≤10% within 2 months prior to the Day 1 visit date
- Ability and willingness to undertake all scheduled visits and assessments
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods during the treatment period and for at least 3 months after the final dose of study treatment

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

  The following are acceptable contraceptive methods: bilateral tubal ligation, male sterilization; hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

  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.
- [redacted]

Ocular Inclusion Criteria for Study Eye

Patients must meet the following ocular inclusion criteria for the study eye for entry in the study:

- Macular thickening secondary to DME involving the center of the fovea with CST ≥325 μm, as measured on Spectralis SD-OCT, or ≥315 μm, as measured on Cirrus SD-OCT or Topcon SD-OCT at screening
- BCVA of 73 to 25 letters, inclusive (20/40 to 20/320 approximate Snellen equivalent), using the ETDRS protocol at the initial testing distance of 4 meters (see the BCVA manual for additional details) on Day 1
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality CFPs (including ETDRS 7 modified fields or 4 wide-angle fields to permit grading of diabetic retinopathy and assessment of the retina) and other imaging modalities.

Exclusion Criteria

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

General Exclusion Criteria

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

- Currently untreated diabetes mellitus or previously untreated patients who initiated oral anti-diabetic medication or insulin within 3 months prior to Day 1
- History of allergy or hypersensitivity to active drug aflibercept and any of its excipients, fluorescein, or any study treatment–related mandatory ingredients (e.g., disinfectants, anesthetics, etc.; see the pharmacy manual for additional details) that is not amenable to treatment
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the RO6867461 or to aflibercept injections, study treatment procedure, dilating drops, or any of the anesthetic and antimicrobial drops used by a patient during the study
- Active cancer within the past 12 months except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of <6 and a stable prostate-specific antigen for >12 months
- Systemic treatment for suspected or active systemic infection

  Ongoing use of prophylactic antibiotic therapy may be acceptable but has to be discussed with the Medical Monitor.

- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis within 6 months prior to Day 1 or anticipated to require hemodialysis or peritoneal dialysis at any time during the study
- History of other disease, other non-diabetic metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a condition that contraindicates the use of the RO6867461 or aflibercept or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator
- Uncontrolled blood pressure (defined as systolic >180 mmHg and/or diastolic >100 mmHg while a patient is at rest)

  If a patient's initial reading exceeds these values, a second reading may be obtained later the same day or on another day during the screening period. If the patient's blood pressure is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1.
- Cerebral vascular accident or myocardial infarction within 6 months prior to Day 1
- Pregnancy or breastfeeding, or intention to become pregnant during the study

  Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to initiation of study treatment. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Participation in an investigational trial that involves treatment with any drug or device (with the exception of vitamins and minerals) within 3 months prior to Day 1
- Administration of systemic pro-angiogenic treatments, such as VEGF-based therapies for the peripheral or coronary ischemia (e.g., limb ischemia or myocardial infarction) within 3 months or 5 half-lives prior to Day 1
- Inability to comply with study or follow-up procedures
- Requirement for continuous use of any medications and treatments indicated in Section 4.4.2, Prohibited Therapy

Ocular Exclusion Criteria for Study Eye

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

- High-risk proliferative diabetic retinopathy (PDR) in the study eye, using any of the following established criteria for high-risk PDR:
  - Any vitreous or pre-retinal hemorrhage
  - Neovascularization elsewhere ≥1/2 disc area within an area equivalent to the mydriatic ETDRS 7 fields on clinical examination or on CFPs
  - Neovascularization at disc ≥1/3 disc area on clinical examination
- Tractional retinal detachment, pre-retinal fibrosis, or epiretinal membrane involving the fovea or disrupting the macular architecture in the study eye
- Active rubeosis
- Uncontrolled glaucoma
- History of retinal detachment or macular hole (Stage 3 or 4)
- Aphakia or implantation of anterior chamber intraocular lens
- IVT anti-VEGF treatment within 3 months prior to Day 1 (applicable to patients whose study eyes were previously treated with IVT anti-VEGF agents) or any IVT anti-VEGF agents to study eye prior to Day 1 (applicable for patients who are treatment naive)
- Treatment with panretinal photocoagulation (PRP) within 3 months prior to Day 1
- Macular (focal or grid) laser within 3 months prior to Day 1
- Any cataract surgery or treatment for complications of cataract surgery with steroids or YAG (yttrium-aluminum-garnet) laser capsulotomy within 3 months prior to Day 1

- Any other intraocular surgery (e.g., corneal transplantation, glaucoma filtration, pars plana vitrectomy, corneal transplant, or radiotherapy)
- Any IVT or periocular (subtenon) corticosteroid treatment within 6 months prior to Day 1
- Any use of medicated intraocular implants, including Ozurdex®, within 6 months of Day 1
- Any use of Iluvien® implants at any time prior to Day 1
- Treatment for other retinal diseases that can lead to macular edema

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

Patients who meet the following exclusion criterion for the fellow eye (non–study eye) will be excluded from study entry:

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

Exclusion Criteria for Both Eyes

Patients who meet the following exclusion criterion for either eye will be excluded from study entry:

- Prior administration of IVT RO6867461 in either eye
- Any history of idiopathic or immune-mediated uveitis in either eye
- Active ocular inflammation or suspected or active ocular or periocular infection in either eye on Day 1

Concurrent Ocular Conditions Exclusion Criteria

Patients who meet the following exclusion criteria related to concurrent ocular conditions will be excluded from study entry:

- Any current or history of ocular disease other than DME that may confound assessment of the macula or affect central vision in the study eye (e.g., choroidal neovascularization, age-related macular degeneration, retinal vein occlusion, uveitis, angioid streaks, histoplasmosis, active or inactive cytomegalovirus, pathological myopia, retinal detachment, macular traction, macular hole, and other)
- Any current ocular condition which, in the opinion of the investigator, is currently causing or could be expected to contribute to irreversible vision loss due to a cause other than DME in the study eye (e.g., foveal atrophy, foveal fibrosis, pigment abnormalities, dense subfoveal hard exudates, or other non-retinal conditions)

End of Study

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

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, [redacted] The end of the study is expected to occur approximately 100 weeks after the last patient is randomized.

Length of the Study

The total length of the study [redacted] from screening of the first patient to the LPLV for patients from the global enrollment phase is expected to be approximately 46 months.

Investigational Medicinal Products

Test Products (Investigational Drugs)

Intravitreal RO6867461 Injections

The 6-mg dose of RO6867461 will be evaluated in this study and will be administered intravitreally to patients randomized to receive RO6867461 Q8W or PTI during the 96-week treatment period.

Patients randomized to receive Q8W treatment will be administered 15 IVT injections of RO6867461 during the 96-week treatment period. Treatment will consist of 6 initial injections (6 mg of RO6867461 Q4W to Week 20), followed by 9 maintenance injections (6 mg of RO6867461 Q8W between Week 24 and Week 96).

The number of IVT injections of RO6867461 administered to patients in the PTI arm will vary, but a minimum of 10 IVT injections of RO6867461 will be administered to patients during the 96-week treatment period. This will consist of minimum of 4 initiating injections (6 mg of RO6867461 Q4W to Week 12), followed by minimum of 6 maintenance injections (6 mg of RO6867461 between Week 16 and Week 96).

Comparator

Intravitreal Aflibercept Injections

A 2-mg dose of aflibercept (Arm C) will be administered intravitreally Q8W to patients randomized to the aflibercept treatment arm during the 96-week treatment period. Patients will receive 15 IVT injections of aflibercept during the 96-week treatment period. Treatment will consist of 5 initiating injections (2 mg of aflibercept Q4W to Week 16), followed by 10 maintenance injections (2 mg of aflibercept Q8W between Week 20 and Week 96).

Non-Investigational Medicinal Products

All three treatment arms (RO6867461 Q8W, RO6867461 PTI, and aflibercept Q8W) will maintain Q4W study visits for the 100-week study duration. To preserve the randomized treatment arm masking, patients will have the sham procedure performed at study treatment visits when they are not treated with either RO6867461 or aflibercept as applicable per their treatment arm schedule.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is the change from baseline in BCVA averaged over Weeks 48, 52, and 56. The BCVA outcome measure is based on the ETDRS visual acuity chart assessed at a starting distance of 4 meters.

The primary comparisons will be the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the RO6867461 arms (Q8W and PTI). Additional analyses based on the per-protocol population will also be conducted.

For the two RO6867461 arms (Q8W and PTI), the following three hypotheses will be tested for each treatment group separately at an overall significance level of $\alpha = 0.05$ using a graph-based testing procedure to control for the overall type I error rate:

- Non-inferiority of RO6867461 compared with aflibercept Q8W in the intent-to-treat (ITT) population
- Superiority of RO6867461 compared with aflibercept Q8W in the treatment-naive population
- Superiority of RO6867461 compared with aflibercept Q8W in the ITT population

If the tests for one treatment sequence are all positive, then $\alpha/2$ will be propagated to the beginning of the other treatment sequence, which will be tested at a significance level of $\alpha = 0.05$. Of note, non-inferiority will be tested one sided at half of the designated significance level.

The non-inferiority tests for the RO6867461 Q8W arm and the RO6867461 PTI arm compared with aflibercept Q8W arm will be conducted with a non-inferiority margin of 4 letters. For each RO6867461 group (Q8W or PTI) the null hypothesis,
H_0: $\mu^{RO6867461} - \mu^{aflibercept} \leq -4$ letters, and the alternative hypothesis,
H_a: $\mu^{RO6867461} - \mu^{aflibercept} > -4$ letters, will be tested, for which $\mu^{RO6867461}$ and $\mu^{aflibercept}$ are the expected change from baseline in BCVA averaged over Weeks 48, 52, and 56 for the treatment group in question (RO6867461 Q8W or PTI) and the active comparator (aflibercept Q8W), respectively.

The change from baseline averaged over Weeks 48, 52, and 56 will be compared between each RO6867461 arm and the aflibercept Q8W arm using a mixed-model repeated measures (MMRM) model. The model will include the change from baseline at Weeks 4–56 as the response variables and will include the categorical covariates of treatment group, visit,

visit-by-treatment group interaction, the continuous baseline value for the response variable (in this case, baseline BCVA), as well as randomization stratification factors as fixed effects. Comparisons between each RO6867461 arm and the aflibercept Q8W arm will be made using a composite contrast over Weeks 48, 52, and 56. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a heterogeneous compound symmetry or an AR(1) covariance structure may be fitted.

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

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

Determination of Sample Size

Determination of sample size is based on patients enrolled in the global enrollment phase. The global enrollment phase will enroll approximately 900 patients. Patients will be randomized in a 1:1:1 ratio to receive treatment with RO6867461 Q8W (Arm A), RO6867461 PTI (Arm B), or aflibercept Q8W (Arm C). The primary comparisons will be the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the RO6867461 arms (Q8W and PTI).

A sample size of approximately 300 patients in each arm will provide greater than 90% power to show non-inferiority of RO6867461 to aflibercept (pairwise comparisons between the active comparator and each of the RO6867461 arms) in the ITT population, using a non-inferiority margin of 4 letters and under the following assumptions:

- Standard deviation (SD) of 11 letters for the change from baseline in BCVA averaged over Week 48, Week 52, and Week 56
- Two-sample *t*-test
- 1.25% one-sided type I error rate
- 10% dropout rate

Assuming 75%–90% of patients recruited will be treatment naive, approximately 225–270 treatment-naive patients will be enrolled per arm. A sample size of 225–270 patients per arm will provide greater than 80% power to show a 3.5-letter superiority of RO6867461 over aflibercept (pairwise comparisons between the active comparator and each of the RO6867461 arms) in the treatment-naive population, using the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 2.5%.

Furthermore, a sample size of approximately 300 patients per arm will provide greater than 80% power to show a 3-letter superiority of RO6867461 over aflibercept (pairwise comparisons between the active comparator and each of the RO6867461 arms) in the ITT population, under the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 2.5%.

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

[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
Ang-2	angiopoietin-2
BCVA	best-corrected visual acuity
CFP	color fundus photograph
CI	center involvement
CST	central subfield thickness
DME	diabetic macular edema
DR	diabetic retinopathy
DRS	diabetic retinopathy severity
DRSS	Diabetic Retinopathy Severity Scale
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FFA	fundus fluorescein angiography
GCP	Good Clinical Practice
HbA_{1c}	hemoglobin A_{1c}
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IL-1b (-6)	interleukin-1b (-6)
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intent to treat
IVT	intravitreal
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MMRM	mixed-model repeated-measures (model)
nAMD	neovascular age-related macular degeneration
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire–25
NPDR	non-proliferative diabetic retinopathy
OCT-A	optical coherence tomography–angiography
PD	pharmacodynamic
PDR	proliferative diabetic retinopathy
PK	pharmacokinetic
PRO	patient-reported outcome
PRP	panretinal photocoagulation
PTI	personalized treatment interval
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
Q16W	every 16 weeks
RBR	Research Biosample Repository
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SOC	standard of care
SS-OCT	swept-source optical coherence tomography
ULN	upper limit of normal
VA	visual acuity
VEGF(-A)	vascular endothelial growth factor(–A)
[redacted]	[redacted]
YAG	yttrium-aluminum-garnet

1. BACKGROUND

1.1 BACKGROUND ON DIABETIC MACULAR EDEMA

Diabetic macular edema (DME), a complication of diabetic retinopathy (DR), can develop at any stage of the underlying disease of retinal microvasculature (Fong et al. 2004). DME occurs with increasing frequency as the underlying DR worsens (Henricsson et al. 1999; Johnson 2009) from non-proliferative DR (NPDR) to proliferative DR (PDR). DME is the most common cause of moderate and severe visual impairment in patients with DR (Ciulla et al. 2003; Davidson et al. 2007; Leasher et al. 2016), and if left untreated can lead to a loss of 10 or more letters in visual acuity (VA) within 2 years in approximately 50% of patients (Ferris and Patz 1984; Ciulla et al. 2003). DME affects approximately 14% of patients with diabetes and can be found in patients with both Type 1 and Type 2 diabetes (Girach and Lund-Andersen 2007). In 2013, the worldwide population of people with diabetes was approximately 382 million, and it is estimated to grow to 592 million by 2035 (International Diabetes Federation 2013).

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

Although macular laser used to be the standard of care (SOC) for treatment of DME, the development of anti-VEGF pharmacotherapy in the past 10 years has led to dramatic improvements in visual outcomes for patients with DME. 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 strong efficacy achieved with anti-VEGF therapies in DME, a significant proportion of patients do not experience clinically meaningful improvements in vision in the real world. Frequent IVT administration is required to achieve, and in some cases, to maintain the observed early benefits of DME treatment over a long period of time.

The current SOC for administration of anti-VEGF injections requires patients to undergo frequent clinical examinations and IVT injections. This imposes a significant burden on patients, caregivers, treating physicians, and the healthcare system.

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

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

1.2 BACKGROUND ON RO6867461

RO6867461 is a humanized full-length bispecific IgG1 antibody that selectively neutralizes VEGF-A and Ang-2, the key factors mediating pathophysiology of diabetic eye disease. RO6867461 was developed using Roche's CrossMab (monoclonal antibody) technology. The VEGF binding and the Ang-2 binding variable regions of RO6867461 bind to VEGF and Ang-2 simultaneously and with high affinity. The Fc portion of RO6867461 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 VEGF and Ang-2 in the vitreous were shown to be upregulated in patients with DR (Rangasamy et al. 2011; Park et al. 2014). In vivo pharmacological evaluations in spontaneous and induced mouse and non-human primate models of neovascularization and in models of intraocular inflammation (uveitis) confirmed the improved anti-angiogenic and anti-inflammatory effects of RO6867461 treatment compared with anti-VEGF monotherapy.

Based on the novel mechanism of action of RO6867461 through selective neutralization of both VEGF and Ang-2, and based on the pathophysiology of diabetic eye disease, it is hypothesized that RO6867461 may lead to stabilization of the pathological ocular vasculature and to improve visual and anatomical outcomes in DME and DR compared with anti-VEGF monotherapies.

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

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The Phase III program will evaluate the efficacy, safety, and pharmacokinetics of RO6867461 when administered to patients every 8 weeks (Q8W) and with a personalized treatment interval (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) (i.e., the number of ETDRS letters). 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 RO6867461 will be assessed.

The Phase II study (BP30099 [BOULEVARD]) provided preliminary evidence of a positive benefit–risk profile for the use of 6-mg IVT injections of RO6867461 for patients with DME and supports further evaluation of RO6867461 in Phase III DME studies.

Additionally, the efficacy, safety, and treatment frequency of IVT RO6867461 administration has been assessed in another retinal disease indication, neovascular age-related macular degeneration (nAMD), in one Phase I study (BP28936) and in two Phase II studies (BP29647 [AVENUE] and CR39521 [STAIRWAY]).

Based on the totality of evidence from the Phase II studies, and taking into account evidence from the preclinical models, it is anticipated that the well-established anti-VEGF mechanism of action combined with anti–Ang-2 targeting in the bispecific RO6867461 molecule will lead to improved efficacy and/or reduced injection burden compared with anti-VEGF monotherapy. This would represent an important advance for patients with DME.

1.3.1 Benefits

The clinical benefit of IVT RO6867461 injections for patients with DME was demonstrated in the Phase II study BP30099. The study met its primary efficacy endpoint, which was the mean change from baseline in BCVA at Week 24 in anti-VEGF treatment–naive patients treated with RO6867461 compared with 0.3 mg of ranibizumab.

Study BP30099 enrolled 229 patients with DME. The study was originally designed to enroll anti-VEGF treatment–naive patients. The protocol was subsequently amended to include an additional cohort of patients (n=61) who were previously treated with anti-VEGF for DME to allow for the exploratory evaluation of the efficacy of RO6867461 in this population.

Anti-VEGF treatment–naive patients were randomized equally into three treatment arms: 6 mg of IVT RO6867461, 1.5 mg of IVT RO6867461, and 0.3 mg of IVT ranibizumab. Patients who were previously treated with anti-VEGF were randomized equally to

receive either 6 mg of IVT RO6867461 or 0.3 mg of IVT ranibizumab. Key demographic and ocular baseline characteristics were generally well balanced. The study consisted of a treatment period (20 weeks in length) and an observational period (up to 16 weeks in length), for a total study duration of up to 36 weeks. Study treatment was administered to patients by IVT injection at every-4-week (Q4W) intervals up to the last injection at Week 20, with the primary endpoint assessed at Week 24. The observational period without treatment lasted up to 16 weeks from Week 20 to Week 36. The observation period allowed for exploration of the durability of pharmacodynamic (PD) effects after the last treatment.

The mean BCVA change from baseline in the anti-VEGF treatment–naive patients treated with 6 mg of RO686746 improved steadily over time, with patients experiencing an average benefit of +3.6 letters (p=0.03; 80% confidence interval [CI]: 1.5 to 5.6 letters) over anti-VEGF monotherapy (adjusted for baseline variables) at Week 24 (1 month after the last monthly dose administered at Week 20), which was statistically significant in a mixed-model repeated measures (MMRM) analysis. In this anti-VEGF treatment–naive population, the mean change in BCVA from baseline in the 6-mg RO6867461 group and the 1.5-mg RO6867461 group at Week 24 was 13.9 letters and 11.7 letters, respectively, relative to 10.3 letters in the 0.3-mg ranibizumab group. The proportion of treatment-naive patients gaining 15 letters or more from baseline over time at Week 24 was 35.3% for the 0.3-mg ranibizumab group relative to 36.0% and 42.5% for the 1.5-mg and 6-mg RO6867461 groups, respectively. In addition to DME benefit, higher rates of improvement in DR severity from baseline (as assessed on the ETDRS Diabetic Retinopathy Severity Scale [DRSS]) were also observed with RO6867461 compared with anti-VEGF monotherapy in the anti–VEGF treatment–naive cohort, with 27.7% and 38.6% of patients (1.5-mg and 6-mg RO6867461, respectively) experiencing a ≥2-step improvement from baseline to Week 24 compared with 12.2% in the 0.3-mg ranibizumab treatment cohort.

For the previously anti-VEGF–treated population, the absolute change from baseline was 9.6 letters and 8.3 letters for the 6-mg RO6867461 group and the anti-VEGF group, respectively. The difference of +1.3 letters was directionally similar to the treatment-naive cohort but was not statistically significant (p=0.635; 80% CI: −2.3 to 5.0). Additionally, the proportion of patients gaining 15 or more letters from baseline over time at Week 24 was 23.2% and 16.8% for the 6-mg RO6867461 and anti-VEGF SOC treatment arms, respectively. The anatomical outcomes showed directionally similar benefits for RO6867461 in this cohort.

Overall, the data from intent-to-treat (ITT) study population (both treatment-naive and previously anti-VEGF–treated patients) suggest consistent benefit of RO6867461 over anti-VEGF monotherapy in the general DME population.

The outcomes in the off-treatment study observation period provided evidence of prolonged duration of effect with RO6867461 compared with anti-VEGF monotherapy.

Assessment of time to disease reactivation up to 16 weeks after the last dose showed an improvement in the duration of the effect of RO6867461 over ranibizumab, as measured by the time to loss of ≥5 ETDRS letters because of DME and an increase ≥50 μm in CST in the treatment-naive patient population in a dose-dependent manner. This improvement in the duration of effect of RO6867461 over ranibizumab was also seen in the previously treated group and the overall patient group.

In summary, the data from Study BP30099 suggested a dose-related benefit favoring the 6-mg dose of RO6867461 relative to the 1.5-mg dose, as measured by both the efficacy outcomes and duration of effect. Based on these results, the 6-mg dose of RO6867461 has been chosen for further clinical development in Phase III studies in patients with DME to explore its benefit compared with SOC IVT anti-VEGF treatment from the following perspectives:

- Potential for superior efficacy outcomes in DME with 6 mg of IVT RO6867461 compared with SOC IVT
- Potential for prolonged treatment duration while achieving and maintaining comparable efficacy with 6 mg of IVT RO6867461 compared with SOC IVT

The Phase III clinical development program will enroll both patients with DME who are naive to anti-VEGF therapy in the study eye and patients who were previously treated with anti-VEGF therapy in the study eye to further explore outcomes on DME in both populations.

1.3.2 Risks

In the Phase I study (BP28936), single and multiple IVT administrations of RO6867461 were well tolerated in patients with nAMD up to the highest dose tested, 6 mg. No deaths and no dose-limiting events were reported.

The Phase II study BP30099 in DME also showed an acceptable tolerability and safety profile, with no new or unexpected safety signals. No serious ocular or systemic adverse events considered related to treatment with RO6867461 were reported. The ocular and systemic safety findings for RO6867461 observed in the Phase II study were generally consistent with the safety profile reported in patients with DME who receive intravitreally administered anti-VEGF products.

Additionally, the safety of IVT RO6867461 administration has been assessed in patients with nAMD in two Phase II studies (BP29647 [AVENUE] and CR39521 [STAIRWAY]). A total of 436 patients have been exposed to at least one dose of RO6867461 to date. No unexpected safety signals have been identified in these studies that would change the anticipated safety profile in the Phase III DME program.

Based on the totality of evidence from the Phase I and Phase II studies, and taking into account evidence from the murine and non-human primate preclinical and toxicology models, it is anticipated that the additional anti–Ang-2 mechanism of action of the

RO6867461 molecule will not lead to an increase in safety risks compared with IVT anti-VEGF monotherapy.

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

1.3.3 Conclusions

The available Phase I and II efficacy and safety data showed a benefit–risk profile that supports further assessment of the efficacy and safety of 6 mg RO6867461 across various treatment intervals compared with anti-VEGF IVT monotherapy in a Phase III DME program.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of RO6867461 when dosed Q8W and with a PTI regimen compared with aflibercept (Eylea®) monotherapy in patients with DME. Specific objectives and corresponding endpoints for the study are outlined in Table 1. An overview of the proposed statistical analyses is described in Section 6.

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of IVT injections of the 6-mg dose of RO6867461 on BCVA outcomes	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) at 1 year [a]
Key Secondary Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of RO6867461 on DR severity outcomes	• Proportion of patients with a ≥2-step DRS improvement from baseline on the ETDRS DRSS at Week 52
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of RO6867461 on additional BCVA outcomes	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) over time • Proportion of patients gaining ≥15, ≥10, ≥5, or ≥0 letters in BCVA from baseline over time • Proportion of patients avoiding a loss of ≥15, ≥10, ≥5, or >0 letters in BCVA from baseline over time • Proportion of patients gaining ≥15 letters or achieving BCVA of ≥84 letters over time • Proportion of patients with BCVA Snellen equivalent of 20/40 or better over time • Proportion of patients with BCVA Snellen equivalent of 20/200 or worse over time
• To evaluate the efficacy of RO6867461 on additional DR outcomes	• Proportion of patients with a ≥2-step DRS improvement from baseline on the ETDRS DRSS over time • Proportion of patients with a ≥3-step DRS improvement from baseline on the ETDRS DRSS over time • Proportion of patients who develop new PDR over time
• To evaluate RO6867461 treatment intervals in the PTI arm	• Proportion of patients in the PTI arm on a Q4W, Q8W, Q12W, or Q16W treatment interval at 1 year and 2 years • Treatment intervals in the PTI arm over time

Table 1 Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate the efficacy of RO6867461 on anatomical outcome measures using SD-OCT	• Change from baseline in CST over time • Proportion of patients with absence of DME (CST <325 μm for Spectralis SD-OCT, or <315 μm for Cirrus SD-OCT or Topcon SD-OCT) over time • Proportion of patients with absence of intraretinal fluid over time • Proportion of patients with absence of subretinal fluid over time • Proportion of patients with absence of intraretinal fluid and subretinal fluid over time
• To evaluate the efficacy of RO6867461 on patient-reported vision-related functioning and quality of life using the NEI VFQ-25	• Change from baseline in NEI VFQ-25 composite score over time
Safety Objective	**Corresponding Endpoints**
• To evaluate the ocular and systemic safety and tolerability of RO6867461	• Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To further evaluate the efficacy of RO6867461 on additional DR outcomes	• Proportion of patients with a ≥2-step or ≥3-step DRS worsening from baseline on ETDRS DRSS over time • Proportion of patients who receive vitrectomy or PRP over time during the study
• To further evaluate the efficacy of RO6867461 on anatomical outcome measures using FFA and/or OCT-A	• Change from baseline in total area of macular non-perfusion and macular ischemia over time • Change from baseline in total area of vascular leakage over time • Proportion of patients with resolution of macular leakage over time • Change from baseline CST neurosensory over time (as measured on SD-OCT) • Change from baseline in total macular volume over time (as measured on SD-OCT)

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objectives (cont.)	Corresponding Endpoints (cont.)
• To further evaluate the efficacy of RO6867461 on patient-reported vision-related functioning and quality of life using the NEI VFQ-25	• Change from baseline in the NEI VFQ-25 Near Activities, Distance Activities, and Driving subscales at 1 year [a] • Proportion of patients with a ≥ 4-point improvement from baseline in NEI VFQ-25 composite score
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the systemic pharmacokinetics of RO6867461	• Plasma concentration of RO6867461 over time
Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to RO6867461 • To evaluate potential effects of ADAs	• Presence of ADAs during the study relative to the presence of ADAs at baseline • Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives	**Corresponding Endpoints**
• To identify biomarkers that are predictive of response to RO6867461, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of RO6867461 activity, or can increase the knowledge and understanding of disease biology	• Concentration of biomarkers of angiogenesis and inflammation in aqueous humor (optional) at baseline and over time and their correlation with PK and/or primary and secondary endpoints at baseline and over time • Relationship between efficacy, safety, PK, immunogenicity, [redacted] • Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., the frequency of study drug administration) over time • Relationship between anatomic measures and visual acuity

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate potential relationships between selected covariates and exposure to RO6867461	• Relationship between selected covariates and plasma or aqueous humor (optional) concentration or PK parameters for RO6867461
• To characterize the aqueous humor (optional) and vitreous (optional) pharmacokinetics of RO6867461	• Aqueous humor (optional) and vitreous (optional) concentration of RO6867461 over time
• To evaluate the drug concentration [redacted]	• [redacted]
• To explore the concentration–effect relationship for visual acuity and other endpoints (e.g., anatomical markers)	• Pharmacokinetics of RO6867461 and the change in BCVA or other endpoints (e.g., anatomical markers) over time

ADA=anti-drug antibody; [redacted]
BCVA=best-corrected visual acuity; CST=central subfield thickness; DR=diabetic retinopathy; DRS=diabetic retinopathy severity; DRSS=Diabetic Retinopathy Severity Scale; ETDRS=Early Treatment Diabetic Retinopathy Study; FFA=fundus fluorescein angiography; IVT=intravitreal; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT-A=optical coherence tomography–angiography; PDR=proliferative diabetic retinopathy; PK=pharmacokinetic; PRP=panretinal photocoagulation; PTI=personalized treatment interval; Q4W = every 4 weeks; Q8W=every 8 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks; SD-OCT=spectral-domain optical coherence tomography; [redacted]

[a] The definition of 1 year for the primary endpoint is the average of the Week 48, 52, and 56 visits.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, double-masked, multicenter, randomized, active comparator–controlled, parallel-group study, evaluating the efficacy, safety, pharmacokinetics, and optimal treatment frequency of RO6867461 administered by IVT injection at 8-week intervals or PTI of approximately 100 weeks' duration (excluding the screening period) to patients with DME.

3.1.1 Overview of Study Design

Approximately 900 patients will be randomized during the global enrollment phase of the study in a 1:1:1 ratio to one of three treatment arms (see Figure 1) at approximately 240 investigational sites globally. The study will randomize patients with DME who are naive to anti-VEGF therapy in the study eye and patients who have previously been treated with anti-VEGF therapy in the study eye, provided that the last treatment was at least 3 months prior to the Day 1 visit (the first study treatment). Site investigators will

be retina specialists or the equivalent outside of the United States (see Section 4.2.2 for additional details).

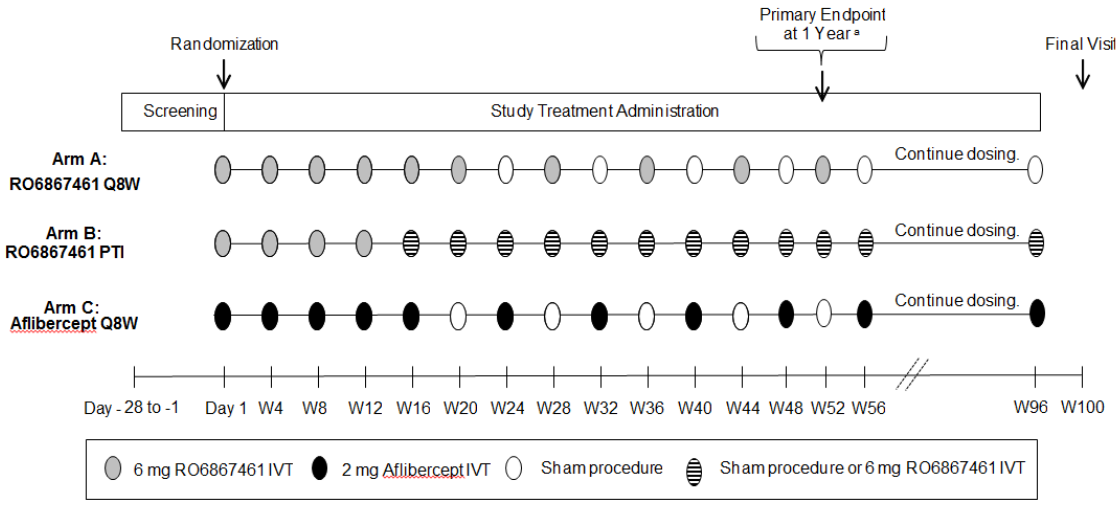
The study treatment arms will be as follows:

- Arm A (administered Q8W) (n=300): Patients randomized to Arm A will receive 6-mg IVT RO6867461 injections Q4W to Week 20, followed by 6-mg IVT RO6867461 injections Q8W to Week 96, followed by the final study visit at Week 100.
- Arm B (PTI) (n=300): Patients randomized to Arm B will receive 6-mg IVT RO6867461 injections Q4W to at least Week 12, followed by PTI dosing (see the PTI dosing criteria below) of 6-mg IVT RO6867461 injections to Week 96, followed by the final study visit at Week 100.
- Arm C (comparator arm) (administered Q8W) (n=300): Patients randomized to Arm C will receive 2-mg IVT aflibercept injections Q4W to Week 16, followed by 2-mg IVT aflibercept injections Q8W to Week 96, followed by the final study visit at Week 100.

Patients in all three treatment arms will complete scheduled study visits Q4W for the entire study duration (100 weeks). A sham procedure will be administered to patients in all three treatment arms at applicable visits to maintain masking among treatment arms (see Figure 1).

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

Figure 1 Study Treatment Schema



IVT=intravitreal; Q8W=every 8 weeks; PTI=personalized treatment interval (see Section 3.1.2 for additional details); W=week.

[a] The definition of 1 year used for the primary efficacy endpoint— defined as the change from baseline in BCVA, as measured on the ETDRS chart at a starting distance of 4 meters at 1 year—is the average of the Week 48, 52, and 56 visits.

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

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

The study will consist of a screening period of up to 28 days (Days −28 to −1) in length and an approximately 96-week treatment period, followed by the final study visit at Week 100. A unique screening number will be assigned to each screened patient through an interactive voice or web-based response system (IxRS).

3.1.1.1 Screening

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

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

The screening and Day 1 (randomization) visits may occur as a combined visit if all assessments are completed and evaluated on the same day or within 2 business days. When screening and the Day 1 visit are completed on the same day, the assessments listed for both visits (see the schedule of activities in Appendix 1) should be conducted only once. A historic hemoglobin A_{1c} (HbA_{1c}) value must be available from within 2 months prior to Day 1 to enable screening and randomization to occur on the same day. If a historic value is used, receipt of screening laboratory results would not be required prior to randomization. If the screening and Day 1 visit are not completed on the same day (but rather within 2 business days), the following safety assessments will be repeated on the day of patient's randomization and study treatment administration: slitlamp examination, indirect ophthalmoscopy, and pre- and post-treatment intraocular pressure (IOP) measurements (recorded on the Day 1 electronic Case Report Form [eCRF] and dated accordingly).

After screening has been completed, eligible patients will have a randomization identification number assigned through the IxRS and will be randomized in a 1:1:1 ratio in order that approximately 300 patients are randomized to each of the three treatment arms. Randomization will be stratified by baseline BCVA ETDRS letter score, as assessed on Day 1 (64 letters or better vs. 63 letters or worse), prior IVT anti-VEGF therapy (yes vs. no), and region (United States and Canada, Asia, and the rest of the world).

3.1.1.2 Screen-Failed Patients

Patients who are not eligible for enrollment (screen failures) may be eligible for re-screening for up to an additional two times during the enrollment period of the study. At re-screening, a new screening number will be assigned to each patient through the IxRS and all screening visit assessments will be performed. At the Day 1 visit, fundus FFA images do not have to be repeated, provided that acceptable FFA images are received by the central reading center within 4 weeks before the new Day 1 visit (randomization) date.

3.1.1.3 Randomization and Visit Schedule

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

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

Starting at the Day 1 visit, randomized patients will have study treatment administered Q4W by the unmasked investigator that will be followed by the safety assessments (finger-counting test and post-dose IOP measurement). After the Day 1 visit, patients will also have safety assessments (see Appendix 1) evaluated by the masked investigator prior to receiving study treatment (for additional details about masking, see Section 4.2). Patients will be instructed to contact the study site at any time if they have any health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 2).

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

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

Note: After the Day 1 visit, if a patient misses a study visit when ocular images are to be obtained (see Appendix 1), the images must be obtained at the next scheduled visit the patient attends.

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

For study masking requirements, see Section 4.2.

Patients who are prematurely discontinued from study treatment but who agree to continue to participate in the study will be encouraged to undergo as many scheduled visits as possible, with emphasis on completing the Week 48, 52, 56, and 100 visits.

Study treatment visits will be scheduled Q4W (±7 days) relative to the Day 1 visit date.

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

Patients who complete study treatment (i.e., the Week 96 visit) will return for the final study visit (Week 100) after a minimum of 28 days have elapsed from their last study

treatment for monitoring of adverse events and final study visit assessments (see Appendix 1).

[redacted]

3.1.2 Treatment Schedule for Patients in the Personalized Treatment Interval Arm (Arm B)

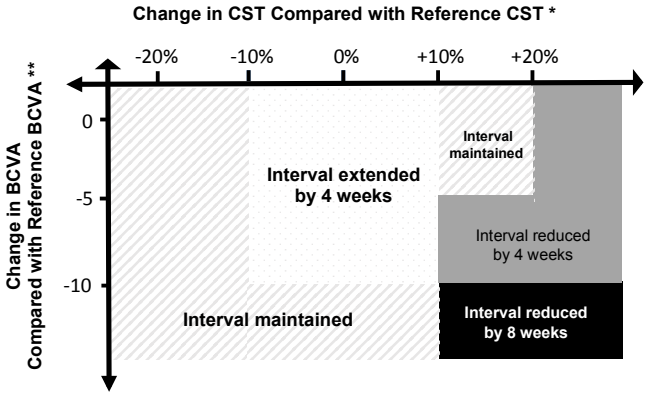
Study drug dosing interval decisions in the PTI arm are automatically calculated by the IxRS based on the algorithm described in this section. Study drug dosing visits are visits when a patient is assigned to receive RO6867461.

3.1.2.1 Study Drug Dosing Interval Determination

Patients randomized to the PTI arm (Arm B) will be treated with RO6867461 on a Q4W dosing interval until the patient's Week 12 visit or later CST meets the predefined reference CST threshold (CST <325 μm for Spectralis SD-OCT, or <315 μm for Cirrus SD-OCT or Topcon SD-OCT). The reference CST is used at study drug dosing visits by the IxRS for interval decision-making.

After a patient's initial reference CST is established, their study drug dosing interval will be increased by 4 weeks to an initial Q8W dosing interval by the IxRS. From this point forward, the study drug dosing interval will be extended, reduced, or maintained based on assessments made at study drug dosing visits. Figure 2 outlines the algorithm used by the IxRS for interval decision-making, which is based on the relative change of the CST and BCVA compared with reference CST and BCVA.

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



All comparisons are made relative to the reference CST* and reference BCVA**. The IxRS will determine the study drug dosing interval based on CST and BCVA data obtained from the study drug dosing visits.

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 ≤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

* Reference center subfoveal thickness (CST): the CST value when the initial CST threshold criteria are met. Reference CST is adjusted if CST decreases by >10% from the previous reference CST for two consecutive study 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.

** Reference best-corrected visual acuity (BCVA): the mean of the three best BCVA scores obtained at any prior study drug dosing visit.

3.1.2.2 Study Drug Dosing Intervals

The IxRS can adjust the study drug dosing interval by 4-week increments to a maximum of every 16 weeks (Q16W) and a minimum of Q4W.

Similar to Arms A and C, patients randomized to the PTI arm (Arm B) will receive a sham procedure at study visits when they are not receiving treatment with RO6867461.

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

Sites will report missed study visits (except of Day 7 visit) and study drug interruption visits to the IxRS for all patients (Arms A, B, and C) to preserve the masking. The following algorithms are only applicable to patients in the PTI arm (Arm B) and are used by the IxRS to automatically determine study drug intervals in the event of the following situations.

3.1.3.1 Missed Study Drug Dosing Visit(s)

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

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

3.1.3.2 Study Drug Interruption at Study Drug Dosing Visit(s)

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

3.1.3.3 Missing CST Value at Study Drug Dosing Visit

If a patient attends a study drug dosing visit, but the CST value is not available for any reason (e.g., OCT machine is not available or is broken), the IxRS will assign the patient to receive study drug at that visit. Generally, the IxRS will maintain the previous drug dosing interval. However, in the event of a concurrent ≥10-letter decrease relative to the

reference BCVA at that study drug dosing visit, the IxRS will reduce the study drug dosing interval by 4 weeks.

3.1.3.4 Missing BCVA Value at Study Drug Dosing Visit

If a patient attends a study drug dosing visit, but the BCVA value is not available for any reason (e.g., patient refuses BCVA examination), the IxRS will assign the patient to receive study drug at that visit. The IxRS will base the study drug dosing interval determination on CST only.

3.1.4 Missed Study Drug Treatment Visit(s) for Patients in the Q8W Treatment Arms

If a patient randomized to treatment Arm A (RO6867461 Q8W) or Arm C (aflibercept Q8W) misses study drug treatment visit(s) after the Q4W initiating doses, the IxRS will assign the patient to receive RO6867461 or aflibercept at the next study visit he or she attends. The Q8W drug treatment interval will be automatically reset by the IxRS from that visit forward, thus 4 weeks later, at the following study visit, the patient will receive sham.

3.1.5 Timely Reporting of BCVA Scores, CST Values, Missed Study Treatment Visits, or Study Treatment Interruptions for All Study Patients

Starting at the Day 1 visit, patients' BCVA scores in all randomized treatment arms (Arms A, B, and C) from each study treatment visit have to be reported by the sites to the IxRS in a timely manner (ideally, within 24 hours of obtaining them). Similarly, OCT images obtained at each study treatment visit have to be forwarded to the central reading center in a timely manner (ideally, within 24 hours of obtaining them). Sites will report in a timely manner in the IxRS the study treatment visits that patients miss. Sites will report in the IxRS the study treatment interruption(s) in order that the correct study treatment (study drug or sham) can be assigned by the system to a patient for a future study treatment visit.

3.1.6 Independent Data Monitoring Committee

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

The iDMC will meet approximately every 6 months (frequency adjustable if required) to evaluate unmasked ocular and systemic (non-ocular) safety events with an emphasis on the evaluation of the rate of ocular inflammation, increased IOP, endophthalmitis, arterial thromboembolic events, and clinically significant decreases in BCVA, which will be prepared for the committee by an independent Data Coordinating Center (iDCC). The iDMC may recommend stopping the study early for safety reasons.

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

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

3.2 END OF STUDY AND LENGTH OF STUDY

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

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, [redacted] The end of the study is expected to occur approximately 100 weeks after the last patient is randomized.

The total length of the study [redacted] from screening of the first patient to the LPLV for patients from the global enrollment phase is expected to be approximately 46 months.

3.3 RATIONALE FOR STUDY DESIGN

A multicenter, double-masked, randomized, comparator-controlled trial design was selected to minimize bias in the evaluation of RO6867461 as a treatment for patients with DME.

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

Optional aqueous humor samples will be collected from consenting patients in regions where optional sampling is approved, with the aim to further understand the ocular pharmacokinetics of RO6867461 as well as to assess biomarkers (see Section 3.3.4). Single (Krohne et al. 2012) and multiple (Campochiaro et al. 2013) aqueous humor samplings have previously been instrumental in the understanding of ocular pharmacokinetics and VEGF suppression (Muether et al. 2012, 2013, 2014; Fauser et al. 2014; Fauser and Muether 2016; Hutton-Smith et al. 2017) and were safely applied in RO6867461 clinical studies in a total of 180 patients.

3.3.1 Rationale for Treatment Arms Dose and Schedule

3.3.1.1 Rationale for RO6867461 Dose and Schedule

The 6-mg dose of RO6867461 will be administered to patients as initiating and maintenance doses in treatment Arm A and Arm B, as outlined in Section 3.1.1.

Dose

The 6-mg dose of RO6867461 selected for this study is based on data from preclinical in vivo and toxicology models, clinical outcomes from Phase I and Phase II studies, and supported by clinical pharmacokinetic (PK) and PD assessments.

The first-in-human study (BP28936) evaluated the safety and tolerability of single and multiple administration of RO6867461 to 24 patients with nAMD, at doses ranging from 0.5 mg to 6 mg. The selection of these doses was based on nonclinical findings and absolute IVT doses administered in toxicology studies. The 6-mg dose of RO6867461 was the highest feasible dose of RO6867461, 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 RO6867461 in patients with DME (n=229 enrolled). The study compared two doses of IVT RO6867461 (1.5-mg RO6867461 and 6-mg RO6867461) with 0.3-mg IVT ranibizumab. The effects of 6-mg IVT RO6867461 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 RO6867461 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 RO6867461, 6 mg and 1.5 mg, were well tolerated and did not result in any new or unexpected safety signals.

As a result, the 6-mg RO6867461 dose has been chosen for further clinical development in Phase III studies in patients with DME. Refer to the 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 Phase III study is designed to allow the assessment of both efficacy and the optimal treatment frequency of the 6-mg IVT RO6867461 dose. The dosing schedule is based on the clinical data from the Phase II study (BP30099 [BOULEVARD]) and the PK and PD assessments of aqueous humor samples from a subset of patients with DME in the Phase II study BP30099.

The mechanism of action of RO6867461 is through neutralization of VEGF and Ang-2. PK and PD assessments of aqueous humor samples from a subset of patients in Study BP30099 demonstrated high suppression of VEGF and Ang-2 for 8 weeks or more with RO6867461, fully supporting the Q8W dosing regimen with a potential to further extend the intervals between injections.

An initiating phase with six IVT injections of 6-mg RO6867461 Q4W was selected for Arm A (RO6867461 Q8W). The rationale for the initial six Q4W doses is based on the continuous BCVA gains seen after each Q4W injection up to Week 24 in the Phase II study (BP30099). The maintenance dosing phase for patients in Arm A (RO6867461 Q8W) will consist of 6 mg of IVT RO6867461 administered to patients Q8W. The rationale for Q8W maintenance phase dosing is based on the evidence of the durability of the 6-mg RO6867461 dose in the 16-week observation period of the Phase II study (after the last dose at Week 20 until the end of observation period at Week 36), and on the VEGF and Ang-2 target neutralization in the aqueous humor in a subset of patients. An additional rationale for the Q8W maintenance dosing schedule for patients in Arm A is that it matches the U.S., Japan, and E.U. approved interval for the active comparator Arm C (aflibercept Q8W) in the Phase III design.

Both the efficacy outcomes from the Phase II study and the variability in individual VEGF and Ang-2 suppression times in the PK/PD aqueous humor assessments indicated a heterogeneous response to treatment and supported a flexible dosing regimen with intervals from Q4W to Q16W. The Phase II study (BP30099) time to disease re-activation data (time to a 50-μm increase in CST or time to a 5-letter worsening in BCVA) following six Q4W doses demonstrated that although some patients with DME may 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 structural model of PK/PD model characterizing the aqueous humor–free VEGF time course showed that there was a substantial proportion of patients with high aqueous humor free-VEGF suppression for whom a Q12W or Q16W regimen could be sufficient to maintain efficacy.

As a result, the Phase III design will assess 6-mg IVT RO6867461 administered at PTIs to patients in Arm B. The PTI regimen aims to achieve maximum efficacy while reducing the IVT injection treatment burden in patients with DME.

3.3.1.2 Rationale for Aflibercept Dose and Schedule

The 2-mg aflibercept doses will be administered to patients in treatment Arm C, as outlined in Section 3.1.1. The aflibercept dose and schedule used in this study are consistent with global recommended dosing posologies (e.g., in the United States, European Union, and Japan) DME product labeling for Eylea (aflibercept) (see Section 3.3.3).

3.3.2 Rationale for Patient Population

This study will be conducted in patients with decreased vision due to DME who meet all of the eligibility criteria for this protocol (for the inclusion and exclusion criteria, see Sections 4.1.1 and 4.1.2, respectively).

Patients who are both naive to anti-VEGF therapy in the study eye and those who have previously been treated with anti-VEGF therapy in the study eye will be randomized.

Inclusion of previously anti-VEGF–treated patients in the study will enable exploratory evaluation of the impact of previous IVT anti-VEGF treatment on the efficacy of RO6867461. The target for participation of previously anti-VEGF–treated patients will be capped at a minimum 10% and a maximum 25% of enrollment. The rationale for capping the number of previously anti-VEGF–treated patients is based on the heterogeneous nature of this population with potentially a history of long-standing DME and irreversible retinal damage that may limit the possibility of detecting additional VA improvements.

3.3.3 Rationale for Control Group

This study is an interventional study, aiming to evaluate the efficacy of RO6867461 compared with a SOC anti-VEGF therapy, aflibercept, for patients with DME. Anti-VEGF therapy is a well-established SOC in patients with DME, and studies with an inactive comparator or macular laser treatment alone are no longer ethically acceptable alternatives given the improvements in visual and anatomical outcomes associated with anti-VEGF treatment.

Aflibercept is an approved anti-VEGF treatment in patients with DME and has demonstrated improvement of BCVA in the target population in controlled, randomized clinical studies (Eylea® [aflibercept] U.S. Package Insert, Eylea® [aflibercept] E.U. Summary of Product Characteristics, and Eylea® [aflibercept] Japan Package Insert). Eylea is the only globally approved anti-VEGF therapy with a Q8W maintenance regimen, facilitating a comparison with the Q8W maintenance regimen of RO6867461 in treatment Arm A.

3.3.4 Rationale for Pharmacodynamic and Biomarker Assessments

PD parameters comprise the primary target engagement markers [redacted] and additional biomarkers.

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 Muethe 2016; Hutton-Smith et al. 2017). Therefore, to increase our understanding of the ocular pharmacokinetics and pharmacodynamics of RO6867461 and its relationship to PTIs, optional aqueous humor samples will be obtained from patients who provide additional optional consent to participate. Aqueous humor and vitreous humor samples will be measured at different timepoints for patients who consent in regions where optional sampling is approved. 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.

The concentration of the molecular targets unbound to RO6867461 [redacted] will be measured in the systemic circulation as part of PD assessments at different timepoints for all patients and at two timepoints for patients who consent in regions where optional sampling is approved.

Moreover, other biochemical entities such as cytokines [redacted] may be analyzed in these specimens in an exploratory analysis. The analysis of these entities aims at the investigation of the role of biochemical and biological processes, such as angiogenesis, inflammation, and oxidative stress in the pathogenesis of DR (Goldberg 2009; Kaul et al. 2010) and DME (Campochiaro 2015) and in the response to RO6867461 treatment. Given that these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

4. MATERIALS AND METHODS

4.1 PATIENTS

Patient Selection and Sex Distribution

Approximately 900 patients with DR and macular edema secondary to diabetes mellitus (Type 1 and 2) will be randomized to the study.

The study will recruit patients who are naive to anti-VEGF therapy in the study eye and those who have previously been treated with anti-VEGF therapy in the study eye. Study participation of previously anti-VEGF–treated patients will be capped at a maximum 25% of enrollment.

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

The protocol allows enrollment of both men and women, provided the entry criteria are met. However, women who are pregnant or breastfeeding will be excluded from the study. The remaining inclusion and exclusion criteria apply to both male and female patients and pertain to issues of patient health performance and safety.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry.

4.1.1.1 General Inclusion Criteria

Patients must meet the following general inclusion criteria for study entry:

- Willingness and the ability to provide signed informed consent

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

- Age ≥18 years
- Documented diagnosis of diabetes mellitus (Type 1 or Type 2), as defined by the American Diabetes Association or per WHO criteria and
  - Current regular use of insulin for the treatment of diabetes

    and/or

  - Current regular use of oral anti-hyperglycemic agents for the treatment of diabetes
- HbA_{1c} of ≤10% within 2 months prior to the Day 1 visit date
- Ability and willingness to undertake all scheduled visits and assessments
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods during the treatment period and for at least 3 months after the final dose of study treatment

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

  The following are acceptable contraceptive methods: bilateral tubal ligation, male sterilization; hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

  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.

- [redacted]

4.1.1.2 Ocular Inclusion Criteria for Study Eye

Patients must meet the following ocular inclusion criteria for the study eye for entry in the study:

- Macular thickening secondary to DME involving the center of the fovea with CST ≥325 μm, as measured on Spectralis SD-OCT, or ≥315 μm, as measured on Cirrus SD-OCT or Topcon SD-OCT at screening

- BCVA of 73 to 25 letters, inclusive (20/40 to 20/320 approximate Snellen equivalent), using the ETDRS protocol at the initial testing distance of 4 meters (see the BCVA manual for additional details) on Day 1
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality CFPs (including ETDRS 7 modified fields or 4 wide-angle fields to permit grading of DR and assessment of the retina) and other imaging modalities.

4.1.2 Exclusion Criteria

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

4.1.2.1 General Exclusion Criteria

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

- Currently untreated diabetes mellitus or previously untreated patients who initiated oral anti-diabetic medication or insulin within 3 months prior to Day 1
- History of allergy or hypersensitivity to active drug aflibercept and any of its excipients, fluorescein, or any study treatment–related mandatory ingredients (e.g., disinfectants, anesthetics, etc.; see the pharmacy manual for additional details) that is not amenable to treatment
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the RO6867461 or to aflibercept injections, study treatment procedure, dilating drops, or any of the anesthetic and antimicrobial drops used by a patient during the study
- Active cancer within the past 12 months except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of <6 and a stable prostate-specific antigen for >12 months
- Systemic treatment for suspected or active systemic infection

  Ongoing use of prophylactic antibiotic therapy may be acceptable but has to be discussed with the Medical Monitor.
- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis within 6 months prior to Day 1 or anticipated to require hemodialysis or peritoneal dialysis at any time during the study
- History of other disease, other non-diabetic metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a condition that contraindicates the use of the RO6867461 or aflibercept or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator
- Uncontrolled blood pressure (defined as systolic $>$180 mmHg and/or diastolic $>$100 mmHg while a patient is at rest)

  If a patient's initial reading exceeds these values, a second reading may be obtained later the same day or on another day during the screening period. If the

patient's blood pressure is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1.

- Cerebral vascular accident or myocardial infarction within 6 months prior to Day 1
- Pregnancy or breastfeeding, or intention to become pregnant during the study

  Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to initiation of study treatment. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Participation in an investigational trial that involves treatment with any drug or device (with the exception of vitamins and minerals) within 3 months prior to Day 1
- Administration of systemic pro-angiogenic treatments, such as VEGF-based therapies for the peripheral or coronary ischemia (e.g., limb ischemia or myocardial infarction) within 3 months or 5 half-lives prior to Day 1
- Inability to comply with study or follow-up procedures
- Requirement for continuous use of any medications and treatments indicated in Section 4.4.2, Prohibited Therapy

4.1.2.2 Ocular Exclusion Criteria for Study Eye

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

- High-risk PDR in the study eye, using any of the following established criteria for high-risk PDR:
  - Any vitreous or pre-retinal hemorrhage
  - Neovascularization elsewhere ≥1/2 disc area within an area equivalent to the mydriatic ETDRS 7 fields on clinical examination or on CFPs
  - Neovascularization at disc ≥1/3 disc area on clinical examination
- Tractional retinal detachment, pre-retinal fibrosis, or epiretinal membrane involving the fovea or disrupting the macular architecture in the study eye
- Active rubeosis
- Uncontrolled glaucoma
- History of retinal detachment or macular hole (Stage 3 or 4)
- Aphakia or implantation of anterior chamber intraocular lens
- IVT anti-VEGF treatment within 3 months prior to Day 1 (applicable to patients whose study eyes were previously treated with IVT anti-VEGF agents) or any IVT anti-VEGF agents to study eye prior to Day 1 (applicable for patients who are treatment naive)
- Treatment with panretinal photocoagulation (PRP) within 3 months prior to Day 1
- Macular (focal or grid) laser within 3 months prior to Day 1

- Any cataract surgery or treatment for complications of cataract surgery with steroids or YAG (yttrium-aluminum-garnet) laser capsulotomy within 3 months prior to Day 1
- Any other intraocular surgery (e.g., corneal transplantation, glaucoma filtration, pars plana vitrectomy, corneal transplant, or radiotherapy)
- Any IVT or periocular (subtenon) corticosteroid treatment within 6 months prior to Day 1
- Any use of medicated intraocular implants, including Ozurdex®, within 6 months of Day 1
- Any use of Iluvien® implants at any time prior to Day 1
- Treatment for other retinal diseases that can lead to macular edema

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

Patients who meet the following exclusion criterion for the fellow eye (non–study eye) will be excluded from study entry:

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

4.1.2.4 Exclusion Criteria for Both Eyes

Patients who meet the following exclusion criterion for either eye will be excluded from study entry:

- Prior administration of IVT RO6867461 in either eye
- Any history of idiopathic or immune-mediated uveitis in either eye
- Active ocular inflammation or suspected or active ocular or periocular infection in either eye on Day 1

4.1.2.5 Concurrent Ocular Conditions Exclusion Criteria

Patients who meet the following exclusion criteria related to concurrent ocular conditions will be excluded from study entry:

- Any current or history of ocular disease other than DME that may confound assessment of the macula or affect central vision in the study eye (e.g., choroidal neovascularization, age-related macular degeneration, retinal vein occlusion, uveitis, angioid streaks, histoplasmosis, active or inactive cytomegalovirus, pathological myopia, retinal detachment, macular traction, macular hole, and other)
- Any current ocular condition which, in the opinion of the investigator, is currently causing or could be expected to contribute to irreversible vision loss due to a cause other than DME in the study eye (e.g., foveal atrophy, foveal fibrosis, pigment abnormalities, dense subfoveal hard exudates, or other non-retinal conditions)

4.2 METHOD OF TREATMENT ASSIGNMENT AND MASKING

4.2.1 Treatment Assignment

After written informed consent has been obtained, all patients will receive a screening number assigned through the IxRS. A patient must satisfy all eligibility criteria (see Sections 4.1.1 and 4.1.2) prior to randomization through the IxRS. As part of the screening process, the central reading center will evaluate CFPs and SD-OCT images to provide an objective, masked assessment of patient eligibility. After all patient eligibility requirements are confirmed, site personnel will contact the IxRS at the Day 1 visit for assignment of a patient identification number (a separate number from the screening number). Patients will be randomized in a 1:1:1 ratio to one of three study treatment arms (RO6867461 Q8W, RO6867461 PTI, or aflibercept Q8W). After randomization and at each study treatment visit (i.e., including Day 1), the IxRS will assign the appropriate study treatment kit to be used. Patients will be randomized on the same day study treatment is to be initiated (the Day 1 visit).

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

- Baseline BCVA ETDRS letter score (≥64 letters vs. <64 letters)
- Prior IVT anti-VEGF treatment (yes vs. no)
- Region (United States and Canada, Asia, and the rest of the world)

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

Patients who are not eligible for enrollment (screen failures) may be eligible for re-screening for up to an additional two times during the enrollment period of the study. At re-screening, a new screening number will be assigned to each patient through the IxRS and all screening visit assessments will be performed. At the Day 1 visit, FFA images do not have to be repeated, provided the central reading center's FFA images were obtained within 4 weeks before the new Day 1 visit (randomization) date.

4.2.2 Masking

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

4.2.2.1 Masked Roles

Principal Investigator

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

Assessor Physician

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

Photographer(s) and OCT Technician(s)

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

Study Coordinator(s)

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

BCVA Examiner

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

Phlebotomist

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

4.2.2.2 Unmasked Roles

Treatment Administrator

At least one investigator will be designated as the treatment administrator and will be unmasked to the patients' treatment assignment. The treatment administrator will be a retina specialist (or the equivalent in ex-U.S. countries). Qualified ophthalmologists (including retina fellows) may be permitted to perform the role of the treatment administrator following Sponsor approval.

The treatment administrator(s) performing the study treatment administration (RO6867461, aflibercept, or sham) will also perform the post-treatment administration vision testing (finger-counting and, if applicable, hand movement and/or light perception tests) and will treat adverse events that occur during or shortly after the study treatment administration. The person in this role, however, will not evaluate the causality of adverse events, which is the responsibility of the masked assessor physician(s). The treatment administrator will also perform post-treatment IOP measurements, as well as optional aqueous humor sample collection.

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

Unmasked Assistant(s) and Pharmacist

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

Number of Unmasked Personnel per Site

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

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

4.2.2.3 Delegation Log

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

4.2.2.4 Role Switching

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

4.2.2.5 Study Backup Staff

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

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

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

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

4.2.2.7 Patient Masking

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

4.2.3 Unmasking

4.2.3.1 Single-Patient Emergency Unmasking

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

4.2.3.2 Single-Patient Non-Emergency Unmasking

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

4.2.3.3 Single-Patient Unmasking for Health Authority Reporting Requirements

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

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is RO6867461 (test product) and will be referred to as either study drug or by the International Non-Proprietary Name or RO number throughout this protocol.

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

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 RO6867461, Aflibercept and Sham

4.3.1.1.1 RO6867461 Formulation

RO6867461 will be supplied by the Sponsor as a sterile liquid for IVT injection in single-use glass vials.

4.3.1.1.2 Aflibercept (Active Comparator) Formulation

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

4.3.1.1.3 Sham Formulation

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

4.3.1.1.4 RO6867461, Aflibercept, and Sham Packaging and Handling

RO6867461 drug product, aflibercept and sham packaging will be overseen by Roche's Clinical Trial Supplies Department and bear labels with the identification required by local law, the protocol number, drug identification, and its concentration.

The packaging and labeling of RO6867461 drug product, aflibercept, and sham will be in accordance with Roche standards and local regulations.

RO6867461 drug product, aflibercept, and sham must be stored according to the details on the product label and the information provided in the pharmacy manual.

For more detailed information on the formulation and handling of RO6867461, aflibercept, and sham, see the pharmacy manual.

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

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

4.3.2.1 Dosage

4.3.2.1.1 Intravitreal RO6867461 Injections

The 6-mg dose of RO6867461 will be evaluated in this study and will be administered intravitreally to patients randomized to receive RO6867461 Q8W or PTI during the 96-week treatment period (see the study treatment schema in Figure 1).

Patients randomized to receive Q8W treatment will be administered 15 IVT injections of RO6867461 during the 96-week treatment period. Treatment will consist of 6 initial injections (6 mg of RO6867461 Q4W to Week 20), followed by 9 maintenance injections (6 mg of RO6867461 Q8W between Week 24 and Week 96).

The number of IVT injections of RO6867461 administered to patients in the PTI arm will vary (see Section 3.1.2.1 for the retreatment criteria), but a minimum of 10 IVT injections of RO6867461 will be administered to patients during the 96-week treatment period. This will consist of minimum of 4 initiating injections (6 mg of RO6867461 Q4W to

Week 12), followed by minimum of 6 maintenance injections (6 mg of RO6867461 between Week 16 and Week 96).

4.3.2.1.2 Intravitreal Aflibercept (Active Comparator) Injections

A 2-mg dose of aflibercept (Arm C) will be administered intravitreally Q8W to patients randomized to the aflibercept treatment arm during the 96-week treatment period (see Figure 1). Patients will receive 15 IVT injections of aflibercept during the 96-week treatment period. Treatment will consist of 5 initiating injections (2 mg of aflibercept Q4W to Week 16), followed by 10 maintenance injections (2 mg of aflibercept Q8W between Week 20 and Week 96).

4.3.2.1.3 Sham Procedure

All three treatment arms (RO6867461 Q8W, RO6867461 PTI, and aflibercept Q8W) will maintain Q4W study visits for the 100-week study duration. To preserve the randomized treatment arm masking, patients will have the sham procedure performed at study treatment visits when they are not treated with either RO6867461 or aflibercept as applicable per their treatment arm schedule (see Figure 1).

4.3.3 Administration

4.3.3.1 RO6867461 or Aflibercept Intravitreal Injections or Sham Procedure

See the pharmacy manual for the pre-treatment procedures, the administration of RO6867461, aflibercept, or sham and the post-treatment procedures for all treated patients.

4.3.4 Study Treatment Preparation

The pharmacist responsible for dispensing the study treatment, or designated unmasked site personnel, will prepare the correct study treatment (RO6867461, aflibercept, or sham) as assigned through the IxRS.

Detailed stepwise instructions for the preparation of RO6867461, aflibercept, or sham for administration, and mandatory materials to be used will be specified by the Sponsor and are detailed in the pharmacy manual.

A specified filter needle must be used for each dose preparation of RO6867461 or aflibercept according to the instructions provided in the pharmacy manual. All materials to prepare and administer study treatments will be provided or reimbursed by the Sponsor, and no other material than specified should be used.

Vials of RO6867461 drug product and vials of aflibercept (the active comparator) are for single-use only (one injection preparation per patient per eye). Vials used for one patient must not be used for any other patient. Partially used vials, remaining RO6867461 drug product or aflibercept vials, as well as administration material must not be reused.

4.3.5 Compliance

Any medication error, including drug overdose, should be noted on Adverse Event eCRF even if it did not result in any adverse event (see Adverse Event eCRF completion guidance and Section 5.4.4).

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Table 2 and Section 5.1.3.1.

4.3.6 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (RO6867461, sham, and aflibercept) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm shipment condition and content. Any damaged shipments will be replaced.

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

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.7 Continued Access to RO6867461

The Sponsor will offer continued access to Roche IMP (RO6867461) 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 (RO6867461) 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 (RO6867461) after completing the study if any of the following conditions are met:

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

- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for 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 prescription drugs or over-the-counter preparations or procedures other than protocol-specified procedural medications (e.g., dilating drops or fluorescein dyes, proparacaine, or antimicrobials [if applicable]) used by a patient within 7 days preceding the Day 1 visit and through the conclusion of the patient's study participation or early termination visit. Patients required to use therapy that is prohibited (see Section 4.4.2) will not be eligible for the study.

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

4.4.1 Permitted Therapy

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 5.1.3.1, Table 2) may apply with cataract surgery.
- Short-term use of topical corticosteroids after cataract surgery, yttrium-aluminum garnet capsulotomy, or peripheral iridotomy
- PRP 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 masked physician, randomized patients may have their fellow (non–study) eye treated with anti-VEGF if they are diagnosed with an ocular condition for which the selected anti-VEGF therapy is approved in the country. Consult with the

region-specific anti-VEGF prescribing information for the recommended dose and frequency of treatment. If the cost of approved anti-VEGF therapy for the fellow eye causes a financial hardship for the patient, the Sponsor will cover the cost of the therapy in accordance with local regulations.

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

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

4.4.2 Prohibited Therapy

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

- Systemic anti-VEGF therapy
- IVT anti-VEGF agents (other than study-assigned aflibercept or RO6867461) in study eye
- IVT, periocular (subtenon), steroid implants (i.e., Ozurdex®, Illuvien®), or chronic topical (ocular) corticosteroids in study eye
- 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)

4.5 STUDY ASSESSMENTS

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

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

4.5.1 Informed Consent Forms and Screening Log

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

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

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, chronic and ongoing conditions (e.g., trauma, cancer, cardiovascular, cerebrovascular, and ophthalmic history), surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 7 days prior to initiation of study treatment (the Day 1 visit) will be recorded.

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

4.5.3 Physical Examinations

A targeted physical examination should include an evaluation of the head, ears, nose and throat. A patient’s height and weight will be recorded as well. If any abnormalities are noted during the study, the patient may be referred to another doctor.

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

4.5.4 Vital Signs

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

4.5.5 Ocular Assessments

Ocular assessments include the following and will be performed at specified timepoints according to the schedule of activities in Appendix 1:

- BCVA assessed on ETDRS chart at a starting distance of 4 meters (perform prior to dilating eyes; see Appendix 4)
- Pre-treatment IOP measurement of both eyes (perform prior to dilating eyes)
- Slitlamp examination (for grading scales for anterior and vitreous cells, see Appendix 3)
- Dilated binocular indirect high-magnification ophthalmoscopy
- Finger-counting test followed by hand motion and light perception tests (when necessary) performed within 15 minutes of post-study treatment in the study eye only by the unmasked treatment administrator.
- At study treatment visits, post-treatment IOP measurement in the study eye only within 30 (±15) minutes by qualified personnel assigned to the unmasked role. If there are no safety concerns after 30 (±15) minutes following the study treatment, the patient will be permitted to leave the clinic. If the IOP value is of concern to the treatment administrator, the patient will remain in the clinic and will be managed in accordance with this physician clinical judgment. The adverse event will be recorded on the Adverse Event eCRF as applicable.

The method of IOP measurement used for a patient must remain consistent throughout the study.

Ocular Imaging

The central reading center(s) will provide sites with the central reading center(s) manual and training materials for specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software (where applicable) will be certified and validated by the reading center(s) as specified in the central reading center manual. All ocular images results will be obtained by trained site personnel at the study sites and forwarded to the central reading center(s) for independent analysis and/or storage (see Appendix 5, Appendix 6, and Appendix 7).

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

Ocular images include the following:

- CFP of both eyes
- FFA of both eyes (performed after laboratory samples are obtained)
- SD-OCT or swept-source OCT (SS-OCT) images of both eyes

  Certain SS-OCT machines may be acceptable; see the central reading center manual.

- Optional OCT-angiography (OCT-A) of both eyes at sites with OCT-A capabilities

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

4.5.6 Concurrent Ocular Procedures

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

4.5.7 Laboratory, Biomarker, and Other Biological Samples

At the scheduled visit, specimens should be obtained prior to study eye treatment and FFA assessments (if applicable). Fasting is not required prior to specimen collection. The specimens will be forwarded to the central laboratory. The central laboratory will either perform the analysis or forward samples to the Sponsor or its designee for analysis and/or storage. Instructions for obtaining, processing, storing, and shipping of all specimens are provided in the laboratory manual. Laboratory supply kits will be provided to the sites by the central laboratory. See Appendix 1 for sample collection timepoints and Appendix 8 for biological sample collection and shipping instructions.

All samples obtained during screening from patients who are not randomized will be discarded.

The following assessments will be performed:

- Hematology: hemoglobin, hematocrit, quantitative platelet count, RBC counts, WBC counts, and differentials, including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, ALP, AST, ALT, and uric acid
- Urinalysis: specific gravity, pH, blood, protein, ketones, glucose, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal)
- Coagulation: activated partial thromboplastin time and prothrombin time
- Urine pregnancy test at screening and 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.
- HbA_{1c}
- Plasma samples for measurement of anti-RO6867461 antibodies

- Plasma samples to measure RO6867461 or aflibercept concentration (mandatory and optional samples from patients who consent to aqueous humor sampling)
- [redacted]

These samples (except for hematology, serum chemistry, urinalysis, coagulation, serum, urine pregnancy tests, and HbA_{1c} that will be destroyed after their analysis during the study) will be stored for up to 5 years after the date of final closure of the associated clinical database.

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

4.5.7.1 Optional Aqueous Humor Samples

Collection and submission of optional aqueous humor 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 4.5.7.1) will not be applicable at that site.

For patients who consent to provide aqueous humor sampling, the aqueous humor sample should be collected just prior to study treatment by a qualified unmasked treatment administrator, using an aseptic procedure and sterile field and according to local guidelines (see Appendix 8 for further details). All efforts should be made to obtain a baseline aqueous humor sample on Day 1 (pre-dose). The schedule of activities (see Appendix 1) provides guidance on recommended visits at which aqueous humor samples should be obtained. Patients who are prematurely discontinued from study treatment but who agree to continue to participate in the study should discontinue collection of optional aqueous humor samples and any associated optional plasma samples. 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 RO6867461 or aflibercept, [redacted]. 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 [redacted] and inflammation [redacted] to identify new therapeutic targets, better understand variability in patient responses to RO6867461, and to support patient selection and/or stratification in future clinical trials.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.9.1), biological samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

4.5.7.2 Optional Unscheduled Collection of Vitreous Samples

Elective vitrectomy for vitreous sample collection is not allowed in the study eye during a patient's study participation; however, if the surgery is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye (see Appendix 8 for further details).

Vitreous humor samples will be analyzed primarily for RO6867461 or aflibercept concentrations. The remaining samples may be analyzed for [redacted], and possibly other biomarkers.

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

4.5.8 Patient-Reported Outcomes

PROs will be assessed using the National Eye Institute Visual Functioning Questionnaire–25 (NEI VFQ-25) (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.

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

4.5.9 Optional Samples for Research Biosample Repository

4.5.9.1 Overview of the Research Biosample Repository

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

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

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.9) will not be applicable at that site. The RBR portion of the Informed Consent Form has to be agreed to and signed by the consenting patient before these samples can be collected and/or mandatory residual samples used.

4.5.9.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to response to RO6867461, to improve the understanding of the biology of VEGF-A and Ang-2, or to better understand the targets or diseases (DR and DME):

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

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

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies.

The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

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

4.5.9.4 Confidentiality

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

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

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

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

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

4.5.9.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.9.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GR40349 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study GR40349.

4.5.9.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Occurrence of any medical condition that the investigator or Sponsor determines may jeopardize the patient’s safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced and will not be allowed to restart study treatment. However, they should be

strongly encouraged to continue their study participation and undergo as many scheduled visits as possible, with emphasis on the Week 48, 52, 56, and 100 visits.

4.6.2 Patient Discontinuation from Study

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

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

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

If a patient discontinues from the study but has not withdrawn informed consent, the site should make every effort to continue to follow-up on serious adverse events, deaths, and adverse events of special interest. In order to avoid loss to follow-up, the investigator should ask the patient at the study start for the contact information of a relative or friend who can be contacted in case the patient cannot be reached. However, patients will not be followed for any reason after consent has been withdrawn. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

Patients who discontinue from the study early but have not withdrawn consent should return for an early termination visit (see Appendix 1) after a minimum of 28 days have elapsed following the last study treatment.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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

5.1.1 Safety Assessments

The schedule of safety assessments to be performed during the study is provided in Appendix 1. After the first study treatment on Day 1, all patients will return for a safety assessment visit on Day 7 (±3 days). Patients will be instructed to contact the site at any time if they have any health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 2).

At sites where the masked investigator's decision is for patients to receive pre- and post-injection antimicrobials, patients will also be asked whether they have taken the prescribed, self-administered, pre- and/or post-injection antimicrobials.

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

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

Note: If an anti-VEGF injection is administered to the non–study (fellow) eye at the same visit as the study eye study treatment (RO6867461, aflibercept, or sham), the study eye treatment must be performed first (see Section 4.4.1 for additional details).

Detailed ocular examinations, including indirect ophthalmoscopy and slitlamp examination, will be performed throughout the study. Blood samples for plasma study drug concentrations, antibodies to RO6867461, and other biomarker samples (see Section 4.5.6) will be obtained from all patients at selected timepoints. The optional aqueous humor and vitreous samples will be obtained from patients who consent to the procedure and sample collection.

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

Patients are discontinued from the study prior to completion (Week 100) will be asked to return for early termination visit assessments after a minimum of 28 days have elapsed following the last study treatment (see Appendix 1). The visit will include assessment of all adverse events (serious and non-serious; ocular and non-ocular). Serious adverse events will be reported in compliance with GCP guidelines.

Treatment interruption and/or treatment discontinuation for adverse events will be determined using the criteria in Section 5.1.3.1, Table 2

5.1.2 Risks Associated with RO6867461

To date, no identified risks for RO6867461 have been observed.

Based on experience with aflibercept and other anti-VEGF therapies, potential risks of RO6867461 include intraocular inflammation, the intravitreal injection-related risks of infectious endophthalmitis, retinal detachment/tear, iatrogenic traumatic cataracts and increased IOP, as well as the systemic risk of arterial thromboembolic events. An independent clinical events coding committee will be established to adjudicate thromboembolic events (myocardial infarcts, strokes, and vascular deaths) reported during the study.

Please see the RO6867461 Investigator's Brochure for more details on the risks of RO6867461.

5.1.3 Management of Patients Who Experience Adverse Events

5.1.3.1 Treatment Interruption: Dose Interruption and Treatment Discontinuation Criteria

Study treatment interruption and/or patient discontinuation from the study treatment for adverse events will be determined using the criteria listed in Table 2. If any of these criteria are met, treatment will be interrupted (or discontinued, if applicable) and will not be resumed earlier than the next scheduled study visit. The reason for study treatment

interruption/discontinuation should be recorded on the appropriate eCRF and, if applicable, on the Adverse Event eCRF.

Table 2 Dose Interruption and Treatment Discontinuation Criteria

Event	Criteria
Intraocular inflammation	• Interrupt study treatment if intraocular inflammation (iritis, iridocyclitis or vitritis) is ≥2+ in the study eye. • Patients with ≥2+ intraocular inflammation may be allowed to resume study treatment subsequently as determined by Medical Monitor and Investigator
Cataract surgery in the study eye	• Interrupt study treatment after cataract surgery in study eye. • Study treatment may be resumed no earlier than 28 days after an uncomplicated cataract surgery and no evidence of post-operational inflammation at that time. For cataract surgery with complications, study treatment may be permitted as determined by Medical Monitor and investigator.
BCVA decrease	• Interrupt study treatment if there is a study treatment–related decrease in BCVA of ≥30 letters in the study eye compared with the last assessment of BCVA prior to the most recent treatment. • Study treatment may be permitted subsequently, as determined by the investigator.
Elevated IOP	• Interrupt study treatment if 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 study treatment if a retinal break is present in the study eye. • Study treatment may be resumed no earlier than 28 days after successful laser retinopexy, as determined by the investigator.

Table 2 Dose Interruption and Treatment Discontinuation Criteria (cont.)

Event	Criteria
Rhegmatogenous retinal detachment or macular hole	• Interrupt study treatment if rhegmatogenous retinal detachment or Stage 3 or 4 macular hole occurs. • Study treatment may be subsequently permitted after discussion with Medical Monitor.
Active infection	• Interrupt study treatment if any of the following are present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye or if the patient requires treatment for an active systemic infection.

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.8 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 the Adverse Event Grading Scale; see Section 5.3.3, Table 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 site staff to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

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

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

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

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

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

- Sight-threatening adverse events: an adverse event is considered to be sight-threatening and should be reported expeditiously if it meets one or more of the following criteria:
  - It causes a decrease of ≥30 letters in VA score (compared with the last assessment of VA prior to the most recent assessment) lasting more than 1 hour.
  - It requires surgical or medical intervention (i.e., conventional surgery, vitrectomy, vitreous tap, or biopsy with IVT injection of anti-infective treatments, or laser or retinal cryopexy with gas, or a medication) to prevent permanent loss of sight.
  - It is associated with severe intraocular inflammation (i.e., endophthalmitis, 4+ anterior chamber cell/flare, or 4+ vitritis; see Section 5.3.5 and Appendix 3 for intraocular inflammation grading scales).

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

For each adverse event recorded on the Adverse Event eCRF, the investigators will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4). For adverse events that occur during or shortly after study treatment, the unmasked investigator may assess the seriousness and severity of the event, but event causality will be assessed by the investigator who is in the masked role.

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until the final study visit at Week 100. For patients who terminate study treatment and from the study early, all adverse events will be reported up to the early termination visit. For patients who discontinue study treatment early (prior to Week 96 treatment) but continue to participate in the study, adverse events will be reported until their last or final study visit.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

Table 3 provides guidance for assessing adverse event severity.

Table 3 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 4). Note: Only the masked investigator will assess all adverse event causality.

- 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 4 Causal Attribution Guidance

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

5.3.5 Procedures for Recording Adverse Events

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

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

For the purposes of reporting events of infection and inflammation, 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 (trace or greater)

  Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, hemorrhage, or other causes.

- Endophthalmitis: diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 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× ULN) in combination with either an elevated total bilirubin (>2× ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

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

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

5.3.5.7 Deaths

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

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

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

5.3.5.8 Preexisting Medical Conditions

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

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

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

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

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

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

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

  The patient has not experienced an adverse event

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

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

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

No safety data related to overdosing of RO6867461 are available.

See Section 5.4.4 for additional medication error reporting details.

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)
- Medication errors, including overdose (see Section 5.4.4 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for Western Hemisphere

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

Mobile Telephone No.: [redacted]

Medical Monitor Contact information for Western Hemisphere

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

Mobile Telephone No.: [redacted]

Medical Monitor Contact Information for Eastern Hemisphere

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

Mobile Telephone No.: [redacted]

Medical Monitor Contact Information for Eastern Hemisphere

Medical Monitor/Roche Medical Responsible: [redacted], M.D., M.Sc., MB, Ch.B.

Telephone No.: [redacted]

Mobile Telephone No.:

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events, and adverse events of special interest will be reported until the final study visit at Week 100. 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 to immediately inform the investigator if they become pregnant during the study or after the last 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

Any 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).

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).

5.4.4 Expedited Reporting Requirements for Cases of Medication Error

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

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

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

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

Special situations are **not in themselves adverse events** but may result in adverse events.

All special situations associated with the masked study treatment, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF in masked manner and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event)

Special situations should be recorded as described below:

- Medication error, including accidental overdose and intercepted medication error: Enter “Medication Error ” on Adverse Event eCRF as the primary event term and check the “Medication error” box.

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

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

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as the final study visit for patients who complete study treatment, i.e., the Week 96 visit; for the patients who discontinue study treatment early but continue to participate in the study, the adverse events reporting period is until their last or final study visit) if the event is believed to be related to prior study drug treatment. The investigator should report these events directly to the Sponsor or its designee, either by faxing or by

scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- RO6867461 Investigator's Brochure
- Aflibercept (Eylea) local prescribing information, such as the E.U. Summary of Product Characteristics, U.S. prescribing information or Package Insert, or other applicable local product labeling

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Approximately 900 patients will be randomized in the global enrollment phase of this study. [redacted]

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

The primary analyses will be performed when all patients from the global enrollment phase have either completed the study through Week 56 or have discontinued from the study prior to Week 56, whichever comes later (i.e., timing is defined as the primary analysis after the LPLV), and all data collected prior to the primary LPLV in the global enrollment phase are in the database and have been cleaned and verified.

Results of the primary analyses, summarized by treatment group, may be reported to the public before completion of the study. However, patients, masked study site personnel,

and central reading center personnel will remain masked to individual treatment assignment until the study is completed, the database is locked, and the study analyses are final.

The final analysis will be performed when all patients from the global enrollment phase have either completed the study through Week 100 or have discontinued early from the study, all data from the global enrollment phase are in the database, and the database is locked.

Unless otherwise specified, the analyses described in this section are based on patients enrolled during the global enrollment phase [redacted]. Details of the planned analyses, including any additional analyses needed to support country-specific or regional marketing applications, will be provided in the Statistical Analysis Plan.

6.1 DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on patients enrolled in the global enrollment phase. The global enrollment phase will enroll approximately 900 patients. Patients will be randomized in a 1:1:1 ratio to receive treatment with RO6867461 Q8W (Arm A), RO6867461 PTI (Arm B), or aflibercept Q8W (Arm C). The primary comparisons will be the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the RO6867461 arms (Q8W and PTI).

A sample size of approximately 300 patients in each arm will provide greater than 90% power to show non-inferiority of RO6867461 to aflibercept (pairwise comparisons between the active comparator and each of the RO6867461 arms) in the ITT population, using a non-inferiority margin of 4 letters and under the following assumptions:

- Standard deviation (SD) of 11 letters for the change from baseline in BCVA averaged over Week 48, Week 52, and Week 56
- Two-sample *t*-test
- 1.25% one-sided type I error rate
- 10% dropout rate

Assuming 75%–90% of patients recruited will be treatment naive, approximately 225–270 treatment-naive patients will be enrolled per arm. A sample size of 225–270 patients per arm will provide greater than 80% power to show a 3.5-letter superiority of RO6867461 over aflibercept (pairwise comparisons between the active comparator and each of the RO6867461 arms) in the treatment-naive population, using the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 2.5%.

Furthermore, a sample size of approximately 300 patients per arm will provide greater than 80% power to show a 3-letter superiority of RO6867461 over aflibercept (pairwise comparisons between the active comparator and each of the RO6867461 arms) in the

ITT population, under the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 2.5%.

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

[redacted]

6.2 ANALYSIS POPULATIONS

The analysis populations used in this section, such as the ITT population, are based on patients enrolled during the global enrollment phase and will not include the [redacted] unless otherwise specified.

6.2.1 Intent-to-Treat Population

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

6.2.2 Treatment-Naive Population

The treatment-naive population is defined as all patients randomized in the study who have not received any IVT anti-VEGF agents in the study eye prior to Day 1. For analyses based on this patient population, patients will be grouped according to the treatment assigned at randomization.

6.2.3 Per-Protocol Population

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

6.2.4 Safety-Evaluable Population

The safety-evaluable population will comprise all patients who receive at least one injection of active study treatment (RO6867461 or aflibercept). For analyses based on this patient population, patients will be grouped according to the actual treatment received up to the Week 56 visit as follows.

- If the only active treatment received by a patient in the study eye is aflibercept, the patient's treatment group will be aflibercept Q8W.
- If the only active treatment received by a patient in the study eye is RO6867461, the patient's treatment group will be as randomized if the patient is randomized to one of the RO6867461 arms; otherwise, the patient's treatment group will be RO6867461 Q8W.
- If a patient received a combination of different active treatments (RO6867461 and aflibercept) in the study eye, the patient's treatment group will be as randomized.

6.2.5 Pharmacokinetic-Evaluable Population

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

6.2.6 Immunogenicity-Analysis population

The immunogenicity analysis population will consist of all patients with at least one plasma sample for anti-drug antibody assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

6.3 SUMMARIES OF CONDUCT OF STUDY

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

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

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

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

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

6.5 EFFICACY ANALYSES

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

The primary comparisons will be the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the RO6867461 arms (Q8W and PTI).

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

6.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in BCVA averaged over Weeks 48, 52, and 56. The BCVA outcome measure is based on the ETDRS VA chart assessed at a starting distance of 4 meters.

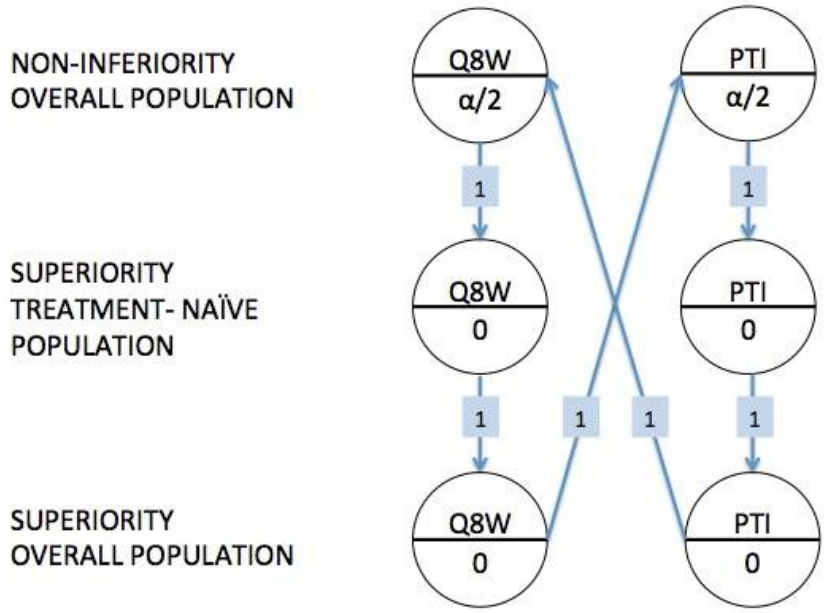
The primary comparisons will be the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the RO6867461 arms (Q8W and PTI). Additional analyses based on the per-protocol population will also be conducted.

For the two RO6867461 arms (Q8W and PTI), the following three hypotheses will be tested for each treatment group separately at an overall significance level of $\alpha = 0.05$ using a graph-based testing procedure (Bretz et al. 2009, 2011) to control for the overall type I error rate:

- Non-inferiority of RO6867461 compared with aflibercept Q8W in the ITT population
- Superiority of RO6867461 compared with aflibercept Q8W in the treatment-naive population
- Superiority of RO6867461 compared with aflibercept Q8W in the ITT population

The order in which hypothesis tests for the primary endpoint will be performed is illustrated in Figure 3, with arrows denoting the direction of α-propagation. If the tests for one treatment sequence are all positive, then $\alpha/2$ will be propagated to the beginning of the other treatment sequence, which will be tested at a significance level of $\alpha = 0.05$. Of note, non-inferiority will be tested one sided at half of the designated significance level shown in Figure 3.

Figure 3 Graph-Based Testing Procedure for the Primary Endpoint



PTI = personalized treatment interval; Q8W = every 8 weeks.
Note: $\alpha = 0.05$.

The non-inferiority tests for the RO6867461 Q8W arm and the RO6867461 PTI arm compared with aflibercept Q8W arm will be conducted with a non-inferiority margin of 4 letters. For each RO6867461 group (Q8W or PTI) the null hypothesis, H_0: $\mu^{RO6867461} - \mu^{aflibercept} \leq -4$ letters, and the alternative hypothesis, H_a: $\mu^{RO6867461} - \mu^{aflibercept} > -4$ letters, will be tested, for which $\mu^{RO6867461}$ and $\mu^{aflibercept}$ are the expected change from baseline in BCVA averaged over Weeks 48, 52, and 56 for the treatment group in question (RO6867461 Q8W or PTI) and the active comparator (aflibercept Q8W), respectively.

The change from baseline averaged over Weeks 48, 52, and 56 will be compared between each RO6867461 arm and the aflibercept Q8W arm using a MMRM model. The model will include the change from baseline at Weeks 4–56 as the response variables and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, the continuous baseline value for the response variable (in this case, baseline BCVA), as well as randomization stratification factors as fixed effects. Comparisons between each RO6867461 arm and the aflibercept Q8W arm will be made using a composite contrast over Weeks 48, 52, and 56. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a heterogeneous compound symmetry or an AR(1) covariance structure may be fitted.

Missing data will be implicitly imputed using the MMRM model, assuming a missing at random missing data mechanism (i.e., the probability that missing data are dependent

on other observed variables but not on the missing data). Data for patients who receive prohibited therapy will be censored at the timing of use of prohibited therapy. Data for patients who discontinue from study drug and do not receive any prohibited therapy after discontinuation of study drug will be included in the analysis.

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

Non-Inferiority Margin

Non-inferiority hypothesis testing for the primary endpoint of the change from baseline in BCVA averaged over Weeks 48, 52, and 56 will be performed using a 4-letter non-inferiority margin based on the VISTA and VIVID aflibercept pivotal DME studies. These studies compared aflibercept to laser control. The 4-letter non-inferiority margin also preserves approximately 50% of the least estimated benefit of aflibercept over control in both VISTA and VIVID studies individually.

The VISTA study randomized 466 patients in the United States and the VIVID study randomized 406 patients in Europe, Japan, and Australia. At Week 52, in VISTA, patients receiving 2 mg of aflibercept Q8W gained 10.7 letters from baseline compared with 0.2 letters for patients in the control arm. The corresponding results from the VIVID study were a gain of 10.7 letters for aflibercept versus 1.2 letters for the control arm.

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

6.5.2 Secondary Efficacy Endpoints

The key secondary endpoint is the proportion of patients with a ≥2-step improvement in DR severity from baseline on the ETDRS DRSS at Week 52.

[redacted]

[redacted]

Additional secondary endpoints are listed in Section 2, Table 1. For all secondary endpoints measured on a continuous scale, the same analysis method and data handling rules as described in Section 6.5.1 for the primary endpoint will be used. For binary secondary endpoints, the proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata defined by randomization factors using the Cochran-Mantel-Haenszel weights (Cochran 1954; Mantel and Haenszel 1959). CIs of the proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be calculated using the normal approximation to the weighted proportions (Mehrota and Railkar 2000). Superiority will be assessed, as appropriate, using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factors.

[redacted]

All secondary endpoints will be assessed at 1 year and at additional timepoints over time during the study. For the purpose of analysis, the definition of 1 year is the average of the Week 48, 52, and 56 visits.

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

6.5.3 Exploratory Efficacy Endpoints

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

6.6 SAFETY ANALYSES

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

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

At the time of the primary analysis, safety summaries will be summarized based on the complete Week 56 data in the safety-evaluable population. In addition, summaries for ongoing safety data (after Week 56 and up to a single specified clinical cutoff date) in the safety-evaluable population will also be summarized. At the time of the final analysis, safety summaries will be produced based on cumulative Week 100 data in the safety-evaluable population.

Verbatim descriptions of treatment-emergent adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and their incidence and severity will be summarized by treatment arm. A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug. Adverse events will be tabulated by System Organ Class and preferred term. In addition, summaries will be generated for serious adverse events, deaths, adverse events leading to discontinuation of study drug, adverse events of special interest, and adverse events judged to be related to study treatment. Separate summaries will be prepared for systemic (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 baseline in pre-dose IOP measurements and changes between pre-dose and post-dose IOP measurements will also be summarized.

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

6.7 PHARMACOKINETIC ANALYSES

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

A non-linear mixed-effects modeling approach (with NONMEM software [Beal and Sheiner 1998]) will be used to analyze the concentration–time data for RO6867461 and aflibercept. Population and individual primary PK parameters (i.e., clearances and volumes) will be estimated. The plasma data collected in this study may be pooled with aqueous humor drug concentrations and with data collected in previous studies as appropriate to update the current population-PK model. The model may be revised if necessary. A covariate modeling approach emphasizing parameter estimation will be implemented for the covariate model development. Potential covariate–parameter relationships will be identified based on mechanistic plausibility and exploratory graphics. Inferences about covariate effects and their clinical relevance will be based on the resulting parameter estimates and measures of estimation precision (asymptotic standard errors). PK parameters such as area under the concentration–time curve and maximum concentration will be derived from the individual post-hoc predictions.

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

6.8 PHARMACODYNAMIC ANALYSES

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

The data collected from this study may be pooled with data from previous studies. The effect of exposure or dosing information on BCVA, aqueous humor [redacted] will be explored using a longitudinal model approach. The influence of various baseline covariates on model parameters will be investigated. The PK–PD or dose–PD relationship will be characterized. Additional PD markers, such as anatomical endpoints, may be included. Additional details about the PK and PD analyses will be provided in the Modeling Analysis Plan. The results will be reported in a separate document from the Clinical Study Report.

6.9 IMMUNOGENICITY ANALYSES

Immunogenicity analyses will be based on the immunogenicity analysis population.

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

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

6.10 BIOMARKER ANALYSES

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

Analyses will be performed to identify biomarkers that are predictive of response to RO6867461, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of RO6867461 activity, or can increase the knowledge and understanding of disease biology.

[redacted]

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of

transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

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

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

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

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the

informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC

policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of GCP guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

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

Approximately 225 sites globally will participate to enroll approximately 900 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. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

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

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of

the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities

Table 1 Study Flowchart: Day 1, Day 7, Week 4 through Week 52, and Early Termination

		Visit Day		Visit Week													ET
	Screening	1[a]	7	4	8	12	16	20	24	28	32	36	40	44	48	52	Visit[b]
Visit Window (days)	–28 to –1	NA	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥ 28)
Main informed consent[c]	x																
Optional aqueous, vitreous and blood sample informed consent[c]	x	x															
Optional (RBR) residual samples and DNA whole blood sample informed consent[c]	x	x															
Review of inclusion and exclusion criteria	x	x															
Demographics (age, sex, and self-reported race/ethnicity)	x																
Medical and surgical history including tobacco history[d]	x																
Physical examination[e]	x																x
Body weight and height	x																
Vital signs[f]	x	x															x
NEI VFQ-25[g]		x							x							x	x
BCVA[h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pre-treatment IOP[i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test[j, k]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

Table 1 Study Flowchart: Day 1, Day 7, Week 4 through Week 52, and Early Termination (cont.)

		Visit Day		Visit Week												ET
	Screening	1[a]	7	4	8	12	16	20	24	28	32	36	40	44	48	52	Visit[b]
Visit Window (days)	–28 to –1	NA	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥ 28)
Whole blood sample (hematology, coagulation [aPTT and PT], serum chemistry, and urinalysis)[j, l]	x																
HbA_{1C}[j]	x															x	x
Optional aqueous humor sample[j, m]		x	x				x	x			x						x
Optional vitreous humor sample[j, n]		Can be collected if vitrectomy is necessary															
Optional whole blood sample for DNA[j, o]		x															
Plasma PK sample[j, o]		x		x						x						x	x
Optional PK plasma sample (if aqueous humor sample is collected)[j, m]			x								x						
Plasma PD sample[j, o]		x		x						x						x	x
Optional PD plasma sample (if aqueous humor sample is collected)[j, m]			x								x						
Plasma ADA sample[j, o]		x		x						x						x	x
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT[p]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Optional OCT-A[p, q]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

Table 1 Study Flowchart: Day 1, Day 7, Week 4 through Week 52, and Early Termination (cont.)

		Visit Day		Visit Week													ET
	Screening	1[a]	7	4	8	12	16	20	24	28	32	36	40	44	48	52	Visit[b]
Visit Window (days)	–28 to –1	NA	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥ 28)
FFA[p]		x					x									x	x
CFP[p]	x						x									x	x
Administration of study treatment[r]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Finger-counting test[s]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	
IOP (post-study treatment)[t]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events[u]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications[v]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures[w]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA=anti-drug antibody; Ang-2=angiopoietin-2; BCVA=best-corrected visual acuity; CFP=color fundus photograph; DME=diabetic macular edema; eCRF=electronic Case Report Form; ET=early termination; FFA=fundus fluorescein angiography; HbA_{1C}=hemoglobin A_{1C}; ICF = Informed Consent Form; IOP=intraocular pressure; NEI VFQ-Q25=National Eye Institute 25-Item Visual Functioning Questionnaire; OCT-A=optical coherence tomography–angiography; PD=pharmacodynamic; PK=pharmacokinetic; RBR=Research Biosample Repository; SD-OCT=spectral-domain optical coherence tomography; SOC=standard of care; VA=visual acuity; VEGF-A=vascular endothelial growth factor–A.

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day, except those at screening. All study visits will be scheduled relative to the date of the Day 1 visit (first study treatment).

There must be a minimum of 21 days between study treatment visits occurring from the Day 1 visit through the Week 96 visit. The final study visit at Week 100 should not occur earlier than 28 days after the last study treatment. SOC treatment for DME in the fellow eye may be provided by the Sponsor as long as the patient remains in the study (see Section 4.4.1). SOC treatments after the ET visit or the final study visit (Week 100) will not be supplied by the Sponsor.

[a] The screening and Day 1 (randomization) visits may occur as a combined visit if all assessments are completed and evaluated within 2 business days. Informed consent must be administered and signed by a patient before any study-specific screening procedure is performed. When screening and randomization are combined and performed in 1 day, assessments listed for both visits should be conducted only once. If the combined visit is conducted within 2 business days, then the following safety assessments will be repeated on the day of patient's randomization and study treatment administration: slitlamp examination, indirect ophthalmoscopy, and pre- and post-treatment IOP measurements (recorded on the Day 1 eCRF and dated accordingly).

[b] Patients who are discontinuing from the study early (prior to the final study visit at Week 100) but have not withdrawn consent should return for an ET visit after a minimum of 28 days have elapsed following their last study treatment.

Appendix 1
Schedule of Activities (cont.)

Table 1 Study Flowchart: Day 1, Day 7, Week 4 through Week 52, and Early Termination (cont.)

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

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

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

[f] Vital signs include measurement of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure; at the Day 1 visit, vital signs should be recorded before study treatment. Vital signs will be measured with the patient in a seated position after resting for 5 minutes.

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

[h] Perform the assessments prior to dilating the eyes.

[i] Perform the assessments prior to dilating the eyes at screening and at each study visit, and if applicable, at the ET visit.

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

[k] Starting on Day 1, collect and perform the urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, collect the serum pregnancy sample and forward it to the central laboratory for testing. If the serum pregnancy test is positive, do not administer study treatment.

[l] Hematology includes hemoglobin, hematocrit, quantitative platelet count, RBC counts, WBC counts, and differentials, including neutrophils, lymphocytes, bands, eosinophils, basophils, and monocytes (absolute). Serum chemistry panel includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, ALP, AST, ALT, and uric acid. Urinalysis includes specific gravity, pH, blood, protein, ketones, glucose, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal). If the screening and Day 1 (randomization) visits occur as a combined visit, a historic HbA1c value must be available from within 2 months prior to Day 1. In this instance, results from the screening samples are not required for randomization.

[m] If a patient consents to collection of optional aqueous humor sample, collect the sample at indicated timepoints prior to study treatment administration. Not applicable for a site that has not been granted approval by a site's Institutional Review Board or Ethics Committee.

[n] If vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. A PK blood sample (for plasma preparation) should also be collected and shipped to the Sponsor. Vitreous humor samples will be analyzed primarily for RO6867461 concentrations and may also be analyzed for aflibercept concentrations. The remaining samples may be analyzed for [redacted] and possibly other biomarkers.

Appendix 1
Schedule of Activities (cont.)

Table 1 Study Flowchart: Day 1, Day 7, Week 4 through Week 52, and Early Termination (cont.)

[o] If the optional whole blood DNA sample is not obtained at the assigned visit (Day 1), the sample may be collected at any subsequent study visit when a blood draw is being performed for other purposes as specified (e.g., PK, 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. At specified visits, the plasma PK, PD, and ADA samples will be collected prior to study treatment.

[p] The central reading center will review SD-OCT and CFP images obtained at screening for determination of patient eligibility. At all subsequent visits, outputs from all types of imaging assessments will be sent to the relevant central reading center. See the central reading center manual for additional details. Note: After randomization, if a patient misses a study visit when ocular images are scheduled, the images should be obtained at the next scheduled visit the patient attends. The baseline FFA may be obtained either at the screening or the Day 1 visit.

[q] To be conducted at sites with OCT-A capability.

[r] At study treatment visits, randomized patients will receive study drug at some visits and sham at other visits or aflibercept at some visits and sham at other visits. The timing of these treatments will depend on the treatment arm to which they are randomized, which will be masked.

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

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

[u] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment (Day 1), all adverse events will be reported until the final study visit or if applicable until the ET visit. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event 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.

[v] Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications such as proparacaine, etc.) used by a patient within 7 days preceding Day 1 and through the conclusion of the patient's study participation or ET visit.

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

Appendix 1
Schedule of Activities (cont.)

Table 2 Study Flowchart: Week 56 through Week 100 and Early Termination

	Week Visit												ET Visit [a]
	56	60	64	68	72	76	80	84	88	92	96	100	
Visit Window (days)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥28 and <35)	(≥28)
Physical examination [b]												x	x
Vital signs [c]												x	x
NEI VFQ-25 [d]												x	x
BCVA [e]	x	x	x	x	x	x	x	x	x	x	x	x	x
Pre-treatment IOP [f]	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [g, h]	x	x	x	x	x	x	x	x	x	x	x	x	x
Whole blood sample (hematology, coagulation [aPTT and PT], serum chemistry, and urinalysis) [g, i]	x												
HbA_{1C} [g]												x	x
Optional aqueous humor sample [f, j]						x	x	x	x				x

Appendix 1
Schedule of Activities (cont.)

Table 2 Study Flowchart: Week 56 through Week 100 and Early Termination (cont.)

	Week Visit												ET Visit [a]
	56	60	64	68	72	76	80	84	88	92	96	100	
Visit Window (days)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(≥28 and <35)	(≥28)
Optional vitreous humor sample [f, k]	Can be collected if vitrectomy is necessary.												
Plasma PK sample [f, k]						x						x	x
Plasma PD sample [f, k]						x						x	x
Plasma ADA sample [f, k]						x						x	x
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x
Indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [l]	x	x	x	x	x	x	x	x	x	x	x	x	x
Optional OCT-A [l, m]	x	x	x	x	x	x	x	x	x	x	x	x	x
FFA [l]											x		x
CFP [l]											x		x
Administration of study treatment [n]	x	x	x	x	x	x	x	x	x	x	x		
Finger-counting test [o]	x	x	x	x	x	x	x	x	x	x	x		
IOP post-treatment [p]	x	x	x	x	x	x	x	x	x	x	x		
Adverse events [q]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [r]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [s]	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

Table 2 Study Flowchart: Week 56 through Week 100 and Early Termination (cont.)

ADA=anti-drug antibody; BCVA=best-corrected visual acuity; CFP=color fundus photograph; DME=diabetic macular edema; eCRF=electronic Case Report Form; ET=early termination; FFA=fundus fluorescein angiography; HbA_{1C}=hemoglobin A_{1C}; IOP=intraocular pressure; NEI VFQ-Q25=National Eye Institute 25-Item Visual Functioning Questionnaire; OCT-A=optical coherence tomography–angiography; PD=pharmacodynamic; PK=pharmacokinetic; SD-OCT=spectral-domain optical coherence tomography; SOC=standard of care; VA=visual acuity; VEGF-A=vascular endothelial growth factor–A.

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day. All study visits will be scheduled relative to the date of the Day 1 visit (first study treatment). There must be a minimum of 21 days between all study treatment visits occurring at the Day 1 visit through the Week 100 visit.

SOC treatment for DME in the fellow (non–study) eye may be provided by the Sponsor as long as the patient remains in the study (see Section 4.4.1). SOC treatment after the ET visit or the final study visit (Week 100) will not be supplied by the Sponsor.

[a] Patients who are discontinuing from the study early (prior to the final study visit at Week 100) but have not withdrawn consent should return for an ET visit after a minimum of 28 days have elapsed following the last study treatment.

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

[c] Vital signs include measurement of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure; at the Day 1 visit, vital signs should be recorded before study treatment. Vital signs will be measured with the patient in a seated position after resting for 5 minutes.

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

[e] Perform the assessments prior to dilating the eyes.

[f] Perform the assessments prior to dilating the eyes, prior to the study treatment, and at the final or ET visit.

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

[h] Starting on Day 1, collect and perform the urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, collect the serum pregnancy sample and forward it to the central laboratory for testing. If the serum pregnancy test is positive, do not administer study treatment.

Appendix 1
Schedule of Activities (cont.)

Table 2 Study Flowchart: Week 56 through Week 100 and Early Termination (cont.)

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

[j] If a patient consents to collection of optional aqueous humor sample, collect the sample at indicated timepoints prior to study treatment administration. Not applicable for a site that has not been granted approval by a site's Institutional Review Board or Ethics Committee.

[k] If vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. A PK blood sample (for plasma preparation) should also be collected and shipped to the Sponsor. Vitreous humor samples will be analyzed primarily for RO6867461 concentrations and may also be analyzed for aflibercept concentrations. The remaining samples may be analyzed for [redacted] and possibly other biomarkers.

[l] The outputs from imaging assessments will be sent to the central reading center. See the central reading center manual for additional details. Note: After randomization, if a patient misses a study visit when ocular images are scheduled, the images should be obtained at the next scheduled visit the patient attends.

[m] To be conducted at sites with OCT-A capability.

[n] At study treatment visits, randomized patients will receive study drug at some visits and sham at other visits or aflibercept at some visits and sham at other visits. The timing of these treatments will depend on the treatment arm to which patients are randomized, which will be masked.

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

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

Appendix 1
Schedule of Activities (cont.)

Table 2 Study Flowchart: Week 56 through Week 100 and Early Termination (cont.)

[q] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment (Day 1), all adverse events will be reported until 28 days after their last study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event 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.

[r] Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications such as proparacaine, etc.) used by the patient within 7 days preceding Day 1 and through the conclusion of the patient's study participation or the ET visit.

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

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 [e]

IOP = intraocular pressure.

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

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

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

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

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

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

Table 1 Grading Scale for Anterior Chamber Flare or Cells

Grade	Description
	Flare
0	No protein is visible in the anterior chamber when viewed by an experienced observer using slitlamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
Trace	Trace amount of protein is detectable in the anterior chamber. This protein is visible only with careful scrutiny by an experienced observer using slitlamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
1+	Slight amount of protein is detectable in the anterior chamber: the presence of protein in the anterior chamber is immediately apparent to an experienced observer using slitlamp biomicroscopy and high magnification, but such protein is detected only with careful observation with the naked eye and a small, bright, focal slit-beam of white light.
2–3+	Moderate amount of protein is detectable in the anterior chamber. These grades are similar to 1+ but the opacity would be readily visible to the naked eye of an observer using any source of a focused beam of white light. This is a continuum of moderate opacification, with 2+ being less apparent than 3+.
4+	A large amount of protein is detectable in the anterior chamber. This grade is similar to 3+, but the density of the protein approaches that of the lens. Additionally, frank fibrin deposition is frequently seen in acute circumstances. It should be noted that because fibrin may persist for a period of time after partial or complete restoration of the blood–aqueous barrier, it is possible to have resorbing fibrin present with lower numeric assignations for flare (e.g., 1+ flare with fibrin).
	Cells
0	No cells are seen in any optical section when a large slit-amp beam is swept across the anterior chamber.
Trace	Few (1–3) cells are observed when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, not every optical section contains circulating cells.
1+	3–10 cells per optical section are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.
2+	10–25 cells are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.

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

Table 1 Grading Scale for Anterior Chamber Flare or Cells (cont.)

Grade	Description
3+	25–50 cells are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells. Keratic precipitates or cellular deposits on the anterior lens capsule may be present.
4+	More than 50 cells are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains cells, or hypopyon is noted. As for fibrin deposition, hypopyon may persist for some period of time after the active exudation of cells into the anterior chamber has diminished or ceased entirely, making it possible to have 1+ circulating cells in the anterior chamber with a resolving hypopyon.

Modified from: Hogan et al. (1959).

Table 2 Grading Scale for Vitreous Cells

Cells in Retro-Illuminated Field	Description	Grade
0	Clear	0
1–20	Few opacities	Trace
21–50	Scattered opacities	1
51–100	Moderate opacities	2
101–250	Many opacities	3
≥251	Dense opacities	4

Modified from: Nussenblatt et al. (1996).

REFERENCES

Hogan MH, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. Am J Ophthalmol 1959;47(5, Part 2):155–70.

Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis: fundamentals and clinical practice. In: Nussenblatt RB, Whitcup SM, Palestine AG, editors. Examination of the patient with uveitis. 2nd revised edition. St Louis: Mosby, 1996; 64.

Appendix 4
Best-Corrected Visual Acuity Testing

SCOPE

The best-corrected visual acuity (BCVA) assessment must be conducted before pupil dilation. BCVA will be measured by trained and certified personnel at the study sites. The visual acuity (VA) examiner must be masked to each patient's study (treated) eye and treatment arm assignment. VA will be measured at the intervals specified in the protocol (see Appendix 1).

EQUIPMENT

The following are needed to conduct the examination:

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

TRAINING AND CERTIFICATION

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

Appendix 5
Color Fundus Photography

SCOPE

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

EQUIPMENT

See the central reading center manual.

PROCEDURE

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

Appendix 6
Fundus Fluorescein Angiography

SCOPE

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

EQUIPMENT

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

Film-based angiography is not acceptable.

DIGITAL IMAGING SYSTEMS AND CERTIFICATION

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

PROCEDURES

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

Appendix 7
Spectral-Domain Optical Coherence Tomography

SCOPE

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

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

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

EQUIPMENT

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

PROCEDURES AND CERTIFICATION

The central reading center 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 RO6867461 concentrations (pharmacokinetics), pharmacodynamics, anti-RO6867461 antibodies, blood DNA sample, laboratory assessment (hematology, serum chemistry, coagulation, and urinalysis), hemoglobin A_{1C} (HgA_{1C}), 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 treating physician from patients who consent to the procedure and sample acquisition. An aqueous humor sample will be collected before the patient's study eye treatment at the visits as indicated in Appendix 1. Please refer to the central laboratory manual for additional details regarding sample collection and shipping information.

OPTIONAL UNSCHEDULED COLLECTION OF VITREOUS HUMOR SAMPLE COLLECTION

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

Appendix 8
Biological Sample Collection and Shipping Instructions (cont.)

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

Vitreous humor samples will be analyzed primarily for RO6867461 concentrations and may also be analyzed for aflibercept concentrations. The remaining samples may be analyzed for [redacted], and possibly other biomarkers.

BIOLOGICAL SAMPLES STORAGE DURATION

The hematology, serum chemistry, urinalysis, coagulation, serum, urine pregnancy tests, and HbA_{1c} samples will be destroyed after their analysis during the study.

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

- 1 - ***version 2000***

Instructions:

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

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

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

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

(Circle One)

READ CATEGORIES:

Excellent	**1**
Very Good	**2**
Good	**3**
Fair	**4**
Poor	**5**

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

(Circle One)

READ CATEGORIES:

Excellent	**1**
Good	**2**
Fair	**3**
Poor	**4**
Very Poor	**5**
Completely Blind	**6**

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

		(Circle One)
READ CATEGORIES:	**None of the time**	**1**
	A little of the time	**2**
	Some of the time	**3**
	Most of the time	**4**
	All of the time?	**5**

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

		(Circle One)
READ CATEGORIES:	**None**	**1**
	Mild	**2**
	Moderate	**3**
	Severe, or	**4**
	Very severe?	**5**

PART 2 - DIFFICULTY WITH ACTIVITIES

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

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

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

(Circle One)

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

No..... 2

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

(Circle One)

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

Gave up 2

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

(Circle One)

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

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

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

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

(Circle One)

No difficulty at all..... 1

A little difficulty..... 2

Moderate difficulty..... 3

Extreme difficulty..... 4

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

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

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

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

Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

PART 3: RESPONSES TO VISION PROBLEMS

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

(Circle One On Each Line)

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

(Circle One On Each Line)

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

SUBSCALE: NEAR VISION

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

(Circle One)

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

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

(Circle One)

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

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

SUBSCALE: DISTANCE VISION

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

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

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Appendix 9
National Eye Institute Visual Functioning Questionnaire–25 (cont.)

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

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

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

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

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

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