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 AND RHINE)

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STATISTICAL ANALYSIS PLAN

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 AND RHINE)**

PROTOCOL NUMBERS: GR40349 and GR40398

STUDY DRUG: Faricimab (RO6867461)

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PLAN PREPARED BY: [redacted], M.Sc.

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STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
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Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
ANCOVA	analysis of covariance
Ang-2	angiopoietin-2
APTC	anti-Platelet Trialist's Collaboration
BCVA	best-corrected visual acuity
[redacted]	[redacted]
CFP	color fundus photograph
CIs	confidence intervals
CMH	Cochran Mantel-Haenszel
CRC	central reading center
CSR	clinical study report
CST	central subfield thickness
DME	diabetic macular edema
DR	diabetic retinopathy
DRS	diabetic retinopathy severity
DRSS	Diabetic Retinopathy Severity Scale
EC	Ethics Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
FAZ	foveal avascular zone
FDA	Food and Drug Administration
FFA	fundus fluorescein angiography
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IOI	intraocular inflammation
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
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated-measures (model)
MNAR	missing not at random

NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire–25
OCT-A	optical coherence tomography–angiography
PD	pharmacodynamic
PDR	proliferative diabetic retinopathy
PK	pharmacokinetic
[redacted]	[redacted]
PTI	personalized treatment interval
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
Q16W	every 16 weeks
SAE	serious adverse event
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SS-OCT	swept-source optical coherence tomography
U.S.	United States
UWF	ultra-wide field
VA	visual acuity
VEGF(– A)	vascular endothelial growth factor(– A)

1. BACKGROUND

Diabetic macular edema (DME), a complication of diabetic retinopathy (DR), can develop at any stage of the underlying disease of retinal microvasculature. DME occurs with increasing frequency as the underlying DR worsens from non-proliferative DR to proliferative DR (PDR). DME is the most common cause of moderate and severe visual impairment in patients with DR, and affects approximately 14% of patients with diabetes. 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. VEGF also upregulates a homeostatic factor, angiopoietin-2 (Ang-2), counteracting vessel stabilization. In summary, both Ang-2 and VEGF-A are recognized as key factors mediating diabetic eye disease pathogenesis.

The development of anti-VEGF pharmacotherapy in the past decade has led to dramatic improvements in visual outcomes for patients with DME. Despite these advancements, a significant proportion of patients do not experience clinically meaningful improvements in vision in the real world. The current standard of care for administration of anti-VEGF injections requires patients to undergo frequent clinical examinations and intravitreal (IVT) injections imposing a significant burden on patients, caregivers, and treating physicians. In addition, anti-VEGF monotherapy does not fully address other pathways, including inflammation and pericyte destabilization, that contribute to worsening of diabetic eye disease. Consequently, patients on anti-VEGF monotherapy may not be gaining as much vision as they could. Taken together, new treatments that target additional pathways could address the above unmet medical needs by improving visual acuity (VA)outcomes and reducing the burden of IVT injections in DME.

Faricimab is a humanized full-length bispecific immunoglobulin 1 antibody that selectively neutralizes Ang-2 and VEGF-A. The Ang-2 binding and the VEGF binding variable regions of faricimab bind to Ang-2 and VEGF independently and simultaneously with high affinity. Based on this novel mechanism of action of faricimab, and existing evidence of upregulated concentrations of both Ang-2 and VEGF in the vitreous in patients with DR, 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. The available Phase I and II efficacy and safety data showed a benefit–risk profile that supports further assessment of the efficacy, durability, and safety of faricimab compared with anti-VEGF IVT monotherapy in a Phase III setting.

The purpose of this document is to provide details of the planned analyses for Phase III studies GR40349 (YOSEMITE) and GR40398 (RHINE). The designs of these studies are identical with the exception of a [redacted], which is planned as part of GR40398 (refer to Section 2.2). An [redacted] was originally considered for GR40349 (YOSEMITE) but was not implemented. In this Statistical Analysis Plan, study collectively refers to both studies GR40349 (YOSEMITE) and GR40398 (RHINE)

and study drug refers to faricimab or aflibercept whereas study treatment refers to faricimab, aflibercept, or the sham procedure.

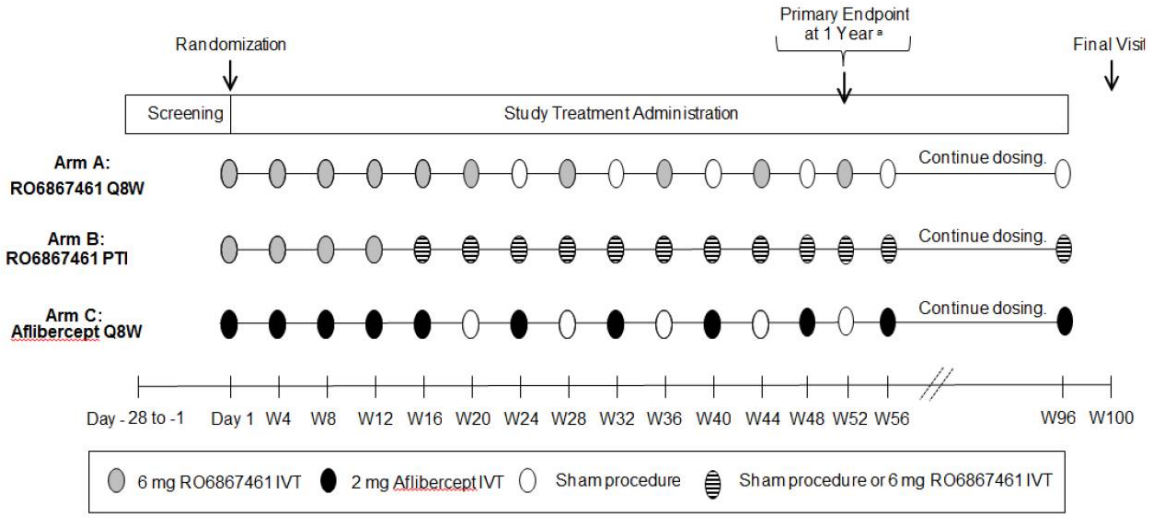
The analyses specified in this document supersede the analysis plan described in the study protocols.

2. STUDY DESIGN

Studies GR40349 (YOSEMITE) and GR40398 (RHINE) are identical Phase III, double-masked, multicenter, randomized, active comparator–controlled, parallel-group studies evaluating the efficacy, safety, pharmacokinetics, and optimal treatment frequency of faricimab when dosed every 8 weeks (Q8W) or on a personalized treatment interval (PTI) regimen compared with aflibercept (Eylea®) monotherapy for approximately 100 weeks duration in patients with DME. For the study schema, see Figure 1.

[redacted]

Figure 1 Study Schema



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

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. 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).

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 every 4 weeks (Q4W) to Week 20, followed by 6 mg IVT faricimab injections Q8W to Week 96.
- 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.
- 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.

Patients in all three treatment arms will complete scheduled study visits Q4W for the study duration and return for a final visit at Week 100. A sham procedure will be administered to patients in all three treatment arms when they are not receiving study treatment to maintain masking among treatment arms.

Refer to Section 3 of the Study Protocols for further details on study design and Appendix 3 of this document for the Schedule of Activities.

Study Drug Dosing Interval Determination for Patients in the Personalized Treatment Interval Arm (Arm B)

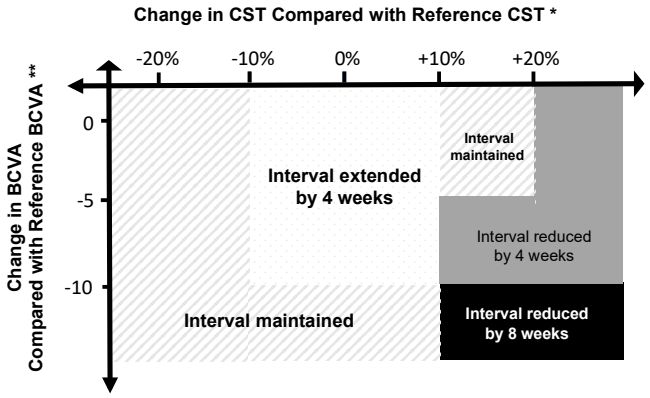
Study drug dosing interval decisions in the PTI arm are automatically calculated by the interactive voice or web-based response system (IxRS) based on the algorithm described in this section. Study drug dosing visits are visits when a patient is assigned to receive faricimab.

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 the central subfield thickness (CST) meets the predefined reference CST threshold (CST < 325 μm for Spectralis spectral-domain optical coherence tomography [SD-OCT], or < 315 μm for Cirrus SD-OCT or Topcon SD-OCT), as determined by the central reading center (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 best-corrected visual acuity (BCVA) compared with reference CST and reference BCVA. 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.

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



BCVA = best-corrected visual acuity; CST = central subfield thickness; IxRS = interactive voice or web-based response system.

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.

* Reference 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 BCVA: the mean of the three best BCVA scores obtained at any prior study drug dosing visit.

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

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1 and Appendix 2.

2.2 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 Intent-to-Treat (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%.

For each unmasked independent Data Monitoring Committee (iDMC) safety review performed prior to the primary analysis, a nominal type I error penalty of 0.0001 will be taken such that efficacy analyses would be performed with a family wise significance

level of 0.0496 (refer to Section 3.3). This type I error adjustment is not expected to impact the sample size or power.

The study protocol mentions that the Sponsor might re-estimate the sample size in a masked manner prior to completing enrollment. However, the sample size re-estimation was not performed and the sample size was not modified due to faster than anticipated enrollment.

[redacted]

2.3 ANALYSIS TIMING

The primary analysis 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 last patient last visit [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. At the time of the primary analysis, the study will be ongoing. Results of the primary analyses, summarized by treatment group, may be reported to the public before completion of the study. 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 have been cleaned and verified.

[redacted]

[redacted]

3. STUDY CONDUCT

3.1 RANDOMIZATION

Using a stratified permuted block randomization method, patients will be randomized in a 1:1:1 ratio so that approximately 300 patients are randomized to each of the three treatment arms (faricimab Q8W, faricimab PTI, aflibercept Q8W). Randomization is 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 [U.S.] and Canada, Asia, and the rest of the world). Randomization will be performed through an IxRS and the first study treatment will be administered on the same day as randomization (i.e., at the Day 1 visit).

Subject randomization and study treatment kit number assignment were audited by an external and independent data coordinating center (iDCC) to ensure that randomization and kit assignment were carried out correctly by the IxRS. This randomization audit was performed on January 25, 2019 (approximately four months after first patient in) with randomization information available for 178 patients available in YOSEMITE and 152 patients in RHINE. No major issues were detected during the audit, and the corresponding report will be provided by the iDCC at study unmasking for the primary analysis.

The same randomization method is implemented for [redacted] (as part of GR40398 [RHINE]).

3.2 INDEPENDENT REVIEW FACILITIES

All ocular images are obtained by trained site personnel at the study sites and forwarded to CRCs, for independent analysis and storage. As part of the screening process, the CRCs evaluate color fundus photographs (CFPs) and SD-OCT images to provide an objective, masked assessment of patient eligibility. During the study treatment period, the CRCs provide a masked evaluation of all ocular images including CFP, fundus fluorescein angiography (FFA), Optional ultra-wide field (UWF) CFP, SD-OCT or swept-source OCT (SS-OCT), and optional OCT−angiography (OCT-A). The data resulting from this masked review of ocular images are forwarded to the Sponsor and additionally, the SD-OCT CST values are forwarded to the IxRS for treatment interval determination.

Potential Anti-Platelet Trialists' Collaboration (APTC) events that are identified during the study are externally adjudicated on an ongoing basis. A dossier of available information on each case of interest is provided to the external expert adjudicators for their review and assessment.

3.3 DATA MONITORING

An iDMC monitors safety and study conduct on an ongoing basis throughout the study. Members of the iDMC are external to the Sponsor and follow a charter that outlines the iDMC's roles and responsibilities. The iDMC meets approximately every 6 months (frequency adjustable as required) to evaluate unmasked ocular and non-ocular safety events. After reviewing the data, the iDMC provides a recommendation to the Sponsor as described in the iDMC Charter. Final decisions rest with the Sponsor. Any outcomes of these data reviews that affect study conduct must be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics Committees (IRBs/ECs).

A nominal type I error penalty of 0.0001 will be taken for each time the iDMC reviews unmasked data prior to the formal analysis of the primary efficacy endpoint. At the time of the primary analysis, it is estimated that four safety interim data reviews will have been conducted by the iDMC; therefore, efficacy analyses would be performed with a family-wise significance level of 0.0496. The final significance level used in the analysis will be adjusted based on the actual number of iDMC review meetings conducted during the study.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

The analysis populations presented in this section are based on patients enrolled during the global enrollment phase of the study and will not include [redacted] (as part of GR40398 [RHINE]), unless otherwise specified. The analysis plan for [redacted] is presented in Section 5.

4.1.1 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.

4.1.2 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 randomization. For analyses based on this patient population, patients will be grouped according to the treatment assigned at randomization.

4.1.3 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 that impacts the efficacy evaluation or the treatment interval determination. For analyses based on this patient population, patients will be grouped according to the actual treatment received 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.

Prior to study unblinding, protocol deviations will be reviewed and a determination of the definition of the population for per protocol analysis will be made.

4.1.4 Safety-Evaluable Population

The safety-evaluable population will comprise all patients who receive at least one injection of active study drug (faricimab or aflibercept) in the study eye. For analyses based on this patient population, patients will be grouped according to the actual treatment received as described in Section 4.1.3.

4.1.5 Pharmacokinetic-Evaluable Population

The pharmacokinetic (PK) analyses will include safety-evaluable patients with at least one plasma sample, provided sufficient dosing information (dose and dosing time) is available, and such patients will be grouped according to treatment received as described in Section 4.1.3.

4.1.6 Immunogenicity-Analysis Population

The immunogenicity prevalence set will consist of all patients randomized to faricimab with at least one determinant anti-drug antibody (ADA) assessment. Patients will be grouped according to treatment received as described in Section 4.1.3, or if no treatment is received prior to study discontinuation, according to treatment assigned.

The immunogenicity incidence set will consist of all patients receiving faricimab with at least one determinant post-baseline ADA assessment. Patients will be grouped according to treatment received as described in Section 4.1.3.

4.2 ANALYSIS OF STUDY CONDUCT

The analysis of study conduct will be based on the ITT population and the treatment-naive population.

The number of patients randomized will be tabulated by country, site, and treatment arm. Patient disposition (the number of patients randomized, treated, and completing through the primary endpoint timing, as well as the end of study) will be tabulated by treatment arm. Premature study drug discontinuation and study discontinuation, as well as reasons for discontinuations, will be summarized. Eligibility criteria deviations and other major protocol deviations will be summarized by treatment arm. The impact of COVID-19 will be assessed by including major protocol deviations related to COVID-19 and by summarizing COVID-19 related intercurrent events by treatment arm.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race/ethnicity and region, and baseline disease characteristics (such as baseline BCVA, ocular assessments, and medical history) will be summarized by treatment as assigned for the ITT population and the treatment-naive population using means, SDs, medians, and ranges for continuous variables, and counts and proportions for categorical variables, as appropriate. In addition, select baseline disease characteristics will be presented by treatment as assigned for patients with evaluable baseline DR severity score.

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

Baseline is defined as the last available measurement obtained on or prior to randomization. Patients with missing baseline assessments will not be imputed.

4.4 EFFICACY ANALYSIS

Efficacy analyses will be based on the ITT population and the treatment-naive population, unless otherwise specified. A supplemental analysis based on the per-protocol population will also be conducted for the primary and key secondary non-inferiority analyses.

Unless otherwise noted, analyses of efficacy outcome measures 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 (U.S. and Canada, Asia, and the rest of the world). The stratification factors as recorded in IxRS will be used.

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 mixed model for repeated measures (MMRM). Binary endpoints will be analyzed using stratified estimation for binomial proportions. The estimates and confidence intervals (CIs) will be provided for the mean (for continuous variables) or proportion (for binary variables) for each of the three treatment arms and for the difference in means or proportions between pairwise

comparisons of active comparator (aflibercept Q8W) and each of the faricimab arms (Q8W and PTI).

4.4.1 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 four meters.

The primary estimand is defined as follows:

- Population(s):
  - Adult patients with DME, either treatment-naive or prior IVT anti-VEGF treated, as defined by the inclusion / exclusion criteria (see Section 4.1.1) (ITT Population)

    OR
  - Adult treatment-naive patients with DME, as defined by the inclusion / exclusion criteria (see Section 4.1.2) (Treatment-Naive Population)
- Variable: Change in BCVA score from baseline averaged over Weeks 48, 52, and 56. BCVA score is based on the ETDRS VA chart assessed at a starting distance of 4 meters
- Intercurrent events:
  - Discontinuation of study treatment due to adverse events (AEs) or lack of efficacy not due to COVID-19: A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event
  - Use of any prohibited systemic treatment or prohibited therapy in the study eye (Section 4.4.2 of Protocol Version 3) not due to COVID-19: A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event
  - Discontinuation of study treatment due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event
  - Use of any prohibited systemic treatment or prohibited therapy in the study eye due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event
  - Missed dose(s) with potentially major impact on efficacy due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event
  - COVID-19 death: A hypothetical strategy will be applied
- Population-level summary: Difference in adjusted mean between each of the two faricimab arms (Q8W and PTI) and aflibercept (Q8W) arm

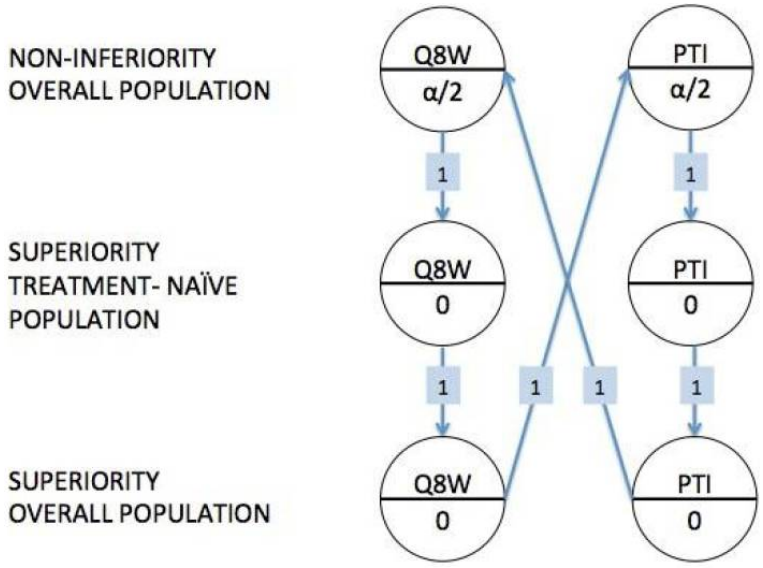
4.4.1.1 Hypothesis Testing and Type I Error Control

For each of the two faricimab arms (Q8W and PTI), the following three hypotheses will be tested separately against the active comparator (aflibercept Q8W) at an overall significance level of $\alpha = 0.0496$ using a graph-based testing procedure (Bretz et al. 2009, Bretz et al. 2011) to control for the overall type I error rate:

- Non-inferiority of faricimab compared with aflibercept Q8W in the ITT population with a non-inferiority margin of 4 letters
- 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 at the $\alpha/2$ (=0.0248) level, then $\alpha/2$ will be propagated to the beginning of the other treatment sequence, which will be tested at a significance level of $\alpha = 0.0496$. Of note, non-inferiority will be tested one-sided at half of the designated significance level shown in Figure 3. If the lower bound of the two-sided confidence limit for the difference in adjusted mean for the treatment group in question (faricimab Q8W or PTI) and the active comparator (aflibercept Q8W) is greater than -4 letters, then that faricimab treatment group in question (Q8W or PTI) is considered non-inferior to aflibercept.

Figure 3 Graph-Based Testing Procedure for the Primary Endpoint



PTI = personalized treatment interval; Q8W = every 8 weeks.
Note: $\alpha = 0.0496$.

[redacted]

4.4.1.2 Analysis Methods

The primary analysis will be performed using a MMRM. The model will include the change from baseline at Weeks 4–56 as the response variable and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), 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 by the MMRM model, assuming a missing at random missing data mechanism. Non-standard BCVA data (assessed by ETDRS BCVA testing with prior visit refraction, test performed by unmasked certified ETDRS BCVA assessor, or by uncertified experienced ETDRS BCVA assessor) will be excluded from the analyses.

4.4.1.3 Sensitivity Analyses

The following sensitivity analysis using a different handling of missing data will be performed for the primary efficacy endpoint to evaluate the robustness of the primary analysis finding:

a) Last observation carried forward:

The estimand and analysis method will be the same as the primary analysis (Section 4.4.1), with the exception that any missing BCVA assessments due to any reason will be imputed using the last available post-baseline observation prior to the occurrence of missing data. Additionally, BCVA assessments after the COVID-19 related

intercurrent event will be censored and will be imputed using the last available post-baseline observation prior to the COVID-19 intercurrent event.

4.4.1.4 Supplementary Analyses

The following supplementary analyses will be performed for the primary efficacy endpoint comparisons to provide further understanding of treatment effect:

a) Per-protocol analysis:

The per-protocol analysis will follow the same intercurrent events, handling of intercurrent events, and analysis method as the primary analysis (Section 4.4.1) with the exception that the analysis will be based on the per-protocol population (Section 4.1.3). Patients with major protocol deviations that impact the efficacy evaluation or the treatment interval determination, whether or not related to COVID-19, will be excluded from the analysis. This analysis will be performed for the non-inferiority assessment only.

b) Analysis using treatment policy strategy for all intercurrent events:

The analysis method, populations, and definition of intercurrent events will be the same as the primary analysis (Section 4.4.1). However, all intercurrent events will follow a treatment policy strategy, where all observed values will be used regardless of the occurrence of the intercurrent event.

c) Analysis using hypothetical strategy for all intercurrent events:

The analysis method, populations, and definition of intercurrent events will be the same as the primary analysis (Section 4.4.1). However, all intercurrent events will follow a hypothetical strategy, where all values will be censored after the occurrence of the intercurrent event.

d) ANCOVA analysis:

The analysis of covariance (ANCOVA) analysis will use the same populations, intercurrent events, and handling of intercurrent events as in the primary analysis. The analysis will be conducted using an ANCOVA model with adjustment for the following covariates: treatment group, baseline BCVA (continuous), as well as randomization stratification factors. The dependent variable in the ANCOVA model is the average of non-missing values of Weeks 48, 52, and 56 assessments in change from baseline in BCVA score (if at least one assessment is available then the average of the non-missing assessments will be used; assessments after the COVID-19 related intercurrent events will be excluded before taking the average). Missing observations will not be imputed.

e) Trimmed Mean Analysis:

The trimmed mean analysis will be used to assess the difference in BVCA between each faricimab treatment group and the active comparator using a truncated distribution, truncating patients with the worst outcome, with the assumption that patients have the worst outcome after non-COVID-19 related intercurrent events. The estimand is defined as follows:

- Population(s):
  - Adult patients with DME, either treatment-naive or prior IVT anti-VEGF treated, as defined by the inclusion / exclusion criteria (see Section 4.1.1) (ITT Population)

    OR
  - Adult treatment-naive patients with DME, as defined by the inclusion / exclusion criteria (see Section 4.1.2) (Treatment-Naive Population)
- Variable: Change in BCVA score from baseline averaged over Weeks 48, 52, and 56. BCVA score is based on the ETDRS VA chart assessed at a starting distance of 4 meters
- Intercurrent events:
  - Discontinuation of study treatment due to AEs or lack of efficacy not due to COVID-19: Assume patients have the worst outcome after the intercurrent event
  - Use of any prohibited systemic treatment or prohibited therapy in the study eye (Section 4.4.2 of Protocol Version 3) not due to COVID-19: Assume patients have the worst outcome after the intercurrent event
  - Discontinuation of study treatment due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event
  - Use of any prohibited systemic treatment or prohibited therapy in the study eye due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event
  - Missed dose(s) with potentially major impact on efficacy due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event
  - COVID-19 death: A hypothetical strategy will be applied
- Population-level summary: Difference in adjusted trimmed mean between each of the two faricimab arms (Q8W and PTI) and aflibercept (Q8W) arm.

The trimmed mean analysis (Permutt and Li 2017) will be performed using an analysis of covariance (ANCOVA) model with adjustment for the following covariates: treatment group, baseline BCVA (continuous), as well as randomization stratification factors. The dependent variable in the ANCOVA model is the average of non-missing values of Weeks 48, 52, and 56 assessments in change from baseline in BCVA score (if at least

one assessment is available then the average of the non-missing assessments will be used; assessments after the COVID-19 related intercurrent events will be excluded before taking the average).

Patients with intercurrent events that are not related to COVID-19 will be considered to have the worst outcomes and will be trimmed from analysis if any of the following occurs:

- They have a non-COVID-19 related intercurrent event prior to Week 48
- They have a missing assessment at Week 48 and have a non-COVID-19 related intercurrent event at Week 48
- They have missing assessments at Weeks 48 and 52, and have a non-COVID-19 related intercurrent event at either one of these two visits
- They have missing assessments at Weeks 48, 52 and 56, and have a non-COVID-19 related intercurrent event at either one of these three visits

Such patients will be referred to as "must be trimmed patients".

Of note, patients in the following scenario will not be considered as "must be trimmed patients". If a patient has a non-missing Week 48 assessment and has a non-COVID-19 related intercurrent event at Week 48, then the change in BCVA from baseline will be calculated using Week 48 assessment only (since BCVA is assessed prior to any treatment administration, it is not expected to have an impact on BCVA even if they occur at the same study visit), and this patient will not be considered as a "must be trimmed patient". Similarly, if a patient has a non-missing Week 52 assessment and has a non-COVID-19 related intercurrent event at Week 52, then the change in BCVA from baseline will be calculated using Week 48 and 52 assessments only. If a patient has a non-missing Week 56 assessment and has a non-COVID-19 related intercurrent event at Week 56, then the change in BCVA from baseline will be calculated using Weeks 48, 52 and 56 assessments.

For the remaining patients without COVID-19 related intercurrent events, if they have at least one BCVA assessment for Weeks 48, 52, and 56, they will be considered "completers". If they have missing assessments at all three visits (Weeks 48, 52, and 56), the missing data will be considered missing at random and these patients will be removed from the analysis.

Patients with intercurrent events due to COVID-19 will be censored after the intercurrent event. If they have at least one BCVA assessment for Weeks 48, 52, and 56 prior to any COVID-19 related intercurrent event, they will be considered "completers". Otherwise, the missing data will be considered missing at random and these patients will be removed from the analysis.

The inferential statistics (i.e., CI, and p-values for the superiority tests only) for the trimmed mean will be based on the permutation test. The treatment assignments will be

permuted in a sufficiently large random sample of possible ways (~30,000 random samples will be generated). The method can be stated in the following four steps:

1. Remove patients whose missing assessments are considered missing at random (see definition above) from the analysis.
2. Order the data based on adjusted values from the ANCOVA model, and trim equal fractions (the trimming fraction will be finalized based on a masked assessment prior to the primary analysis) from both treatment arms.

   The adjusted values are determined as follows. An ANCOVA model as specified above will be fitted for all completers. The estimated treatment effect will be discarded and the coefficients for the covariates will be kept to calculate the adjusted value $Y - \beta' X$ for each patient, for which Y is the change in BCVA score averaged over Weeks 48, 52 and 56, X is the matrix for the covariates— baseline BCVA (continuous), and randomization stratification factors of baseline BCVA score, prior IVT anti-VEGF therapy, and region, and β is the estimated coefficient matrix for the covariates.

   These adjusted values will be used to rank the data within each treatment group. The “must be trimmed” patients will always be ranked the lowest (regardless of whether their adjusted values are available) and trimmed from the analyses. The best $(1-0.1)*100\%(=90\%)$ in each group will be used for the analysis specified in Step 3. If multiple patients have the same adjusted values, they will be ranked randomly relative to each other prior to trimming.

3. Refit the ANCOVA model (as specified above) to the trimmed data set, and compute the difference in trimmed mean between two treatment groups.
4. Repeat steps 2 and 3, 30,000 times based on augmented datasets with the treatment assignment randomly permuted according to the original randomization procedures (blocked randomization stratified by baseline BCVA score, prior IVT anti-VEGF therapy, and region).

When the proportion of the "must be trimmed patients" in either treatment group in the permuted data exceeds the planned trimmed fraction, the trimming fraction will be chosen adaptively as the greater of the proportions of the "must be trimmed patients" in the two treatment groups.

f) Multiple imputation:

The populations, intercurrent events, and handling of intercurrent events will be the same as in the primary analysis, however missing primary endpoint BCVA data will be imputed via multiple imputation. As in the primary analysis, intercurrent events related to COVID-19 will follow a hypothetical strategy where all values are censored after the intercurrent event, and intercurrent events not related to COVID-19 will follow a treatment policy strategy where all observed values are used regardless of the occurrence of the intercurrent event. The analysis will be performed using an ANCOVA

model in the same way as described above for the ANCOVA analysis (item d in Section 4.4.1.4).

Missing BCVA data resulting from intercurrent events related to COVID-19 will be assumed to be missing at random (MAR). Missing BCVA data for reasons that have not been specified as an intercurrent event will also be assumed MAR. Intercurrent events not related to COVID-19 that result in missing data will be assumed to be missing not at random (MNAR). Each arm will be imputed separately. The missing BCVA values for patients with MAR data will be imputed first while excluding the patients with MNAR data; the MNAR values will then subsequently be imputed. Imputation will only be performed for patients with missing BCVA data at all three primary endpoint timepoints (Weeks 48, 52, and 56), where a single value for each patient will be imputed. If at least one of the primary endpoint timepoint values is available after censoring from COVID-19 related intercurrent events, the averaged value will be used in the ANCOVA analysis and no imputation will be conducted.

For BCVA data that is MAR, the fully conditional specification predicted mean matching method will be used for imputation (SAS Institute 2018). This method imputes by selecting a value from a set of observed values whose predicted values are closest to the predicted value for the missing value from a simulated regression model. The regression model will be fit with observed values of BCVA at each timepoint j as the dependent variable, and BCVA at each prior timepoint, baseline BCVA (continuous), and the stratification factors as covariates. The BCVA values that are missing will be imputed sequentially.

$BCVA_j = \beta_0 + (\beta_1 * BCVA_1) + \ldots + (\beta_{j-1} * BCVA_{j-1}) + (\beta_j *$baseline BCVA [continuous]$) + (\beta_{j+1} *$baseline BCVA [>=64 letters vs. <63 letters]$) + (\beta_{j+2} *$prior IVT anti-VEGF therapy$) + (\beta_{j+3} *$region$)$

where j=1, 2, …, 12 such that $BCVA_j$ is the BCVA value at Week 4*j.

The number of observations whose corresponding predicted values are closest to the predicted values of the missing data will be set to 30 patients in the relevant treatment arm.

For BCVA data that is MNAR, an approximate Bayesian bootstrap method will be used for imputation. These patients will be assumed to have worse outcomes compared to the rest of the population and will be imputed from patients with non-missing BCVA data with the worst outcomes.

Suppose there are n_1 patients with at least one assessment from Weeks 48, 52, and 56 (i.e. patients with non-missing primary endpoint data after censoring for COVID-19 related intercurrent events), and n_0 patients that are missing all three assessments. The imputation steps will be as follows:

1. Among patients with at least one assessment from Weeks 48, 52, and 56, identify 10% of the patients with the worst values for change in BCVA score from

baseline averaged over the non-missing values of Weeks 48, 52, and 56. Call this Y_{obs}.

2. Draw n_1 observations randomly with replacement from Y_{obs} to create a new data set Y_{obs}*.

3. Draw n_0 values randomly with replacement from Y_{obs}* to obtain the missing values.

The imputation will be implemented in SAS using the three standard steps to generate inference from imputed data: imputation step, analysis step, and pooling step. The number of imputations will be set to 100.

1. The missing data will be filled in 100 times to generate 100 imputed datasets.
2. Each of the 100 imputed datasets will be analyzed using the ANCOVA model
3. The results from the 100 imputed data sets will be combined for inference following the methodology developed by Rubin (1987).

The SAS codes for multiple imputation will be added to a separate table/listing/graph mockup document (Data Analysis Plan – Module 2) prior to the study unmasking; and will also be included in the Analysis Data Reviewer's Guide.

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 Key Secondary Endpoint

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

The estimand for the key secondary endpoint is defined as follows:

- Population(s):
  - Adult patients with DME, either treatment-naive or prior IVT anti-VEGF treated, as defined by the inclusion / exclusion criteria (see Section 4.1.1) (ITT Population)

    OR
  - Adult treatment-naive patients with DME, as defined by the inclusion / exclusion criteria (see Section 4.1.2) (Treatment-Naive Population)
- Variable: Patient with ≥2-step DRS improvement from baseline on the ETDRS DRSS at Week 52
- Intercurrent events:
  - Discontinuation of study treatment due to AEs or lack of efficacy not due to COVID-19: A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event
  - Use of any prohibited systemic treatment or prohibited therapy in the study eye (Section 4.4.2 of Protocol Version 3) not due to COVID-19: A treatment policy

strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event

  - Discontinuation of study treatment due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event
  - Use of any prohibited systemic treatment or prohibited therapy in the study eye due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event
  - Missed dose(s) with potentially major impact on efficacy due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event
  - COVID-19 death: A hypothetical strategy will be followed
- Population-level summary: Difference in proportions between each of the two faricimab arms (Q8W and PTI) and aflibercept (Q8W) arm

4.4.2.2 Hypothesis Testing and Type I Error Control

Of note, non-inferiority will be tested one-sided at half of the designated significance level. If the lower 97.52% confidence limit for the difference in adjusted proportions for the treatment group in question (faricimab Q8W or PTI) and the active comparator (aflibercept Q8W) is greater than −10%, then that faricimab treatment group in question (Q8W or PTI) is considered non-inferior to aflibercept.

4.4.2.3 Analysis Methods

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 the randomization stratification factors of baseline BCVA score (64 letters or better vs. 63 letters or worse), prior IVT anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world) using the Cochran Mantel-Haenszel (CMH) weights (Cochran 1954; Mantel and Haenszel 1959). Confidence intervals of the proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be calculated using the normal approximation to the weighted proportions (Mehrotra and Railkar 2000). Superiority will be assessed, as

appropriate, using a CMH test stratified by the randomization stratification factors. If the response rate is low, an unstratified analysis may also be performed. Due to a small number of patients enrolled from Asia, the Asia and rest of the world regions will be combined to calculate the CMH weighted estimates and for the CMH analyses.

Analysis will be based on observed data, missing ETDRS DRSS assessments will not be imputed.

4.4.2.4 Supplementary Analyses

The following supplementary analyses will be performed for the key secondary efficacy endpoint to provide further understanding of the treatment effect:

a) Per-protocol analysis:

The per-protocol analysis will follow the same intercurrent events, handling of intercurrent events, and analysis method as for the key secondary endpoint (Section 4.4.2.1) with the exception that the analysis will be based on the per-protocol population (Section 4.1.3). Patients with major protocol deviations that impact the efficacy evaluation or the treatment interval determination, whether or not related to COVID-19, will be excluded from the analysis. This analysis will be performed for the non-inferiority assessment only.

b) Analysis using a composite strategy for non-COVID-19 related intercurrent events:

The populations and analysis method will be the same as the key secondary endpoint (Section 4.4.2.1) with the exception that a composite strategy will be followed where patients with an intercurrent event not due to COVID-19 prior to Week 52 will be considered as not achieving a $\geq$2-step improvement in DRS from baseline on the ETDRS DRSS at Week 52 (treatment failure). Patients with COVID-19 related intercurrent events will be censored after the intercurrent event.

c) Analysis using treatment policy strategy for all intercurrent events:

The analysis method, populations, and definition of intercurrent events will be the same as the key secondary endpoint (Section 4.4.2.1). However, all intercurrent events will follow a treatment policy strategy, where all observed values will be used regardless of the occurrence of the intercurrent event.

d) Analysis using hypothetical strategy for all intercurrent events:

The analysis method, populations, and definition of intercurrent events will be the same as the key secondary endpoint (Section 4.4.2.1). However, all intercurrent events will follow a hypothetical strategy, where all values will be censored after the occurrence of the intercurrent event.

4.4.3 Additional Secondary Endpoints

The binary secondary endpoints will be analyzed using the estimand, analysis method and data handling rules following those for the key secondary endpoint (Section 4.4.2.1),

as well as using descriptive statistics after censoring observations following COVID-19 related intercurrent events as described in Section 4.4.2.1.

The continuous secondary endpoints will be analyzed using the estimand, analysis method and data handling rules following those for the primary endpoint (Section 4.4.1) as well as using descriptive statistics after censoring observations following COVID-19 related intercurrent events as described in Section 4.4.1.

The secondary endpoints are noted below. Endpoints measured at 1 year correspond to changes from baseline averaged over Weeks 48, 52 and 56.

- Proportion of patients gaining:
  - ≥15 letters in BCVA from baseline at 1 year
  - ≥10 letters in BCVA from baseline at 1 year
  - ≥5 letters in BCVA from baseline at 1 year
  - ≥0 letters in BCVA from baseline at 1 year
- Proportion of patients avoiding loss of:
  - ≥15 letters in BCVA from baseline at 1 year
  - ≥10 letters in BCVA from baseline at 1 year
  - ≥5 letters in BCVA from baseline at 1 year
- Proportion of patients with a≥3-step DRS improvement from baseline on the ETDRS DRSS at Week 52
- Proportion of patients gaining≥15 letters from baseline or achieving BCVA of ≥84 letters at 1 year
- Proportion of patients with BCVA Snellen equivalent of 20/40 (BCVA-ETDRS ≥ 69 letters) or better at 1 year
  - Different strata will be used for the CMH analyses: the difference between the two treatment groups will be estimated using the same approach as the key secondary endpoint but stratified by baseline BCVA Snellen equivalent of 20/40 or better vs. worse than 20/40
- Proportion of patients with BCVA Snellen equivalent of 20/200 (BCVA-ETDRS ≤38 letters) or worse at 1 year
- Proportion of patients who developed new PDR at Week 52
  - PDR is defined as achieving ETDRS DRSS score of 61 or greater on the 7-field / 4-wide field CFP image assessment reported by the reading center at Week 52
- Proportion of patients who developed high-risk PDR at Week 52
  - High-risk PDR is defined as reaching ETDRS DRSS score of 71 or greater on the 7-field/4-wide field CFP image assessment reported by the reading center at Week 52
- Change in CST from baseline at 1 year

  - CST is defined as the distance between ILM and Bruch's membrane (BM), as measured in μm as assessed by CRC
- Proportion of patients with absence of DME at 1 year
  - Absence of DME is defined as achieving a CST of <325μm
- Proportion of patients in the PTI arm on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 52 and Week 96
  - For the faricimab PTI arm, treatment interval will be defined as follows:

    At Week 52: the treatment interval decision determined/followed at Week 52

    At Week 96: the treatment interval decision determined/followed at Week 96
- Proportion of patients in the PTI arm at Week 52 who achieved a Q12W or Q16W treatment interval without an injection interval decrease below Q12W
- Proportion of patients with absence of intraretinal fluid at Week 52
  - Intraretinal fluid is as measured in the central subfield (center 1 mm)
- Proportion of patients with absence of subretinal fluid at baseline at Week 52
  - Subretinal fluid is as measured in the central subfield (center 1 mm)
- Proportion of patients with absence of intraretinal and subretinal fluid at Week 52
- Change from baseline in National Eye Institute Visual Functioning Questionnaire–25 (NEI VFQ-25) composite score at Week 52

Additionally, the following secondary endpoints will be assessed over time, with results presented for each study visit:

- Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) over time
- Proportion of patients gaining $\geq 15, \geq 10, \geq 5, \geq 0$ letters in BCVA from baseline over time
- Proportion of patients avoiding a loss of $\geq 15, \geq 10, \geq 5$ letters in BCVA from baseline over time
- Proportion of patients gaining ≥15 letters from baseline or achieving BCVA of ≥ 84 letters over time
- Proportion of patients with BCVA Snellen equivalent of 20/40 (BCVA-ETDRS $\geq$ 69 letters) or better over time
  - Different strata will be used for the CMH analyses: the difference between the two treatment groups will be estimated using the same approach as the key secondary endpoint but stratified by baseline BCVA Snellen equivalent of 20/40 or better vs. worse than 20/40
- Proportion of patients with BCVA Snellen equivalent of 20/200 (BCVA-ETDRS ≤38 letters) or worse over time

- Proportion of patients with:
  - ≥2-step DRS improvement from baseline on the ETDRS DRSS over time
  - ≥3-step DRS improvement from baseline on the ETDRS DRSS over time
  - ≥4-step DRS improvement from baseline on the ETDRS DRSS over time
- Change from baseline in CST over time
- Proportion of patients with absence of DME over time
- Proportion of patients with "retina dryness" over time
  - Retina dryness is defined per CST when estimated in the absence of qualitative fluid compartment outputs on OCT (achieving a CST of <280 μm)
- Proportion of patients in the PTI arm on a Q4W, Q8W, Q12W, or Q16W treatment interval over time
  - For the faricimab PTI arm, treatment intervals at a given visit will be defined as the treatment interval decision determined/followed at that visit
- Proportion of patients with absence of intraretinal fluid over time
- Proportion of patients with absence of subretinal fluid over time
- Proportion of patients with absence of intraretinal and subretinal fluid over time
- Change from baseline in NEI VFQ-25 composite score over time

4.4.4 Exploratory Efficacy Endpoints

The following exploratory endpoints will be summarized using descriptive statistics by including the mean, standard deviation, median, and range for continuous endpoints, and counts and percentages for categorical endpoints. Patients with COVID-19 related intercurrent events will be censored after the intercurrent event.

- Proportion of patients who receive vitrectomy during the first year
  - Analysis will be presented based on the ITT population (Section 4.1.1) and among patients with an evaluable baseline DR severity score
- Proportion of patients who receive panretinal photocoagulation (PRP) during the first year
  - Analysis will be presented based on the ITT population (Section 4.1.1) and among patients with an evaluable baseline DR severity score
- Change from baseline in vascular leakage area in the macula over time
- Proportion of patients with absence of macular leakage over time
  - Absence is defined as an area of leakage within the macula of 0 mm^2
- Change from baseline in vascular leakage area in the total retinal area over time
- Proportion of patients with absence of total retinal leakage over time
  - Absence is defined as an area of leakage within the total retinal area of 0 mm^2

- Change from baseline in the area of ischemic non perfusion within the macula over time
- Proportion of patients with absence of macular ischemic non perfusion (capillary loss) over time
  - Absence is defined as an area of ischemic non perfusion within the macula of 0 to 0.1 mm^2
- Change from baseline in the area of ischemic non perfusion within the total retinal area over time
- Proportion of patients with absence of ischemic non-perfusion within the total retinal area over time
  - Absence is defined as an area of ischemic non perfusion within the total retinal area of 0 to 1 mm^2
- Change from baseline in vascular density in the superficial capillary plexus at Week 52
  - Data from Optovue and Cirrus machines will be analyzed jointly. If enough gradable images, analyses may be conducted by machine type
- Change from baseline in vascular density in the deep capillary plexus at Week 52
- Change from baseline in FAZ (foveal avascular zone) area at Week 52
  - Data from Optovue and Cirrus machines will be analyzed jointly. If enough gradable images, analyses may be conducted by machine type.
- Change from baseline in neurosensory CST over time
- Change from baseline in total macular volume over time
- Change from baseline in the NEI VFQ-25 Near Activities, Distance Activities, and Driving subscales over time
- Proportion of patients with $\geq$ 4-point improvement from baseline in NEI VFQ-25 composite score over time
- Proportion of patients who develop new PDR over time
- Proportion of patients who progressed to high-risk PDR over time
- Proportion of patients with:
  - $\geq$ 2-step DRS worsening from baseline on the ETDRS DRSS over time
  - $\geq$ 3-step DRS worsening from baseline on the ETDRS DRSS over time
  - $\geq$ 4-step DRS worsening from baseline on the ETDRS DRSS over time

4.4.5 Subgroup Analyses

The following subgroups will be analyzed with respect to the primary efficacy endpoint and key secondary endpoint using the same method as specified above for each respective endpoint. Forest plots will be presented to summarize the results. The

subgroup categories may be combined if there is not enough representation of a specific subpopulation.

- Baseline BCVA (≥64 letters and ≤63 letters)
- Region (U.S. and Canada, Asia, and the rest of the world)
- Prior IVT anti-VEGF therapy (yes and no)
- Baseline DR severity (<47, 47-53 and >53 ETDRS DRSS)
- Baseline HbA1c (≤8% and >8%)
- Age (<65 years and ≥65 years)
- Gender (female and male)
- Race (White, Black or African American, Asian, and other)

In addition, the proportion of patients with ≥2, ≥3, ≥4 step DRS improvement from baseline on the ETDRS DRSS will be summarized using the same method as described for the key secondary endpoint, as well as using descriptive statistics, in the following subgroups:

- Patients with DRSS 47 or worse at baseline
- Patients with DRSS 53 or worse at baseline
- Patients with PDR (DRSS 61 or worse) at baseline regardless if they had PRP prior to the study
- Patients with PDR (DRSS 61 or worse) at baseline who did not have PRP prior to the study

4.5 PHARMACOKINETIC ANALYSES

PK analyses will be based on the pharmacokinetic-evaluable population.

Listings of individual plasma and aqueous humor faricimab (RO6867461) concentrations will be provided by treatment arm with summary statistics. Mean faricimab (RO6867461) plasma and aqueous humor concentration versus time data will be plotted.

In addition, the population PK analysis will be performed. The previous Population PK analysis of plasma and aqueous humor of faricimab (RDR 1092579) that was conducted on the data from Phase II Studies BP29647 and CR39521 in patients with neovascular age related macular degeneration and from the Phase II Study BP30099, in patients with DME will be updated with the PK data from the present Studies GR40349 and GR40398. Structural model refinement will be driven by the data and will be based on various goodness of fit indicators.

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). The potential effect of ADA on the kinetics of faricimab will be assessed. PK parameters, such as area under the concentration–time curve and maximum concentration, will be derived from the individual post-hoc predictions. Additional PK analyses may be conducted as appropriate.

Details of the population PK analyses will be described in a Modeling and Simulation Analysis Plan. The result of the population PK analyses will be reported in a document separate from the clinical study report (CSR) and may include data from [redacted]

4.6 PHARMACODYNAMIC ANALYSES

Pharmacodynamic (PD) analyses will be based on the safety-evaluable population.

PD biomarker analyses will be focused primarily on, but not limited to, the change in Ang-2 and VEGF. Graphical displays and summaries of the absolute values or change from baselines (or as appropriate, percent change from baseline) will be provided. The data collected from this study may be pooled with data from previous studies and the results of such analyses will be reported in a document separate from the CSR. The effect of exposure or dosing information on BCVA, CST, aqueous humor [redacted] may be explored using a longitudinal modeling approach if appropriate. The influence of various baseline covariates on model parameters may be investigated. The PK–PD or dose–PD relationship will be characterized as appropriate and results will be reported in a document separate from the CSR.

4.7 IMMUNOGENICITY ANALYSES

Immunogenicity analyses will be based on the immunogenicity-analysis population (immunogenicity prevalence set or immunogenicity incidence set, as appropriate, as defined in Section 4.1.6).

4.7.1 Sample Anti-Drug Antibody (ADA) Status

The following properties of each sample will be listed by patient:

- ADA status (from the confirmatory assay): ADA positive (yes) or ADA negative (no) and titer value for the ADA positive sample.

4.7.2 Patient ADA Status

The ADA status will be listed by patient using the immunogenicity incidence set and summarized according to treatment received.

- Treatment-boosted ADA-positive: number and percent of patients with at least one treatment-boosted ADA-positive sample. The numerator is the number of patients with an ADA-positive sample at baseline and any post-baseline samples with a titer that is equal or greater than 4-fold baseline titer. The denominator is the total number of patients in the immunogenicity incidence set.
- Treatment-induced ADA-positive: number and percent of patients with at least one treatment-induced ADA-positive sample. The numerator is the number of patients with an ADA-negative or missing sample at baseline and any post-baseline positive sample. The denominator is the total number of patients in the immunogenicity incidence set. Among the treatment –induced ADA-positive, the number of patients with transient (ADA positive result detected (a) at only one post-baseline sampling time point (excluding last timepoint) OR (b) at 2 or more timepoints during treatment where the first and last ADA positive samples are separated by a period of $<$16 weeks, irrespective of any negative samples in between) and persistent (ADA positive result detected (a) at the last post-baseline sampling time point, OR (b) at 2 or more time points during treatment where the first and last ADA positive samples are separated by a period $=$ 16 weeks, irrespective of any negative samples in between) will be listed.
- Treatment-unaffected ADA-positive patient: number and percent of patients with an ADA-positive baseline sample (level of pre-existing ADAs) that does not change following drug administration. The numerator is the number of patients with ADA-positive sample post-baseline having titer lower than 4-fold the ADA-positive baseline titer. The denominator is the total number of patients in the immunogenicity incidence set.
- ADA-negative: number and percent of patients without positive ADA during the study period or if they are ADA positive at baseline but without positive ADA post-baseline (numerator). The denominator is the total number of patients in the immunogenicity incidence set.
- ADA incidence (i.e., ADA-positive in %): number and percent of patients with at least one treatment-induced or treatment-boosted ADA-positive sample. The numerator is the number of patients positive for boosted or induced ADA. The denominator is the total number of patients in the immunogenicity incidence set.

The following summaries, both overall and by time point (including baseline) will be provided using the immunogenicity prevalence set, according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned. For summaries by time point, the numerator is the number of patients at that time point with determinant samples:

- ADA prevalence: number and percent of patients with at least one ADA-positive sample at any timepoint (including baseline). The numerator is the number of ADA positive patients at each timepoint and overall timepoints. The denominator is the total number of evaluable patients in the study at corresponding timepoints.

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

4.8 BIOMARKER ANALYSES

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

Baseline values will be used to evaluate predictive biomarkers in the context of efficacy, PK, safety, and/or immunogenicity endpoints. In addition, whole genome sequencing data will be analyzed in the context of this study and may be explored in aggregate with data from other studies to increase researcher's understanding of disease pathobiology and faricimab treatment response, and guide the development of new therapeutic approaches. The results from these analyses will be reported in a document separate from the CSR.

4.9 SAFETY ANALYSES

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

Safety will be assessed through descriptive summary of ocular and non-ocular AEs, deaths, and ocular assessments. Clinically significant laboratory abnormalities and clinically significant vital sign abnormalities will be reported as AEs and evaluated as part of the AE 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. At the time of the final analysis, safety summaries will be produced based on cumulative Week 100 data in the safety-evaluable population.

Baseline for safety analyses is defined as the last available measurement prior to first exposure to study drug.

4.9.1 Exposure of Study Medication

Exposure to study drug (number of study drug administrations and duration of treatment) will be summarized by treatment group for the study eye in the safety-evaluable population.

Duration of treatment is the time from first study drug (faricimab or aflibercept) to the earlier of

- Date of treatment discontinuation or date of study treatment completion
- The analysis cutoff date

Pre-randomization and concomitant systemic medications, ocular medications for the study eye, and ocular medications for the fellow eye will be summarized separately by treatment group.

4.9.2 Adverse Events

All verbatim AE terms will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA), and the incidence and severity will be summarized by treatment arm.

For safety analyses, unless otherwise specified, only treatment-emergent AEs will be included in the analyses. A treatment-emergent AE is defined as any new AE reported or any worsening of an existing condition on or after the first dose of study drug. Adverse events with missing onset date will be considered to be treatment emergent. Adverse events with partially missing onset date will also be included as treatment emergent when the month (if it was recorded) and the year occur on or later than the month and year of the study treatment start date.

Frequency tables, including patient incidence rates by treatment arm, will be provided for the events listed below. In addition, graphical presentations will be included, as applicable. For ocular AEs, events in the study eye and fellow eye will be summarized separately.

- Ocular AEs and serious adverse events (SAEs)
- Non-ocular AEs and SAEs
- Adverse events of special interest defined as follows:
  - Cases of potential drug-induced liver injury that include elevated alanine aminotransferase or aspartate aminotransferase in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6 of Protocol Version 3)
  - Suspected transmission of an infectious agent by the study drug
  - Sight-threatening AEs
- AEs leading to discontinuation of study treatment
- Treatment related ocular AEs and SAEs as determined by the Investigator
- Externally adjudicated APTC events
- Intraocular inflammation (IOI)
- Retinal vascular occlusive disease
- Deaths

Adverse events associated with suspected or confirmed COVID-19 will also be provided.

4.9.3 Ocular Assessments

Results of the following ocular assessments will be summarized by treatment group, by timepoint, using descriptive summaries and graphical presentations (as applicable):

- intraocular pressure (IOP)
- slitlamp examination

- indirect ophthalmoscopy

Changes from baseline in pre-dose IOP measurements and changes between pre-dose and post-dose IOP measurements will be summarized. The presence of IOI and vitreous hemorrhage, as determined on slitlamp examination, will be tabulated by grade (according to grading scales for flares and cells in Appendix 3 of Protocol Version 3). The presence of retinal break or detachment as determined from ophthalmoscopy will be tabulated.

4.9.4 Laboratory Data

Laboratory data will be collected at baseline and Week 56 only (Section 4.5.7 of Protocol Version 3). Laboratory assessments will be summarized by treatment group, by timepoint, using descriptive summaries.

4.9.5 Vital Signs

Vital signs will be collected at screening, randomization and Week 100 or early termination visit only. These data can be used for interpretation of some AEs, no general summary is planned.

4.10 MISSING DATA

For efficacy analyses, the handling of missing data during analysis is specified in the efficacy analysis section (Section 4.4.1.2 and Section 4.4.2.3).

For safety analyses, missing data will not be imputed.

4.11 INTERIM ANALYSES

No interim efficacy or futility analyses are planned. The iDMC will review the interim safety analyses approximately every 6 months.

[redacted]

[redacted]

6. REFERENCES

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Appendix 1
Protocol Synopsis (Study GR40349)

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*)*
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]

Appendix 2
Protocol Synopsis (Study GR40398)

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 (RHINE)**
PROTOCOL NUMBER:	GR40398
VERSION NUMBER:	3
EUDRACT NUMBER:	2017-005105-12
IND NUMBER:	119225
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	• Presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs	• 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, 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 should be conducted only once. *The following conditions have to be met for a combined visit to occur:*

- [redacted]
- A historic hemoglobin A1c (HbA1c) 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]

[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.
- [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 *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 $\leq$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]

Appendix 3
Schedule of Assessments

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 3
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 3
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]	*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 3
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 3
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 3
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 3
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 3
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]											*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 3
Schedule of Activities (cont.)

Week 56 through Week 100 and Early Termination

	Week Visit												ET
	56	60	64	68	72	76	80	84	88	92	96	100	Visit [a]
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 3
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 (and UWF CFP at applicable sites) 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 3
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.