Official Title: A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate The Efficacy and Safety of Faricimab in Patients With Neovascular Age-Related Macular Degeneration (Tenaya And Lucerne)

NCT Number: NCT03823300

Document Date: SAP Version 1: 15-October-2020

STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FARICIMAB IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (TENAYA AND LUCERNE)**

PROTOCOL NUMBERS: GR40306 and GR40844

STUDY DRUG: Faricimab (RO6867461)

VERSION NUMBER: 1.0

IND NUMBER: 119225

EUDRACT NUMBER: 2018-002152-32 (GR40306)
2018-004042-42 (GR40844)

SPONSOR: F. Hoffmann-La Roche Ltd

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

DATE FINAL: See electronic date stamp below.

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
15-Oct-2020 11:17:55	Company Signatory	[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse events
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
Ang-2	angiopoietin-2 (protein)
Anti-VEGF	anti-vascular endothelial growth factor
APTC	Anti-Platelet Trialists' Collaboration
BCVA	best-corrected visual acuity
BM	Bruch's membrane
CDE	(China) Center for Drug Evaluation
CFP	color fundus photograph
CI	confidence interval
CMH	Cochran Mantel-Haenszel
CNV	choroidal neovascularization
CRC	central reading center
CSR	clinical study report
CST	central subfield thickness
EC	Ethics Committee
ETDRS	early treatment diabetic retinopathy study
FFA	fundus fluorescein angiography
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
ICGA	indocyanine green angiography
ILM	internal limiting membrane
IOI	intraocular inflammation
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intent-to-treat
IVT	intravitreal
IxRS	interactive voice or web-based response system
LLD	low-luminance deficit
LPLV	last patient, last visit
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MNAR	missing not at random
nAMD	neovascular age-related macular degeneration

NEI VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
OCT	optical coherence tomography
OCT-A	optical coherence tomography–angiography
PD	pharmacodynamic
PED	pigment epithelial detachment
PK	pharmacokinetic
PTI	personalized treatment interval
Q12W	every 12 weeks
Q16W	every 16 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
RPE	retinal pigment epithelium
SAE	serious adverse event
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
U.S.	United States
VA	visual acuity
VEGF (–A)	vascular endothelial growth factor (–A)

1. BACKGROUND

Neovascular age-related macular degeneration (nAMD) is a form of advanced AMD that causes rapid and severe visual loss and remains a leading cause of visual impairment in the elderly. In nAMD, choroidal neovascularization (CNV) leaks fluid, lipids, and blood into the outer retina causing severe, irreversible loss of central vision if left untreated.

Treatment of nAMD has been markedly improved by the introduction of biological molecules that target vascular endothelial growth factor (-A) (VEGF-A). The impressive benefit of anti-VEGF therapies and their ability to restore vision has been widely recognized since the first approval of Lucentis® (ranibizumab) in 2006. A key challenge with currently available anti-VEGF treatments is the requirement for long-term frequent administration to maintain vision gains. Real-world data suggest that many patients with nAMD do not receive treatment at the optimal frequency, and this under-treatment in clinical practice is associated with lower visual acuity (VA) gains compared with those observed in controlled clinical trials. Under-treatment of nAMD in clinical practice reflects the burden of frequent therapy on patients, caregivers, and the healthcare system.

Faricimab is a novel humanized bispecific immunoglobulin 1 monoclonal antibody that selectively binds to angiopoietin-2 (Ang-2) and VEGF-A. Nonclinical studies have shown that Ang-2 and VEGF-A act in concert to regulate the vasculature and to increase retinal endothelial cell permeability such that simultaneous inhibition of Ang-2 and VEGF-A with faricimab led to a greater reduction in the leakiness and severity of CNV lesions compared with inhibition of either target alone. Furthermore, data from the completed Phase II studies also support the hypothesis that targeting Ang-2 has the potential to extend the durability of effect beyond anti-VEGF therapy alone in nAMD. Taken together, data from earlier non-clinical and clinical studies, as well as the clear unmet need for less-frequent dosing in nAMD, support the evaluation of faricimab in a Phase III study.

The purpose of this document is to provide details of the planned analyses for Phase III studies GR40306 (TENAYA) and GR40844 (LUCERNE). The designs of these studies are identical with the exception of the country participating in the extension study. A Japan extension study is planned as part of GR40306 and a China extension is planned as part of GR40844 (refer to Section 2.2). In this Statistical Analysis Plan, study collectively refers to both studies GR40306 (TENAYA) and GR40844 (LUCERNE), and study drug refers to faricimab or aflibercept whereas study treatment refers to faricimab, aflibercept, or the sham procedure.

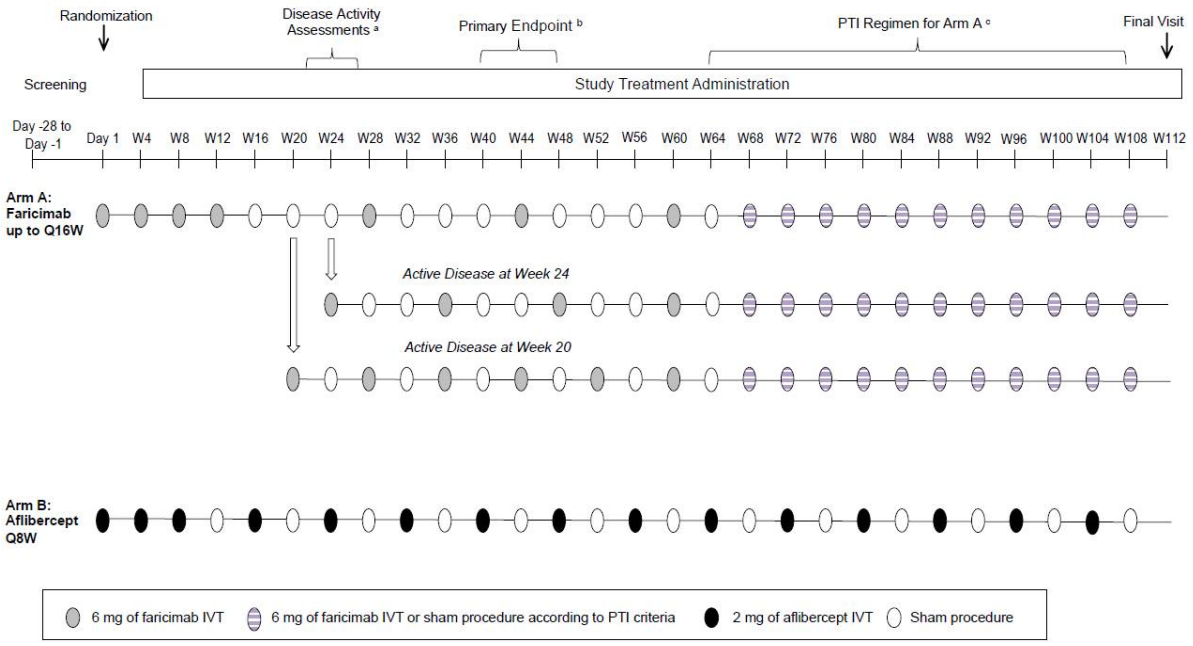
The analyses specified in this document supersede the analysis plan described in the study protocols.

2. STUDY DESIGN

Studies GR40306 (TENAYA) and GR40844 (LUCERNE) are identical Phase III, multicenter, randomized, active comparator-controlled, double-masked, parallel-group, 112-week studies, evaluating the efficacy, safety, durability, and pharmacokinetics of the 6 mg dose of faricimab administered at up to 16-week intervals compared with aflibercept monotherapy every 8 weeks (Q8W) in patients with nAMD. For the study schema, see Figure 1.

Patient recruitment is expected to take longer in Japan and China; therefore, a specific Japan and China enrollment plan has been established as part of Studies GR40306 and GR40844, respectively. After the global enrollment phase of these studies has been completed, additional patients will be enrolled in a Japan and China extension to ensure a total enrollment that is sufficient to support registration in Japan and in the People's Republic of China, respectively (refer to Section 2.2.1 and Section 2.2.2).

Figure 1 Study Schema



BCVA=best-corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; IVT=intravitreal; PTI=personalized treatment interval; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; W=week.

[a] At Weeks 20 and 24, patients will undergo a disease activity assessment. Patients with anatomic or functional signs of disease activity at these timepoints will receive Q8W or Q12W dosing, respectively, rather than Q16W dosing.

[b] The primary endpoint is the change from baseline in BCVA (as assessed on the ETDRS chart at a starting distance of 4 meters) based on an average at Weeks 40, 44, and 48.

[c] From Week 60 (when all patients in Arm A are scheduled to receive faricimab) onward, patients in Arm A will be treated according to a PTI dosing regimen (between Q8W and Q16W).

Approximately 640 patients will be enrolled globally during the global enrollment phase of the study and randomized in a 1:1 ratio to one of two treatment arms:

- Arm A (n = 320): Patients randomized to Arm A will receive 6 mg of intravitreal (IVT) faricimab every 4 weeks (Q4W) up to Week 12 (4 injections). At Week 20 and Week 24, protocol-defined assessment of disease activity determines patients' treatment frequency (a fixed regimen every 8, 12, or 16 weeks) until Week 60. From Week 60 onward, all patients will be treated according to a personalized treatment interval (PTI) dosing regimen (up to Week 108).
- Arm B (n = 320): Patients randomized to Arm B will receive 2 mg of IVT aflibercept Q4W up to Week 8 (3 injections), followed by 2 mg of IVT aflibercept Q8W up to Week 108.

Weeks 20 and 24 Disease Activity Criteria for Patients Randomized to Arm A

At Weeks 20 and 24, a protocol-defined assessment of disease activity performed for all patients. Patients in Arm A with active disease at Week 20 will be treated at that visit and continue with a Q8W dosing regimen of faricimab. Patients in Arm A with active disease at Week 24 (excluding those with active disease at Week 20) will be treated at that visit and to continue with a Q12W dosing regimen of faricimab. Patients in Arm A who do not have active disease at Week 20 and Week 24 will be treated with a Q16W dosing regimen of faricimab. Patients in Arm A will continue receiving faricimab on a fixed regimen every 8, 12, or 16 weeks until Week 60. Patients in Arm B will receive aflibercept Q4W up to Week 8, followed by Q8W up to Week 108.

Determination of active disease at Weeks 20 and 24 will be made if any of the following criteria are met:

- Increase > 50 μm in central subfield thickness (CST) compared with the average CST value over the previous two scheduled visits (Weeks 12 and 16 for the Week 20 assessment and Weeks 16 and 20 for the Week 24 assessment) Or
- Increase ≥ 75 μm in CST compared with the lowest CST value recorded at either of the previous two scheduled visits Or
- Decrease ≥ 5 letters in best-corrected visual acuity (BCVA) compared with average BCVA value over the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator) Or
- Decrease ≥ 10 letters in BCVA compared with the highest BCVA value recorded at either of the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator) Or
- Presence of new macular hemorrhage (as determined by the investigator), owing to nAMD activity

Additional considerations at Week 24: If there is significant nAMD disease activity at Week 24 that does not meet the criteria above, but which in the opinion of the investigator would otherwise warrant treatment, following Sponsor notification through the interactive voice or web-based response system (IxRS), patients randomized to

Arm A will receive 6 mg of faricimab at Week 24 and will continue to receive repeated 12 weekly treatments until Week 60.

Personalized Treatment Interval Disease Activity Criteria for Patients Randomized to Arm A

From Week 60 (when all patients in Arm A are scheduled to receive faricimab) to Week 108, patients in Arm A will be treated according to a PTI dosing regimen (Q8W, every 12 weeks [Q12W], or every 16 weeks [Q16W]). At study drug dosing visits, treatment intervals may be maintained or adjusted (i.e., increased by 4 weeks, or decreased by 4 or 8 weeks), based on CST, BCVA, and clinical assessment as mentioned below Table 1.

Table 1 Personalized Treatment Interval Algorithm

Dosing Interval	Criteria
Interval extended by 4 weeks (to a maximum of Q16W)	• Stable CST[a] compared with the average of the last two study drug dosing visits, and no increase ≥ 50 μm in CST (compared with the lowest on-study drug dosing visit measurement) **and** • No decrease ≥ 5 letters in BCVA[b] compared with the average from the last two study drug dosing visits, and no decrease ≥ 10 letters in BCVA[b] compared with the highest on-study drug dosing visit measurement **and** • No new macular hemorrhage[c]
Interval reduced (to a minimum Q8W) If one of the criteria is met, the interval will be reduced by 4 weeks. If two or more criteria are met or one criterion includes new macular hemorrhage, the interval will be reduced to an 8-week interval. [d]	• Increase ≥ 50 μm in CST compared with the average from the last two study drug dosing visits or ≥ 75 μm compared with the lowest on-study drug dosing visit measurement **or** • Decrease ≥ 5 letters in BCVA [b] compared with average of last two study drug dosing visits or decrease ≥ 10 letters in BCVA [b] compared with the highest on-study drug dosing visit measurement **or** • New macular hemorrhage [c]
Interval maintained	If extension or reduction criteria have not been met

BCVA = best-corrected visual acuity; CST = central subfield thickness; nAMD = neovascular age-related macular degeneration; Q8W = every 8 weeks; Q16W = every 16 weeks.

[a] Where stability is defined as a change of CST of less than 30 μm.

[b] Change in BCVA should be attributable to nAMD disease activity (as determined by investigator).

[c] Refers to macular hemorrhage owing to nAMD activity (as determined by investigator).

[d] Patients whose treatment interval is reduced by 8 weeks from Q16W to Q8W will not be allowed to return to a Q16W interval during the study.

Patients in both treatment arms will complete scheduled study visits Q4W for the entire study duration and return for a final visit at Week 112. A sham procedure will be administered to patients in both treatment arms at study visits with no study treatment administration 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.

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, which will enroll approximately 640 patients. Patients will be randomized in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B). The primary comparison will be between the active comparator (aflibercept Q8W) and the faricimab up to Q16W arm.

A sample size of approximately 320 patients in each arm will provide greater than 90% power to show non-inferiority of faricimab to aflibercept in the change in BCVA averaged over Weeks 40, 44, and 48 in the intent-to-treat (ITT) population, using a non-inferiority margin of 4 letters, and under the following assumptions:

- No difference in the mean change from baseline in BCVA between two treatment arms
- Standard deviation (SD) of 14 letters for the change from baseline in BCVA averaged over Weeks 40, 44, and 48
- Two-sample t-test
- 2.5% one-sided type I error rate
- 10% dropout rate

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 0.0497 (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 may elect to cap the recruitment of patients in certain baseline BCVA strata to ensure appropriate patient representation. In addition, it states that the Sponsor might re-estimate the sample size in a masked manner prior to completing enrollment. However, a recruitment cap was not introduced and the sample size re-estimation was not performed nor the sample size modified due to faster than anticipated enrollment.

2.2.1 Sample Size for the Japan Extension (as part of GR40306 [TENAYA])

After the global enrollment phase of the GR40306 (TENAYA) has been completed, additional patients will be enrolled in a Japan extension to ensure a total enrollment that is sufficient to support registration in Japan. It is anticipated that approximately 132 patients will be enrolled at approximately 45 sites (including patients who have already enrolled during the global enrollment phase). The data from Japan patients enrolled during the global enrollment phase of the study will be included in the primary analysis of the study. Data from patients enrolled during the Japan extension will not be included in the primary analyses but will be considered in the Japan subpopulation analysis (see Section 5).

2.2.2 Sample Size for the China Extension (as part of GR40844 [LUCERNE])

After the global enrollment phase of the GR40844 (LUCERNE) has been completed, additional patients will be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in the People's Republic of China. It is anticipated that approximately 90 patients will be enrolled at approximately 15 sites (including patients who have already enrolled during the global enrollment phase). The China extension may include current residents of mainland China, Hong Kong, or Taiwan enrolled at China Center for Drug Evaluation (CDE) –recognized sites. The data from China patients enrolled during the global enrollment phase of the study will be included in the primary analysis of the study. Data from patients enrolled during the China extension will not be included in the primary analyses but will be considered in the China subpopulation analysis (see Section 6).

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 48 or have discontinued from the study prior to Week 48, 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 central reading center (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 112 or have discontinued early from the study, all data from the global enrollment phase are in the database and have been cleaned and verified.

Additional analyses of efficacy endpoints may be performed between the primary analysis and final analysis to support marketing applications.

2.3.1 Analysis Timing for the Japan Subpopulation Analysis (as part of GR40306 [TENAYA])

Primary analysis for the Japan subpopulation will be performed when all patients from Japan (i.e., during both the global enrollment phase and the Japan extension of GR40306 [TENAYA]) have either completed the study through Week 48 or have discontinued from the study prior to Week 48, whichever comes later, and all data collected are in the database, cleaned and verified.

A final analysis for the Japan subpopulation will be performed when all patients from Japan (i.e., during both the global enrollment phase and the Japan extension) have either completed the study through Week 112 or have discontinued early from the study, all data are in the database, and the database is locked.

2.3.2 Analysis Timing for the China Subpopulation Analysis (as part of GR40844 [LUCERNE])

Primary analysis for the China subpopulation will be performed when all patients from China (i.e., during both the global enrollment phase and the China extension of GR40844 [LUCERNE]) have either completed the study through Week 48 or have discontinued from the study prior to Week 48, whichever comes later, and all data collected are in the database, cleaned and verified.

A final analysis for the China subpopulation will be performed when all patients from China (i.e., during both the global enrollment phase and the China extension) have either completed the study through Week 112 or have discontinued early from the study, all data are in the database, and the database is locked.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Using a stratified permuted block randomization method, patients will be randomized in a 1:1 ratio so that approximately 320 patients are randomized to receive treatment with faricimab (Arm A) or aflibercept (Arm B). Randomization is stratified by baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score as assessed on Day 1 ($\geq$74 letters, 73–55 letters, and $\leq$54 letters), low-luminance deficit (LLD; $<$33 letters and $\geq$33 letters), 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 August 14, 2019 (approximately six months after first patient in) with randomization information available for 230 patients available in TENAYA and 277 patients in LUCERNE. No major issues were detected during the audit, and corresponding report will be provided by the iDCC at study unmasking for the primary analysis.

The same randomization method is implemented for the Japan extension (as part of GR40306 [TENAYA]) and for the China extension (as part of GR40844 [LUCERNE]).

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), fundus fluorescein angiography (FFA), and optical coherence tomography (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, FFA, indocyanine green angiography (ICGA), 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 spectral-domain optical coherence tomography (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 three safety interim data reviews will have been conducted by the iDMC; therefore, efficacy analyses would be performed with a family-wise significance level of 0.0497. 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 the Japan extension (as part of GR40306 [TENAYA]) or China extension (as part of GR40844 [LUCERNE]), unless otherwise specified. The analysis plans for the Japan and China extensions are presented in Section 5 and Section 6, respectively.

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 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. If by error, a patient receives a combination of different active study drugs (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.

4.1.3 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 4.1.2.

4.1.4 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 4.1.2.

4.1.5 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 4.1.2. 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 4.1.2.

4.2 ANALYSIS OF STUDY CONDUCT

The analysis of study conduct will be based on the ITT population.

The number of patients randomized will be tabulated by country, site, and treatment arm. Patient disposition (the number of patients randomized, treated, and completing through the primary endpoint timing, as well as 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 using means, SDs, medians, and ranges for continuous variables, and counts and proportions for categorical variables, as appropriate.

Exposure to study drug (number of study drug administrations and duration of treatment) will be summarized 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, unless otherwise specified. A supplemental analysis based on the per-protocol population will also be conducted for the primary endpoint.

Unless otherwise noted, analyses of efficacy outcome measures will be stratified by baseline BCVA ETDRS letter score as assessed on Day 1 ($\geq$74 letters, 73–55 letters, and $\leq$54 letters), LLD ($<$33 letters and $\geq$33 letters), 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 comparison will be between the active comparator (aflibercept Q8W) and the faricimab up to Q16W arm.

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 treatment group and the difference in means or proportions between two treatment groups. All CIs will be two-sided and at the 95.03% level.

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in BCVA averaged over Weeks 40, 44, and 48. 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: Adult treatment-naive patients with nAMD, as defined by the inclusion / exclusion criteria (see Section 4.1.1) (ITT Population)
- Variable: Change in BCVA score from baseline averaged over Weeks 40, 44, and 48. 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 4.4.3 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 faricimab (up to Q16W) and aflibercept (Q8W) arms

4.4.1.1 Hypothesis Testing and Type I Error Control

The primary comparison will be to test non-inferiority of faricimab (up to Q16W) compared with aflibercept (Q8W) in the ITT population. The non-inferiority test will be

conducted with a non-inferiority margin of four letters at the one-sided 0.02485 significance level. For the primary efficacy endpoint, if the lower bound of a two-sided 95.03% CI for the difference in adjusted means of the two treatments is greater than −4 letters (the non-inferiority margin), then faricimab is considered non-inferior to aflibercept.

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 4–48 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 the two treatment arms will be made using a composite contrast over Weeks 40, 44, and 48. 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 (MAR) 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 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 4.1.2). 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.

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

The analysis method, population, 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, population, 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 population, 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 40, 44, and 48 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 analysis will be used to assess the difference in BVCA between two treatment groups 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: Adult treatment-naive patients with nAMD, as defined by the inclusion / exclusion criteria (see Section 4.1.1) (ITT Population)
- Variable: Change in BCVA score from baseline averaged over Weeks 40, 44, and 48. 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 4.4.3 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 faricimab (up to Q16W) and aflibercept (Q8W) arms

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 40, 44, and 48 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 40
- They have missing assessment at Week 40 and have a non-COVID-19 related intercurrent event at Week 40
- They have missing assessments at Weeks 40 and 44, and have a non-COVID-19 related intercurrent event at either one of these two visits
- They have missing assessments at Weeks 40, 44 and 48, 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 40 assessment and has a non-COVID-19 related intercurrent event at Week 40, then the change in BCVA from baseline will be calculated using Week 40 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 a as "must be trimmed patient”. Similarly, if a patient has a non-missing Week 44 assessment and has a non-COVID-19 related intercurrent event at Week 44, then the change in BCVA from baseline will be calculated using Week 40 and 44 assessments only. 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 Weeks 40, 44 and 48 assessments only.

For the remaining patients without COVID-19 related intercurrent events, if they have at least one BCVA assessment for Weeks 40, 44, and 48, they will be considered "completers". If they have missing assessments at all three visits (Weeks 40, 44, and 48), the missing data will be considered MAR 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 40, 44, and 48 prior to any COVID-19 related intercurrent event, they will be considered "completers". Otherwise, the missing data will be considered MAR and these patients will be removed from the analysis.

The inferential statistics (i.e., 95.03% CI) 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 MAR (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 40, 44, and 48; X is the matrix for the covariates – baseline BCVA (continuous), and randomization stratification factors of baseline BCVA score, LLD, 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, LLD, 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 population, 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 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 40, 44, and 48), 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 (FCS) 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]) + (β_{j+1}*baseline BCVA ($\geq$74 letters, 73–55 letters, $\leq$54 letters)]) + (β_{j+2}*LLD) + (β_{j+3}*region)

where j=1, 2, …, 10 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 40, 44, and 48 (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 40, 44, and 48, identify 10% of the patients with the worst values for change in BCVA score from baseline averaged over the non-missing values of Weeks 40, 44, and 48. 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 Endpoints

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 binary secondary endpoints will be analyzed using the population, intercurrent events, and handling of intercurrent events as described in Section 4.4.1 with the following analysis method.

The proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be estimated using the weighted average of

the observed proportions and the differences in observed proportions over the strata defined by randomization stratification factor of baseline BCVA score (≥74 letters, 73–55 letters, and ≤54 letters), LLD (<33 letters and ≥33 letters), 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). 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.

In addition, the binary endpoints will be summarized using descriptive statistics after censoring observations following COVID-19 related intercurrent events as described in Section 4.4.1.

The primary comparison for the following secondary endpoints will be faricimab (up to Q16W) vs. aflibercept (Q8W)

The secondary endpoints are:

- Proportion of patients gaining:
  - ≥15 letters in BCVA from baseline averaged over Weeks 40, 44 and 48
  - ≥10 letters in BCVA from baseline averaged over Weeks 40, 44 and 48
  - ≥5 letters in BCVA from baseline averaged over Weeks 40, 44 and 48
  - ≥0 letters in BCVA from baseline averaged over Weeks 40, 44 and 48
- Proportion of patients avoiding a loss of:
  - ≥15 letters in BCVA from baseline averaged over Weeks 40, 44 and 48
  - ≥10 letters in BCVA from baseline averaged over Weeks 40, 44 and 48
  - ≥5 letters in BCVA from baseline averaged over Weeks 40, 44 and 48
- Proportion of patients gaining ≥15 letters from baseline or achieving BCVA of ≥84 letters averaged over Weeks 40, 44 and 48
- Proportion of patients with BCVA Snellen equivalent of 20/40 (BCVA-ETDRS ≥69 letters) or better averaged over Weeks 40, 44 and 48
  - Different strata will be used for the CMH analyses: the difference between the two treatment groups will be estimated using the same approach as described above 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 averaged over Weeks 40, 44 and 48

- Proportion of patients in the faricimab arm on a Q8W, Q12W, and Q16W treatment interval at Weeks 48, 60, and 112
  - For the faricimab arm, treatment interval will be defined as follows:

    At Week 48: the treatment interval decision followed at Week 48

    At Week 60: the treatment interval decision followed at Week 60

    At Week 112: the treatment interval decision followed at Week 112
- Number of study drug injections received through Weeks 48, 60, and 112
- Change from baseline in CST (ILM-RPE) based on an average at Weeks 40, 44, and 48
  - CST is defined as the distance between internal limiting membrane (ILM) and retinal pigment epithelium (RPE), as measured in μm as assessed by CRC.
- Change from baseline in total area of CNV lesion at Week 48 and Week 112
- Change from baseline in total area of leakage at Week 48 and Week 112

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

- Change from baseline in BCVA over time
- Proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, ≥ 0 letters in BCVA from baseline over time
- Proportion of patients avoiding a loss of ≥ 15, ≥ 10, ≥ 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 described above 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 $\leq$38 letters) or worse over time
- Change from baseline in CST (ILM-RPE) over time
- Proportion of patients with absence of intraretinal fluid over time
  - Intraretinal fluid is as measured in the central subfield (center 1 mm)
- Proportion of patients with absence of subretinal fluid over time
  - Subretinal fluid is as measured in the central subfield (center 1 mm)
- Proportion of patients with absence of intraretinal and subretinal fluid over time

- Proportion of patients with absence of pigment epithelial detachment (PED) over time
  - PED is as measured in the central subfield (center 1 mm)

The following efficacy endpoints are considered for the purpose of the marketing authorization application for European Medicine Agency (EMA):

- Change from baseline in BCVA averaged over Weeks 52, 56, and 60
- Change from baseline in CST (ILM-RPE) averaged over Weeks 52, 56, and 60
- Proportion of patients gaining $\geq$ 15 letters in BCVA from baseline averaged over Weeks 52, 56, and 60
- Proportion of patients avoiding a loss of $\geq$ 15 letters in BCVA from baseline averaged over Weeks 52, 56, and 60

4.4.3 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.

- Change from baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) composite score over time
- Change from baseline in CST (ILM-BM) based on an average at Weeks 40, 44, and 48
  - CST is defined as the distance between ILM and Bruch's membrane (BM), as measured in μm as assessed by CRC.
- Change from baseline in CST (ILM-BM) over time
- Change from baseline in PED height over time
  - PED height is defined as RPE + PED thickness at the foveal center, as measured in μm

Analysis for the following endpoints will be presented by pooling across machine type used to obtain the images. If enough gradable images available, analysis may be conducted by machine type.

- Proportion of patients with choriocapillaris drop out dropout over time assessed using OCT-A
- Change from baseline in lesion area over time, as assessed using OCT-A
- Change from baseline in vascular density over time, as assessed using OCT-A

4.4.4 Subgroup Analyses

The following subgroups will be analyzed with respect to the primary efficacy 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 (≥74 letters, 73–55 letters, and ≤54 letters)
- Region (U.S. and Canada, Asia, and the rest of the world)
- Low-luminance deficit (<33 letters and ≥33 letters)
- CNV lesion subtype (classic, predominantly classic, minimally classic, and occult)
- CNV lesion area (<1 mm^2, 1-3 mm^2 and >3 mm^2)
- Total CNV lesion area (<1 mm^2, 1-3 mm^2 and >3 mm^2)
- Age (<75 years and ≥75 years)
- Gender (female and male)
- Race (White, Asian, and other)

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 diabetic macular edema will be updated with the PK data from the present Studies GR40306 and GR40844. 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 the Japan and China extensions.

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 free VEGF-A and Ang-2 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 4.1.5).

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 48 data in the safety-evaluable population. For the purpose of the marketing authorization application for EMA, safety summaries will also be summarized based on the cumulative Week 60 data in the safety-evaluable population. At the time of the final analysis, safety summaries will be produced based on cumulative Week 112 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 AEs 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 48 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, Week 48, Week 60 and Week 112 or early termination visit. Vital signs will be summarized by treatment group, by timepoint, using descriptive summaries.

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).

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.

5. JAPAN SUBPOPULATION ANALYSIS

A separate analysis will be performed for the Japan subpopulation, where data from all patients enrolled in Japan (i.e., during both the global enrollment phase and the Japan extension of GR40306 [TENAYA]) will be combined and summarized.

Analyses described in this section will include all data from the Japan subpopulation as defined in Section 2.3.1.

The analysis populations will be equally defined as per Section 4.1 but will be based only on patients who enroll in Japan. Analyses of study conduct will be performed as described in Section 4.2. Summaries of demographics, stratification factors, disease history, baseline disease characteristics, and patient treatment history will be produced as described in Section 4.3. Primary and key efficacy endpoints for the Japan subpopulation will be summarized using descriptive statistics after censoring observations following COVID-19 related intercurrent events. Similarly, key PK, ADA and safety data for the Japan subpopulation will also be summarized.

No formal statistical testing of the comparison between faricimab (up to Q16W) and the active comparator aflibercept (Q8W) is planned for the Japan subpopulation and the clinical data will be descriptively summarized. The Japan subpopulation results will be interpreted in the context of results from the global enrollment phase. Thus, the consideration of whether the Japan subpopulation data is consistent with the results

from the primary analysis will be based on the totality of the data, including the direction of efficacy and safety profiles.

6. CHINA SUBPOPULATION ANALYSIS

A separate analysis will be performed for the China subpopulation, where data from all patients enrolled in China (i.e., during both the global enrollment phase and the China extension of GR40844 [LUCERNE]) will be combined and summarized.

Analyses described in this section will include all data from the China subpopulation as defined in Section 2.3.2.

The analysis populations will be equally defined as per Section 4.1 but will be based only on patients who enroll at a CDE–recognized site in mainland China, Hong Kong, or Taiwan. Analyses of study conduct will be performed as described in Section 4.2. Summaries of demographics, stratification factors, disease history, baseline disease characteristics, and patient treatment history will be produced as described in Section 4.3. Primary and key efficacy endpoints for the China subpopulation will be summarized using descriptive statistics after censoring observations following COVID-19 related intercurrent events. Similarly, key PK, ADA and safety data for the China subpopulation will also be summarized.

No formal statistical testing of the comparison between faricimab (up to Q16W) and the active comparator aflibercept (Q8W) is planned for the China subpopulation and the clinical data will be descriptively summarized. The China subpopulation results will be interpreted in the context of results from the global enrollment phase. Thus, the consideration of whether the China subpopulation data is consistent with the results from the primary analysis will be based on the totality of the data, including the direction of efficacy and safety profiles.

7. REFERENCES

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Appendix 1
Protocol Synopsis (Study GR40306)

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR–CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FARICIMAB IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (TENAYA)**
PROTOCOL NUMBER:	GR40306
VERSION NUMBER:	3
EUDRACT NUMBER:	2018-002152-32
IND NUMBER:	119225
TEST PRODUCT:	Faricimab (RO6867461)
PHASE:	Phase III
INDICATION:	Neovascular age-related macular degeneration
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, durability, and pharmacokinetics of the 6-mg dose of faricimab administered at up to 16-week intervals compared with aflibercept monotherapy every 8 weeks (Q8W) in patients with choroidal neovascularization (CNV) secondary to age-related macular generation (AMD), also known as neovascular AMD (nAMD). Specific objectives and corresponding endpoints for the study are outlined in the following table.

In this protocol, study drug refers to faricimab or aflibercept and study treatment refers to faricimab, aflibercept, or the sham procedure.

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 compared with aflibercept	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) based on an average at Weeks 40, 44, and 48
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of faricimab on additional BCVA outcomes	• Change from baseline in BCVA over time • Proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, or ≥ 0 letters in BCVA from baseline over time • Proportion of patients avoiding loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline over time • Proportion of patients with BCVA Snellen equivalent of 20/40 or better over time • Proportion of patients gaining ≥ 15 letters or achieving BCVA of ≥ 84 letters over time • Proportion of patients with BCVA Snellen equivalent of 20/200 or worse over time
• To evaluate the frequency of study drug administration	• Proportion of patients on a Q8W, Q12W, and Q16W treatment interval at Weeks 48, 60, and 112 • Number of study drug injections received through Weeks 48, 60, and 112
• To evaluate the efficacy of faricimab on anatomic outcome measures using OCT	• Change from baseline in CST based on an average at Weeks 40, 44, and 48 • Change from baseline in CST 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 and subretinal fluid over time • Proportion of patients with absence of intraretinal cysts over time • Proportion of patients with absence of pigment epithelial detachment over time
• To evaluate the efficacy of faricimab on anatomic outcome measures using FFA	• Change from baseline in total area of CNV lesion at Week 48 and Week 112 • Change from baseline in total area of CNV leakage at Week 48 and Week 112

Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the ocular and non-ocular safety and tolerability of faricimab	• Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events
Exploratory Efficacy Objectives	**Corresponding Endpoint**
• 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
Pharmacokinetic Objectives	**Corresponding Endpoints**
• 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 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 evaluate the drug concentration (exposure)-effect relationship for free Ang-2 and free VEGF-A • To characterize the aqueous humor (optional) and vitreous (optional) pharmacokinetics of faricimab	• Relationship between pharmacokinetics of faricimab and concentration of free Ang-2 and VEGF-A in aqueous humor (optional), plasma, and/or vitreous (optional) over time • Aqueous humor (optional) and vitreous (optional) concentration of faricimab over time
• To explore 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

Objectives and Corresponding Endpoints (cont.)

Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives (cont.)	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, or other biomarker endpoints and genetic polymorphisms at loci, including, but not limited to, Ang-2 and VEGF-A • Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., frequency of study drug administration) over time • Relationship between anatomic measures and visual acuity • Relationship between LLD and/or low-luminance BCVA and BCVA or other endpoints (e.g., anatomical markers) at baseline, Week 48, and Week 112

ADA=anti-drug antibody; Ang-2=angiopoietin-2; BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; CST=central subfield thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; FFA=fundus fluorescein angiography; IVT=intravitreal; LLD = low-luminance deficit; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT=optical coherence tomography; PK=pharmacokinetic; Q8W = every 8 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks; VEGF-A=vascular endothelial growth factor–A.

Note: Additional exploratory efficacy objectives may be evaluated using color fundus photographs, OCT, FFA, optional OCT-angiography, and optional indocyanine green angiography and will be detailed in the Statistical Analysis Plan.

Study Design

Description of Study

This is a Phase III, multicenter, randomized, active comparator–controlled, double-masked, parallel-group, 112-week study to investigate the efficacy, safety, durability, and pharmacokinetics of faricimab administered at up to 16-week intervals to treatment-naive patients with nAMD.

Overview of Study Design

Approximately 640 patients will be enrolled globally and randomized in a 1:1 ratio to one of two treatment arms:

- Arm A (faricimab up to every 16 weeks [Q16W]) (n=320): Patients randomized to Arm A will

receive 6 mg of intravitreal (IVT) faricimab every 4 weeks (Q4W) up to Week 12 (4 injections). At Week 20, a protocol-defined assessment of disease activity requires patients in Arm A with active disease to be treated at that visit and to continue with a Q8W dosing regimen of faricimab. A second protocol-defined assessment of disease activity at Week 24 requires patients in Arm A with active disease (excluding those with active disease at Week 20 and therefore receiving a Q8W dosing regimen of faricimab) to be treated at that visit and to continue with an every 12-week (Q12W) dosing regimen of faricimab. Patients receiving faricimab who do not have active disease according to the protocol-defined criteria at Week 20 and Week 24 will be treated with a Q16W dosing regimen of faricimab. Patients will continue receiving faricimab on a fixed regimen every 8, 12, or 16 weeks until Week 60 according to the disease activity assessments made at Weeks 20 and 24.

From Week 60 (when all patients in Arm A are scheduled to receive faricimab) onward, all patients in Arm A will be treated according to a personalized treatment interval (PTI) dosing regimen (up to Week 108).

- Arm B (comparator arm) (Q8W) (n = 320): Patients randomized to Arm B will receive 2 mg of IVT aflibercept Q4W up to Week 8 (3 injections), followed by 2 mg of IVT aflibercept Q8W up to Week 108.

Patients in both treatment arms will complete scheduled study visits Q4W for the entire study duration (112 weeks). A sham procedure will be administered to patients in both treatment arms at study visits with no study treatment administration to maintain masking among treatment arms.

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

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

The study will consist of a screening period of up to 28 days (Days −28 to −1) in length and an approximately 108-week treatment period, followed by the final study visit at Week 112 (at least 28 days after the last study treatment administration). 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 each 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.

The screening and Day 1 (randomization) visits may occur as a combined visit if all assessments (with the exception of informed consent, which may be obtained earlier) are completed *and evaluated on the same day or* within 2 business days.

During screening, a patient's eligibility will be assessed, including a central reading center review of color fundus photographs (CFPs), optical coherence tomography (OCT), and fundus fluorescein angiography (FFA), to ensure that CNV secondary to AMD meets the ocular criteria for the study.

After screening and *pre-treatment* Day 1 assessments have been completed, eligible patients will have a randomization identification number assigned to them through the IxRS and will be randomized in a 1:1 ratio in order that approximately 320 patients are randomized to each of the two treatment arms. Randomization will be stratified by baseline best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score as assessed on Day 1 (≥ 74 letters, 73–55 letters, and ≤ 54 letters), low-luminance deficit (LLD; < 33 letters and ≥ 33 letters), and region (United States and Canada, Asia, and the rest of the world).

Randomization and Visit Schedule

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

Note: If a site has an unexpected issue (e.g., the IxRS is not able to assign the study kit), a patient's *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 *administration*: *urine pregnancy test (if appropriate),* slitlamp examination, indirect ophthalmoscopy, and pre-treatment IOP measurements (recorded on the Day 1 eCRF and dated accordingly).

Randomized 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). Afterward, all study patients will have a safety assessment visit on Day 7 ($\pm$3 days) evaluated by the masked investigator. At subsequent scheduled visits, patients will have safety assessments evaluated by the masked investigator prior to receiving study treatment (for additional details about masking). Study treatment administration and study-related assessments will occur Q4W (starting on Day 1), as outlined in the schedule of activities). The sham procedure will be delivered to patients in all arms throughout the study as applicable.

At Weeks 20 and 24, a protocol-defined assessment of disease activity performed for all patients in the study requires patients with active disease receiving faricimab (Arm A) to be treated with an 8 weekly or 12 weekly dosing regimen, respectively, until Week 60. Patients receiving faricimab who do not have active disease according to the protocol-defined criteria will be treated with a 16 weekly dosing regimen until Week 60.

From Week 60 (when all patients in Arm A are scheduled to receive faricimab) to Week 108, patients in Arm A will be treated according to a PTI dosing regimen (Q8W, Q12W, or Q16W). At study drug dosing visits treatment intervals may be maintained or adjusted (i.e., increased by 4 weeks, or decreased by 4 or 8 weeks), based on OCT, BCVA, and clinical assessment.

Patients in Arm B will receive aflibercept Q4W up to Week 8, followed by Q8W up to Week 108.

Patients will receive the assigned therapy up to and including Week 108 and return for a final visit at Week 112. After the final visit, adverse events should be followed. Assessments performed in case of an unscheduled safety visit(s) are at the discretion of the investigator.

Patients who prematurely discontinue 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 40, 44, 48, 60, and 112 visits.

Patients who wish to discontinue from the study prior to completion but have not withdrawn consent 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.

Weeks 20 and 24 Disease Activity Criteria

Determination of active disease at Weeks 20 and 24 will be made if any of the following criteria are met:

- Increase $>$50 μm in central subfield thickness (CST) compared with the average CST value over the previous two scheduled visits (Weeks 12 and 16 for the Week 20 assessment and Weeks 16 and 20 for the Week 24 assessment)

  Or

- Increase $\geq$75 μm in CST compared with the lowest CST value recorded at either of the previous two scheduled visits

  Or

- Decrease $\geq$5 letters in BCVA compared with average BCVA value over the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)

  Or

- Decrease ≥ 10 letters in BCVA compared with the highest BCVA value recorded at either of the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)

  Or

- Presence of new macular hemorrhage (as determined by the investigator), owing to nAMD activity

Additional considerations at Week 24: If there is significant nAMD disease activity at Week 24 that does not meet the criteria above, but which in the opinion of the investigator would otherwise warrant treatment, following Sponsor notification through the IxRS, patients randomized to Arm A will receive 6 mg of faricimab at Week 24 and will continue to receive repeated 12 weekly treatments. Patients randomized to Arm A who meet the disease activity criteria at Week 20 will remain on their Q8W dosing schedule and will not receive treatment at Week 24. Patients randomized to Arm B will remain on their Q8W dosing schedule and will receive aflibercept at Week 24.

Personalized Treatment Interval Disease Activity Criteria

Starting at Week 60, when all patients in Arm A are scheduled to receive faricimab, the study drug dosing interval for patients in Arm A will be extended, reduced, or maintained based on assessments made at study drug dosing visits. Study drug dosing interval decisions during the PTI regimen phase for Arm A are automatically calculated by the IxRS based on the algorithm described in the following table. The decision will be made based on data from visits at which patients received study drug. Patients will receive a sham procedure at study visits when they are not receiving treatment with faricimab.

Personalized Treatment Interval Algorithm

Dosing Interval	Criteria
Interval extended by 4 weeks (to a maximum of Q16W)	• *Stable CST[a] compared with the average of the last 2 study drug dosing visits,* and no increase ≥50 μm in CST *(*compared with the lowest on-study drug dosing visit measurement*)* **and** • No decrease ≥5 letters in BCVA[b] compared with the average from the last two study drug dosing visits, and no decrease ≥10 letters in BCVA[b] compared with the highest on-study drug dosing visit measurement **and** • No new macular hemorrhage[c]
Interval reduced (to a minimum Q8W) If one of the criteria is met, the interval will be reduced by 4 weeks. If two or more criteria are met or one criterion includes new macular hemorrhage, the interval will be reduced to an 8-week interval.[d]	• Increase ≥ 50 μm in CST compared with the average from the last two study drug dosing visits or ≥75 μm compared with the lowest on-study drug dosing visit measurement **or** • Decrease ≥5 letters in BCVA[b] compared with average of last two study drug dosing visits or decrease ≥10 letters in BCVA[b] compared with the highest on-study drug dosing visit measurement **or** • New macular hemorrhage[c]
Interval maintained	If extension or reduction criteria have not been met

BCVA=best-corrected visual acuity; CST=central subfield thickness; nAMD=neovascular age-related macular degeneration; Q8W=every 8 weeks; Q16W=every 16 weeks.

[a] *Where stability is defined as a change of CST of less than 30 μm.*

[b] Change in BCVA should be attributable to nAMD disease activity (as determined by investigator).

[c] Refers to macular hemorrhage owing to nAMD activity (as determined by investigator).

[d] Patients whose treatment interval is reduced by 8 weeks from Q16W to Q8W will not be allowed to return to a Q16W interval during the study.

Japan Enrollment Plan

Patient recruitment is expected to take longer in Japan; therefore, a specific Japan enrollment plan has been established. After the global enrollment phase of the study has been completed, additional patients may be enrolled in a Japan extension to ensure a total enrollment that is sufficient to support registration in Japan. It is anticipated that approximately 110 patients will be enrolled at approximately 45 sites. All Japanese patients enrolled in the global enrollment phase of the study will be included in the primary analysis of the study. Data from patients enrolled during the Japan extension will not be included in the primary analyses.

Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will monitor safety and study conduct on an ongoing basis throughout the study. 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 as required) to evaluate unmasked ocular and non-ocular safety events, with 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. 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 640 patients will be enrolled at approximately 200 sites globally.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

General Inclusion Criteria

Patients must meet the following general criteria for study entry:

- 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 ≥ 50 years on Day 1
- Ability to comply with the study protocol, in the investigator's judgment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive measures that result in failure rate < 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. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For patients enrolled in the *Japan* extension at *Japanese* sites: current residents of *Japan*

Ocular Inclusion Criteria for Study Eye

Patients must meet the following ocular criteria for study entry:

- Treatment-naive CNV secondary to AMD (nAMD)
- Subfoveal CNV or juxtafoveal*/extrafoveal* CNV with a subfoveal component related to the CNV activity *identified* by FFA or OCT (*where CNV activity is defined as showing evidence of* subretinal fluid, subretinal hyper-reflective material, *or* leakage)

- CNV lesion of any type (i.e., predominantly classic, minimally classic, or occult [including polypoidal choroidal vasculopathy and retinal angiomatous proliferation]) that exhibits **all** of the following characteristics:
  - A total lesion size (including blood, atrophy, fibrosis, and neovascularization) of ≤9 disc areas on FFA
  - A CNV component area of ≥ 50% of the total lesion size on FFA
  - Active CNV confirmed on FFA (evidence of leakage)
  - CNV exudation confirmed on OCT (presence of fluid)
- BCVA of 78 to 24 letters, inclusive (20/32 to 20/320 approximate Snellen equivalent), using the ETDRS protocol and assessed at the initial testing distance of 4 meters on Day 1
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

Exclusion Criteria

Patients who meet any of the following 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:

- Any major illness or major surgical procedure within 1 month before screening
- Active cancer within the 12 months prior to Day 1 except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤6 and a stable prostate-specific antigen for >12 months
- Requirement for continuous use of any *prohibited* medications and treatments
- Systemic treatment for suspected or active systemic infection on Day 1

  Ongoing use of prophylactic antibiotic therapy may be acceptable if approved after discussion with the Medical Monitor
- Uncontrolled blood pressure, defined as systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg while a patient is at rest on Day 1

  If a patient's initial reading exceeds these values, a second reading may be taken later on 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 (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1
- History of other disease, metabolic dysfunction, physical examination finding, or *historical or current* clinical laboratory findings giving reasonable suspicion of a condition that contraindicates the use of the investigational drug 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
- 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.
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab or aflibercept injections, study-related procedure preparations (including fluorescein), dilating drops, or any of the anesthetic and antimicrobial preparations used by a patient during the study
- 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

Ocular Exclusion Criteria for Study Eye

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

- CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis
- Any history of macular pathology unrelated to AMD affecting vision or contributing to the presence of intraretinal or subretinal fluid
- Presence at screening of central serous chorioretinopathy
- Retinal pigment epithelial tear involving the macula on Day 1
- On FFA/CFP:
  - Subretinal hemorrhage of $>$ 50% of the total lesion area and/or that involves the fovea
  - Fibrosis or atrophy of $>$ 50% of the total lesion area and/or that involves the fovea
- Any concurrent intraocular condition (e.g., amblyopia, aphakia, retinal detachment, cataract, diabetic retinopathy or maculopathy, or epiretinal membrane with traction) that, in the opinion of the investigator, could either reduce the potential for visual improvement or require medical or surgical intervention during the study
- Current vitreous hemorrhage on Day 1
- Uncontrolled glaucoma
- Spherical equivalent of refractive error demonstrating more than 8 diopters of myopia

  For patients who have undergone prior refractive or cataract surgery, the preoperative refractive error should not have exceeded −8 diopters of myopia.
- Any prior or concomitant treatment for CNV or vitreomacular-interface abnormalities, including, but not restricted to, IVT treatment (e.g., anti-vascular endothelial growth factor [VEGF], steroids, tissue plasminogen activator, ocriplasmin, C_3F_8, air), periocular pharmacological intervention, argon laser photocoagulation, verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or ocular surgical intervention
- 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., pars plana vitrectomy, glaucoma surgery, corneal transplant, or radiotherapy)
- Prior periocular pharmacological or IVT treatment (including anti-VEGF medication) for other retinal diseases

Ocular Exclusion Criteria for Fellow (Non–Study) Eye

Patients who meet the following exclusion criterion for the fellow eye (non-study eye) *at both the screening and Day 1 visits* 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 criteria for either eye will be excluded from study entry:

- Prior IVT administration of faricimab in either eye
- History of idiopathic or autoimmune-associated uveitis in either eye
- Active ocular inflammation or suspected or active ocular or periocular infection in either eye on Day 1

End of Study

The study consists of two enrollment phases: the global enrollment phase, during which patients will be recruited globally, and an optional *Japan* extension, during which additional patients may be enrolled to support registration in *Japan*.

The end of this study is defined as the date when the last patient, last visit occurs, including patients from the optional *Japan* extension. The end of the study is expected to occur approximately 112 weeks after the last patient is randomized.

Length of Study

The total length *of the study* (excluding the *Japan* extension) from screening of the first patient to the end of the *study* is expected to be approximately 48 months.

Investigational Medicinal Products

Test Products (Investigational Drugs)

Intravitreal Faricimab

Patients randomized to Arm A will receive 6 mg of IVT faricimab Q4W up to Week 12 (4 injections). At Week 20, protocol-defined assessment of disease activity requires patients in Arm A with active disease to be treated with a Q8W dosing regimen of 6 mg of faricimab (i.e., injections at Weeks 20, 28, 36, 44, 52, and 60).

A second protocol-defined assessment of disease activity at Week 24 requires patients in Arm A with active disease, excluding those with active disease at Week 20 and therefore receiving a Q8W dosing regimen of 6 mg of IVT faricimab) to be treated with a Q12W dosing regimen of 6 mg of IVT faricimab (i.e., injections at Weeks 24, 36, 48, and 60).

Patients receiving faricimab who do not have active disease according to the protocol-defined criteria at Week 20 or Week 24 will be treated with 6 mg of IVT faricimab Q16W (i.e., injections at Weeks 28, 44, and 60).

From Week 60 (when all patients in Arm A are scheduled to receive study drug) to Week 108, patients in Arm A will be treated according to a PTI dosing regimen (between Q8W and Q16W). At study drug dosing visits, treatment intervals may be maintained or adjusted (i.e., increased by 4 weeks or decreased by 4 or 8 weeks), based on OCT, BCVA, and clinical assessment. Patients will therefore receive between 10 and 16 injections over the study treatment period (Day 1 to Week 108).

Comparator

Intravitreal Aflibercept (Active Comparator) Injections

For patients randomized to the active comparator (Arm B), a 2-mg dose of aflibercept will be administered intravitreally Q8W after 3 consecutive monthly doses during the 108-week treatment period. Patients will receive 15 IVT injections of aflibercept during the 108-week treatment period. This will consist of three initiating injections (2 mg of aflibercept Q4W to Week 8), followed by 12 maintenance injections (2 mg of aflibercept Q8W at Weeks 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96, and 104).

Non-Investigational Medicinal Products

Sham Procedure

Both treatment arms (faricimab up to Q16W and aflibercept Q8W) will maintain Q4W study visits for the duration of the study. To preserve masking of the randomized treatment arm, 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 40, 44, and 48. The BCVA outcome measure is based on the ETDRS visual acuity chart assessed at a starting distance of 4 meters.

The primary comparison will be to test non-inferiority of faricimab compared with aflibercept in the intent-to-treat (ITT) population. Additional analysis based on the per-protocol population will also be conducted.

The non-inferiority test will be conducted with a non-inferiority margin of 4 letters at a 0.025 one-sided significance level. The null hypothesis, H_0: $\mu^{faricimab} - \mu^{aflibercept} \leq -4$ letters and the alternative hypothesis, H_a: $\mu^{faricimab} - \mu^{aflibercept} > -4$ letters, will be tested, for which $\mu^{faricimab}$ and $\mu^{aflibercept}$ are the expected change from baseline in BCVA averaged over Weeks 40, 44, and 48 for the faricimab up to Q16W arm and the active comparator (aflibercept Q8W), respectively.

The change from baseline averaged over Weeks 40, 44, and 48 will be compared between the faricimab up to Q16W arm and the aflibercept Q8W arm using a mixed model for repeated measures (MMRM). The model will include the change from baseline at Weeks 4–48 as the response variable 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 the two treatment arms will be made using a composite contrast over Weeks 40, 44, and 48. 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 (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 prohibited therapy after discontinuation of study drug will be included in the analysis.

Additional details about the planned analyses, as well as supplementary and sensitivity analyses using other imputation methods for missing data, analysis using the trimmed mean approach for patients who receive prohibited therapy or discontinue study drug due to lack of efficacy or adverse events, 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 640 patients.

Patients will be randomized in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B). The primary comparison will be between the active comparator (aflibercept Q8W) and the faricimab up to Q16W arm.

A sample size of approximately 320 patients in each arm will provide greater than 90% power to show non-inferiority of faricimab to aflibercept in the change in BCVA averaged over Weeks 40, 44, and 48 in the ITT population, using a non-inferiority margin of 4 letters, and under the following assumptions:

- No difference in the mean change from baseline in BCVA between two treatment arms
- Standard deviation (SD) of 14 letters for the change from baseline in BCVA averaged over Weeks 40, 44, and 48
- Two-sample *t*-test
- 2.5% one-sided type I error rate
- 10% dropout rate

To ensure appropriate patient representation, the Sponsor may elect to cap the recruitment of patients in certain baseline BCVA strata. If implemented, details of the cap will be described in the Statistical Analysis Plan.

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 taken 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.

Additional patients may be randomized during the *Japan* extension to support a *Japan* marketing application. If implemented, details of the *Japan* extension will be described in the Statistical Analysis Plan.

Appendix 2
Protocol Synopsis (Study GR40844)

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR–CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FARICIMAB IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (LUCERNE)**
PROTOCOL NUMBER:	GR40844
VERSION NUMBER:	3
EUDRACT NUMBER:	2018-004042-42
IND NUMBER:	119225
TEST PRODUCT:	Faricimab (RO6867461)
PHASE:	Phase III
INDICATION:	Neovascular age-related macular degeneration
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, durability, and pharmacokinetics of the 6-mg dose of faricimab administered at up to 16-week intervals compared with aflibercept monotherapy every 8 weeks (Q8W) in patients with choroidal neovascularization (CNV) secondary to age-related macular generation (AMD), also known as neovascular AMD (nAMD). Specific objectives and corresponding endpoints for the study are outlined in the following table.

In this protocol, study drug refers to faricimab or aflibercept and study treatment refers to faricimab, aflibercept, or the sham procedure.

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 compared with aflibercept	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) based on an average at Weeks 40, 44, and 48
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of faricimab on additional BCVA outcomes	• Change from baseline in BCVA over time • Proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, or ≥ 0 letters in BCVA from baseline over time • Proportion of patients avoiding loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline over time • Proportion of patients with BCVA Snellen equivalent of 20/40 or better over time • Proportion of patients gaining ≥ 15 letters or achieving BCVA of ≥ 84 letters over time • Proportion of patients with BCVA Snellen equivalent of 20/200 or worse over time
• To evaluate the frequency of study drug administration	• Proportion of patients on a Q8W, Q12W, and Q16W treatment interval at Weeks 48, 60, and 112 • Number of study drug injections received through Weeks 48, 60, and 112
• To evaluate the efficacy of faricimab on anatomic outcome measures using OCT	• Change from baseline in CST based on an average at Weeks 40, 44, and 48 • Change from baseline in CST 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 and subretinal fluid over time • Proportion of patients with absence of intraretinal cysts over time • Proportion of patients with absence of pigment epithelial detachment over time
• To evaluate the efficacy of faricimab on anatomic outcome measures using FFA	• Change from baseline in total area of CNV lesion at Week 48 and Week 112 • Change from baseline in total area of CNV leakage at Week 48 and Week 112

Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the ocular and non-ocular safety and tolerability of faricimab	• Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events
Exploratory Efficacy Objectives	**Corresponding Endpoint**
• 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
Pharmacokinetic Objectives	**Corresponding Endpoints**
• 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 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 evaluate the drug concentration (exposure)-effect relationship for free Ang-2 and free VEGF-A To characterize the aqueous humor (optional) and vitreous (optional) pharmacokinetics of faricimab	• Relationship between pharmacokinetics of faricimab and concentration of free Ang-2 and free VEGF-A in aqueous humor (optional), plasma, and/or vitreous (optional) over time • Aqueous humor (optional) and vitreous (optional) concentration of faricimab over time
• To explore 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

Objectives and Corresponding Endpoints (cont.)

Exploratory Pharmacokinetic, Pharmacodynamic, and Biomarker Objectives (cont.)	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, or other biomarker endpoints and genetic polymorphisms at loci, including, but not limited to, Ang-2 and VEGF-A • Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., frequency of study drug administration) over time • Relationship between anatomic measures and visual acuity • Relationship between LLD and/or low-luminance BCVA and BCVA or other endpoints (e.g., anatomical markers) at baseline, Week 48, and Week 112

ADA=anti-drug antibody; Ang-2=angiopoietin-2; BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; CST=central subfield thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; FFA=fundus fluorescein angiography; IVT=intravitreal; LLD = low-luminance deficit; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT=optical coherence tomography; PK=pharmacokinetic; Q8W = every 8 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks; VEGF-A=vascular endothelial growth factor–A.

Note: Additional exploratory efficacy objectives may be evaluated using color fundus photographs, OCT, FFA, optional OCT-angiography, and optional indocyanine green angiography and will be detailed in the Statistical Analysis Plan.

Study Design

Description of Study

This is a Phase III, multicenter, randomized, active comparator–controlled, double-masked, parallel-group, 112-week study to investigate the efficacy, safety, durability, and pharmacokinetics of faricimab administered at up to 16-week intervals to treatment-naive patients with nAMD.

Overview of Study Design

Approximately 640 patients will be enrolled globally and randomized in a 1:1 ratio to one of two treatment arms:

- Arm A (faricimab up to every 16 weeks [Q16W]) (n=320): Patients randomized to Arm A will

receive 6 mg of intravitreal (IVT) faricimab every 4 weeks (Q4W) up to Week 12 (4 injections). At Week 20, a protocol-defined assessment of disease activity requires patients in Arm A with active disease to be treated at that visit and to continue with a Q8W dosing regimen of faricimab. A second protocol-defined assessment of disease activity at Week 24 requires patients in Arm A with active disease (excluding those with active disease at Week 20 and therefore receiving a Q8W dosing regimen of faricimab) to be treated at that visit and to continue with an every 12-week (Q12W) dosing regimen of faricimab. Patients receiving faricimab who do not have active disease according to the protocol-defined criteria at Week 20 and Week 24 will be treated with a Q16W dosing regimen of faricimab. Patients will continue receiving faricimab on a fixed regimen every 8, 12, or 16 weeks until Week 60 according to the disease activity assessments made at Weeks 20 and 24.

From Week 60 (when all patients in Arm A are scheduled to receive faricimab) onward, all patients in Arm A will be treated according to a personalized treatment interval (PTI) dosing regimen (up to Week 108).

- Arm B (comparator arm) (Q8W) (n = 320): Patients randomized to Arm B will receive 2 mg of IVT aflibercept Q4W up to Week 8 (3 injections), followed by 2 mg of IVT aflibercept Q8W up to Week 108.

Patients in both treatment arms will complete scheduled study visits Q4W for the entire study duration (112 weeks). A sham procedure will be administered to patients in both treatment arms at study visits with no study treatment administration to maintain masking among treatment arms.

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

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

The study will consist of a screening period of up to 28 days (Days −28 to −1) in length and an approximately 108-week treatment period, followed by the final study visit at Week 112 (at least 28 days after the last study treatment administration). 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 each 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.

The screening and Day 1 (randomization) visits may occur as a combined visit if all assessments (with the exception of informed consent, which may be obtained earlier) are completed *and evaluated on the same day or* within 2 business days.

During screening, a patient's eligibility will be assessed, including a central reading center review of color fundus photographs (CFPs), optical coherence tomography (OCT), and fundus fluorescein angiography (FFA), to ensure that CNV secondary to AMD meets the ocular criteria for the study.

After screening and *pre-treatment* Day 1 assessments have been completed, eligible patients will have a randomization identification number assigned to them through the IxRS and will be randomized in a 1:1 ratio in order that approximately 320 patients are randomized to each of the two treatment arms. Randomization will be stratified by baseline best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score as assessed on Day 1 (≥ 74 letters, 73–55 letters, and ≤ 54 letters), low-luminance deficit (LLD; < 33 letters and ≥ 33 letters), and region (United States and Canada, Asia, and the rest of the world).

Randomization and Visit Schedule

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

Note: If a site has an unexpected issue (e.g., the IxRS is not able to assign the study kit), a patient's *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 *administration*: *urine pregnancy test (if appropriate),* slitlamp examination, indirect ophthalmoscopy, and pre-treatment IOP measurements (recorded on the Day 1 eCRF and dated accordingly).

Randomized 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). Afterward, all study patients will have a safety assessment visit on Day 7 ($\pm$3 days) evaluated by the masked investigator. At subsequent scheduled visits, patients will have safety assessments evaluated by the masked investigator prior to receiving study treatment (for additional details about masking). Study treatment administration and study-related assessments will occur Q4W (starting on Day 1), as outlined in the schedule of activities). The sham procedure will be delivered to patients in all arms throughout the study as applicable.

At Weeks 20 and 24, a protocol-defined assessment of disease activity performed for all patients in the study requires patients with active disease receiving faricimab (Arm A) to be treated with an 8 weekly or 12 weekly dosing regimen, respectively, until Week 60. Patients receiving faricimab who do not have active disease according to the protocol-defined criteria will be treated with a 16 weekly dosing regimen until Week 60.

From Week 60 (when all patients in Arm A are scheduled to receive faricimab) to Week 108, patients in Arm A will be treated according to a PTI dosing regimen (Q8W, Q12W, or Q16W). At study drug dosing visits treatment intervals may be maintained or adjusted (i.e., increased by 4 weeks, or decreased by 4 or 8 weeks), based on OCT, BCVA, and clinical assessment.

Patients in Arm B will receive aflibercept Q4W up to Week 8, followed by Q8W up to Week 108.

Patients will receive the assigned therapy up to and including Week 108 and return for a final visit at Week 112. After the final visit, adverse events should be followed. Assessments performed in case of an unscheduled safety visit(s) are at the discretion of the investigator.

Patients who prematurely discontinue 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 40, 44, 48, 60, and 112 visits.

Patients who wish to discontinue from the study prior to completion but have not withdrawn consent 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.

Weeks 20 and 24 Disease Activity Criteria

Determination of active disease at Weeks 20 and 24 will be made if any of the following criteria are met:

- Increase $>$50 μm in central subfield thickness (CST) compared with the average CST value over the previous two scheduled visits (Weeks 12 and 16 for the Week 20 assessment and Weeks 16 and 20 for the Week 24 assessment)

  Or

- Increase $\geq$75 μm in CST compared with the lowest CST value recorded at either of the previous two scheduled visits

  Or

- Decrease $\geq$5 letters in BCVA compared with average BCVA value over the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)

  Or

- Decrease ≥ 10 letters in BCVA compared with the highest BCVA value recorded at either of the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)

  Or

- Presence of new macular hemorrhage (as determined by the investigator), owing to nAMD activity

Additional considerations at Week 24: If there is significant nAMD disease activity at Week 24 that does not meet the criteria above, but which in the opinion of the investigator would otherwise warrant treatment, following Sponsor notification through the IxRS, patients randomized to Arm A will receive 6 mg of faricimab at Week 24 and will continue to receive repeated 12 weekly treatments. Patients randomized to Arm A who meet the disease activity criteria at Week 20 will remain on their Q8W dosing schedule and will not receive treatment at Week 24. Patients randomized to Arm B will remain on their Q8W dosing schedule and will receive aflibercept at Week 24.

Personalized Treatment Interval Disease Activity Criteria

Starting at Week 60, when all patients in Arm A are scheduled to receive faricimab, the study drug dosing interval for patients in Arm A will be extended, reduced, or maintained based on assessments made at study drug dosing visits. Study drug dosing interval decisions during the PTI regimen phase for Arm A are automatically calculated by the IxRS based on the algorithm described in the following table. The decision will be made based on data from visits at which patients received study drug. Patients will receive a sham procedure at study visits when they are not receiving treatment with faricimab.

Personalized Treatment Interval Algorithm

Dosing Interval	Criteria
Interval extended by 4 weeks (to a maximum of Q16W)	• *Stable CST[a] compared with the average of the last 2 study drug dosing visits,* and no increase ≥50 μm in CST *(*compared with the lowest on-study drug dosing visit measurement*)* **and** • No decrease ≥5 letters in BCVA[b] compared with the average from the last two study drug dosing visits, and no decrease ≥10 letters in BCVA[b] compared with the highest on-study drug dosing visit measurement **and** • No new macular hemorrhage[c]
Interval reduced (to a minimum Q8W) If one of the criteria is met, the interval will be reduced by 4 weeks. If two or more criteria are met or one criterion includes new macular hemorrhage, the interval will be reduced to an 8-week interval.[d]	• Increase ≥ 50 μm in CST compared with the average from the last two study drug dosing visits or ≥75 μm compared with the lowest on-study drug dosing visit measurement **or** • Decrease ≥5 letters in BCVA[b] compared with average of last two study drug dosing visits or decrease ≥10 letters in BCVA[b] compared with the highest on-study drug dosing visit measurement **or** • New macular hemorrhage[c]
Interval maintained	If extension or reduction criteria have not been met

BCVA=best-corrected visual acuity; CST=central subfield thickness; nAMD=neovascular age-related macular degeneration; Q8W=every 8 weeks; Q16W=every 16 weeks.

[a] *Where stability is defined as a change of CST of less than 30 μm.*

[b] Change in BCVA should be attributable to nAMD disease activity (as determined by investigator).

[c] Refers to macular hemorrhage owing to nAMD activity (as determined by investigator).

[d] Patients whose treatment interval is reduced by 8 weeks from Q16W to Q8W will not be allowed to return to a Q16W interval during the study.

China Enrollment Plan

Patient recruitment is expected to take longer in China; therefore, a specific China enrollment plan has been established. After the global enrollment phase of the study has been completed, additional patients may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in the People's Republic of China. *It is anticipated that approximately 64 patients will be enrolled at approximately 15 sites*. The China extension may include current residents of mainland China, Hong Kong, or Taiwan enrolled at China Center for Drug Evaluation (CDE)–recognized sites. *The data from those China* patients *who are* enrolled *during* the global enrollment phase of *the* study will be included in the primary analysis of the study. Data from patients enrolled during the China extension will not be included in the primary analyses.

Independent Data Monitoring Committee

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

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The iDMC will meet approximately every 6 months (frequency adjustable as required) to evaluate unmasked ocular and non-ocular safety events, with 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. 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 640 patients will be enrolled at approximately 200 sites globally.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

General Inclusion Criteria

Patients must meet the following general criteria for study entry:

- 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 ≥ 50 years on Day 1
- Ability to comply with the study protocol, in the investigator's judgment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive measures that result in failure rate < 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. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For patients enrolled in the China extension at China CDE–recognized sites: current residents of mainland China, Hong Kong, or Taiwan

Ocular Inclusion Criteria for Study Eye

Patients must meet the following ocular criteria for study entry:

- Treatment-naive CNV secondary to AMD (nAMD)
- Subfoveal CNV or juxtafoveal*/extrafoveal* CNV with a subfoveal component related to the CNV activity *identified* by FFA or OCT (*where CNV activity is defined as showing evidence of* subretinal fluid, subretinal hyper-reflective material *or* leakage)

- CNV lesion of any type (i.e., predominantly classic, minimally classic, or occult [including polypoidal choroidal vasculopathy and retinal angiomatous proliferation]) that exhibits **all** of the following characteristics:
  - A total lesion size (including blood, atrophy, fibrosis, and neovascularization) of ≤9 disc areas on FFA
  - A CNV component area of ≥ 50% of the total lesion size on FFA
  - Active CNV confirmed on FFA (evidence of leakage)
  - CNV exudation confirmed on OCT (presence of fluid)
- BCVA of 78 to 24 letters, inclusive (20/32 to 20/320 approximate Snellen equivalent), using the ETDRS protocol and assessed at the initial testing distance of 4 meters on Day 1
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

Exclusion Criteria

Patients who meet any of the following 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:

- Any major illness or major surgical procedure within 1 month before screening
- Active cancer within the 12 months prior to Day 1 except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤6 and a stable prostate-specific antigen for >12 months
- Requirement for continuous use of any *prohibited* medications and treatments
- Systemic treatment for suspected or active systemic infection on Day 1

  Ongoing use of prophylactic antibiotic therapy may be acceptable if approved after discussion with the Medical Monitor
- Uncontrolled blood pressure, defined as systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg while a patient is at rest on Day 1

  If a patient's initial reading exceeds these values, a second reading may be taken later on 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 (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1
- History of other disease, metabolic dysfunction, physical examination finding, or *historical or current* clinical laboratory findings giving reasonable suspicion of a condition that contraindicates the use of the investigational drug 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
- 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.
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab or aflibercept injections, study-related procedure preparations (including fluorescein), dilating drops, or any of the anesthetic and antimicrobial preparations used by a patient during the study
- 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

Ocular Exclusion Criteria for Study Eye

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

- CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis
- Any history of macular pathology unrelated to AMD affecting vision or contributing to the presence of intraretinal or subretinal fluid
- Presence at screening of central serous chorioretinopathy
- Retinal pigment epithelial tear involving the macula on Day 1
- On FFA/CFP:
  - Subretinal hemorrhage of $>$ 50% of the total lesion area and/or that involves the fovea
  - Fibrosis or atrophy of $>$ 50% of the total lesion area and/or that involves the fovea
- Any concurrent intraocular condition (e.g., amblyopia, aphakia, retinal detachment, cataract, diabetic retinopathy or maculopathy, or epiretinal membrane with traction) that, in the opinion of the investigator, could either reduce the potential for visual improvement or require medical or surgical intervention during the study
- Current vitreous hemorrhage on Day 1
- Uncontrolled glaucoma
- Spherical equivalent of refractive error demonstrating more than 8 diopters of myopia

  For patients who have undergone prior refractive or cataract surgery, the preoperative refractive error should not have exceeded –8 diopters of myopia.
- Any prior or concomitant treatment for CNV or vitreomacular-interface abnormalities, including, but not restricted to, IVT treatment (e.g., anti-vascular endothelial growth factor [VEGF], steroids, tissue plasminogen activator, ocriplasmin, C_3F_8, air), periocular pharmacological intervention, argon laser photocoagulation, verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or ocular surgical intervention
- 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., pars plana vitrectomy, glaucoma surgery, corneal transplant, or radiotherapy)
- Prior periocular pharmacological or IVT treatment (including anti-VEGF medication) for other retinal diseases

Ocular Exclusion Criteria for Fellow (Non–Study) Eye

Patients who meet the following exclusion criterion for the fellow eye (non-study eye) *at both the screening and Day 1 visits* 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 criteria for either eye will be excluded from study entry:

- Prior IVT administration of faricimab in either eye
- History of idiopathic or autoimmune-associated uveitis in either eye
- Active ocular inflammation or suspected or active ocular or periocular infection in either eye on Day 1

End of Study

The study consists of two enrollment phases: the global enrollment phase, during which patients will be recruited globally, and an optional China extension, during which additional patients may be enrolled to support registration in the People's Republic of China.

The end of this study is defined as the date when the last patient, last visit occurs, including patients from the optional China extension. The end of the study is expected to occur approximately 112 weeks after the last patient is randomized.

Length of Study

The total length $of\ the\ study$ (excluding the China extension) from screening of the first patient to the end of the $study$ is expected to be approximately 48 months.

Investigational Medicinal Products

Test Products (Investigational Drugs)

Intravitreal Faricimab

Patients randomized to Arm A will receive 6 mg of IVT faricimab Q4W up to Week 12 (4 injections). At Week 20, protocol-defined assessment of disease activity requires patients in Arm A with active disease to be treated with a Q8W dosing regimen of 6 mg of faricimab (i.e., injections at Weeks 20, 28, 36, 44, 52, and 60).

A second protocol-defined assessment of disease activity at Week 24 requires patients in Arm A with active disease, excluding those with active disease at Week 20 and therefore receiving a Q8W dosing regimen of 6 mg of IVT faricimab) to be treated with a Q12W dosing regimen of 6 mg of IVT faricimab (i.e., injections at Weeks 24, 36, 48, and 60).

Patients receiving faricimab who do not have active disease according to the protocol-defined criteria at Week 20 or Week 24 will be treated with 6 mg of IVT faricimab Q16W (i.e., injections at Weeks 28, 44, and 60).

From Week 60 (when all patients in Arm A are scheduled to receive study drug) to Week 108, patients in Arm A will be treated according to a PTI dosing regimen (between Q8W and Q16W). At study drug dosing visits, treatment intervals may be maintained or adjusted (i.e., increased by 4 weeks or decreased by 4 or 8 weeks), based on OCT, BCVA, and clinical assessment. Patients will therefore receive between 10 and 16 injections over the study treatment period (Day 1 to Week 108).

Comparator

Intravitreal Aflibercept (Active Comparator) Injections

For patients randomized to the active comparator (Arm B), a 2-mg dose of aflibercept will be administered intravitreally Q8W after 3 consecutive monthly doses during the 108-week treatment period. Patients will receive 15 IVT injections of aflibercept during the 108-week treatment period. This will consist of three initiating injections (2 mg of aflibercept Q4W to Week 8), followed by 12 maintenance injections (2 mg of aflibercept Q8W at Weeks 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96, and 104).

Non-Investigational Medicinal Products

Sham Procedure

Both treatment arms (faricimab up to Q16W and aflibercept Q8W) will maintain Q4W study visits for the duration of the study. To preserve masking of the randomized treatment arm, 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 40, 44, and 48. The BCVA outcome measure is based on the ETDRS visual acuity chart assessed at a starting distance of 4 meters.

The primary comparison will be to test non-inferiority of faricimab compared with aflibercept in the intent-to-treat (ITT) population. Additional analysis based on the per-protocol population will also be conducted.

The non-inferiority test will be conducted with a non-inferiority margin of 4 letters at a 0.025 one-sided significance level. 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 40, 44, and 48 for the faricimab up to Q16W arm and the active comparator (aflibercept Q8W), respectively.

The change from baseline averaged over Weeks 40, 44, and 48 will be compared between the faricimab up to Q16W arm and the aflibercept Q8W arm using a mixed model for repeated measures (MMRM). The model will include the change from baseline at Weeks 4–48 as the response variable 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 the two treatment arms will be made using a composite contrast over Weeks 40, 44, and 48. 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 (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 prohibited therapy after discontinuation of study drug will be included in the analysis.

Additional details about the planned analyses, as well as supplementary and sensitivity analyses using other imputation methods for missing data, analysis using the trimmed mean approach for patients who receive prohibited therapy or discontinue study drug due to lack of efficacy or adverse events, 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 640 patients.

Patients will be randomized in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B). The primary comparison will be between the active comparator (aflibercept Q8W) and the faricimab up to Q16W arm.

A sample size of approximately 320 patients in each arm will provide greater than 90% power to show non-inferiority of faricimab to aflibercept in the change in BCVA averaged over Weeks 40, 44, and 48 in the ITT population, using a non-inferiority margin of 4 letters, and under the following assumptions:

- No difference in the mean change from baseline in BCVA between two treatment arms
- Standard deviation (SD) of 14 letters for the change from baseline in BCVA averaged over Weeks 40, 44, and 48
- Two-sample *t*-test
- 2.5% one-sided type I error rate
- 10% dropout rate

To ensure appropriate patient representation, the Sponsor may elect to cap the recruitment of patients in certain baseline BCVA strata. If implemented, details of the cap will be described in the Statistical Analysis Plan.

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 taken 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.

Additional patients may be randomized during the China extension to support a China marketing application. If implemented, details of the China extension will be described in the Statistical Analysis Plan.

Appendix 3
Schedule of Assessments

Screening through Week 48 Assessments

		Visit Day		Visit Week												
	Screening [a]	1 [a]	7	4	8	12	16	20	24	28	32	36	40	44	48	ET [b]
Day(s) (Visit window)	–28 to –1	N/A	(±3)	28 (±7)	56 (±7)	84 (±7)	112 (±7)	140 (±7)	168 (±7)	196 (±7)	224 (±7)	252 (±7)	280 (±7)	308 (±7)	336 (±7)	(≥28)
Informed consent [c]	x															
Sample informed consent [c] for optional aqueous, vitreous, and blood samples	x															
Optional (RBR) residual samples and DNA whole blood sample informed consent [c]	x															
Review of inclusion and exclusion criteria	x	x														
Demographic data	x															
Medical history [d]	x															
Targeted physical examination [e]	x															x
Body weight and height	x															
Vital signs [f]	x	x													x	x
NEI VFQ-25 [g]		x							x						x	x
BCVA [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Low-luminance BCVA		x													x	
Pre-treatment IOP [i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Screening through Week 48 Assessments (cont.)

		Visit Day		Visit Week												
	Screening [a]	1 [a]	7	4	8	12	16	20	24	28	32	36	40	44	48	
Day(s) (Visit window)	–28 to –1	N/A	(±3)	28 (±7)	56 (±7)	84 (±7)	112 (±7)	140 (±7)	168 (±7)	196 (±7)	224 (±7)	252 (±7)	280 (±7)	308 (±7)	336 (±7)	ET [b] (≥28)
Pregnancy test [j]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
*Whole blood sample (*hematology, chemistry panel, coagulation*)*, and urinalysis [k]	x														x	
Optional aqueous humor sample [l]		x	x				x	x	x	x						x
Optional vitreous humor sample [m]		If elective vitrectomy is performed [m]														
Optional PK plasma sample (if vitreous humor sample collected) [m]		*If elective vitrectomy is performed and vitreous humor sample collected* [m]														
Optional blood sample for RBR [n]		x														
Mandatory plasma PK sample [o]		x		x			x	x							x	x
Optional PK plasma sample (if aqueous humor sample is collected)			x [p]													
Mandatory plasma PD sample [o]		x		x			x	x							x	x
Optional PD plasma sample (if aqueous humor sample is collected)			x [p]													
Mandatory plasma sample for ADAs [o]		x		x				x							x	x
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Screening through Week 48 Assessments (cont.)

		Visit Day		Visit Week												
	Screening [a]	1 [a]	7	4	8	12	16	20	24	28	32	36	40	44	48	ET [b]
Day(s) (Visit window)	–28 to –1	N/A	(±3)	28 (±7)	56 (±7)	84 (±7)	112 (±7)	140 (±7)	168 (±7)	196 (±7)	224 (±7)	252 (±7)	280 (±7)	308 (±7)	336 (±7)	(≥28)
Indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
OCT [q]	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
FFA [q]	x														x	x
CFP [q]	x														x	x
Optional ICGA [q, s]	x														x	
Disease activity assessment [t]								x	x							
Administration of study treatment		x		x	x	x	x	x	x	x	x	x	x	x	x	
Finger counting test [u]		x		x	x	x	x	x	x	x	x	x	x	x	x	
Post-treatment IOP [v]		x		x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events [w]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [x]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [y]		x	x	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; eCRF = electronic Case Report Form; ET = early termination; FFA = fundus fluorescein angiography; ICGA = indocyanine green angiography; IOP = intraocular pressure; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT = optical coherence tomography; OCT-A = optical coherence tomography–angiography; PD = pharmacodynamic; PK = pharmacokinetic; RBR = Research Biosample Repository; VA = visual acuity.

Screening through Week 48 Assessments (cont.)

Notes: *All ocular assessments are to be performed on both eyes unless stated otherwise. All assessments are to be performed on the same day, except during screening.*

All study visits will be scheduled relative to the date of the Day 1 visit (first study treatment). There must be a minimum of 21 days between all study visits occurring from Week 4 through Week 108. All assessments should be performed prior to dosing, unless otherwise specified. *Fellow eye anti-VEGF treatment approved by the country regulatory agency for ocular use* may be covered by the Sponsor only as long as the patient remains in the study (for details, refer to Section 4.4.2).

[a] The screening and Day 1 (randomization) visits may occur as a combined visit if all assessments are completed and evaluated within 2 business days. Informed consent must be administered and signed by a patient before any study-specific screening procedure is performed. When screening and randomization are combined and performed on 1 day, assessments listed for both visits should be conducted only once. If the combined visit is conducted within 2 business days, then the following safety assessments will be repeated on the day of patient's randomization and study treatment administration: slitlamp examination, indirect ophthalmoscopy, and pre- and post-treatment IOP measurements (recorded on the Day 1 eCRF and dated accordingly). *Verify that the patient has not started any prohibited medication.*

[b] Patients who discontinue from the study early (prior to the final study visit at Week 112) 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, and smoking history, will be recorded at baseline.

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

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

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

[h] To be performed prior to other ocular assessments. Perform the assessments prior to dilating the eyes.

[i] The same method should be used throughout the study period. Perform *measurements* prior to dilating the eyes. At screening and on Day 7, IOP should be performed, although study treatment will not be given.

Screening through Week 48 Assessments (cont.)

[j] All women of childbearing potential (including those who had had a tubal ligation) will have a urine pregnancy test performed at screening and prior to each study treatment at subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. If positive, do not administer study treatment. Perform urine pregnancy test before FFA (if applicable).

[k] Hematology includes hemoglobin, hematocrit, quantitative platelet count, RBC counts, WBC counts, and differentials, including neutrophils, bands, lymphocytes, basophils, eosinophils, 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. Coagulation includes activated partial thromboplastin time and prothrombin time. 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 screening and Day 1 visits are combined, historical laboratory data obtained within 2 months of Day 1 may be used at the Principal Investigator's discretion.*

[l] 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. Not applicable* for a site that has not been granted approval by a site's Institutional Review Board or Ethics Committee. The sample at ET is not required if there are any safety concerns.

[m] If elective vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. A PK blood sample (for plasma preparation) should also be collected and shipped to the Sponsor. Vitreous humor samples will be analyzed primarily for faricimab concentrations or aflibercept concentrations. The remaining samples may be analyzed for VEGF and Ang-2 concentrations and possibly other biomarkers.

[n] *Not applicable* for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. If the optional RBR 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 and ADA sampling, and/or hematology or chemistry).

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

[p] PK and PD samples on Day 7 should be collected only from patients consenting to optional aqueous humor sampling.

[q] *OCT and FFA images obtained at screening will be reviewed by the CRC to determine patient eligibility. At all subsequent visits, please forward imaging outputs from all devices to the CRC. Please see the CRC manual for further details on image requirements.* ***Please remember to forward all OCT images to the CRC as soon as possible. If OCT imaging data is missing due to a missed visit or a problem with the OCT device, please notify the CRC as soon as possible.*** Note: After randomization, if a patient misses a study visit when ocular images are scheduled, the images should be obtained at the next scheduled visit the patient attends.

Screening through Week 48 Assessments (cont.)

[r] Optional OCT-A of both eyes to be conducted at sites with agreed OCT-A capability.

[s] Optional ICGA of both eyes performed at sites with agreed ICGA capability. ICGA should be performed after laboratory samples are obtained and, *if images are taken sequentially,* after all other imaging has been performed. *If standard of care at a site, it is acceptable to perform ICGA in parallel with FFA.*

[t] Assessment of disease activity should be conducted per the specified criteria outlined in Section 3.1.1.4.

[u] The finger counting test should be conducted within 15 minutes of study drug or sham administration for the study eye only.

[v] Post-treatment IOP measurement to be conducted in the study eye only *at* 30 (±15) minutes by qualified personnel assigned to the unmasked role. If there are no safety concerns *at* 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. The same method should be used throughout the study period.

[w] 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 drug, all adverse events will be reported until 28 days after the final dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event(s) that are believed to be related to prior administration of study treatment. The investigator should follow each adverse event until: the event has resolved to baseline grade or better; the event is assessed as stable by the investigator; the patient is lost to follow-up; or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[x] All medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment (the Day 1 visit) until 28 days after the final dose of study drug should be recorded.

[y] 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.

Week 52 through Week 112 Assessments

	Visit Week																
	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	
Day (Visit window)	364 (±7)	392 (±7)	420 (±7)	448 (±7)	476 (±7)	504 (±7)	532 (±7)	560 (±7)	588 (±7)	616 (±7)	644 (±7)	672 (±7)	700 (±7)	728 (±7)	756 (±7)	784 (±7) [a]	ET [b] (≥28)
Targeted physical examination [c]																x	x
Vital signs [d]			x													x	x
NEI VFQ-25 [e]			x													x	x
BCVA [f]	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x
Low-luminance BCVA			x													x	
Pre-treatment IOP [g]	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x
Pregnancy test [h]	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x
Optional aqueous humor sample [i]				x	x	x	x										x
Optional vitreous humor sample [j]	If elective vitrectomy is performed [j]																
Optional PK plasma sample (if vitreous humor sample is collected) [j]	*If elective vitrectomy is performed and vitreous humor sample collected* [j]																
Plasma PK sample [k]							x									x	x
Plasma PD sample [k]							x									x	x
Plasma sample for ADAs [k]							x									x	x
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Week 52 through Week 112 Assessments (cont.)

	Visit Week																
	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	
Day(s) (Visit window)	364 (±7)	392 (±7)	420 (±7)	448 (±7)	476 (±7)	504 (±7)	532 (±7)	560 (±7)	588 (±7)	616 (±7)	644 (±7)	672 (±7)	700 (±7)	728 (±7)	756 (±7)	784 (±7) [a]	ET [b] (≥28)
Indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
OCT [l]	x	x	x	x	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	x	x	x	x
FFA [l]			x													x	x
CFP [l]			x													x	x
Optional ICGA [l, n]			x													x	
Administration of study treatment	x	x	x	x	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	x	x	x	x		
Post-treatment IOP [p]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Adverse events [q]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [r]	x	x	x	x	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	x	x	x	x

ADA = anti-drug antibody; BCVA = best-corrected visual acuity; CFP = color fundus photograph; eCRF = electronic Case Report Form; ET = early termination; FFA = fundus fluorescein angiography; ICGA = indocyanine green angiography; IOP = intraocular pressure; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT = optical coherence tomography OCT-A = optical coherence tomography–angiography; PD = pharmacodynamic; PK = pharmacokinetic; VA = visual acuity.

Week 52 through Week 112 Assessments (cont.)

Notes: There must be a minimum of 21 days between all study visits occurring from Week 4 through Week 108. All assessments should be performed prior to dosing, unless otherwise specified. Standard-of-care treatment for nAMD in the fellow eye may be covered by the Sponsor only as long as the patient remains in the study (for details, refer to Section 4.4.2).

[a] The Week 112 visit must occur ≥28 days and <35 days after the actual date of the Week 108 visit.

[b] Patients who discontinue from the study early but have not withdrawn consent should return for an ET visit 28 days following the last study treatment.

[c] 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.

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

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

[f] To be performed prior to other ocular assessments. Perform the assessments prior to dilating the eyes.

[g] The same method should be used throughout the study period. Perform *measurements* prior to dilating the eyes.

[h] All women of childbearing potential (including those who have had a tubal ligation) will have a urine pregnancy test performed at prior to each study treatment and at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. If positive, do not administer study treatment. Perform urine pregnancy test before FFA (if applicable).

[i] If a patient consents to collection of optional aqueous humor sample, collect the sample at the indicated timepoints prior to study treatment administration. Not applicable for a site that has not been granted approval by a site's Institutional Review Board or Ethics Committee. The sample at ET is not required if there are any safety concerns.

[j] If elective vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. A PK blood sample (for plasma preparation) should also be collected and shipped to the Sponsor. Vitreous humor samples will be analyzed primarily for faricimab concentrations or aflibercept concentrations. The remaining samples may be analyzed for VEGF and Ang-2 concentrations, and possibly other biomarkers.

Week 52 through Week 112 Assessments (cont.)

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

[l] *Please forward imaging outputs from all devices to the CRC. Please see the CRC manual for further details on image requirements.* ***Please remember to forward all OCT images to the CRC as soon as possible, particularly from Week 60 onwards when images need to be read and data submitted to IxRS before the next study visit. If OCT imaging data is missing due to a missed visit or a problem with the OCT device, please notify the CRC as soon as possible so that they may update the IxRS system accordingly.*** Note: If a patient misses a study visit when ocular images are scheduled, the images should be obtained at the next scheduled visit the patient attends.

[m] Optional OCT-A of both eyes to be conducted at sites with agreed OCT-A capability.

[n] Optional ICGA of both eyes performed at sites with agreed ICGA capabilities. ICGA should be performed after laboratory samples are obtained and *if images are taken sequentially,* after all other imaging has been performed. *If standard of care at a site, it is acceptable to perform ICGA in parallel with FFA.*

[o] The finger counting test should be conducted within 15 minutes of study drug or sham administration for the study eye only.

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

[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 drug, all adverse events will be reported until 28 days after the final dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event(s) that are believed to be related to prior administration of study treatment. The investigator should follow each adverse event until: the event has resolved to baseline grade or better; the event is assessed as stable by the investigator; the patient is lost to follow-up; or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[r] All medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment (the Day 1 visit) until 28 days after the final dose of study drug should be recorded.

[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 ET visit.