Official Title: An Exploratory, Prospective, Multi-Center, Open-Label, Single-Arm, Interventional, Phase IIb Study to Investigate Aqueous Humor and Multimodal Imaging Biomarkers in Intravitreal Treatment-Naïve Patients with Diabetic Macular Edema Treated with Faricimab (R06867461) -Altimeter Study

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STATISTICAL ANALYSIS PLAN

AN EXPLORATORY, PROSPECTIVE, MULTI-CENTER, OPEN-LABEL, SINGLE-ARM, INTERVENTIONAL, PHASE IIB STUDY TO INVESTIGATE AQUEOUS HUMOR AND MULTIMODAL IMAGING BIOMARKERS IN INTRAVITREAL TREATMENT-NAÏVE PATIENTS WITH DIABETIC MACULAR EDEMA TREATED WITH FARICIMAB (RO6867461) - ALTIMETER STUDY

PROTOCOL NUMBER:	MR41926
STUDY DRUG:	Faricimab (RO6867461)
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PLAN PREPARED BY:	[redacted] Cytel [redacted], Roche
DATE FINAL:	See electronic date stamp below

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AC	anterior chamber
AE	adverse event
AH	aqueous humor
AI	artificial intelligence
ALT	alanine aminotransferase
AMD	age-related Macular Degeneration
Ang-2	angiopoietin-2
AO	adaptive optics
AST	aspartate transaminase
BCVA	best corrected visual acuity
BP	blood pressure
CFP	color fundus photographs
CI	confidence interval
CRC	central reading center
CRO	Contract research organization
CST	central subfield thickness
CTCAE	Common Terminology Criteria for Adverse Events
DM	diabetes mellitus
DME	diabetic macular edema
DR	diabetic retinopathy
DRIL	disorganization of retinal inner layers
DRSS	Diabetic Retinopathy Severity Scale
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	Electronic data capture
EoS	End of Study
ETDRS	Early Treatment Diabetic Retinopathy Study
ETV	Early termination visit
FAZ	foveal avascular zone
FDA	Food and Drug Administration
FFA	fundus fluorescein angiography
HbA_{1c}	hemoglobin A_{1c}
HIPAA	Health Insurance Portability and Accountability Act
HRF	hyper-reflective foci
ICF	Informed Consent Form

ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IOP	intraocular pressure
IRB	Institutional Review Board
IRF	intraretinal fluid
IVT	intravitreal
IxRS	interactive voice/web response system
LPLV	last patient, last visit
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NA	not applicable
nAMD	neovascular age-related macular degeneration
NCI	National Cancer Institute
NCT	National Clinical Trials
NEI	National Eye Institute
NGS	next-generation sequencing
NPDR	non-proliferative diabetic retinopathy
OCT	optical coherence tomography
PDR	proliferative diabetic retinopathy
PK	pharmacokinetic
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD-OCT	spectral domain optical coherence tomography
SD-OCT-A	spectral-domain optical coherence tomography angiography
SFV	safety follow-up visit
SoA	schedule of assessments
SOC	standard of care
SRF	subretinal fluid
SS-OCT	swept-source optical coherence tomography
SS-OCT-A	swept-source optical coherence tomography angiography
SUN	Standardization of Uveitis Nomenclature
ULN	upper limit of normal
UWF	ultra-wide field

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1. BACKGROUND

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

With advances in imaging technology, DME is now often diagnosed by optical coherence tomography (OCT) rather than the traditional Early Treatment Diabetic Retinopathy Study (ETDRS) ophthalmoscopy-based criteria. On a molecular level, DME is a result of a vascular endothelial growth factor-A (VEGF-A)-mediated increase in vessel permeability and loss of pericytes, consequent to hypoxia-mediated release of pro-angiogenic, hyperpermeability, and pro-inflammatory mediators (Antonetti et al. 1999).

VEGF also upregulates a homeostatic factor, angiopoietin-2 (Ang-2), which acts as an antagonist of the Tie2 receptor tyrosine kinase on endothelial cells, counteracting vessel stabilization maintained through Ang-1-dependent Tie2 activation. Therefore, Ang-2 acts as a vascular destabilization factor, rendering the vasculature more elastic and amenable to endothelial barrier breakdown and sprouting. The excess of Ang-2 and VEGF in the retinal tissues promotes vessel destabilization, vascular leakage, and neovascularization. Ang-2 is also involved in inflammatory pathways such as lymphocyte recruitment. In summary, both VEGF-A and Ang-2 are recognized as key factors mediating diabetic eye disease pathogenesis (Aiello et al. 1994; Davis et al. 1996; Maisonpierre et al. 1997; Gardner et al. 2002; Joussen et al. 2002; Fiedler et al. 2003).

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

Faricimab (also known as RO6867461) is a humanized full-length bispecific IgG1 antibody that selectively neutralizes VEGF-A (hereafter referred to as "VEGF") and Ang-2, the key factors mediating pathophysiology of diabetic eye disease. Faricimab was developed using Roche's CrossMab (monoclonal antibody) technology.

Faricimab has been approved in 45 countries worldwide, including Australia, Canada, EU, Japan, Switzerland, UK, and the US for the treatment of DME and neovascular (wet) age-related macular degeneration (nAMD).

The clinical benefit of faricimab injections for patients with DME was demonstrated in the Phase II study (BP30099 [BOULEVARD]). The data from Study BP30099 (BOULEVARD) suggested a dose-related benefit favoring the 6-mg dose of faricimab relative to the 1.5-mg dose, as measured by both the efficacy outcomes and duration of effect. Based on these results, the 6-mg dose of faricimab has been chosen for further clinical development in Phase III studies in patients with DME to explore its benefit compared with SOC IVT anti-VEGF treatment.

The Phase III clinical development program in DME (YOSEMITE: Study GR40349, and RHINE: Study GR40398) enrolled both patients with DME who were naive to anti-VEGF therapy in the study eye and patients who were previously treated with anti-VEGF therapy in the study eye to further explore outcomes on DME in both populations. Enrollment into these 2 ongoing studies has been completed in 2019. Both studies met their primary endpoint (Wykoff et al. 2022) and faricimab was generally well tolerated, with no new or unexpected safety signals identified.

As of May 2022, approximately 2700 patients have received at least one dose of faricimab in the completed and ongoing clinical studies. Overall, the updated analysis through Week 100/112 of the pivotal Phase III studies and final analysis from the supportive Phase II studies in patients with DME/DR and nAMD showed that faricimab has a comparable safety profile to aflibercept and ranibizumab. The safety data indicate that faricimab was generally well tolerated, and no new or unexpected safety signals were identified.

Please refer to the protocol for the references cited above and for further details on faricimab background.

2. STUDY DESIGN

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

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

- AH taps from the study eye will be collected on Day 1 (baseline) and the Day 112 visit (i.e., prior to injections 1 and 5).

- Multimodal retinal imaging will be applied at the screening visit, Day 1 (baseline), and throughout the study (see Appendix 2)

Approximately 35 global study sites will enroll approximately 80 patients who are treatment-naïve in the study eye. However, the Sponsor may increase the sample size up to 100 patients, to compensate for those patients who completed the study without having a full set of Day 1 (baseline) and Day 112 visit analyzable AH samples collected. The aim of this increase is to achieve 60 patients with analyzable Day 1 (baseline) and Day 112 visit AH samples (see Section 2.3). The Sponsor may decide to stop the enrollment as soon as the target of 60 analyzable sets of AH samples is reached. Patients will receive 6 doses (one 6 mg faricimab IVT injection Q4W) starting at Day 1 and ending on the Day 140 visit. Patients will return for a safety follow-up visit (SFV) after ≥28 days and within <35 days following their last study treatment. Patients who discontinue from the study or treatment early (prior to the SFV) but have not withdrawn consent (and have not been lost to follow-up) should return for an early termination visit (ETV) after ≥28 days have elapsed following their last study treatment (visit should occur within <35 days of the patient's last study treatment).

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

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

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

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

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

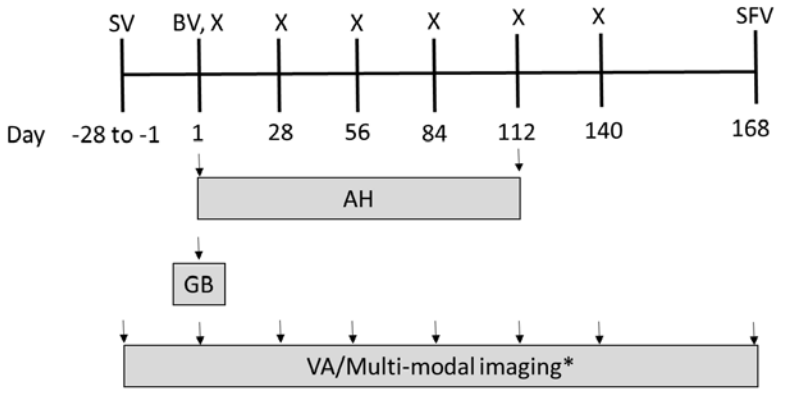
- Screening period: up to 28 days (i.e., up to 4 weeks)
- Treatment period: 140 days (±7 days) (i.e., approximately 20 weeks)
- Safety follow-up period: 28 days to 35 days (i.e., approximately 4 to 5 weeks)

A patient is considered to have completed the study if he/she has completed the last scheduled procedure (i.e. he/she has completed the Safety Follow-up visit) shown in the schedule of assessments.

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

Figure 1 presents an overview of the study design.

Figure 1 Study Design



SV: screening visit
BV: baseline visit
X: 6 mg faricimab (RO6867461) IVT injection
SFV: safety follow-up visit
AH: aqueous humor tap
GB: genomic blood draw
VA: visual acuity tests
* Multi-modal imaging detailed in the Schedule of Assessments

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

2.2.1 Exploratory Endpoints

To explore the associations over time between clinical assessments, multimodal imaging assessments, AH biomarker patterns and genetic polymorphisms:

- Proportion of patients with a ≥2-step ETDRS DRSS improvement from baseline over time
- Proportion of patients with a ≥3-step ETDRS DRSS improvement from baseline over time
- Changes from baseline in BCVA (as measured on the ETDRS chart) over time
- Changes from baseline in IRF (intraretinal fluid) over time
- Changes from baseline in SRF (subretinal fluid) over time
- Changes from baseline in CST over time
- Changes from baseline in multimodal imaging over time including:
    - Central retinal thickness
    - Foveal avascular zone (FAZ) / retinal nonperfusion
    - Vessel density
    - Periphery status (ischemia and proliferation)
    - Microaneurysm location, number, and turnover
    - Ischemic area
- Changes from baseline in AH biomarker patterns over time including:
    - Proteins, including but not limited to: cytokines, chemokines, and growth-, angiogenesis-, and complement-related factors, etc.
    - Metabolites, including but not limited to: lipids, sugars, amino acids, etc.
- Genetic polymorphisms via standard clinical genotyping
- Advanced analytics tools (e.g., artificial intelligence-based tools) for the assessment of clinically relevant features

2.2.2 Pharmacokinetic Endpoints

Not Applicable.

2.2.3 Safety Endpoints

The Safety endpoints are:

- Incidence and severity of adverse events
- Description of ocular assessments
- Study treatment exposure and Anti-VEGF exposure for fellow eye
- Laboratory assessments (only HbA1c assessments)
- Concomitant medication
- Concurrent ocular procedures

2.3 DETERMINATION OF SAMPLE SIZE

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

The Sponsor has increased the sample size up to 99 patients, to compensate for those patients who completed the study without having a full set of Day 1 (baseline) and Day 112 visit analyzable* AH samples collected. The aim of this increase was to achieve 60 patients with analyzable* Day 1 (baseline) and Day 112 visit AH samples.

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

2.4 ANALYSIS TIMING

Only final analysis will be performed at the end of Study once all patients have completed the Week 24 (Day 168 visit) visit or have discontinued from the study prior to Week 24, all data collected through Week 24 are in the database, the data have been cleaned and verified, and the database is locked.

The results of the statistical analyses described in this SAP will be included in a Clinical Study Report (CSR). As this is an open-label study, no formal interim analyses are planned. Nevertheless, exploratory analyses of selected endpoints may be performed during the course of the study (e.g., after all patients have completed the Day 28 visit and the necessary data are available).

3. STUDY CONDUCT

3.1 RANDOMIZATION

Not Applicable

3.2 INDEPENDENT REVIEW FACILITY

All ocular images results are obtained by trained site personnel at the study sites and forwarded to the CRC for independent analysis and/or storage. As part of screening process, the CRCs evaluate Spectral Domain-Optical Coherence Tomography (SD-OCT) images and Color Fundus Photography (FP-7M) to provide an objective assessment of patient eligibility. During the study treatment, the CRCs provide an evaluation of all ocular images including: Ultra-Widefield Color Fundus Photography (UWF-C), Ultra-Widefield Fluorescein Angiography (UWF-FA), Spectral Domain and Swept Source Optical Coherence Tomography (SD-OCT and (if capable) SS-OCT), Spectral Domain or Swept Source Optical Coherence Tomography Angiography (SD-OCTA and SS-OCTA), Color Fundus Photography – Modified 7 Field (FP-7M) and Adaptive Optics (AO; to be collected at selected study sites).

3.3 DATA MONITORING

Not Applicable.

4. STATISTICAL METHODS

For continuous variables, descriptive statistics (e.g., number of patients [n], mean, standard deviation [SD], median, 25th and 75th percentiles, minimum, maximum) will be calculated and summarized.

For categorical variables, the number and percentage in each category will be displayed.

Statistical methods for exploratory endpoints are detailed in the Exploratory Analyses section below.

Unless otherwise specified, statistical tests will be two-sided and the statistical significance level will be 5%. Corresponding 95% CIs will be presented as appropriate. Although multiple statistical tests may be conducted, due to the exploratory nature of the study no adjustments to the Type 1 error rate for multiplicity will be made.

The analyses outlined in this SAP supersede those specified in the protocol.

4.1 ANALYSIS POPULATIONS

4.1.1 Modified Intent-To-Treat Population

The modified intent-to-treat (mITT) population is defined as all patients enrolled in the study that received any amount of study treatment.

4.1.2 Per Protocol Population

Not Applicable.

4.1.3 Pharmacokinetic-Evaluable Population

Not Applicable.

4.1.4 Safety-Evaluable Population

Safety-evaluable population (SE) is defined as all patients enrolled who received at least one injection of study treatment.

4.2 ANALYSIS OF STUDY CONDUCT

The number of patients enrolled will be tabulated by country and site.

Patient disposition information will be summarized as follows:

- Number and percentage of patients enrolled
- Number and percentage of patients in the mITT population and SE population
- Number and percentage of patients who complete study treatment
- Number and percentage of patients who discontinue study treatment and the reasons for study treatment discontinuation
- Number and percentage of patients who complete study
- Number and percentage of patients who discontinue study and the reasons for study discontinuation

Major protocol violations, including violations of inclusion/exclusion criteria collected during the study via PDMS will be summarized.

The impact of COVID-19 will be assessed by summarizing major protocol deviations related to COVID-19 and by summarizing COVID-19 related intercurrent events.

4.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

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

The following demographic and baseline characteristics will be summarized for the mITT population:

- Age (years) as continuous variable and age in category < 65 years, ≥ 65 years
- Gender (Male and Female)
- Self-reported race and ethnicity
- Region
- Female reproductive status
- Smoking history (never, current, former)
- Diabetes mellitus (Type 1, Type 2)
- Baseline HbA1c as continuous and in category < 6.5 %, ≥ 6.5 - < 8 % and ≥ 8%
- Systolic blood pressure (mmHg) as continuous variable and its category <140 mmHg, >=140 and <160 mmHg and >=160 mmHg
- Diastolic blood pressure (mmHg) as continuous variable
- Blood pressure (mmHg) in category (> 160 systolic or > 90 diastolic, <= 140 systolic and <= 85 diastolic and <= 120 systolic and <= 80 diastolic)

Baseline ocular characteristics:

- Baseline ocular characteristics description will be done in study eye and fellow eye (analyzed separately).
    - Study eye selection (Eligible eye (right, left, bilateral) and selected eye (right, left)).
    - Diabetic macular edema (Yes/No) (for fellow eye only)

- Diabetic macular edema status at baseline (Resolved/Ongoing) (for fellow eye only)

- Duration since Diabetic macular edema initial diagnosis Onset (in months) and its category (≤ 3 months and >3 months) (date of baseline visit – onset date of Diabetic macular edema diagnosis +1) / 30.4375.

- Baseline BCVA

- Baseline ocular assessments

    - Center subfield thickness (CST)

    - Macular Ischemic Non-Perfusion (Yes/No): Absence is defined as Total area of capillary non perfusion within the macula of 0 to 0.1 mm2.

    - Macular leakage (Yes/No): Absence is defined as Total area of fluorescein leakage within the macula of 0 mm2

    - Intraocular Pressure (mmHg)

    - Lens status (phakic, pseudophakic, aphakic, other)

    - Global Diabetic retinopathy status (ETDRS scale into 12 step) from Ultra-widefield Fundus Photography (UWF-C)

    - Diabetic retinopathy status (ETDRS scale into 12 step) from Color Fundus Photography (FP-7M

A listing of Demographics and relevant baseline characteristics will be presented.

General medical history and baseline conditions:

For each medical history and baseline conditions recorded medical history (MH), the term entered by the investigator describing the event (the “reported term”) will be assigned a standardized term (the “Preferred Term” [PT]) and assigned to a superclass term (the “System Organ Class” [SOC]) on the basis of the MedDRA World Health Organization (WHO) dictionary of terms.

The general medical history and baseline conditions will be summarized by SOC and PT.

Prior ocular surgeries and procedures

The description will be done in the study eye and fellow eye (analyzed separately).

- Did the subject have any prior ocular surgeries or procedures? (Yes/No)
- Prior ocular surgery or procedure was for ocular inflammatory disease (Yes/No)
- Number and percentages of patients per ocular surgeries or procedure. (Radiation therapy / Submacular surgery)

Prior medications

Previous medications (defined as treatment started and ended before start date of trial treatment) will be summarized by frequency tables according to the Anatomic Therapeutic Chemical (ATC) classification system using the WHO Drug dictionary.

Prior Ocular Therapies/Treatments

The description will be done in the study eye and fellow eye (analyzed separately).

- Did the subject have any prior ocular therapies/treatments? (Yes/No)
- Number and percentages of patients by ocular therapies/treatments (Laser Photocoagulation, Photodynamic Therapy Visudyne, Lucentis, Macugen, Avastin, Intravitreal Steroids, Subtenon Steroids, Topical Steroids, Dietary Supplement, Other).

4.4 EXPLORATORY ANALYSIS

The objective of this study is to explore the associations over time between clinical assessments, multimodal imaging assessments, AH biomarker patterns, and genetic polymorphisms of treatment-naïve DME patients treated with faricimab on the basis of the endpoints listed in Section 2.2.1.

All exploratory outcomes will be analyzed in the modified intent-to-treat (mITT) population.

Variables will be summarized descriptively at each timepoint in addition to change from baseline.

Continuous outcomes as Change from baseline at each timepoint will be analyzed using a mixed model for repeated measures (MMRM).

Patients with COVID-19 related intercurrent events will be censored after occurrence of these intercurrent events. COVID-19 related intercurrent events are defined as follows:

- Discontinuation of study treatment due to COVID-19
- Use of any prohibited systemic treatment or prohibited therapy in the study eye due to COVID-19
- Missed dose(s) with potentially major impact on BCVA and anatomical endpoints due to COVID-19
- COVID-19 death

Intercurrent events that are not related to COVID-19 will be handled using a treatment policy where all observed values will be used regardless of the occurrence of the intercurrent event. Those are defined as follows:

- Discontinuation of study treatment due to adverse events (AEs) or lack of efficacy not due to COVID-19
- Use of any prohibited systemic treatment or prohibited therapy in the study eye not due to COVID-19

In addition to the analyses listed in this SAP, the associations between AH biomarkers, imaging and clinical assessments will be analyzed and reported separately. Specifications of these analyses will be detailed in a separate document. These analyses may include but are not limited to univariate summaries, scatterplots and correlation coefficients, pairwise correlation matrices, heat maps.

4.4.1 Exploratory Endpoints

All exploratory endpoints will be analyzed in the study eye, over time from baseline up to week 20 or Safety Follow-up period week 24 if the assessment is available (See Appendix 2: Schedule of Assessments).

4.4.1.1 Ocular and multimodal imaging assessments

Best-corrected visual acuity (BCVA)

BCVA score is based on the ETDRS VA chart assessed at a starting distance of 4 meters. The BCVA score (actual value and change from Baseline) will be summarized over time.

A listing of BCVA score over time will be presented.

Change from Baseline in BCVA score over time will be analyzed using a longitudinal mixed effects model repeated measures (MMRM). The model's fixed effects will include visit along with the following covariates:

- Baseline BCVA score
- Age (continuous)
- Region (U.S/Canada and the rest of the world (ROW))

Visit will be treated as a repeated variable within a patient. Patient and visit will be treated as factor variables. An unstructured variance-covariance structure will be applied to model the within-patient errors. If there are convergence issues with the model, then an AR (1) covariance structure may be fitted. The model will be fitted using the Restricted Maximum Likelihood method (REML). Denominator degrees of freedom will be estimated using Satterthwaite's approximation.

Graphical presentation for least square means and 95% confidence intervals will be used to illustrate trends over time.

Diabetic Retinopathy Severity Score (DRSS)

The ETDRS DRSS score (actual value and change from baseline) assessed from Ultra-widefield Fundus Photography (UWF-C) and from Color Fundus Photography (FP-7M) will be summarized over time presenting the following proportion of patients along with a two-sided 95% Clopper-Pearson exact confidence interval:

- Number and percentage of patients with >=2 step ETDRS DRSS improvement from baseline
- Number and percentage of patients with >=3 step ETDRS DRSS improvement from baseline

These proportions will be described graphically (bar chart) to illustrate trends over time

Intraretinal fluid (IRF) and Subretinal fluid (SRF)

The IRF/SRF assessed from Spectral Domain-Optical Coherence Tomography (SD-OCT) will be described as below:

Proportion of patients along with a two-sided 95% Clopper-Pearson exact confidence interval:

- Number and percentage of patients with Absence and Presence of intraretinal fluid over time:

        - Absence of IRF is defined as IRF-Cystoid Spaces equals to Absent, or Definite outside center subfield only.

        - Presence of IRF is defined as IRF-Cystoid Spaces equals to Questionable, or Definite only noncystoid center subfield involved, or Definite cystoid center subfield involved.

    - Number of patients with recurrence of IRF over time (i.e. Number of patients with recurrence of IRF over time are defined as patients with presence of IRF at any of the post baseline timepoints (week 4, week 8, week 12, week 16, week 20 and week 24) regardless of their baseline status..)

    - Number and percentage of patients with Absence and Presence of subretinal fluid over time:

        - Absence of SRF is defined as SRF equals to Absent or Definite outside center subfield only.

        - Presence of SRF is defined as SRF equals to Questionable or Definite center subfield involved.

    - Number of patients with recurrence of SRF over time (i.e., Number of patients with recurrence of SRF over time are defined as patients with presence of SRF at any of the post baseline timepoints (week 4, week 8, week 12, week 16, week 20 and week 24) regardless of their baseline status.)

Additionally, the time to IRF resolution will be defined as the number of days from Baseline to first absence of IRF. The Kaplan-Meier method will be used to estimate the survival function for the time to first IRF resolution. Kaplan-Meier rates and Greenwood 95% CI using log-log transformation will be presented at week 4, week 8, week 12, week 16, week 20 and week 24. Kaplan-Meier plots (presented as cumulative incidence) will be produced. Patients without IRF resolution, discontinued from treatment, will be censored at the last IRF assessment. The patients with absence of IRF at baseline are not considered at risk, therefore, they will be excluded from the analysis.

The same analysis will be produced for the time to SRF resolution.

Retinal thickness using Spectral Domain-Optical Coherence Tomography (SD-OCT)

The measurement of Central subfield thickness (CST ILM-RPE) (actual value and change from Baseline) will be summarized over time up to week 20 and Safety Follow-up period

week 24). In addition, the change from baseline in CST will be analyzed using a longitudinal MMRM. The model's fixed effects will include visit along with the baseline CST ILM-RPE value, age and region covariates.

The same analyses will be performed on Center Point Thickness (CPT ILM-RPE) and on macular volume (Center SubField Volume ILM-RPE, the center subfield (CSF) is the circular region centered on the anatomic fovea with a radius of 500 microns).

Additionally, the time to first absence of DME will be analyzed. The first absence of DME is defined as the number of days from baseline to first time reaching CST (ILM-RPE) < 305 um. The Kaplan-Meier method will be used to estimate the survival function for the time to first absence of DME. Kaplan-Meier rates and Greenwood 95% CI using log-log transformation will be presented at week 4, week 8, week 12, week 16, week 20 and week 24. Kaplan-Meier plots (presented as cumulative incidence) will be produced.

Patients without absence of DME discontinued from treatment, will be censored at the last CST assessment.

Outcome measures using Ultra-widefield Fluorescein Angiography (UWF-FA)

The UWF-FA imaging type was scheduled at screening post-eligibility visit and week 20. The screening visit will be considered as Baseline visit.

The baseline actual value and change from baseline to week 20 will be summarized for the following endpoints:

- Total area of capillary Non-perfusion within the macula ETDRS grid
- Distance of the capillary Non-perfusion to the Center of Fovea
- Perimeter length of total capillary Non-perfusion
- Total area of capillary Non-perfusion within the eye
- Total area of assessable retina for capillary Non-perfusion
- Total area of visible retina
- Total area of fluorescein leakage within the ETDRS grid
- Distance of the fluorescein leakage to the Center of the Fovea
- Perimeter length of total fluorescein leakage

- Total area of leakage within the eye

The following proportion of patients along with a two-sided 95% Clopper-Pearson exact confidence interval will be summarized at Baseline and week 20:

- Number and percentage of patients with absence of macular ischemic non perfusion (capillary loss):
    - Absence defined as total area of capillary non perfusion within the macula of 0 to 0.10 mm^2
- Number and percentage of patients with absence of ischemic non perfusion within the Total Retinal Area:
    - Absence defined as total area of Capillary non perfusion within the eye of 0 to 1 mm2
- Number and percentage of patients with absence of Macular leakage:
    - Absence is defined as total area of fluorescein leakage within the macula of 0 mm2

The number of patients and percentage at baseline and week 20 visit will be described for the following endpoints:

- Change in fluorescein leakage within ETDRS grid from Screening Visit
- Absence of New Vessels on Disc (NVD)
- Absence of New Vessels Elsewhere (NVE) within 7 field grid
- Absence of New Vessels Elsewhere (NVE) beyond 7 field grid

Adaptive optics

For Adaptive optics assessments, the number of patients who underwent these assessments at baseline and week 20 visit will be summarized.

4.4.1.2 Aqueous Humor Biomarker assessment

The AH sample is collected at Baseline and at the week 16 visit.

The number of patients with sample collection will be summarized at Baseline and week 16.

The analysis of changes from baseline in AH biomarker patterns over time will be reported in a separate document as per section 4.4.

4.4.2 Sensitivity Analyses

Not Applicable.

4.4.3 Subgroup Analyses

The exploratory endpoints will be summarized by the following subgroups, provided that they include at least 30 patients:

- Baseline BCVA (≥ 64 letters and ≤ 63 letters)
- Baseline DR severity (<47, ≥ 47- ≤ 53, > 53 ETDRS DRSS)
- Baseline HbA1c (≤ 8 %, > 8 %)
- Age (< 65 years, ≥ 65 years)
- Gender (Female and Male)

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

No pharmacokinetic or pharmacodynamic analyses are planned in this study.

4.6 SAFETY ANALYSES

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

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

4.6.1 Exposure of Study Treatment

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

For the Fellow eye, the anti-VEGF treatment duration, number of administrations and the conditions/diagnosis for which the treatment was given will be described.

4.6.2 Adverse Events

For each recorded adverse event (AE), the term entered by the investigator describing the event (the "reported term") will be assigned a standardized term (the "Preferred Term" [PT]) and assigned to a superclass term (the "System Organ Class" [SOC]) based on the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

Treatment emergent adverse events (TEAEs) will be summarized by SOC and PT. At each level of summarization (at least one event, SOC and PT), patients reporting more than one AE will be counted only once. For TEAEs by grade (intensity), the highest grade will be reported. The table results will be sorted by descending frequency of SOC and PT within each SOC.

Definitions

Treatment emergent adverse events (TEAE): AEs with an observed or imputed date of onset on or after the start date of trial treatment. If the onset date of the AE is prior to the day of first dose, the AE will be considered treatment emergent only if the most extreme intensity is greater than the initial intensity (i.e., the intensity for a given AE increases and its end date is on or after the date of the first dose). An AE with a completely missing, non-imputed start date will be assumed to be treatment emergent unless the AE has a complete, non-imputed end date that is prior to the date of the first dose.

Imputation of incomplete date: in order to evaluate if an AE is treatment-emergent, incomplete dates will be imputed as follows:

1. If year is not missing and is after the year of first dose:
    a. If month is missing, then month will be imputed as January.
    b. If day is missing, then day will be imputed as the first of the month.
2. If year is not missing and is the same as the year of the first dose:
    a. If month is missing, then impute the month as the month of the first dose date.
    b. If day is missing, and the month is the same as the month of the first dose date, then impute day as the day of the first dose date.
    c. If day is missing but month is after the month of first dose date, then impute day as the first day of the month.
3. If year is missing then impute the year as the year of the first dose date:
    a. If month is missing, then impute the month as the month of the first dose date.
    b. If day is missing, then impute the day as the day of the first dose date.

4. If the start date is completely missing, but the AE is either ongoing or the end date is after the first dose date then impute the start date as the first dose date.
5. For any cases involving the rules above, if the AE end date is before the AE start date, then leave the AE start date missing and assume that AE is treatment emergent for the purpose of the analysis. Further, if the AE end date is complete and occurs prior to first dose date, leave the AE start date missing and assume that AE is not treatment emergent.

Output Conventions

All analyses of AE data will be performed using the PTs unless otherwise specified.

For all summary tables, the AEs will be sorted by SOC (in decreasing order of overall incidence) and then by PT (in decreasing order of overall incidence). All summaries and listings of AEs will be based on the Safety-evaluable population. Summaries of AEs will be generated to summarize the incidence of treatment emergent AEs only (TEAE and AE are used exchangeable).

Frequency tables, including patient incidence rates will be provided for the events listed below. For ocular AEs, events in the study eye and fellow eye will be summarized separately:

Overview of AE, including

- Ocular AEs and Serious ocular AEs (SAEs)
- Non-Ocular AEs and Serious non-ocular AEs (SAEs)
- Ocular AEs and SAEs leading to study drug discontinuation
- Non-Ocular AEs and SAEs leading to study drug discontinuation
- Adverse events of special interest defined as follows:
    - Case of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in protocol
    - Suspected transmission of an infectious agent by the study drug
    - Causes a decrease of >= 30 letters in VA Score lasting more than 1 hour
    - Requires surgical or medical intervention to prevent permanent loss of sight
    - Associated with severe intraocular inflammation
- Ocular AEs and Serious AEs (SAEs) related to the study treatment (only for study eye)
- Ocular AEs and Serious AEs (SAEs) related to the Anti-VEGF therapy (only for fellow eye)
- Non-Ocular ATE (Arterial Thromboembolic Events) and Cerebrovascular

Hemorrhagic

- AEs of Intraocular Inflammation
- AEs of retinal vascular occlusive disease
- Deaths
- AE of Infectious endophthalmitis
- AE of Rhegmatogeneous retinal detachment
- AE of Retinal tear
- AE leading to study discontinuation

Summary tables presenting the number and percentage of patients who experienced an AE will be summarized by SOC and PT. The AE by severity (mild, moderate, severe) will be also tabulated by SOC and PT.

4.6.3 Additional Safety Analyses Performed for COVID-19

From MedDRA 25.0, a COVID-19 SMQ (narrow) is available. This SMQ includes the preferred terms relevant to COVID-19 infection, and these terms will be used to assess the impact of COVID-19. Patients with AEs from this COVID-19 SMQ (narrow) will be considered to have a confirmed or suspected COVID-19 infection.

A listing of all confirmed and suspected COVID-19 Adverse events will be produced.

In addition to presenting the suspected/confirmed COVID-19 infections, a listing of AEs associated with COVID-19 during the study will be presented. An AE associated to COVID-19 is defined as an AE reported ≤7 days before and ≤30 days after any reported AE suggesting a confirmed COVID-19 infection according COVID-19 SMQ (narrow).

4.6.4 Ocular assessments

Results of the following ocular assessments will be summarized by time point, using descriptive summaries and graphical presentations (If applicable):

- Intraocular pressure (IOP)
- Slit lamp 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 Anterior chamber cell, Vitreous cell, Vitreous hemorrhage, Anterior chamber flare and cataract as determined on slit lamp examination will be tabulated by grade (according to grading scales for flares and cells in Appendix 3 of Protocol Version 4).

The presence of posterior vitreous detachment or retinal break or detachment as determined from ophthalmoscopy will be tabulated. The type of retinal detachment (i.e. involving or not macula) will be also described.

4.6.5 Laboratory Data

Pregnancy Test:

Pregnancy test results collected will be listed as "positive" or "negative" with the date of the pregnancy test for women with a pregnancy test recorded.

HbA1c results:

HbA1c will be summarized at baseline, week 16 and week 24 visit using descriptive statistics. Data from other unscheduled assessments will not be included in this summary or analysis.

Descriptive statistics will be used to summarize the following:

- HbA1c at baseline, at week 16 and week 24
- Hba1c in categories (< 6.5 %, ≥ 6.5 - < 8 % and ≥ 8%)

A listing of HbA1c at each visit will be also presented.

4.6.6 Vital Signs

Vital signs will be collected at screening, Safety Follow-up visit only. These data can be used for interpretation of some AEs, no general summary is planned.

4.6.7 Concomitant medications

Concomitant medications (defined as treatment started on or after baseline visit or treatment started before baseline visit and ended/ongoing during the treatment period) will be summarized by frequency tables according to the Anatomic Therapeutic Chemical (ATC) classification system using the WHO Drug dictionary.

Medication with a partial start date will be considered as concomitant except if the end date is before study treatment date.

A listing of ocular concomitant medications in the study eye will be presented.

4.6.8 Concurrent ocular procedures

Number and percentages of patients with concurrent ocular procedures as well as the Disease category of concurrent ocular procedures will be tabulated (study eye, fellow eye analyzed separately).

4.7 MISSING DATA

For exploratory and safety analyses, missing data will not be imputed, except for the MMRM analyses where missing data will be implicitly imputed by the MMRM model, assuming a missing at random missing data mechanism. The data will be used up to discontinuation.

4.8 INTERIM ANALYSES

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

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Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

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

Objectives and Endpoints

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

Objectives and Corresponding Endpoints

Exploratory Objective	Exploratory Endpoints

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

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

Study Design

Description of Study

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

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

Patients will receive 6 doses (one 6 mg faricimab intravitreal [IVT] injection every 28 days [Q4W]) starting at Day 1 and ending on the Day 140 visit. Patients will return for a safety follow up visit (SFV) after ≥28 days and within <35 days following their last study treatment. Patients

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

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

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

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

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

Screening

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

Screen-Failed Patients

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

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

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

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

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

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

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

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

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

Number of Patients

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

Target Population

Inclusion Criteria

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

Informed Consent

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

Age

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

Type of DME Patients and Disease Characteristics

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

5. Hemoglobin A_{1c} (HbA_{1c}) ≤10% (historic values up to 2 months before the screening visit will be permissible; otherwise, the study site may collect a sample for analysis at screening)
6. Patients who are IVT treatment-naïve in the study eye (i.e., have not received previous treatment with any anti-vascular endothelial growth factor-A (VEGF-A) IVT or any corticosteroids periocular or IVT in the study eye).

Ocular Inclusion Criteria for Study Eye

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

Contraception

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

Exclusion Criteria

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

Medical Conditions

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

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

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

Prior/Concomitant Therapy

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

Ocular Exclusion Criteria for Study Eye

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

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

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

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

End of Study and Length of Study

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

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

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

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

Investigational Medicinal Products

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

Statistical Methods

Exploratory Analyses

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

Determination of Sample Size

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

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

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

Interim Analyses

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

Appendix 2
Schedule of Assessments

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

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

AE = adverse event; AH = aqueous humor; AO = adaptive optics; BCVA = best corrected visual acuity; BP = blood pressure; CFP = color fundus photography; eCRF = electronic case report form; ETDRS = Early Treatment Diabetic Retinopathy Study; ETV = early termination visit; HbA_{1c} = hemoglobin A1c; IOP = intraocular pressure; IVT = intravitreal; NA = not applicable; SD-OCT-A = spectral-domain optical coherence tomography angiography; SAE = serious adverse event; SD-OCT = spectral domain optical coherence tomography; SFV = safety follow-up visit; SS-OCT = swept-source optical coherence tomography; SS-OCT-A = swept-source optical coherence tomography angiography; UWF-CFP = ultra-wide field color fundus photography; UWF-FFA = ultra-wide field fundus fluorescein angiography; VEGF = vascular endothelial growth factor; WOCBP = women of childbearing potential.

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

All assessments are to be performed on the same day, except those at screening. All study visits will be scheduled relative to the date of the day 1

visit (first study treatment). The SFV (or ETV, as applicable) should not occur earlier than 28 days after the last study treatment. The fellow eye anti-VEGF treatment approved by the country regulatory agency for ocular use may be covered by the Sponsor as long as the patient remains in the study (see Protocol Section 4.4.1). The fellow eye anti-VEGF treatments after the ETV or the SFV will not be covered by the Sponsor.

a. Patients who discontinue the study or treatment early (prior to the SFV) but have not withdrawn consent (and have not been lost to follow-up) should return for an ETV after a minimum of 28 days have elapsed following their last study treatment (visit should occur within <35 days of the patient's last study treatment).
b. Informed consent must be administered and documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment at the day 1 visit.
c. 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 AE eCRF.
d. Vital signs include measurement of temperature, heart rate, and systolic and diastolic BP.
e. Required for WOCBP only. A negative serum pregnancy test is required for enrollment (i.e., at the screening visit). If any urine pregnancy test is positive during the treatment period or the safety follow-up period, it must be confirmed by a serum pregnancy test. If the serum pregnancy test is positive during the treatment period, do not administer study treatment. A pregnancy test (serum or urine, as applicable) must always be timed to occur before administration of the fluorescein for the UWF-FFA; a negative test is required before administration of the fluorescein.
f. Medical history, including clinically significant diseases, chronic and ongoing conditions (e.g., trauma, cancer, cardiovascular, cerebrovascular, and ophthalmic comorbidities/history), surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history will be recorded at the screening visit and reconfirmed at baseline visit.
g. Record in the eCRF any concomitant medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment within 7 days preceding the baseline visit and through the conclusion of the patient's study participation or early termination visit.
h. Record all concurrent ocular procedures performed on the both the study and non-study eye (fellow eye) between the day 1 visit after study treatment and the SFV or the ETV.
i. Both refraction and BCVA must be performed prior to pupil dilation (study eye and non-study eye), the faricimab IVT injection in the study eye and, if applicable, the anti-VEGF treatment in the non-study eye. Screening BCVA (not baseline) used for eligibility. Both refraction and BCVA will be assessed at every study visit (as indicated in the table above) for the study eye, but only at the screening visit, the baseline visit, and the SFV / ETV for the non-study eye (fellow eye).
j. Performed prior to the faricimab IVT injection (study eye) and, if applicable, the anti-VEGF treatment (non-study eye). All imaging procedures will be performed at every study visit (as indicated in the table above) for the study eye, but only at the baseline visit and the SFV / ETV for the non-study eye (fellow eye).
k. If the study site has the capability to perform SS-OCT-A and SD-OCT-A, the study site must perform SS-OCT-A only. If the study site does not have the capability to perform SS-OCT-A, then the study site must perform SD-OCT-A. Similarly, if the study site has the capability to perform SS-OCT and SD-OCT, the study site must perform SS-OCT only. If the study site does not have the capability to perform SS-OCT, then the

study site must perform SD-OCT.

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

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

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

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

p. After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study treatment (day 1), all AEs will be reported until the patient's SFV or the ETV. After this period, the Sponsor should be notified if the investigator becomes aware of any SAEs that are believed to be related to prior study drug treatment. The investigator should follow each AE 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 SAEs considered to be related to study drug or study-related procedures until a final outcome can be reported.

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

r. Historic values up to 2 months before the screening visit will be permissible; otherwise, the study site may collect a sample for analysis at screening. Patients who have a blood sample for the assessment of HbA_{1c} collected at screening will not require an additional HbA_{1c} sample collection at day 1. However, patients who did not require a blood sample for the assessment of HbA_{1c} at screening (i.e., an available historic HbA_{1c} value ≤ 2 months old) will be required to have an additional HbA_{1c} sample collection at day 1. All patients will require an HbA_{1c} sample collection at the SFV or the ETV.

Appendix 3
Unscheduled Safety Assessment Visit

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

BP=blood pressure; IOP=intraocular pressure.

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

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

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

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

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

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

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

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

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

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

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

Appendix 5
Refraction and Best-Correct Visual Acuity Testing

SCOPE

The refraction and best-corrected visual acuity (BCVA) assessment must be conducted before pupil dilation (study eye and non-study eye). The refraction and BCVA will be measured by trained and certified personnel at the study sites. Both refraction and BCVA will be assessed at every study visit for the study eye, but only at the screening visit and the SFV / ETV for the non-study eye (fellow eye) (see Appendix 2).

EQUIPMENT

The following are needed to conduct the examination:

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

TRAINING AND CERTIFICATION

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

Appendix 6
Color Fundus Photography

SCOPE

Stereo color fundus photographs (CFP) using 7-modified field imaging and ultra-wide field color fundus photography (UWF-CFP; Optos®) will be obtained by trained personnel at the study sites. Color fundus photographs using 7-modified field imaging and UWF-CFP will be performed for the study eye and the non-study eye (when indicated) at specified timepoints according to the schedule of activities in Appendix 2.

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

EQUIPMENT

See the Image Acquisition Guidelines for equipment details.

PROCEDURE AND CERTIFICATION

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

Appendix 7
Ultra-Wide Field Fundus Fluorescein Angiography

SCOPE

Fundus fluorescein angiography using the ultra-wide field (UWF; Optos®) imaging will be performed at the study sites by trained personnel who are certified by the central reading center (CRC). The fundus fluorescein angiograms will be performed for the study eye and the non-study eye (when indicated) at specified timepoints according to the schedule of activities in Appendix 2. Analysis (if applicable) of fundus fluorescein angiograms will be performed by the CRC.

EQUIPMENT

See the Image Acquisition Guidelines for equipment details.

DIGITAL IMAGING SYSTEMS AND CERTIFICATION

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

PROCEDURES AND CERTIFICATION

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

Appendix 8
Spectral-Domain Optical Coherence Tomography, Swept-Source Optical Coherence Tomography, and Swept-Source Optical Coherence Tomography Angiography / Spectral-Domain Optical Coherence Tomography Angiography

SCOPE

Spectral-domain optical coherence tomography (SD-OCT), swept-source optical coherence tomography (SS-OCT), and swept-source optical coherence tomography angiography (SS-OCT-A) / spectral-domain optical coherence tomography angiography (SD-OCT-A) will be performed on at the study sites by trained personnel who are certified by the central reading center (CRC). SD-OCT, SS-OCT, and SS-OCT-A / SD-OCT-A imaging will be performed for the study eye and the non-study eye (when indicated) at specified timepoints according to the schedule of activities in Appendix 2.

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

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

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

EQUIPMENT

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

PROCEDURES AND CERTIFICATION

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

Appendix 9
Adaptive Optics (Selected Study Sites Only)

Acceptability of the site's adaptive optics (AO) data collection capabilities will be determined prior to selecting the study sites involved in this optional data collection. AO will be performed for the study eye and the non-study eye (when indicated) at specified timepoints according to the schedule of activities in Appendix 2.

Appendix 10
Biological Sample Collection and Shipping Instructions

BIOLOGICAL SAMPLE COLLECTION

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

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

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

BIOLOGICAL SAMPLES STORAGE DURATION

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

Signature Page for Statistical Analysis Plan - MR41926
System identifier: RIM-CLIN-462303

Approval Task	[redacted] Company Signatory 17-Jan-2023 14:04:16 GMT+0000