NIS PROTOCOL (PRIMARY DATA COLLECTION)

TITLE:	**REAL-WORLD, LONG-TERM DATA COLLECTION TO GAIN CLINICAL INSIGHTS INTO FARICIMAB (FAREAL STUDY)**
PROTOCOL NUMBER:	MR45586
VERSION NUMBER:	1.0
STUDIED MEDICINAL PRODUCTS	FARICIMAB
AUTHOR:	Maria Salling Eghøj, MD, FEBO F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124, 4070 Basel, Switzerland
DATE FINAL:	See electronic date stamp below

STUDY INITIATOR:	F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124, 4070 Basel, Switzerland
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany
COUNTRIES OF STUDY POPULATION:	This study will be conducted in 18 countries (region Europe and Israel).

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
11-Jul-2024 14:26:36	Company Signatory	Fernandez Garcia, Ignacio (fernani9)

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PROTOCOL ACCEPTANCE FORM

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PROTOCOL NUMBER:	MR45586
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STUDIED MEDICINAL PRODUCTS	Faricimab
STUDY INITIATOR:	F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124, 4070 Basel, Switzerland
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany

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

Treating Physician's Name
(print)

Treating Physician's Signature Date

Please return a copy of this form to your Site Operations Representative. Please retain the signed original for your study files.

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AMD	age-related macular degeneration
AST	aspartate aminotransferase
BCVA	best-corrected visual acuity
CI	confidence interval
CME	cystoid macular edema
CRO	contract research organization
CST	central subfield thickness
CTCAE	common terminology criteria for adverse events
CUP	compassionate use programs
DME	diabetic macular edema
DR	diabetic retinopathy
EAS-EL	Enrolled Analysis Set - Eye-Level
EAS-PL	Enrolled Analysis Set - Patient-Level
EC	Ethics Committee
eCRF	electronic case report form
EFAS-EL	Effectiveness Analysis Set - Eye-Level
EFAS-PL	Effectiveness Analysis Set - Patient-Leve
EMA	European Medicines Agency
EDC	electronic data capture
ERM	epiretinal membrane
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GDPR	general data protection regulation
GPP	Good Pharmacoepidemiology Practice
HCP	Healthcare professional
ICH	International Council for Harmonisation
IRB	institutional review board
IRF	intraretinal fluid
ISO	International Organization for Standardization
IVT	intravitreal treatment
logMAR	Logarithm of the Minimum Angle of Resolution

Abbreviation	Definition
MAH	marketing authorization holder
MAP	Market Access Program
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measurement
MNV	macular neovascular membrane
nAMD	neovascular age-related macular degeneration
NCI	National Cancer Institute
NIS	non-interventional study
O&P	Observe and Plan
OCT	optical coherence tomography
PCV	polypoidal choroidal vasculopathy
PDC	prospective data collection
PED	pigment epithelial detachment
PRN	pro re nata
PSP	patient support program
PT	preferred term
PTAP	post trial access programs
PTI	Personalized Treatment interval
RCT	randomized clinical trial
RPE	retinal pigment epithelium
RVO	retinal vein occlusion
RWD	real-world data
SAE	serious adverse event
SAP	statistical analysis plan
SAS-EL	Safety Analysis Set – Eye-Level
SAS-PL	Safety Analysis Set – Patient-Level
SD	standard deviation
SD-OCT	spectral domain optical coherence tomography
SDU	Secondary data use
SDV	source data verification
SOC	System Organ Class
SRF	subretinal fluid
SS-OCT	swept-source optical coherence tomography
T&E	treat-and-extend
ULN	upper limit of normal

Abbreviation	Definition
VA	visual acuity
VEGF	vascular endothelial growth factor
WHO-DD	World Health Organization Drug Dictionary
YAG laser	yttrium aluminum garnet laser

2 SYNOPSIS

TITLE:	**REAL-WORLD, LONG-TERM DATA COLLECTION TO GAIN CLINICAL INSIGHTS INTO FARICIMAB (FAREAL STUDY)**
PROTOCOL NUMBER:	MR45586
VERSION NUMBER:	1.0
DATE OF SYNOPSIS:	See electronic date stamp
STUDIED MEDICINAL PRODUCTS	Faricimab
MAIN AUTHOR:	**Maria Salling Eghøj, MD, FEBO** F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124, 4070 Basel, Switzerland
INDICATION:	Neovascular Age-related Macular Degeneration (nAMD), Diabetic Macular Edema (DME)
STUDY INITIATOR:	F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124, 4070 Basel, Switzerland
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany

Research Question and Objectives

The FaReal study aims to evaluate the effectiveness, safety, clinical insights and treatment patterns in patients treated with faricimab, in neovascular age-related macular degeneration (nAMD) or diabetic macular edema (DME) in at least one eye, in real-world routine clinical practice over a 2-year patient follow-up period. Additionally, the FaReal study also aims to describe and evaluate health economic aspects of previous anti-VEGF treatments and current treatment with faricimab.

Primary and Secondary Objectives

Primary Objective	Primary Analysis
To evaluate the functional effectiveness of faricimab in nAMD and DME on visual acuity (VA) at 12 months in the real-world setting.	• Change in VA (approximate Early Treatment Diabetic Retinopathy Study (ETDRS) letter score - see Appendix 3) from index date* to month 12.

Secondary Objectives	Secondary Analyses
To evaluate the functional effectiveness of faricimab in nAMD and DME on VA at specified intervals during the conduct of the study in the real-world setting.	• Change in VA (approximate ETDRS letter score - see Appendix 3) from index date* to months 3, 6 and 24.
To evaluate the anatomical effectiveness of faricimab in nAMD and DME on central subfield thickness (CST) reduction	• Change in CST from index date* to months 3, 6, 12 and 24 months (as measured per local standard clinical practice).
To describe retinal treatment patterns throughout study period	• Number and percentage of eyes in each treatment regimen (i.e., Fixed regimen, T&E, PRN, Other - see Appendix 5) at 3, 6, 12 and 24 months of observation. • Number of intravitreal injections per eye per year per indication overall (at month 12 and 24). • Number of intravitreal injections in loading phase** for treatment naïve and anti-VEGF pre-treated patients (per pre-treatment type) • Total number of visits, number of visits with or without treatment (observational) at 3, 6, 12 and 24 months of observation. • Number and percentage of eyes with treatment switch from faricimab, including reason for switch, at 3, 6, 12 and 24 months of observation for treatment naïve and pre-treated patients (per pre-treatment type).
To describe durability of faricimab treatment within different patient groups (indication, treatment naïve/pre-treated)	• Number and percentage of eyes obtaining treatment intervals of Q8W, Q12W, Q16W and other at 12 months and 24 months of observation for treatment naïve and pre-treated patients (per pre-treatment type).
To evaluate the correlation/association between retinal treatment characteristics (durability and treatment patterns) and change in VA over time in nAMD and DME	• Change in VA (approximate ETDRS letter score - see Appendix 3) from index date* to months 3, 6, 12 and 24, in relation to: ○ Treatment regimen (Fixed, T&E, PRN, Other - see Appendix 5) ○ Number of intravitreal treatments ○ Total number of visits ○ Treatment intervals ○ Type of pre-treatment and number of previous injections for preceding regimen at index date ○ Length of diagnosis of disease at index date

CST = central subfield thickness, DME = diabetic macular edema, ETDRS = Early Treatment Diabetic Retinopathy Study, nAMD = neovascular age-related macular degeneration, PRN = pro re nata, T&E = Treat-and-Extend, VA = visual acuity, VEGF = vascular endothelial growth factor

*Index date is defined as the date of first faricimab treatment on eye-level. If both eyes are treated with faricimab and the treatment start dates are different, each start date will be used as index date for the respective eye.

**Loading phase is defined as per local label (for nAMD and DME)

Safety Objective

Safety Objective	Safety Analysis
To evaluate the ocular and systemic safety and tolerability for faricimab in nAMD and DME in the real-world setting.	• Incidence, severity, duration, and outcomes of ocular and non-ocular adverse events.

DME = diabetic macular edema, nAMD = neovascular age-related macular degeneration

Exploratory Objectives

Exploratory Objectives	Exploratory Analyses
To evaluate changes over time in presence/absence of retinal fluid, as determined by imaging assessments according to investigator evaluation as per routine clinical practice, in relation to the number of treatments, treatment regimen, and investigator-determined disease activity.	• Presence/absence of fluid in relation to the number of treatments including loading dose, treatment regimen, and investigator-determined disease activity: ○ Proportion of eyes with presence/absence of intraretinal fluid (IRF) over time (index date*, months 3, 6, 12, 24) ○ Proportion of eyes with presence/absence of subretinal fluid (SRF) over time (index date*, months 3, 6, 12, 24) ○ Proportion of eyes with presence/absence of IRF and SRF over time (index date*, months 3, 6, 12, 24) ○ Proportion of eyes with absence/presence of either IRF, SRF or both from index date* over time (index date, months 3, 6, 12, 24) ○ Proportion of eyes with absence/presence of serous pigment epithelial detachment (PED) from index date* over time and change in height of PED if measured (index date*, months 3, 6, 12, 24)
To describe changes in VA over time in relation to presence/absence of fluid or PED	• Change in VA (approximate ETDRS letter score - see Appendix 3) from index date* to months 3, 6, 12 and 24 for eyes in each fluid group at index date (no fluid present, presence of IRF,

Exploratory Objectives	Exploratory Analyses
	presence of SRF, presence of serous PED, presence of both IRF & SRF)
To describe distribution of patients according to change in VA in nAMD and DME in the real-world setting.	• Number and proportion of eyes, over time (from index date* to months 3, 6, 12 and 24), with approximate ETDRS letter score[1] of: ○ 70 or more (20/40 Snellen equivalent). ○ 36 to 69 (between 20/40 and 20/200 Snellen equivalent). ○ 35 or less (20/200 Snellen equivalent). • Proportion of eyes gaining ≥15, ≥10, ≥5, or >0 letters in VA[1] from index date* over time. • Proportion of eyes losing ≥15, ≥10, ≥5, or >0 letters in VA[1] from baseline* over time.
To evaluate changes over time in presence/absence of anatomical features	nAMD specific endpoints: Number and percentage of eyes with the following, at index date* and months 3, 6, 12, 24: • presence/absence of atrophy • presence/absence of fibrosis • presence/absence of PED (also adding height of PED if measured) • presence/absence of hemorrhage DME specific endpoints: Number and percentage of eyes with the following, at index date* and months 3, 6, 12, 24: • presence/absence of epiretinal membrane (ERM)
To evaluate the health economic perspective and specific treatment patterns of anti-VEGF treatment in nAMD and DME	For eyes pre-treated with any anti-VEGF: • Type of anti-VEGF treatments received before index date* • Time spent on each pre-treatment • Number of previous injections for previous treatment • Treatment interval of the last preceding treatment before entering the study. For all eyes (both naïve and pre-treated) the below will be described following the index date: • Number and percentage of eyes in each treatment regimen (i.e., Fixed regimen, T&E, PRN, Other - see Appendix 5). • Number of injections per eye per year per indication. • Total number of visits, number of visits with or without treatment (observational), and time intervals between treatments, per year.

DME = Diabetic macular edema, ERM = Epiretinal Membrane, ETDRS = Early Treatment Diabetic Retinopathy Study, IRF = intraretinal fluid, nAMD = neovascular age-related macular degeneration, PED - pigment epithelial detachment, PRN = pro re nata, SRF = subretinal fluid, T&E = Treat-and-Extend, VA = visual acuity, VEGF = vascular endothelial growth factor

*Index date is defined as the date of first faricimab treatment on eye-level. If both eyes are treated with faricimab and the treatment start dates are different, each start date will be used as index date for the respective eye.

[1] Approximate ETDRS letter score conversion table can be found in Appendix 3 .

Study Design

The FaReal study is a primary data collection, non-interventional, prospective, multinational, multicenter study designed to collect real-world data on patients treated with faricimab in nAMD and DME in the real-world routine clinical practice. Participation in this study will not change or influence a patient's care in any way, and treatment decisions will be made by the treating physician independently of the patient's decision to participate in this study.

This study aims to enroll approximately 850 patients from approximately 65 sites (in 18 countries in region Europe and Israel).

Adult patients fulfilling the eligibility criteria who sign informed consent (as required per local regulations) will be enrolled and followed up prospectively from enrollment until completion of 2 years participation, death, withdrawal of consent, participation in an investigational ophthalmology clinical trial, early termination of the study, or discontinuation of the study site, whichever occurs first. Patients are free to withdraw participation at any time.

Note: If a patient discontinues from faricimab or switches to another treatment, the patient should continue to participate in this study until completion of 2 years of participation, death, withdrawal of consent, participation in an investigational ophthalmology clinical trial, early termination of the study, or discontinuation of the study site, whichever occurs first.

All patient visits will be conducted according to usual local clinical practice. Data recorded at each visit will be collected, including some data that may not be routinely recorded in patient medical records but is part of the clinical routine for a specific patient. Where applicable, analysis will be conducted at specific time points (e.g., 3, 6, 12 and 24 months from index date). The derivation of the analysis value per time point will be described in the Statistical Analysis Plan (SAP) and may use data from visits placed in the appropriate window for analysis (e.g., ±30 days, ±60 days around the timepoint of interest). Subgroup analyses will also be performed, for example by region, country, baseline characteristics, or other factors, as defined in the SAP.

Anonymized data will be shared with the medical and scientific community to foster research and support evidence generation. The data elements collected will address different types of research questions through registry-based studies such as secondary data use (SDU) studies.

Start Date of Study

Patient enrollment will be initiated at each site, upon approval from regulatory authorities and Institutional Review Boards (IRBs)/Ethics Committees (ECs), as per local regulation and site agreement implementation and approval of faricimab treatment in nAMD and/or DME according to local labeling. The study start date will be the date of the first patient enrolled.

Study Duration

The expected duration of the study is up to 4 years, depending on the enrollment period duration. This includes approximately 1 to 2 years of recruitment and 2 years of follow-up of every patient (unless the patient discontinues early from the study).

End of Study

The study ends when all participants have either completed at least 2 years of follow-up or have ended their participation in the study due to death, withdrawal of consent, participation in an investigational ophthalmology clinical trial, early termination of the study, or discontinuation of the study site, whichever occurs first.

Baseline Date and Index Date

Baseline is defined as the date when a patient initiates treatment with faricimab in at least one eye (first eye in case of both eyes being treated).

Index date is defined as the date when treatment is initiated at the eye-level. If both eyes are treated with faricimab and the treatment start dates are different, each start date will be used as the index date for the respective eye.

Enrollment Date

Enrollment date is the date the patient signs the Informed Consent Form to participate in this study.

Enrollment date cannot occur earlier than index/baseline date.

Target Population

The main patient population for this study are new users of faricimab approved in nAMD and DME in at least one eye.

Patients must meet the following criteria for study entry:

1. Adult patients (≥18 years), who have provided signed informed consent, as required per local regulations.

2. Patients as defined by local regulations and local faricimab product label, who are initiating treatment with faricimab at time of enrollment or have initiated treatment with faricimab within 3 months prior to patient enrollment, in DME or

nAMD in at least one eye according to the investigator's discretion in routine clinical practice for anti-VEGF treatment naïve and pre-treated patients.

3. Patients have received at least one faricimab treatment (the first dose) in the study eye.

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

1. Concomitant participation of the patient in any investigational ophthalmology clinical trial that includes receipt of any ophthalmological investigational drug or procedure within the last 28 days prior to enrollment.

2. Current participation in any interventional clinical study

3. Active ocular inflammation or suspected/active ocular infection in either eye.

4. Patients in whom the study eye has been treated with faricimab for more than 3 months prior to enrollment.

5. Patients treated with faricimab who have and are currently participating in patient support programs that are Market Research and Patient Support Programs (MAPs) including Post Trial Access Programs (PTAP) and Compassionate Use Programs (CUP), will be excluded from selection.

6. Patients with non-ocular sight threatening disease which have an effect on primary endpoint (VA) eg: apoplexia.

7. Hypersensitivity to the active substance or any of the excipients of Vabysmo (as per label)

Studied Medicinal Products

The studied medicinal product within this study is faricimab.

The dosing and treatment duration of faricimab are at the discretion of the physician and agreement of the patient, in accordance with local clinical practice and local labeling.

Variables

Only variables obtained according to routine clinical practice can and should be documented in this study.

The variables collected at index date, enrollment (incl. retrospective data) and during follow-up fall into the following categories:

Primary and Secondary Effectiveness Variables

- Visual Acuity (VA) on approximate ETDRS letter score (see Appendix 3) (by eye) in nAMD and DME (including date, method of VA assessment - scale and type of correction), as measured per local clinical practice.
- Treatment regimens (i.e., Fixed regimen, treat-and-extend (T&E), PRN, Other - see Appendix 5).
- Faricimab intravitreal injections/dates of treatments
- Visits with or without treatment (observational), dates of visits.
- Eyes with treatment switch, including date and reason for switch.
- Eyes obtaining treatment intervals of Q8W, Q12W, Q16W and other
- Loading dose of intravitreal injections
- Central Subfield Thickness (CST) and anatomical observations (including method, software settings and type of optical coherence tomography [OCT]) (as measured per local standard clinical practice).

Exploratory Effectiveness Variables

- Imaging assessments (by eye), as per routine clinical practice (during visits for the retinal indications) e.g.:
  - IRF
  - SRF
  - serous PED and height if measured.

➢ Specific Exploratory Variables for nAMD

- Eyes with presence/absence of atrophy*
- Eyes with presence/absence of fibrosis**
- Eyes with presence/absence of serous PED*** (also height of PED if measured)
- Eyes with presence/absence of hemorrhage****

➢ Specific Exploratory Variables for DME

- Eyes with presence/absence of ERM in the central 3 mm (as evaluated by the treating physician)

Health Economic Evaluation Variables (for All Eyes - Both Naïve and Pre-treated)

- For eyes pre-treated with any intravitreal anti-VEGF:
  - Type of intravitreal anti-VEGF treatments received before index date
  - Number and dates of previous anti-VEGF treatments

- Treatment interval of the last preceding anti-VEGF treatment before entering the study.

- For all eyes (both naïve and pre-treated) the below will be collected following the index date:
  - Treatment regimen (i.e., Fixed regimen, T&E, PRN, Other).
  - Number of intravitreal faricimab injections (with date).
  - Number of visits with or without treatment (observational) with dates.

Safety Variables

- Safety events (all ocular and non-ocular adverse events [AEs]) including, date, seriousness, severity and outcome.

Other Variables of Interest

- Patients' characteristics of interest include but are not limited to:
  - Demographic characteristics
  - Relevant medical history: ocular and non-ocular (ocular - by eye where applicable):
    - Comorbidities (ocular and non-ocular)
    - Prior intravitreal anti-VEGF treatments (type, dates) – by eye - until entry into the current study
    - Previous intravitreal treatments (IVT) other than anti-VEGF and other ocular treatments
  - Surgical history: macular laser, surgical procedures, corneal transplant, cataract surgery, vitrectomy, peripheral laser treatment, yttrium aluminum garnet (YAG) laser treatment, corneal surgery, steroid implant.
  - Concomitant medications (ocular and non-ocular)
  - Specific baseline***** characteristics:
    - For nAMD patients:
      - Type of membrane (1-3 macular neovascular membrane (MNV), polypoidal choroidal vasculopathy (PCV), cystoid macular edema (CME))
      - Pigment epithelial detachment (PED) or disruption within the retinal pigment epithelium
      - Duration of the disease
      - Presence/absence of atrophy*
      - Presence/absence of fibrosis**
    - For DME patients:
      - Severity of diabetes (HbA1c levels),

- Duration of diabetes
- Diabetes type
- Duration of DME
- DME classification (central involvement /non-central involvement). Central is defined as central 3 mm.
- Presence/absence of proliferative diabetic retinopathy
- Presence/absence of ERM in the central 3 mm

*Atrophy definition: Defined as cRORA (complete loss of photoreceptors and retinal pigment epithelium (RPE) in the central 3 mm), atrophy is to be assessed as per the treating physician (Sadda S et al 2018, Guymer RH et al 2020, Savastano MC et al 2020).

**Fibrosis: Hyperreflective material below the neurosensory retina on OCT (may have a multilaminar appearance) accompanied by different amounts of RPE destruction & photoreceptor loss. It is to be evaluated by the treating physician in the central 3 mm. (Willoughby AS et al 2015, Gräfe MGO et al 2020).

***Serous PED: Separation between the RPE and the inner most aspect of Bruch´s membrane. Is to be evaluated in the central 3 mm.

****Hemorrhage to be evaluated by the treating physician in the central 3 mm

*****Baseline characteristics will be documented at the timepoint of faricimab treatment initiation (index date) for the respective eye included in the study

- Treatment and management (by eye) during the study period, from index date until the end of study participation, include but not limited to:
    - Treatments received for the indications (nAMD, DME)
    - Treatment discontinuation/termination
    - Details of other procedures that could potentially elevate/deteriorate VA.

- Imaging assessments (by eye) during the study period from index date until end of study participation, include but not limited to:
    - optical coherence tomography (OCT)-imaging assessment type, machine used, and the results of CST, IRF, SRF, PED. Images will not be collected.

The primary effectiveness variable is VA. VA will be collected as measured per local practice and will then be entered from source data into electronic case report form (eCRF) using the approximate Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

Data Sources

Patients' data will be recorded on eCRFs and stored in the electronic data capture (EDC) system. All clinical data will be processed and stored in a database. All data will be pseudo-anonymized, and each patient will have a unique code so that the information of the same patients can be linked.

Data Analysis

Full details of the statistical analysis to be conducted will be provided in the SAP.

The following 2 cohorts will be defined and analyzed:

- Cohort 1: Patients receiving faricimab for nAMD in at least one eye
- Cohort 2: Patients receiving faricimab for DME in at least one eye.

Within each cohort, sub-cohorts will be defined as per treatment history at eye-level when initiating faricimab for this study as described below.

The following sub-cohorts will be considered:

A. Treatment naïve sub-cohort:

   Patient-eyes initiating faricimab intravitreal treatment that have never had any anti-VEGF intravitreal treatment

B. Previously treated with anti-VEGF sub-cohort

   Patient-eyes initiating faricimab intravitreal treatment after being previously treated with any intravitreal anti-VEGF.

Sub-cohort Details per Cohort

Cohort 1	**Cohort 2**
Patients receiving faricimab for nAMD in at least one eye	**Patients receiving faricimab for DME in at least one eye**
A. Treatment naïve sub-cohort:	A. Treatment naïve sub-cohort:
Patient-eyes newly initiating faricimab intravitreal treatment* in at least one eye that has never had any anti-VEGF intravitreal treatment	Patient-eyes newly initiating faricimab intravitreal treatment* in at least one eye that has never had any anti-VEGF intravitreal treatment
B. Pre-treated sub-cohort:	B. Pre-treated sub-cohort:
Patient-eyes newly initiating faricimab intravitreal treatment* after being previously treated with intravitreal anti-VEGF	Patient-eyes newly initiating faricimab intravitreal treatment* after being previously treated with intravitreal anti-VEGF

DME = diabetic macular edema, nAMD = neovascular age-related macular degeneration, VEGF = vascular endothelial growth factor

*Patient-eyes newly initiating faricimab intravitreal treatment: patient-eyes initiated treatment during 3 months prior to enrollment.

Patients may be part of several sub-cohorts as analysis will be carried out at eye-level (regardless of whether it is the right or left eye).

Unless otherwise specified, statistical analyses will be performed per cohort and per sub-cohort.

Patients' demographics as well as medical history (ocular and non-ocular) will be summarized using descriptive statistics. Baseline ocular characteristics and information on prior ocular treatments will be summarized descriptively.

Patient and eye disposition (e.g., enrolled, treated, switched therapy, early discontinuation, study completers) will be summarized using the Safety Analysis Sets.

Continuous variables will be summarized descriptively using mean, median, standard deviation (SD), first quartile, third quartile, minimum, and maximum. Categorical outcomes will be summarized using numbers and percentages in each category.

The primary effectiveness endpoint is the change in VA (approximate ETDRS letter score - see Appendix 3) from index date to month 12 in nAMD and DME. Both actual values at index date and month 12 and change from index date in VA (approximate ETDRS letter score - see Appendix 3) to month 12 will be summarized descriptively.

The key secondary endpoints are the change in VA (approximate ETDRS letter score - see Appendix 3) from index date to months 3, 6, and 24 in nAMD and DME, and the change in CST from index date to months 3, 6, 12 and 24 (as measured per local standard clinical practice). All primary, secondary and exploratory effectiveness outcomes will be analyzed using the Effectiveness Analysis sets.

The Safety Endpoint is the incidence of ocular and non-ocular AEs. Non-ocular AEs will be assessed at the patient-level for the Safety Analysis Set. Ocular AEs will be assessed on the eye-level for the Safety Analysis Set. The incidence of AEs and serious adverse events (SAEs) will be summarized descriptively by the Medical Dictionary for Regulatory Activities (MedDRA) primary System Organ Class (SOC) and Preferred Term (PT) for the Safety Analysis Set.

Cumulative incidence and rates per 100 patient-years or 100 patient-eye years (for eye-level events) (or 1,000 patient-years, etc., as appropriate) of AEs and SAEs will be calculated. The number and percentage of patients (or eyes) experiencing AEs and SAEs, as well as the number of events will be displayed by SOC, PT, and by severity. The AE outcomes and duration of AEs will be summarized descriptively using the Safety Analysis Sets.

Study Size/Determination of Sample Size

No formal sample size calculation linked to hypothesis testing has been done for this descriptive study. Sample sizes will be calculated for each of the treatment naïve and pre-treated sub-cohorts of Cohort 1 (nAMD) and Cohort 2 (DME).

For the primary endpoint change from baseline in VA to month 12, we calculate the precision of the 95% confidence interval for the mean change in VA given the sample size anticipated to be enrolled by the sites, and assuming a range of standard deviations (SD) that was reported in the literature for treatment naïve patients, and assuming a 5% drop-out rate. Precision is defined as the width of the confidence interval of the mean change in VA from 0 to 12 months. We anticipate that the SD will be equal or lower for pre-treated patients, as their VA might have stabilized by the time they enroll into the study.

Cohort & Sub-cohort	SampleSize	Precision at SD=12	Precision at SD=14
Treatment naïve patients in nAMD	240	3	3.6
Pre-treated patients in nAMD	360	2.5	3
Treatment naïve patients in DME	100	5	5.6
Pre-treated patients in DME	150	4	4.6

DME = diabetic macular edema, nAMD = neovascular age-related macular degeneration, SD = Standard Deviation

3 PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by the Marketing Authorization Holder or designee.

Protocol amendments will be submitted to the Institutional Review Boards (IRBs)/Ethics Committees (ECs) and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in Site Operations Representative or contact information).

Substantial protocol amendments/updates so far: none.

4 RATIONALE AND BACKGROUND

Retinal vascular diseases, which are often characterized by leakage of fluid, hemorrhage, and fibrous scarring in the eye, include dry and wet forms of age-related macular degeneration (AMD), diabetic retinopathy (DR) and diabetic macular edema (DME), and retinal vein occlusion (RVO). These diseases are major causes of visual impairment and blindness worldwide (Daien et al., 2019; Duphare et al., 2020; Li et al., 2020).

DME is a complication of DR, which is one of the most common microvascular complications of diabetes. Nearly 100 million people worldwide have some signs of macular edema secondary to diabetes. In a literature review by Diabetes Atlas (Thomas, 2019), for the period between 2015 and 2018, the global prevalence of DR (any type) was 27.0%, comprising 25.2% non-proliferative DR and 1.4% proliferative DR, while the global prevalence of DME was 4.6%. The highest prevalence of DR and DME has been reported in African countries (Ethiopia, Tanzania, South Africa, Zambia) at 33.8%, Middle East and North Africa region at 33.8% (one study in Iran), and the Western Pacific region (Singapore, Australia, Hong Kong, New Zealand, Indonesia, China) at 36.2%. The lowest prevalence has been reported in Europe at 20.6% and South-East Asia at 12.5%. In the Occident, the prevalence of any diabetic eye disease was 40.3% in the United States (US) with the prevalence of sight threatening DR 8.2%; while in Europe, the prevalence was found to be 25.7% for DR and 3.7% for DME (Li et al., 2020). It is predicted that the total numbers of inhabitants from the European Union with diabetic eye disease will likely increase from 6.4 million persons as of 2020 to 8.6 million in 2050 (Li et al., 2020).

The critical pathophysiology of DME involves disruption of the blood–retinal barrier, which separates retinal photoreceptors from the vasculature; however, the process is complicated and involves various inflammatory markers upregulated by advanced glycation end products, hyperglycemia, and diabetes. Vasoconstriction caused by diabetes upregulates the expression of vascular endothelial growth factor (VEGF), and this leads to development of macular edema by causing retinal fluid leakage (Ndisang, 2014; Duphare et al., 2020).

Furthermore, the cytokine angiopoietin-2 (Ang-2) and VEGF-A cause destabilization of retinal blood vessels, formation of new leaky blood vessels, and increase in inflammation (Scholz et al., 2015; Sahni et al., 2019). Thus, in recent years, DME management has involved an increased focus on improving these key physiological targets.

Another retinal complication and a leading cause of vision impairment is AMD. AMD is a neurodegenerative disease of the central retina, which is characterized by choroidal neovascularization (CNV) and causes irreversible destruction of the macula and loss of the sharp, central vision (fine detailed vision) required for important everyday activities such as reading, driving, recognizing faces (Holekamp, 2019). As per a systematic review (until 2013) and meta-analysis, 8.7% of the population worldwide had any AMD, and it is projected to affect nearly 288 million people by the year 2040 (Wong et al., 2014). It is well established that early AMD may progress to dry AMD or wet AMD, the latter one is also referred to as neovascular age-related macular degeneration (nAMD) (Chakravarthy et al., 2020). The pathophysiology of nAMD involves the growth of immature blood vessels toward the outer retina from the underlying choroid, along with fluid leak below or within the retina (Ambati, 2012). The cytokines VEGF-A and Ang-2

have been observed to play a pivotal role in neovascularization and vascular complications of nAMD as described previously. Of note, higher levels of Ang-2 correlate with the higher disease severity of nAMD, thus indicating worse best-corrected visual acuity (BCVA) and greater central macular thickness (Ng et al., 2017). Therefore, VEGF and the associated regulators are currently key therapeutic targets for treatment developments for retinal pathologies involving angiogenesis (i.e., nAMD and DME) (Khan, 2020).

Considering the critical pathogenesis of these retinal complications, the emergence of anti-VEGF agents has been a resounding success and breakthrough in the treatment of retinal vascular disorders. Individuals on this treatment usually benefit from this therapy, at least for the first few years, if treated sufficiently to control the neovascular activity.

However, in the long-term, the real-world visual acuity (VA) results have been reported to decline, which could be attributed to less frequent treatment over time, late complications (atrophy and fibrosis), and having a more diverse patient population than clinical trials (including those with comorbidities) (Holz et al., 2015; Jaffe et al., 2019; Ciulla et al., 2018; Khanani et al., 2020). These factors can all impact the outcomes and may lead to loss of vision. Results from landmark registries have confirmed that the number of intravitreal anti-VEGF injections is an important factor linked with better long-term VA related treatment outcomes after 1 and 2 years of therapy (Gillies et al., 2015; Wecker et al., 2017; Westborg et al., 2017; Holz et al., 2020b). Thus, understanding such treatment drivers and risk factors contributing to the differences in real-world outcomes compared to the outcomes in controlled clinical trials is critical to providing maximum and long-term benefits to each individual from the available therapies, with lower societal costs.

An important treatment outcome for anti-VEGF therapy besides improvement of BCVA (defined as the best possible vision that an eye can achieve with the help of an intervention), is a completely dry retina, as the retinal fluid is a biomarker of disease activity. However, evidence suggests that this may not be necessary or desired. Some reports on nAMD indicate that tolerating a certain level of subretinal fluid (SRF) might be desirable and associated with better VA (i.e., the clarity or sharpness of vision) (Jaffe et al., 2019). In the FLUID study (Guymer et al., 2019), patients treated with ranibizumab treat-and-extend regimen (T&E) for 24 months with tolerance for SRF up to 200 µm, achieved visual outcomes non-inferior to those with no tolerance to SRF. Another study showed that during the nAMD treatment with anti-VEGF, a greater variation in the retinal thickness was associated with worse BCVA, as well as development of fibrosis and macular atrophy, among the analyzed patients (Evans et al., 2020). Thus, exploring associations between functional and morphological parameters through long-term real-world observations would be beneficial.

A recent (2019) systematic literature review indicated that there are numerous existing real-world data (RWD) sources on patients with retinal disease treated with anti-VEGFs; however, very few of these have covered the holistic aspects of management of such patients. None of the studies have analyzed treatment patterns across different regions or the treatment regimen dependent outcomes in this cohort of population. Lastly, the safety outcomes (ocular and non-ocular adverse events [AEs]) were reported in only 30% (n=19) of the analyzed RWD sources (Daien et al., 2019).

Thus, a valuable addition to this existing literature would be a study that develops a robust database that can provide information on overall aspects of treatment and management of these patients. This would inform and assist the healthcare professionals (HCPs) in making sound clinical decisions for individuals on anti-VEGFs and anti-VEGF/Ang-2 in retinal indications.

Faricimab is a novel, bispecific antibody used to treat retinal diseases like nAMD, DME and RVO. It works by targeting 2 key pathways involved in these diseases: VEGF-A and angiopoietin-2 (Ang-2). Faricimab's dual target inhibition disrupts abnormal new blood vessel formation (neovascularization), stabilizes vascular leakage, and targets chronic inflammation, key pathophysiological processes and characteristic of these retinal conditions (Sahni et al., 2019; Sharma et al., 2020). Phase III trials, nAMD - TENAYA/LUCERNE (Heier et al., 2022), DME - YOSEMITE/RHINE (Wykoff et al., 2022; Wong et al., 2023), have shown promising results for faricimab, offering improved efficacy and extended dosing intervals compared to aflibercept.

The European Medicines Agency (EMA) approved faricimab for the treatment of nAMD and DME in September 2022, based on pivotal clinical trial data. However, these randomized clinical trials (RCTs) are usually conducted under very controlled, protocol specific settings, in well-defined patient populations, which may differ in disease severity, patient demographics, treatment patterns and adherence to treatment in the real-world setting.

Real-world evidence studies, such as FaReal, are essential for complementing the findings of clinical trials, providing insights into treatment outcomes in diverse patient populations, assessing long-term effectiveness and safety, understanding treatment patterns, evaluating healthcare resource utilization, and facilitating comparative effectiveness research. These studies play a crucial role in informing clinical practice, optimizing treatment strategies, and improving patient care in the management of retinal diseases.

4.1 STUDY RATIONALE

Since the approval of anti-VEGF therapies, many countries and regions have set up retinal registries, observational studies, and databases containing information on patients with retinal diseases (Daien et al., 2019). However, data captured within these different data sources are not always consistent and complete with respect to collecting information on the overall management of the patients treated with anti-VEGFs in retinal indications. The FaReal study therefore aims to fill the existing knowledge gaps by collecting long-term data on patients treated with faricimab, in order to:

- Evaluate the real-world evidence of faricimab (functional and anatomic effectiveness, durability, and safety) in nAMD and DME in a multi-country, regional setting.
- Describe the treatment patterns and explore the association between treatment patterns and effectiveness of faricimab.
- Evaluate the impact of treatment patterns on change in VA over time.
- Evaluate health economic aspects of previous anti-VEGF treatments and current treatment with faricimab.

The insights gathered in this study may help to further advance personalized healthcare initiatives in ophthalmology and allow a broader real-world evidence collection within EU countries, in a standardized data collection format.

5 RESEARCH QUESTION AND OBJECTIVES

5.1 RESEARCH QUESTION

The FaReal study aims to evaluate the effectiveness, safety, clinical insights and treatment patterns in patients treated with faricimab, in nAMD or DME (in at least one eye), in real-world routine clinical practice over a 2-year patient follow-up period. Additionally, the FaReal study also aims to describe and evaluate health economic aspects of previous anti-VEGF treatments and current treatment with faricimab.

5.2 OBJECTIVES

5.2.1 Primary and Secondary Objectives

Primary Objective	**Primary Analysis**
To evaluate the functional effectiveness of faricimab in nAMD and DME on visual acuity (VA) at 12 months in the real-world setting.	• Change in VA (approximate Early Treatment Diabetic Retinopathy Study (ETDRS) letter score - see Appendix 3) from index date* to month 12.

Secondary Objectives	**Secondary Analyses**
To evaluate the functional effectiveness of faricimab in nAMD and DME on VA at specified intervals during the conduct of the study in the real-world setting.	• Change in VA (approximate ETDRS letter score - see Appendix 3) from index date* to months 3, 6 and 24.
To evaluate the anatomical effectiveness of faricimab in nAMD and DME on central subfield thickness (CST) reduction	• Change in CST (defined as the CST measured by the used OCT) from index date* to months 3, 6, 12 and 24 months (as measured per local standard clinical practice).

Secondary Objectives	Secondary Analyses
To describe retinal treatment patterns throughout study period	• Number and percentage of eyes in each treatment regimen (i.e., Fixed regimen, T&E, PRN, Other - see Appendix 5) at 3, 6, 12 and 24 months of observation. • Number of intravitreal injections per eye per year per indication overall (at month 12 and 24). • Number of intravitreal injections in loading phase** for treatment naïve and anti-VEGF pre-treated patients (per pre-treatment type) • Total number of visits, number of visits with or without treatment (observational) at 3, 6, 12 and 24 months of observation • Number and percentage of eyes with treatment switch from faricimab, including reason for switch, at 3, 6, 12 and 24 months of observation for treatment naïve and pre-treated patients (per pre-treatment type).
To describe durability of faricimab treatment within different patient groups (indication, treatment naïve/pre-treated)	• Number and percentage of eyes obtaining treatment intervals of Q8W, Q12W, Q16W and other at 12 months and 24 months of observation for treatment naïve and pre-treated patients (per pre-treatment type).
To evaluate the correlation/association between retinal treatment characteristics (durability and treatment patterns) and change in VA over time in nAMD and DME	• Change in VA (approximate ETDRS letter score - see Appendix 3) from index date* to months 3, 6, 12 and 24, in relation to: ○ Treatment regimen (Fixed, T&E, PRN, Other - see Appendix 5) ○ Number of intravitreal treatments ○ Total number of visits ○ Treatment intervals ○ Type of pre-treatment and number of previous injections for preceding regimen at index date ○ Length of diagnosis of disease at index date

CST = central subfield thickness, DME = diabetic macular edema, ETDRS = Early Treatment Diabetic Retinopathy Study, nAMD = neovascular age-related macular degeneration, PRN = pro re nata, T&E = Treat-and-Extend, VA = visual acuity, VEGF = vascular endothelial growth factor

*Index date is defined as the date of first faricimab treatment on eye-level. If both eyes are treated with faricimab and the treatment start dates are different, each start date will be used as index date for the respective eye.

**Loading phase is defined as per local label (for nAMD and DME)

5.2.2 Safety Objective

Safety Objective	Safety Analysis
To evaluate the ocular and systemic safety and tolerability for faricimab in nAMD and DME in the real-world setting.	● Incidence, severity, duration, and outcomes of ocular and non-ocular adverse events.

DME = diabetic macular edema, nAMD = neovascular age-related macular degeneration

5.2.3 Exploratory Objectives

Exploratory Objectives	Exploratory Analyses
To evaluate changes over time in presence/absence of retinal fluid, as determined by imaging assessments according to investigator evaluation as per routine clinical practice, in relation to the number of treatments, treatment regimen, and investigator-determined disease activity	● Presence/absence of fluid in relation to the number of treatments including loading dose, treatment regimen, and investigator-determined disease activity: ○ Proportion of eyes with presence/absence of intraretinal fluid (IRF) over time (index date*, months 3, 6, 12, 24) ○ Proportion of eyes with presence/absence of subretinal fluid (SRF) over time (index date*, months 3, 6, 12, 24) ○ Proportion of eyes with presence/absence of IRF and SRF over time (index date*, months 3, 6, 12, 24) ○ Proportion of eyes with absence/presence of either IRF, SRF or both from index date* over time (index date, months 3, 6, 12, 24) ○ Proportion of eyes with absence/presence of serous pigment epithelial detachment (PED) from index date* over time and change in height of PED if measured (index date*, months 3, 6, 12, 24)
To describe changes in VA over time in relation to presence/absence of fluid or PED	● Change in VA (approximate ETDRS letter score - see Appendix 3) from index date* to months 3, 6, 12 and 24 for eyes in each fluid group at index date (no fluid present, presence of IRF, presence of SRF, presence of serous PED, presence of both IRF & SRF)
To describe distribution of patients according to change in VA in nAMD and DME in the real-world setting.	● Number and proportion of eyes, over time (from index date* to months 3, 6, 12 and 24), with approximate ETDRS letter score[1] of:

Exploratory Objectives	Exploratory Analyses
	○ 70 or more (20/40 Snellen equivalent). ○ 36 to 69 (between 20/40 and 20/200 Snellen equivalent). ○ 35 or less (20/200 Snellen equivalent). ● Proportion of eyes gaining ≥15, ≥10, ≥5, or >0 letters in VA[1] from index date* over time. ● Proportion of eyes losing ≥15, ≥10, ≥5, or >0 letters in VA[1] from index date* over time.
To evaluate changes over time in presence/absence of anatomical features	nAMD specific endpoints: Number and percentage of eyes with the following, at index date* and months 3, 6, 12, 24: ● presence/absence of atrophy[2] ● presence/absence of fibrosis[3] ● presence/absence of serous PED[4] (also adding height of PED if measured) ● presence/absence of hemorrhage[5] DME specific endpoints: Number and percentage of eyes with the following, at index date* and months 3, 6, 12, 24: ● presence/absence of epiretinal membrane (ERM)[6]
To evaluate the health economic perspective and specific treatment patterns of anti-VEGF treatment in nAMD and DME	For eyes pre-treated with any anti-VEGF: ● Type of anti-VEGF treatments received before index date* ● Time spent on each pre-treatment ● Number of previous injections for previous treatment ● Treatment interval of the last preceding treatment before entering the study. For all eyes (both naïve and pre-treated) the below will be described following the index date: ● Number and percentage of eyes in each treatment regimen (i.e., Fixed regimen, T&E, PRN, Other - see Appendix 5). ● Number of injections per eye per year per indication. ● Total number of visits, number of visits with or without treatment (observational), and time intervals between treatments, per year.

DME = Diabetic macular edema, ERM = Epiretinal Membrane, ETDRS = Early Treatment Diabetic Retinopathy Study, IRF = intraretinal fluid, nAMD = neovascular age-related macular degeneration, OCT= optical coherence tomography, PED = pigment epithelial detachment, PRN = pro re nata, RPE= retinal pigment epithelium, SRF = subretinal fluid, T&E = Treat-and-Extend, VA = visual acuity, VEGF = vascular endothelial growth factor

*Index date is defined as the date of first faricimab treatment on eye-level. If both eyes are treated with faricimab and the treatment start dates are different, each start date will be used as index date for the respective eye.

[1] Approximate ETDRS letter score conversion table can be found in Appendix 3

[2] Atrophy definition: Defined as cRORA (Complete loss of photoreceptors and the retinal pigment epithelium (RPE) in the central 3 mm), atrophy is to be assessed as per the treating physician (Sadda S et al 2018, Guymer RH et al 2020, Savastano MC et al 2020).

[3] Fibrosis: Hyperreflective material below the neurosensory retina on OCT (may have a multilaminar appearance) accompanied by different amounts of RPE destruction & photoreceptor loss. It is to be evaluated by the treating physician in the central 3 mm (Willoughby AS et al 2015, Gräfe MGO et al 2020).

[4] Serous PED: Separation between the RPE and the inner most aspect of Bruch´s membrane. Is to be evaluated in the central 3 mm.

5 Hemorrhage to be evaluated by the treating physician in the central 3mm

6 ERM: to be evaluated by the treating physician in the central 3 mm

6 RESEARCH METHODS

6.1 STUDY DESIGN

6.1.1 Overview of Study Design

The FaReal study is a non-interventional, prospective, multinational, multicenter study designed to collect real-world data on patients treated with faricimab in nAMD and DME in the real-world routine clinical practice with primary prospective data collection (NIS PDC) and retrospective collection of prior medical/treatment history data from medical records.

Participation in this study will not change or influence a patient's standard of care in any way. The decision to start treatment with faricimab must be taken independently by the treating physician and before the decision to invite the patient into the study.

This study aims to enroll approximately 850 patients from approximately 65 sites (in 18 countries in region Europe and Israel). The expected duration of the study is approximately 4 years.

Adult patients fulfilling the eligibility criteria who sign informed consent (as required per local regulations) will be enrolled and followed up prospectively from enrollment until completion of 2 years of participation, death, withdrawal of consent, participation in an investigational ophthalmology clinical trial, early termination of the study, or discontinuation of the study site, whichever occurs first. Patients are free to withdraw participation at any time.

Retrospective data will be collected for pre-treated patients pertaining to their previous anti-VEGF treatments.

All patient visits will be conducted according to usual local clinical practice. No study-specific visits are mandated by the study protocol, no patient visits or remote consultations are mandated by the study protocol, and no additional tests will be performed on patients due to their participation in this study. Data will be collected only when patients present for their routine visits or are contacted remotely. Retrospective data from enrolled patients will be collected from the patient's medical history.

Data recorded at each visit will be collected, including some data that may not be routinely recorded in patient medical records but is part of the clinical routine for a specific patient. Where applicable, analysis will be conducted at specific time points (e.g., 3, 6, 12 and 24 months from index date). The derivation of the analysis value per time point will be described in the Statistical Analysis Plan (SAP) and may use data from visits placed in the appropriate window around the timepoint of interest for analysis (e.g., ±30 days, ±60 days). Subgroup analyses, for example by region, country, baseline characteristics, or other factors, will be performed as defined in the SAP. Further details of the planned analyses are provided in Section 6.7 and will be fully described in the SAP.

The study population is intended to reflect the real-world use of faricimab treatment; therefore, minimal inclusion and exclusion criteria will be used. The study population will comprise patients treated with faricimab, for nAMD (Cohort 1) or DME (Cohort 2). Cohorts 1 and 2 will each be further divided into 2 sub-cohorts: treatment naïve (first-line) sub-cohort and anti-VEGF pre-treated (second-line) sub-cohort. For further details please refer to Section 6.7.

Approximately 40% of the patients in Cohort 1 and Cohort 2 (treatment naïve sub-cohorts) will be enrolled after the decision to initiate intravitreal faricimab treatment has been taken as part of routine clinical practice as first-line treatment. The remaining patients in Cohort 1 and 2 (pre-treated sub-cohorts) may already have received intravitreal anti-VEGF treatment previously.

After enrolment, patients in both cohorts will be prospectively followed up during the faricimab treatment period (estimated as approximately 2 years). Patients who discontinue faricimab treatment for this study or switch to another treatment will be followed up until completion of 2 years of participation, death, withdrawal of consent, participation in an investigational ophthalmology clinical trial, early termination of the study, or discontinuation of the study site, whichever occurs first.

Treatment after switch from faricimab in both cohorts will be according to standard of care and as deemed appropriate by the treating physicians.

Anonymized data will be shared with the medical and scientific community to foster research and support evidence generation. The data elements collected will address different types of research questions through registry-based studies such as secondary data use (SDU) studies.

Start Date of Study

Patient enrollment will be initiated at each site, upon approval from regulatory authorities and IRBs)/ ECs, as per local regulation and site agreement implementation and approval of faricimab treatment in nAMD and/or DME according to local labeling. The study start date will be the date of the first patient enrolled.

Study Duration

The expected duration of the study is up to 4 years, depending on the enrollment period duration. This includes approximately 1 to 2 years of recruitment and 2 years for follow-up of every patient (unless the patient discontinues early from the study).

Baseline Date and Index Date

Baseline is defined as the date when a patient initiates treatment with faricimab in at least one eye (first eye in case of both eyes being treated).

Index date is defined as the date when treatment is initiated at the eye-level. If both eyes are treated with faricimab and the treatment start dates are different, each start date will be used as the index date for the respective eye.

Enrollment Date

Enrollment date is the date the patient signs the Informed Consent Form to participate in this study.

Enrollment date cannot occur earlier than index/baseline date.

End of Study

The study ends when all participants have either completed at least 2 years of follow-up or have ended their participation in the study due to death, withdrawal of consent, participation in an investigational ophthalmology clinical trial, early termination of the study, or discontinuation of the study site, whichever occurs first.

The end of the study date will be the date on which the last information pertaining to the last included patient is recorded in the database.

6.1.2 Rationale for Study Design

The prospective observational design offers the opportunity to explore the use, effectiveness, and safety of faricimab in nAMD and DME in a real-world clinical setting and to collect desired information by defining uniform data collection methods.

Typically, for clinical trials, the outcome of BCVA is used to analyze the efficacy of intravitreal treatments (IVTs); however, BCVA is seldom measured in the routine clinical practice. VA and its change over time is considered a standard endpoint to measure effectiveness of these treatments in the real-world setting. Therefore, it has been chosen as the primary effectiveness endpoint of the FaReal study to explore faricimab approved in nAMD and DME in a long-term real-world setting with a broader patient population. In routine clinical practice, VA measurements will be done at distinct timepoints using different methods; thus, the date of each measurement will be recorded from all routine visits and, where applicable, analyzed as per the appropriate window period planned around these timepoints. The results will be documented as measured per local practice and will then be converted automatically in the electronic case report form (eCRF) to the approximate early treatment DR study (ETDRS) letter score for comparability.

Key secondary effectiveness objectives will evaluate the impact of retinal treatment patterns on VA in terms of treatment frequency, monitoring visit frequency, total visit frequency, and time interval between treatments. The observational study design will allow the required information on real-world retinal treatment patterns to be collected and explored to meet these objectives.

The study also includes a Safety Endpoint of evaluating the ocular and systemic safety/tolerability of faricimab approved in nAMD and DME. This study design allows the collection of all ocular and non-ocular AEs (serious and non-serious) to allow comprehensive data collection for this endpoint.

Regular interim analyses will be performed throughout the study duration to evaluate effectiveness and safety of faricimab. Additional details on these can be found in section Interim and Final Analyses and Timing of Analyses (Section 6.7.5).

6.1.3 Number of Patients Observed in the Study

This study aims to enroll a total of approximately 850 patients treated with faricimab (n=600 patients with nAMD and n=250 patients with DME), who will be contributing data for one or both eyes, to enable meaningful analysis of study cohorts, sub-cohorts and subgroups by baseline characteristics, and other factors. Sub-cohorts will include treatment naïve patients (approximately 240 nAMD and 100 DME patients) and patients previously treated with anti-VEGF (approximately 360 and 150 patients in the nAMD and DME cohorts, respectively).

Cohort	Total**	Sub-cohorts (by Treatment Status)		% Treatment Naïve*
		treatment naïve**	pre-treated**	
nAMD	600 (70%)	240 (70%)	360 (70%)	40%
DME	250 (30%)	100 (30%)	150 (30%)	40%
Overall	850 (100%)	340 (100%)	510 (100%)	40%

DME = diabetic macular edema, nAMD = neovascular age-related macular degeneration

*Row percentage
**Column percentage

Recruitment will be open until approximately 850 patients have been recruited. The recruitment period may be expanded at the Marketing Authorization Holder (MAH)'s discretion.

6.1.4 Sites

Approximately 65 sites in Europe and Israel, with commercial availability/reimbursement and access to the faricimab, will be included. Additional centers may be added or substituted as required.

6.2 POPULATION

The main patient population for this study, that is new users of faricimab (initiated treatment at enrollment or within 3 months prior to enrollment) in nAMD or DME in at least one eye, has been chosen to allow the capture of the baseline information as it will coincide around the time of study enrollment.

The study will recruit patients who are naïve to anti-VEGF intravitreal therapy in the study eye and those who have previously been treated with anti-VEGF intravitreal therapy in the study eye. Overall, study participation of patients previously treated with intravitreal anti-VEGF will be capped at a maximum of approximately 60% in each

indication. Expected proportion of nAMD and DME patients in the study population is 70% and 30%, respectively.

Patients must meet the following criteria for study entry:

1. Adult patients (≥18 years), who have provided signed informed consent, as required per local regulations.
2. Patients, as defined by local regulations and local faricimab product label, who are initiating treatment with faricimab at time of enrollment or have initiated treatment with faricimab within 3 months prior to patient enrollment, in DME or nAMD in at least one eye according to the investigator's discretion in routine clinical practice for anti-VEGF treatment naïve and pre-treated patients.
3. Patients have received at least one faricimab treatment (the first dose) in the study eye.

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

1. Concomitant participation of the patient in any investigational ophthalmology clinical trial that includes receipt of any ophthalmological investigational drug or procedure within the last 28 days prior to enrollment
2. Current participation in any interventional clinical study
3. Active ocular inflammation and/or suspected/active ocular infection in either eye
4. Patients in whom the study eye has been treated with faricimab for more than 3 months prior to enrollment
5. Patients treated with faricimab who have and are currently participating in patient support programs (PSP) that are Market Research and Patient Support Programs (MAP) including Post Trial Access Programs (PTAP) and Compassionate Use Programs (CUP)
6. Patients with non-ocular sight threatening disease which have an effect on primary endpoint (VA), e.g.: apoplexia
7. Hypersensitivity to the active substance or any of the excipients of Vabysmo (as per label)

6.2.1 Rationale for Patient Population

This study aims to collect data from a broad real-world patient population treated with faricimab in nAMD and DME, as per clinical practice and labeling under EMA label or Food and Drug Administration (FDA) label (Israel) authorization and as per country label requirement. Therefore, minimal eligibility criteria will be applied to ensure a broad population.

As the primary objective of this study is to evaluate the effectiveness of faricimab for nAMD and DME on VA at 12 months after treatment initiation in the real-world setting, eligibility criteria focus on those patients' eye(s) that are initiating treatment at the time of enrollment. It is acknowledged that the effectiveness of faricimab may be different depending on whether an eye was previously treated with anti-VEGFs. Treatment naïve eyes are of particular scientific and medical interest as effectiveness and safety

outcomes will not be hindered by any long-term effects of previous treatments. Furthermore, a prospective follow-up of patients will enable a better recording of safety data, which is an important objective of this study.

Treatment naïve patients and pre-treated patients will be recruited in this study. Patients who had previously received intravitreal anti-VEGF treatment will be enrolled to assess the effectiveness of faricimab in switch patients and to incorporate the health economic aspects of previous treatments. The number of participants with prior intravitreal anti-VEGF therapy will be limited to 60% as the maximum proportion of the total and each indication enrolled.

The rationale for capping the number of pre-treated participants is based on the heterogeneous nature of this population with potentially a history of long-standing disease and irreversible retinal damage that may limit the possibility of detecting additional VA improvements.

6.2.2 Recruitment Procedure

To best understand the real-world effectiveness and safety of faricimab for treatment of nAMD and DME, treating physicians are requested to ensure adequate enrollment among both anti-VEGF naïve patients and patients pre-treated with anti-VEGF so that a sufficient number of treated eye data within each sub-cohort of interest are available for analysis.

Treating physicians will explain the study to patients, addressing any questions or concerns. Treatment decisions will be determined by the treating physician and must be made independently of the patient's decision to participate in this study. When required by local regulations, the physician decision to treat with faricimab must be documented prior to the patient's enrollment.

6.2.3 Dosage, Administration, and Compliance

The dosing and treatment duration of faricimab received by participants of this NIS is at the discretion of the treating physician, in accordance with local clinical practice and local labeling.

6.2.4 Concomitant Medication and Treatment

Concomitant treatment is at the discretion of the treating physician, in accordance with real-world clinical practice. Concomitant medications (ocular and non-ocular) prescribed in this study at the beginning of the observation period or introduced during the observation period will be documented in the eCRF at index date and throughout the study, if applicable.

6.3 VARIABLES

The data collection overview is presented in Table 1. The data collection schedule is presented in Appendix 2 , which outlines variables that will be collected at index date, enrollment (incl. retrospective data) and during follow-up.

The eCRF will serve as the primary reference for information regarding parameters collected in the study.

Table 1: Variables to be Collected in this Study

Category	Variable
Demographic characteristics at enrollment	● Year of birth ● Sex (Female, Male, Other) ● Smoking status (Current Smoker, Former Smoker, Never Smoker)
Specific baseline characteristics (disease information[a]) at index date	● Type of disease (nAMD, DME) and date of diagnosis (month/year) ● For nAMD patients: ○ Duration of disease before study inclusion ○ Type of membrane (1-3 MNV, polypoidal choroidal vasculopathy (PCV), cystoid macular edema (CME)) ○ Pigment epithelial detachment (PED)[c] or disruption within the retinal pigment epithelium ○ Duration of the disease ○ Presence/absence of atrophy[b] ○ Presence/absence of fibrosis[d] ● For DME patients: ○ Severity of diabetes (HbA1c) ○ Duration of diabetes (date of diagnosis) ○ Diabetes type ○ Duration of DME ○ DME classification (non-central or central involvement). Central is defined as central 3 mm ○ Presence/absence of proliferative diabetic retinopathy ○ Presence/absence of ERM in the central 3 mm
Relevant medical history (ocular - by eye where applicable)	● Ocular comorbidities ● Non-ocular comorbidities ● Previous intravitreal treatments (IVT) other than anti-VEGF and other ocular treatments ● Surgical history: macular laser, surgical procedures, corneal transplant, cataract surgery vitrectomy, YAG laser treatment, peripheral laser treatment, cornea surgery, steroid implant
Prior treatment and management (by eye) for health economic analysis perspectives (for eyes with previous anti-VEGF treatment)	● Type of intravitreal anti-VEGF treatments received before index date. ● Date of first anti-VEGF treatment ● Time spent on each pre-treatment. ● Number of previous injections for previous treatments ● Treatment interval of the last preceding anti-VEGF treatment before entering the study.
Treatment and management (by eye) for health economic analysis perspectives (pre-treated and treatment naïve eyes), from index date until end of study	● Treatment regimen (i.e., Fixed regimen, T&E, PRN, Other) ● Number of injections per eye per year per indication (nAMD, DME). ● Total number of visits, number of visits with or without treatment (observational), and time intervals between treatments, per year.
Treatment and management (by eye) during study period, from index date until end of study	● Treatments received for the indications nAMD, DME (type of treatment: anti-VEGF injection, laser therapy, corticosteroid injections or steroid implants), with date of therapy. ● Therapy switch: (date and reason)

Category	Variable
	● Treatment discontinuation/termination (date and reason) ● Details of other procedures that could potentially elevate/deteriorate visual acuity (VA) ● Treatment regimen (Fixed regimen, T&E, PRN, Other) ● Number (dates) of injections ● Number of loading dose intravitreal injections (per eye) ● Number (dates) of visits with and without treatment (observational) ● Treatment intervals of Q8W, Q12W, Q16W and other ● CST over time (as measured per local standard clinical practice), by eye, (including method, software settings and type of OCT) ● Eyes with presence of IRF ● Eyes with presence of SRF ● Eyes with presence of serous PED, height of PED (if measured) ● Eyes with presence of atrophy[b] ● Eyes with presence of fibrosis ● Eyes with presence of hemorrhage ● Eyes with presence of ERM
Concomitant medications (ocular and non-ocular), from index date until end of study	● Ocular concomitant medications (type, indication and treatment time) ● Non-ocular concomitant medication (type, indication and treatment time)
Visual acuity (VA) by eye, from index date until end of study	● VA (as measured per local clinical practice) including method of VA assessment - scale and type of correction (e.g., Best-corrected, Corrected, Pinhole, Uncorrected), and date of assessment.
Imaging assessments (by eye) as per routine clinical practice (during visits for the retinal indications), from index date until end of study *Note: Diagnostic images for this study will not be stored, hence assessment of images by investigators must be well-defined.*	● Optical coherence tomography (OCT)-imaging assessment type (e.g. SD-OCT, SS-OCT), machine used ● Results, including: ○ SRF assessment (presence/absence) ○ IRF assessment (presence/absence) ○ CST assessment (numerically) ○ Serous PED assessment (presence/absence and height of PED if measured)
Safety events (all ocular and non-ocular AEs), from index date until end of study	● Type of AE: ○ AE/SAE ○ AESI ○ Ocular/non-ocular ● Onset date and resolution date ● Outcome ● Seriousness ● Severity ● Action taken ● Relationship to therapy (i.e., related or unrelated) ● For ocular events: eye(s) affected

AE = adverse event, AESI = adverse events of special interest, anti-VEGF = anti-vascular endothelial growth factor, CME = cystoid macular edema, CST = central subfield thickness, DME = diabetic macular edema, ERM = epiretinal membrane, HbA1c = Hemoglobin A1c, IRF = intraretinal fluid, IVT = intravitreal treatment,

MNV = macular neovascular membrane, nAMD = neovascular age-related macular degeneration, OCT = optical coherence tomography, PCV = polypoidal choroidal vasculopathy, PED = pigment epithelial detachment, PRN = pro re nata, RPE= retinal pigment epithelium, SAE = serious adverse event, SD-OCT = spectral domain optical coherence tomography, SRF = subretinal fluid, SS-OCT= swept-source optical coherence tomography, T&E = treat-and-extend, VA = visual acuity, YAG laser = yttrium aluminum garnet laser

[a] To be assessed as per the treating physician.
[b] Atrophy definition: Defined as cRORA (complete loss of photoreceptors and the RPE) in the central 3 mm), atrophy is to be assessed as per the treating physician (Sadda S et al 2018, Guymer RH et al 2020, Savastano MC et al 2020).
[c] Serous PED: Separation between the RPE and the inner most aspect of Bruch´s membrane. Is to be evaluated in the central 3 mm.
[d] Fibrosis: Hyperreflective material below the neurosensory retina on OCT (may have a multilaminar appearance) accompanied by different amounts of RPE destruction & photoreceptor loss. It is to be evaluated by the treating physician in the central 3 mm (Willoughby AS et al 2015, Gräfe MGO et al 2020).

6.3.1 Visual Acuity

The primary effectiveness variable is VA. VA will be collected at index date and at all available follow-up measurements. Information on the scale and type of correction (e.g., Best-corrected, Corrected, Pinhole, Uncorrected) during assessment, and the date of assessment, will be collected for each VA assessment, as available per routine clinical practice. If possible, and within routine clinical practice, it is recommended that the patient is assessed in the same manner across visits.

VA will be collected as measured per local practice and will then be converted automatically in the eCRF to the approximate ETDRS letter score (Gregori et al., 2010). Details of the conversion to approximate ETDRS letter score are outlined in Appendix 3 .

6.4 DATA SOURCES

Patients' data will be recorded in the database via eCRFs and stored in the electronic data capture (EDC) system. All clinical data will be processed and stored in a database. All data will be pseudo-anonymized, and each patient will have a unique code so that the information of the same patients can be linked.

6.4.1 Collection of Data on the eCRF

Patients' data will be recorded on eCRFs. The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient medical records should be entered on the eCRF as soon as they become available.

6.4.2 Data Collected During the Observation Period

During the observational period, assessments are routinely performed in accordance with current guidelines and local standard of care. When performed during the observational period, available results will be documented in the eCRF.

Please see Appendix 2 for the data collection overview (as per standard of care).

6.4.3 Safety Data Collection

Clinical AEs serious and non-serious will be recorded in the eCRF during the entire observation period, with physician's assessment of severity (mild, moderate, severe) and

relationship to therapy (i.e., related or unrelated), defined by the International Organization for Standardization (ISO) Adverse Event Categorization Guidelines as described in Appendix 4.3.15.

6.5 PATIENT, STUDY AND SITE DISCONTINUATION

6.5.1 Patient Discontinuation

Patients have the right at any time and for any reason to withdraw their consent to have data collected and used for the study.

Patients starting participation in a Roche Patient Support Program (PSP) after enrollment in this study will have to be evaluated for future participation in the study by the Medical Monitor in order to ensure that the PSP will not have any influence on the treatment choice of the treating physician.

Reasons for discontinuation include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Patient is entering an investigational ophthalmology clinical trial
- Patient is no longer attending the participating site
- AE
- Death

6.5.2 Discontinuation from Treatment with Studied Medicinal Product

The decision for treatment discontinuation lies with the treating physician and is not regulated by this protocol.

If a patient discontinues from faricimab treatment or switches to another treatment, even if faricimab is not being received in either eye, the patient should continue to participate in this study until the end of study participation (defined in Section 6.1.1).

6.5.3 Study and Site Discontinuation

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

- Patient enrollment is unsatisfactory
- Quality or compliance issues at the site

Roche will notify the physician if the study is placed on hold, or if the study is discontinued.

Roche has the right to discontinue a site at any time. Reasons for discontinuation of a site may include, but are not limited to, the following:

- Recruitment is unsatisfactory
- Poor study protocol adherence
- Inaccurate or incomplete study data recording

- Non-compliance with the Guidelines for Good Pharmacoepidemiology Practice (GPP) or any other pertinent local law or guideline

6.6 DATA MANAGEMENT

6.6.1 Data Quality Assurance

A contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data will be collected in the eCRF via EDC. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will perform oversight of the data management of this study. The CRO will produce eCRF specifications for the study based on the Roche templates, including quality checking to be performed on the data.

All clinical data will be processed and stored in a database.

The eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures. The CRO will comply with the Roche procedures regarding archiving and record management.

6.6.2 Electronic Case Report Forms

A study designated EDC system will be used. Sites will receive training and have access to a manual for appropriate eCRF completion. The eCRFs will be submitted electronically and should be handled in accordance with instructions from the CRO.

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

At the end of the study, the physician will receive the data related to patients from his or her site in an electronically readable format (e.g., on a compact disc). Data must be kept with the study records. Acknowledgment of receipt of the data is required.

6.6.3 Source Data Documentation

The Site Operations Representatives will perform ongoing source data verification (SDV) as defined in the Clinical Monitoring Plan to confirm that critical protocol data (i.e., source data) entered in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents (where applicable).

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

Before study initiation, the types of source documents that contain study-relevant information will be defined in the Clinical Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered in the eCRF must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 6.8.4.

To facilitate SDV, the physicians and institutions must provide the MAH, and the Clinical Research Associates belonging to the contacted CRO, direct access to applicable source documents and reports for study-related monitoring, MAH audits, and IRB/EC review. The participating sites must also allow inspection by applicable health authorities.

6.7 STATISTICAL CONSIDERATIONS

Analyses will be performed using available data; however, due to the real-world, observational nature of this study, missing values are expected. Missing data will not be imputed unless otherwise specified in the SAP.

This is a NIS designed to collect RWD. It is expected that visits will not occur at a set schedule. Where applicable, to evaluate specified outcomes over time, analysis time points (e.g., 3, 6, 12, 24 months) will be defined. The listed time points are selected time points of interest; other time points may be specified in the SAP. Windowing of the visits will be relative to the time points of interest (i.e., ±number of days from time point of interest).

Unless otherwise specified, statistical analyses will be performed per cohort and per sub-cohort.

The following 2 cohorts will be defined and analyzed:

- Cohort 1: Patients receiving faricimab for nAMD in at least one eye.
- Cohort 2: Patients receiving faricimab for DME in at least one eye.

Within each cohort, 2 sub-cohorts will be defined (treatment naïve and pre-treated) based on treatment history at eye-level when initiating faricimab for this study as described in Table 2. Schematic view of sub-cohorts is presented in Figure 1 below.

Table 2: Sub-cohort Details per Cohort

Cohort 1	Cohort 2
Patients receiving faricimab for nAMD in at least one eye	**Patients receiving faricimab for DME in at least one eye**
A. Treatment naïve sub-cohort: Patient-eyes newly initiating faricimab intravitreal treatment* in at least one eye that has never had any anti-VEGF intravitreal treatment	**A. Treatment naïve sub-cohort:** Patient-eyes newly initiating faricimab intravitreal treatment* in at least one eye that has never had any anti-VEGF intravitreal treatment
B. Pre-treated sub-cohort: Patient-eyes newly initiating faricimab intravitreal treatment* after being previously treated with intravitreal anti-VEGF	**B. Pre-treated sub-cohort:** Patient-eyes newly initiating faricimab intravitreal treatment* after being previously treated with intravitreal anti-VEGF

DME = Diabetic macular edema, nAMD = neovascular age-related macular degeneration, VEGF = vascular endothelial growth factor

*Patient-eyes newly initiating faricimab intravitreal treatment: patient-eyes initiated treatment during 3 months prior to enrollment.

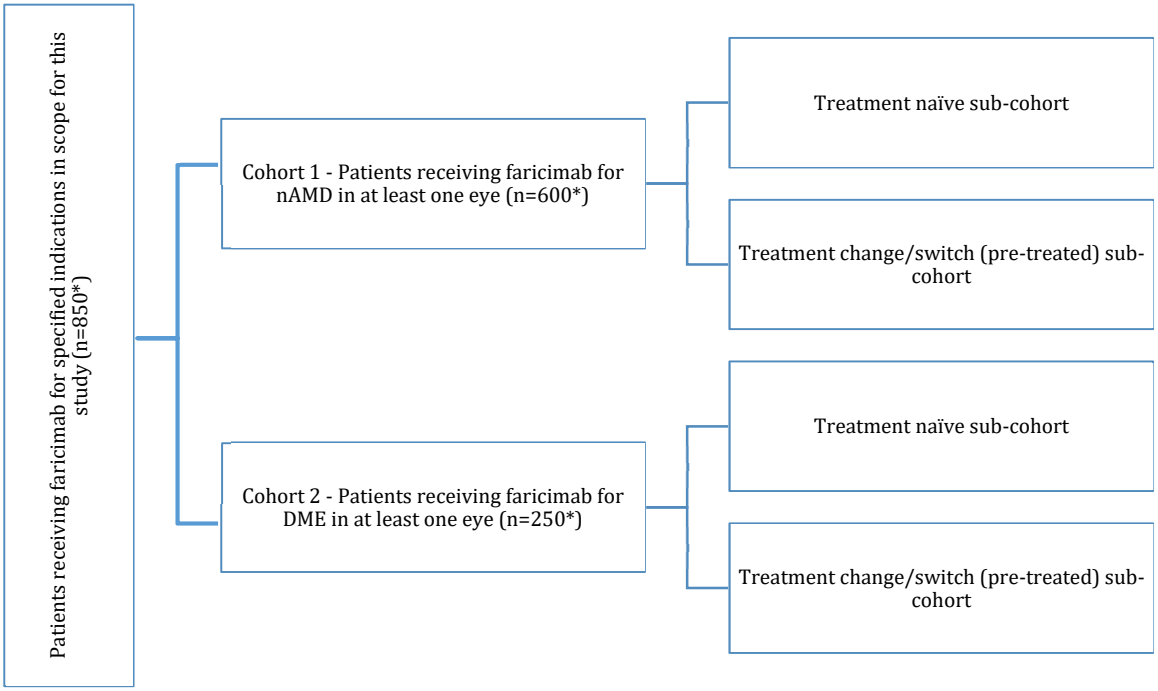

Figure 1. Schematic View of Sub-cohorts

* Estimated figure based on calculated overall Sample Size

DME = diabetic macular edema, nAMD = neovascular age-related macular degeneration

Patients may be part of several sub-cohorts as analyses will be carried out at eye-level (regardless of whether it is the right or left eye).

Patients' demographics as well as medical history will be summarized for each cohort and sub-cohort using descriptive statistics. Baseline ocular characteristics and information on prior ocular treatments will be summarized descriptively.

Patient and eye disposition will be summarized overall, by cohort and sub-cohort.

Continuous variables will be summarized descriptively using mean, median, standard deviation (SD), first quartile, third quartile, minimum, and maximum. Categorical outcomes will be summarized using numbers and percentages in each category. Corresponding 95% confidence intervals (CIs) will be provided for statistical estimates if applicable.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the SAP.

6.7.1 Analyses Sets

The analysis sets will be defined at 2 different levels.

- Eye-level analysis set applies to data that is collected separately for each eye.
- Patient-level analysis set applies to data that is collected for each patient.

All eyes in scope of an analysis will contribute to the analysis data set for that analysis. A participant who has 2 eyes meeting the scope of the analysis will contribute data on both eyes for the analysis.

6.7.1.1 Enrolled Analysis Set / Safety Analysis Set

Patient-Level

The Enrolled Analysis Set/Safety Analysis Set- Patient-Level (EAS-PL, SAS-PL) will consist of patients who meet all inclusion and none of the exclusion criteria, and who received at least one dose of faricimab in nAMD of DME indications.

Eye-Level

The Enrolled Analysis Set/Safety Analysis Set - Eye-Level (EAS-EL, SAS-EL) will consist of eyes with indication and treatment in scope for this study from patients who meet all inclusion criteria and none of the exclusion criteria, and who received at least one dose of faricimab in nAMD of DME indications.

The Enrolled Analysis Sets in this study are identical to the corresponding Safety Analysis Sets, because according to the inclusion criteria, only patients who have received at least one faricimab injection at enrollment or prior to enrollment can be included in the study.

6.7.1.2 Effectiveness Analysis Set

Patient-Level

The Effectiveness Analysis Set - Patient-Level (EFAS-PL) will consist of patients who meet all inclusion and none of the exclusion criteria, and who received at least one dose of faricimab in nAMD of DME indications and provide data for VA at least at the index date and one post-index visit.

Eye-Level

The Effectiveness Analysis Set - Eye-Level (EFAS-EL) will consist of eyes with indication and treatment in scope of the study from patients who meet all inclusion and none of the exclusion criteria, and who received at least one dose of faricimab in nAMD of DME indications, with VA measurements at least at the index date and one post-index visit.

6.7.2 Effectiveness Analyses

6.7.2.1 Primary Effectiveness Analyses

Primary effectiveness analyses will be performed per cohort and per sub-cohort, at the eye-level, for the EFAS-EL.

The primary effectiveness endpoint is the change in VA (approximate ETDRS letter score) from index date to month 12 per nAMD and DME and per treatment naïve and pre-treated sub-cohorts. VA will be measured as per the local practice at index date and at month 12. To allow statistical analysis of the different clinical methods used to measure VA, the assessments will be automatically converted to the approximate ETDRS letter score. The approximate ETDRS letter score conversion table can be found in Appendix 3 .

Both actual values at index date and month 12 and change from index date in VA (approximate ETDRS letter score) to month 12 will be summarized descriptively.

6.7.2.2 Secondary Effectiveness Analyses

Secondary effectiveness analyses will be performed on eye-level per cohort (nAMD/DME) and per sub-cohort (treatment naïve and pre-treated eyes) for the effectiveness dataset (EFAS-EL).

Change in VA (approximate ETDRS letter score) will be estimated from index date to months 3, 6, 24.

Actual VA values as well as change from index date in VA (approximate ETDRS letter score) will be summarized descriptively and graphically at index date, months 3, 6, and 24. Change in VA will also be described according to treatment regimen (Fixed, T&E, PRN, Other), number of intravitreal treatments, total number of visits, time interval between treatments, pre-treatment type (specified therapeutic) and number of previous injections for preceding regimen at index date.

In addition, mean change in VA from index date to month 12 will be estimated using Mixed Model for Repeated Measurement (MMRM). The model will use all the data collected up until the point of analysis. Complete model specifications will be detailed in the SAP.

Both actual values and change from index date in CST will be summarized descriptively at index date, months 3, 6, 12 and 24 using mean, median, SD, first quartile, third quartile, minimum, and maximum.

The number and percentage of eyes in each treatment regimen (i.e., Fixed regimen, T&E, PRN, Other) will be calculated and summarized at index date, months 3, 6, 12 and 24.

The number and percentage of treatments (faricimab injections) received in each eye, from index date to months 3, 6, 12, 24 will be calculated and summarized by study cohort and pre-treatment type.

The number of faricimab intravitreal treatments (on eye-level), per year, per nAMD and DME, and per treatment naïve and pre-treated sub-cohorts will be calculated and summarized descriptively using mean, median, SD, first quartile, third quartile, minimum, and maximum.

Total number of visits (with or without treatment) and time interval between treatments, per year, per nAMD and DME, and per treatment naïve and pre-treated sub-cohorts will be summarized descriptively using mean, median, SD, first quartile, third quartile, minimum, and maximum.

The number of loading dose intravitreal injections in treatment naïve and pre-treated patients (per pre-treatment type) by nAMD and DME will be calculated and summarized.

Cumulative time spent in each treatment regimen (i.e., Fixed regimen, T&E, PRN, Other), per nAMD and DME, and per treatment naïve and pre-treated sub-cohorts will be summarized descriptively using mean, median, SD, first quartile, third quartile, minimum, and maximum.

The number and percentage of eyes obtaining treatment intervals of Q8W, Q12W, Q16W and other at 12 months and 24 months will be calculated and summarized by study cohort and for treatment naïve and pre-treated patients (by pre-treatment type).

The number and percentage of eyes discontinuing faricimab treatment in each cohort will be calculated at months 3, 6, 12, and 24 (the reason for treatment discontinuation will be reported at the same time periods).

The number and percentage of eyes switching treatment regimen or treatment type and reason for switch at months 3, 6, 12 and 24 will be calculated and summarized per nAMD and DME.

Time to first treatment switch will be calculated per nAMD and DME and summarized using Kaplan-Meier estimate.

Number and percentage of eyes switched from faricimab to a non-faricimab product will be calculated and summarized at index date, months 3, 6, 12 and 24.

Number, type and frequency of ocular concomitant and subsequent medications received during the study period will be calculated and summarized descriptively by eye.

6.7.3 Safety Analyses

The Safety Population will consist of all consented patients who receive faricimab in nAMD and DME. Summary tables and listings will be based on the Safety Population (SAS-EL or SAS-PL).

The Safety Endpoint is the incidence of ocular and non-ocular AEs.

Non-ocular AEs/serious adverse events (SAEs) will be assessed at patient-level, per cohort and per sub-cohort, for the SAS-PL.

Ocular AEs/SAEs will be assessed at eye-level, per faricimab and any other anti-VEGF treatment, per cohort (nAMD, DME) and per sub-cohort (treatment naïve and pre-treated eyes), for the SAS-EL.

The incidence of AEs/SAEs will be summarized descriptively by Medical Dictionary for Regulatory Activities (MedDRA) Primary System Organ Class (SOC) and Preferred Term (PT). Cumulative incidence and rates per 100 patient-years or 100 patient-eye years (for eye-level events) (or per 1,000 patient-years, etc., as appropriate) of AEs and SAEs will be calculated.

The number and percentages of patients (or eyes) experiencing AEs and SAEs as well as the number of events will be displayed by SOC, PT, and by severity. AE outcome and duration of AE will be summarized descriptively. For all outcome measures, events with onset through end of study will be summarized at the final analysis.

6.7.4 Exploratory Analyses

Exploratory analyses will be performed per cohort (nAMD, DME) and per sub-cohort (treatment naïve and pre-treated), at the eye-level, for effectiveness dataset.

The following parameters will be summarized descriptively per eye, per nAMD/DME and per sub-cohort, at index date, 3, 6, 12 and 24 months:

- Number and percentage of eyes with absence/presence of IRF
- Number and percentage of eyes with absence/presence of SRF
- Number and percentage of eyes with absence/presence of IRF and SRF
- Number and percentage of eyes with absence/presence of either IRF, SRF or both
- Number and percentage of eyes with presence/absence of serous PED
- Change in height of serous PED (if measured) over time summarized descriptively using mean, median, SD, first quartile, third quartile, minimum, and maximum

The following categories will be calculated and summarized descriptively per nAMD and DME and per treatment naïve and pre-treated sub-cohorts at index date, 3, 6, 12 and 24 months, for the EFAS-EL:

- Number and percentage of eyes with approximate ETDRS letter score of 70 or more

- Number and percentage of eyes with approximate ETDRS letter score of 36 to 69
- Number and percentage of eyes with approximate ETDRS letter score of 35 or less

The change from index date to 3, 6, 12, 24 months in the following variables will be calculated and summarized descriptively for the EFAS-EL:

- Number and percentage of eyes gaining ≥15 letters in approximate ETDRS letter score
- Number and percentage of eyes gaining ≥10 letters in approximate ETDRS letter score
- Number and percentage of eyes gaining ≥5 letters in approximate ETDRS letter score
- Number and percentage of eyes gaining >0 letters in approximate ETDRS letter score
- Number and percentage of eyes losing ≥15 letters in approximate ETDRS letter score
- Number and percentage of eyes losing ≥10 letters in approximate ETDRS letter score
- Number and percentage of eyes losing ≥5 letters in approximate ETDRS letter score
- Number and percentage of eyes losing >0 letters in approximate ETDRS letter score

Time from index date to first achieving VA measurement of 70 letters or more will be calculated and summarized for eyes with an index VA measurement below 70 letters. This analysis will be done for the EFAS-EL, at the eye-level, using a Kaplan-Meier analysis.

Time from index date to first VA measurement below 70 letters will be calculated and summarized for eyes with an index VA measurement equal or greater than 70 letters. This analysis will be done for the EFAS-EL, at the eye-level, using a Kaplan-Meier analysis.

Both actual values and change from index date in VA (approximate ETDRS letter score) will be summarized descriptively for the EFAS-EL and graphically at index date, and each time point, per cohort and sub-cohort in each fluid group at index date (no fluid, SRF, IRF, both SRF and IRF, serous PED), using mean, SD, median, first quartile, third quartile, minimum, and maximum.

Both actual values and change from index date in VA (approximate ETDRS letter score) will be summarized descriptively for the EFAS-EL and graphically at index date and each time point, per cohort and sub-cohort in each treatment regimen (i.e., Fixed regimen, T&E, PRN, Other), using mean, SD, median, first quartile, third quartile, minimum, and maximum.

Both actual values and change from index date in VA (approximate ETDRS letter score) will be summarized descriptively for the EFAS-EL and graphically, at index date and each time point.

6.7.4.1 Specific Exploratory Analyses for nAMD and DME

The following will be summarized descriptively per eye for the nAMD cohort (per treatment naïve and pre-treated sub-cohorts) at index date, 3, 6, 12 and 24 months based on effectiveness dataset:

- Number and percentage of eyes with presence/absence of atrophy
- Number and percentage of eyes with presence/absence of fibrosis
- Number and percentage of eyes with presence/absence of PED
- Number and percentage of eyes with presence/absence of hemorrhage

The above will be displayed graphically with change from index date in VA (approximate ETDRS letter score) and graphically at index date, months 3, 6, 12 and 24 per eye in each cohort (nAMD, DME) and sub-cohort.

The following will be summarized descriptively for the DME patients at index date, 3, 6, 12 and 24 months:

- Number and percentage of eyes with presence/absence of ERM

The above will be displayed graphically with change from index date in VA (approximate ETDRS letter score) and graphically at index date, months 3, 6, 12 and at 24 per eye in each cohort (nAMD, DME) and sub-cohort.

6.7.4.2 Specific Exploratory Analyses for Health Economic Perspective

Exploratory analyses for health economic perspective will be performed per cohort (nAMD, DME) and per sub-cohort (treatment naïve and pre-treated), at the eye-level, based on effectiveness dataset.

The following will be calculated for anti-VEGF pre-treated eyes (pre-treated sub-cohorts) in nAMD and DME and summarized descriptively:

- Type of anti-VEGF treatments received before index date
- Time spent on each pre-treatment
- Number of previous injections for previous treatment
- Treatment interval of the last preceding treatment before entering the study.

The following will be collected prospectively starting at index date, calculated per cohort (nAMD, DME) and sub-cohort (treatment naïve and pre-treated) and summarized descriptively (at index date, 3, 6, 12, 24 months):

- Number and percentage of eyes in each treatment regimen (i.e., Fixed regimen, T&E, PRN, Other).
- Number of injections per eye per year.

- Total number of visits (per eye per year)
- Number of visits with treatment (per eye per year)
- Number of visits without treatment (observational) per eye per year
- Time intervals between treatments, per eye per year.

6.7.4.3 Concomitant Medication and Treatment

Ocular concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The most recent version of WHO-DD will be used.

Ocular concomitant medications will be summarized by cohort (nAMD, DME) and sub-cohort (treatment naïve and pre-treated) for the SAS-EL.

6.7.4.4 Subgroup Analyses

In addition to analyses per cohort and per sub-cohort, the following subgroups within cohorts and sub-cohorts will be considered in the analyses as appropriate:

- VA (approximate ETDRS letter score) categories, e.g., VA at index date, or eyes with off-chart values
- Treatment regimen (Fixed, T&E, PRN, Other - see Appendix 5)
- Fluid group at index date (no fluid, SRF, IRF, both SRF and IRF)
- Number of intravitreal treatments collected prospectively
- Total number of visits
- Number of faricimab treatment visits
- Number of monitoring visits
- Treatment interval
- Type of pre-treatment and number of previous intravitreal injections for preceding regimen at index date
- Length of diagnosis of disease at index date

Analyses will be performed based on effectiveness dataset.

This list is not exhaustive and can be subject to change; other subgroups of interest may be defined in the SAP.

6.7.5 Interim and Final Analyses and Timing of Analyses

The final analysis will be conducted after the last patient has exited the study. No formal confirmatory effectiveness or safety interim analyses are planned.

Exploratory interim analyses of selected endpoints are planned to be performed during the course of the study on an annual basis (depending on the available data); the timing and details will be provided in the SAP. The SAP may be modified during the course of the study, as required.

6.7.6 Determination of Sample Size

No formal sample size calculation linked to hypothesis testing has been done for this descriptive study. Sample sizes will be calculated for each of the treatment naïve and pre-treated sub-cohorts of cohort 1 (nAMD) and cohort 2 (DME).

For the primary endpoint change from baseline in VA to month 12, we calculate the precision of the 95% CIs for the mean change in VA given the sample size anticipated to be enrolled by the sites, and assuming a range of standard deviations (SD) that was reported in the literature (Kern et al., 2021; Kiss et al., 2020; Holz et al., 2020a; Mitchell et al., 2018; Mitchell et al., 2020; Lotery et al., 2017) for treatment naïve patients, and assuming a 5% drop-out rate. Precision is defined as the width of the confidence interval of the mean change in VA from 0 to 12 months. We anticipate that the SD will be equal or lower for pre-treated patients, as their VA might have stabilized by the time they enroll into the study. The estimated number of patients per cohort/sub-cohort is presented in Table 3.

Table 3: Sample Size for the Primary Effectiveness Variable - Change in VA at 12 months

Cohort & Sub-cohort	Sample Size	Precision at SD=12	Precision at SD=14
Treatment naïve patients in nAMD	240	3	3.6
Pre-treated patients in nAMD	360	2.5	3
Treatment naïve patients in DME	100	5	5.6
Pre-treated patients in DME	150	4	4.6

DME = diabetic macular edema, nAMD = neovascular age-related macular degeneration, SD = Standard Deviation, VA = visual acuity

6.8 STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

6.8.1 Study Documentation

The treating physician must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms (as required per local regulations), and documentation of IRB/EC and governmental approval/notification as per local requirements. In addition, at the end of the study, the treating physician will receive the patient data, which will include an audit trail containing a complete record of all changes to the data.

Roche shall ensure that the data set and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

6.8.2 Site Audits and Inspections

The treating physician will permit Roche to audit facilities and records relevant to this study.

The treating physician will also permit national and local health authorities to inspect facilities and records relevant to this study.

6.8.3 Use of Site Computerized Systems

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

6.8.4 Retention of Records

Archiving at the study site has to be done for at least 5 years after the final study report or first publication of study results, whichever comes later, or according to local regulation.

Records and documents pertaining to the conduct of this study must be retained by Roche for at least 25 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, which is subject to local regulations.

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

All supporting functional parties will comply with the Roche procedures regarding archiving and record management.

6.8.5 Administrative Structure

Development of the study documents and a general oversight over the conduct of the study is the responsibility of Roche core study management team, which includes medical, regulatory, safety, statistician, data management, RWD representative, patient partnership, and operational lead.

Training materials, feasibility and site selection, contract negotiations, regulatory submissions, quality, completeness and consistency of data collection, as well as the initiation, monitoring, and closure of the sites are to be done within the work frame of the CRO quality management system and in accordance with CRO’s policies and procedures, including quality control.

Setting up an integrated data repository with all functionalities and flexibility to ensure its connection with other data sources, data transformation, and transferring of all data to the relevant internal Roche databases will be a responsibility of the CRO.

The Steering Committee will be closely involved at the beginning of the study as well as throughout the study duration.

6.9 LIMITATIONS OF THE RESEARCH METHOD

The study might be limited by the factors described below:

- Data on effectiveness of non-Roche products will not be collected, which limits the ability to compare the effectiveness of faricimab with non-Roche products that are used in routine clinical practice.
- Although the study will enroll a large number of patients from multiple countries overall, the patients within each country will be enrolled from a few selected sites. This may limit the representativeness of the results to the underlying population within each country. Also, due to logistics barriers, consecutive enrollment is not mandated and the patients who choose or are invited to enroll in the study may differ from those who are not (e.g., relatively healthier individuals choose to enroll in the study); this will limit the representativeness of the results.
- The primary effectiveness endpoint of VA may be measured using different methods depending on the local clinical practice, leading to heterogeneity in the assessment methods. However, the change in VA will be analyzed by approximate ETDRS letter score for comparability and will be calculated for each eye. It is anticipated that measurements over time for the same eye at the same site will generally be conducted using a consistent method, thus limiting the impact of heterogeneity on the outcome.
- The flexible inclusion criteria, allowing inclusion of difficult-to-treat patients, and variable treatment schedules as well as treatment decisions based on respective clinical practice guidelines across countries and regions might result in variations in the study outcomes. Thus, the study may have a lower internal validity. However, such variety of data will help shed light on the critical factors that HCPs from different countries consider while making clinically important decisions for diverse patient populations in a real-world setting.
- The data to be captured for this study will be collected from the ophthalmologic sites, and not from any other healthcare providers. Information on non-ocular AEs may therefore not be recorded in the data at the ophthalmologic sites and may be underreported.
- This being an observational study, only the data available from routine clinical practice will be collected; thus, there could be some missing data. This can be minimized by raising queries for any additional information that the site may have, which can be used to complete the essential information regarding the patients and thereby be included in the study. Despite this, some study data may remain missing. The impact of any missing data on the study outcomes will be explored at the analysis and/or reporting stage.

7 PROTECTION OF HUMAN SUBJECTS

7.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research is conducted.

7.2 INFORMED CONSENT

The Roche sample Informed Consent Form will be provided to the sites as required per local regulations. If applicable, it will be provided in a certified translation of the local language. Roche must review and approve any proposed deviations from the Roche's sample Informed Consent Forms, or any alternate Consent Forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission, if applicable. The final Consent Forms approved by the IRB/EC must be provided to the MAH for archiving and health authority submission purposes according to local requirements.

As required per local regulations, the Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before the start of documentation of his or her data in the eCRF. The case history or clinical records for each patient shall document the informed consent process and that the written informed consent was obtained prior to first documentation of this patient's data in the eCRF.

By providing informed consent, the patient confirms that he/she has been informed about the study and agrees to pseudonymous data collection, pooling of data with similar scientific data (if applicable), and the possibility of monitoring activities.

The patient data may be used or shared for the purposes of this study and for research related to retinal indications (nAMD, DME) for which faricimab is approved, common pathways (links) among diseases, the use of faricimab in disease therapy.

Anonymized data will be shared with the medical and scientific community to foster research and support evidence generation. The data elements collected will address different types of research questions through registry-based studies such as SDU studies.

Secondary data use studies (SDU)

The data elements collected will address different types of research questions through SDU studies. An SDU study has a research plan and aims to answer a specific research question with data that have been collected as part of the FaReal dataset. To meet General Data Protection Regulation (GDPR) and local data privacy requirements, researchers will only be given access to anonymized patient data from the global dataset (i.e., patient data pooled from all countries participating in the study).

It is the accountability of the treating physician to ascertain that the patient has understood the information and to obtain written informed consent from each patient participating in the study. As required per local regulations, a copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or site file and must be available for verification by Site Operations Representative at any.

7.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Site Operations Representative in consultation with the Scientific Responsible and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

In addition to the requirements for collecting and reporting all AEs, adverse events of special interest (AESI) and SAEs to the MAH, treating physicians must comply with requirements for AE reporting to the local health authority and IRB/EC.

7.4 CONFIDENTIALITY

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

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

Roche, including affiliates, collaborators, and licensees may use study data labeled with the patient ID numbers. Study data may also be shared with independent researchers or government agencies, but only after personal information that can identify the patient has been removed. Patients' study data may be combined with other patients' data and/or linked to other data collected from the patients. Patients' study data may be used to help better understand why people get diseases, how to best prevent, diagnose and treat diseases, and to develop and deliver access to new medicines, medical devices, and healthcare solutions to advance patient care.

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

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

8 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

8.1 SAFETY REPORTING REQUIREMENTS FOR STUDIED MEDICINAL PRODUCTS

8.1.1 Safety Parameters and Definitions

The reporting requirements in this section apply to all studied medicinal products. For safety reporting requirements of non-studied medicinal products, see Section 8.2.

Safety assessments will consist of monitoring and recording SAEs, non-serious AEs, and AESI, as per standard medical practice. In addition to the definitions below, refer to Appendix 4.3.15 for the ISO adverse event categorization guidelines for the classification of AEs.

8.1.1.1 Adverse Events

According to the International Council for Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation patient administered a

pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Appendix 4.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram, x-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

Note: AEs should be reported listing the underlying cause (if known) of the event as the primary event term (see Appendix 4.3.3).

8.1.1.2 Assessment of Serious Adverse Events (Immediately Reportable to the Marketing Authorization Holder), Non-serious Adverse Events of Special Interest (AESI) and Other Non-serious Adverse Events

8.1.1.2.1 Serious Adverse Events

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient’s ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine
- Is a significant medical event in the physician’s judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) criteria; see Appendix 4); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF (for detailed instructions, see Appendix 4).

SAEs are required to be reported by the treating physician to the MAH immediately (i.e., no more than 24 hours after learning of the event).

8.1.1.2.2 Adverse Events of Special Interest (Immediately Reportable to the Marketing Authorization Holder)

AESI for this study include the following:

- Cases of potential medicine-induced liver injury that include an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Appendix 4).
- Suspected transmission of an infectious agent by the study medicine, as defined below:
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study medicine is suspected.
- Ocular AESI for faricimab are defined as any of the events that meet one of the following criteria:
    - the AE causes a decrease of approximately 30 letters in VA (compared with the last assessment of VA prior to the most recent treatment) lasting more than 1 hour.
    - the AE requires surgical intervention (i.e., conventional surgery, vitrectomy, vitreous tap, or biopsy with intravitreal injection of anti-infective medications, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
    - the AE is associated with severe intraocular inflammation (e.g., endophthalmitis, 4+ anterior chamber cell/flare or 4+ cells/flare in the vitreous).

AESIs are required to be reported by the treating physician to the MAH immediately (i.e., no more than 24 hours after learning of the event).

8.1.1.2.3 Non-Serious Adverse Events other than Adverse Events of Special Interest

All non-serious AEs (in addition to AESI) must be collected according to the appropriate level of MedDRA classification.

8.1.1.3 Serious Health Threat (Immediately Reportable to the MAH)

A serious health threat is defined as a signal from any AE that indicates an imminent risk of death or a serious deterioration in the health of patients, users, or other persons, and that requires prompt remedial action for other patients, users, or other persons. A serious health threat is required to be reported by the treating physician to the MAH

immediately (i.e., no more than 24 hours after learning of the event) are described in Section 8.1.3.1.

8.1.1.4 Exemption of Specific Adverse Events from Collection

Not applicable for this study.

8.1.2 Methods and Timing for Capturing and Assessing Safety Parameters

The physician is accountable for ensuring that all AEs collected as per protocol (see Section 8.1.1.1 for definition) are recorded in the AE section of the eCRF and reported to the MAH in accordance with instructions provided in this section and in Section 8.1.3.

For each AE recorded in the AE section of the eCRF, the physician will assess seriousness (see Section 8.1.1.2), severity (see Appendix 4.1), and causality (see Appendix 4.2).

8.1.2.1 Adverse Event Reporting Period

Qualified HCPs will seek information on AEs at each patient contact. All AEs subject to the collecting and reporting requirements outlined in this protocol, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and in the AE section of the eCRF.

Once the patient is enrolled in the study, AEs will be collected from index date (i.e., date of treatment initiation with faricimab) until the end of his or her observation period. After this period, the HCP is not required to actively monitor patients for AEs; but if the treating HCP becomes aware of any related AEs to any medicinal product, they should be notified to the competent authority in the Member State where the reactions occurred or to the MAH of the suspected medicinal product, but not to both (to avoid duplicate reporting).

8.1.2.2 Procedures for Recording Adverse Events

HCPs should use correct medical terminology/concepts and MedDRA coding when recording AEs in the AE section of the eCRF. Colloquialisms and abbreviations should be avoided.

See Appendix 4 for further specific instructions regarding:

- IVT-related reactions
- Diagnosis versus signs and symptoms
- AEs occurring secondary to other AEs
- Persistent or recurrent AEs
- Abnormal laboratory values
- Abnormal vital sign values
- Abnormal liver function tests
- Deaths
    - All events with an outcome or consequence of death should be classified as SAEs and reported to the MAH immediately. In certain circumstances, however, suspected adverse reactions with fatal outcome may not be subject to expedited reporting (see Section 8.3). All deaths that occur during the

protocol-specified AE reporting period, regardless of relationship to study medicine, must be recorded in the AE section of the eCRF and be immediately reported to the MAH

- Pre-existing medical conditions
- Lack of therapeutic efficacy
- Hospitalization or prolonged hospitalization
- Overdoses, misuses, abuses, off-label use, occupational exposure, or medication error
- Quality defects, falsified medicinal products and product complaints
- Drug interactions

8.1.3 Reporting Requirements from Healthcare Professional to Marketing Authorization Holder

8.1.3.1 Immediate Reporting Requirements from Healthcare Professional to Marketing Authorization Holder

Certain events require immediate reporting to allow the MAH and the regulatory authorities to take appropriate measures to address potential new risks associated with the use of the medicine. The HCP must report such events to the MAH immediately; under no circumstances should reporting take place more than 24 hours after the HCP learns of the event. The following is a list of events that the HCP must report to the MAH within 24 hours after learning of the event, regardless of relationship to study medicine:

- SAEs
- Non-serious AESI
- Pregnancies

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

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

For reports of SAEs and AESI, including follow-up, HCPs should record all case details that can be gathered immediately (i.e., within 24 hours) in the AE page of the eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety by the EDC system.

In the event that the EDC system is temporarily unavailable, please refer to Section 8.1.3.3.

HCPs must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

8.1.3.2 Reporting Requirements for Non-Serious Adverse Events

For all non-serious AEs, including follow-up reports, HCPs must record all case details that can be gathered within 30 calendar days of learning of the event on the AE section of the eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety to allow appropriate reporting to relevant competent authorities.

In the event that the EDC system is temporarily unavailable, please refer to Section 8.1.3.3.

8.1.3.3 If EDC System is Temporarily Unavailable

In the event that the EDC system is temporarily unavailable, a completed paper reporting form and fax coversheet should be faxed/scanned to Roche Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the event) or within 30 calendar days for non-serious AEs if not AESI, using the fax number or email address provided to treating physicians.

Once the system is available again, all information should additionally be entered and submitted via the EDC system.

8.1.3.4 Reporting Requirements for Pregnancies/Breastfeeding

8.1.3.4.1 Pregnancies/Breastfeeding in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the physician if they become pregnant during the study or within 28 days after the last intravitreal injection. A Pregnancy Report should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy) and sent to Roche Drug Safety. Pregnancy should not be recorded in the AE eCRF. The treating physician should discontinue the medicinal product and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until the conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the AE section of the eCRF. In addition, the treating physician will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk should be reported to Roche Drug Safety.

8.1.3.4.2 Pregnancies in Female Partners of Male Patients

Not applicable for this study.

8.1.3.4.3 Abortions

Any abortion should be classified as an SAE (as the MAH considers abortions to be medically significant), recorded in the AE section of the eCRF, and reported to the MAH immediately (i.e., no more than 24 hours after learning of the event; see Section 8.1.3.1).

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

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

8.1.3.4.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to the medicine should be classified as an SAE, recorded in the AE section of the eCRF, and reported to the MAH immediately (i.e., no more than 24 hours after learning of the event; see Section 8.1.3.1).

8.1.4 Follow-Up of Patients after Adverse Events

8.1.4.1 HCP Follow-Up

The HCP should follow each AE until the event has resolved to baseline grade or the event is assessed as stable by the HCP, 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 the studied medicinal product until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented in the AE section of the eCRF and in the patient's medical record to facilitate SDV.

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

8.1.4.2 Marketing Authorization Holder Follow-Up

For all AEs, the MAH or a designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case. AE follow-up should be documented in the AE section of the eCRF.

8.2 SAFETY REPORTING REQUIREMENTS FOR NON-STUDIED PRODUCTS

Although AE information is not being actively solicited for non-studied products, the treating physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a product) that come to their attention to the MAH of the suspected product, or to the concerned competent authorities via the national spontaneous reporting system.

In addition, the following should also be reported if occurring during exposure to a marketed medicinal product, even in the absence of AEs:

- Pregnancy
- Breastfeeding

- Abnormal laboratory findings
- Overdose, abuse, misuse, off-label use, medication error, or occupational exposure
- Reports of lack of efficacy
- Product quality defects and falsified medicinal products
- Data related to a suspected transmission of an infectious agent via a medicinal product
- Drug interactions (including drug/drug, drug/food, drug/device, and drug/alcohol)

When a patient is not exposed to a marketed medicinal product, but the HCP/consumer becomes aware of the potential for a medication error, or an intercepted medication error, this should also be reported.

8.3 REPORTING OF PRODUCT COMPLAINTS WITHOUT ADVERSE EVENTS

Report Roche product complaints without AEs, where Product Complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market, to basel.complaint_manager_pharma@roche.com. Report non-Roche-product complaints as per local regulation.

9 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, Roche is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. Roche will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the treating physician must agree to submit all manuscripts or abstracts to the MAH prior to submission for publication or presentation. This allows Roche to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the treating physician.

In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter studies only in their entirety or by region and not as individual center data. In this case, a coordinating physician will be designated by mutual agreement.

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

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

Specification of Publication Plan

The publication plan for this study will be prepared as a separate document.

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11 APPENDICES

Appendix 1 List of Stand-Alone Documents Not Included in the Protocol

Country appendix, if applicable

Appendix 2 Data Collection Overview (as per Standard of Care)

Data Collection Schedule for FaReal Study

Data Collection[1]	Retrospective Data Collection	Data Collection at Enrollment Visit[7] / Baseline/Index Visit[8]	Data Collected During Prospective Observational Period[9]	
			Month 3, 6, 12 and 24 visits	Any other routine visits
Informed consent (as required per local regulations)		x		
Eligibility[2]		x		
Demographic characteristics (year of birth, sex, smoking status)		x		
Disease information (including type of disease and date of diagnosis, disease characteristics)[3]		x	x	x
Medical and surgical history (ocular, by eye where applicable)[3]		x		
Prior treatment and management, by eye (treatment details, details of other procedures)[3]	x			
Treatment and management (by eye) during study period (treatment details, treatment regimen/management plan including monitoring and injection visit intervals, planned and actual visit dates and reasons for delays if applicable, treatment switch and treatment discontinuation/termination)[3]		x	x	x
Concomitant medications (ocular)		x	x	x

VA (Method of VA Assessment - Scale and Type of Correction and other assessments)[4]		**x**	**x**	**x**
Imaging assessments (type, machine used, and the results) by eye, as per routine clinical practice (during visits for the retinal indications)[5]		**x**	**x**	**x**
Safety events (all ocular and non-ocular AEs)[6]		**x**	**x**	**x**

AE = adverse event, SAE = serious adverse event, VA = visual acuity.

1. Variables obtained according to routine clinical practice. No additional diagnostic or monitoring procedures shall be applied to the patients.
2. Signed informed consent must be obtained before any data collection.
3. Images taken as per routine clinical practice for the specified indications of interest will not be collected for this study.
4. The following will be collected from index date (i.e., date of treatment initiation with faricimab) until the end of the observational period: SAEs and non-serious AEs (including severity of all AEs and AEs of special interest).
5. Enrollment is the date the patient signs the Informed Consent Form to participate in this study.
6. Baseline is the date when a patient initiates treatment with faricimab in at least one eye. Index date is the date when treatment is initiated at the eye-level. If both eyes are treated with faricimab and the treatment start dates are different, each start date will be used as index date for the respective eye.
7. The prospective observational period starts one day post-enrollment.
8. Baseline is the date when a patient initiates treatment with faricimab in at least one eye. Index date is the date when treatment is initiated at the eye-level. If both eyes are treated with faricimab and the treatment start dates are different, each start date will be used as index date for the respective eye.
9. The prospective observational period starts one day post-enrollment.

Appendix 3 Error! Reference source not found.Conversion Table for Visual Acuity

Snellen acuity and Logarithm of the Minimum Angle of Resolution (LogMAR) acuity score will be converted to approximate Early Treatment Diabetic Retinopathy Study (ETDRS) letter score (Gregori et al.,2010; Holladay, 1997). The general formulas are:

- Approximate ETDRS (letter score) = 85 + 50 × log (Snellen fraction); or:
- Approximate ETDRS (letter score) = 85 – 50 × LogMAR.

Table 1. Conversion of Visual Acuity Measurements Between Snellen Fraction, logMAR, ETDRS Letter Scores, ETDRS Equivalent Snellen Fraction, and Approximate ETDRS Letter Scores

Snellen Fraction	ETDRS Equivalent Snellen Fraction	logMAR*	ETDRS Letter Score	Approximate ETDRS Letter Score†
1/200 (CF)		2.30		0
2/200		2.00		2
	20/800	1.60	5	5
6/200		1.52		9
	20/640	1.51	10	10
	20/500	1.40	15	15
20/400	20/400	1.30	20	20
	20/320	1.20	25	25
20/300		1.18		26
	20/252	1.10	30	30
20/250		1.10		30
20/200	20/200	1.00	35	35
	20/160	0.90	40	40
	20/125	0.80	45	45
20/100	20/100	0.70	50	50
20/80	20/80	0.60	55	55
20/70		0.54		58
	20/63	0.50	60	60
20/60		0.48		61
20/50	20/50	0.40	65	65
20/40	20/40	0.30	70	70
	20/32	0.20	75	75
20/30		0.18		76
	20/25	0.10	80	80
20/20	20/20	0.00	85	85
	20/16	−0.10	90	90
20/15		−0.12		91
	20/13	−0.19	95	95
	20/10	−0.30	100	100

*Snellen converted to logMAR = −1 × log(Snellen fraction).
†Snellen converted to approximate ETDRS letters = 85 + 50 × log(Snellen fraction), which may be rounded to the nearest letter.
CF, counting fingers.

Holladay TJ. Proper Method for calculating Average Visual Acuity. Journal of Refractive Surgery 1997;13:388-91.

Gregori N Z, Feuer, W., & Rosenfeld, P. (2010). Novel Method for Analyzing Snellen Visual Acuity Measurements. Retina. The Journal of Retinal and Vitreous Diseases 2010;30:1046-49.

The following approximate conversion will be used for off-chart values (Mollan et al., 2021):

Off-chart Categories	Snellen feet	Snellen meter	Snellen decimal	LogMAR	ETDRS
NLP	20/20000	6/6000	0.001	3	0
LP	20/10000	6/3000	0.002	2.7	0
HM	20/4000	6/1200	0.005	2.3	0
CF	20/2000	6/600	0.01	1.9	2

Abbreviations:
CF= counting fingers, ETDRS= Early Treatment Diabetic Retinopathy Study, HM= hand movement, LogMAR= Logarithm of the Minimum Angle of Resolution, LP= light perception, NLP= no light perception.

Mollan SP, Fu DJ, Chuo C, et al. Predicting the immediate impact of national lockdown on neovascular age-related macular degeneration and associated visual morbidity: an INSIGHT Health Data Research Hub for Eye Health report. British Journal of Ophthalmology Published Online First: 13 September 2021. doi: 10.1136/bjophthalmol-2021-319383

Appendix 4 Methods for Assessing and Recording Adverse Events

Appendix 4.1 Assessment of Severity of Adverse Events

The table below provides guidance for assessing adverse event (AE) severity.

Adverse Event Severity Grading Scale

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

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (SAE) (see Section 8.1.1.2).

Appendix 4.2 Assessment of Causality of Adverse Events

Physicians should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study medicine, indicating “yes” or “no” accordingly. Refer to Appendix 4.3.15 ISO AE categorization guidelines for the classification of AEs.

The following guidance should be taken into consideration:

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

Appendix 4.3 Procedures for Recording Adverse Events

Appendix 4.3.1 Injection Reactions

AEs that occur during or within 24 hours after studied medicinal product administration should be captured as individual signs and symptoms in the AE section of the electronic case report form (eCRF) rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of anaphylactic reaction).

Appendix 4.3.2 Diagnosis versus Signs and Symptoms

For AEs, other than injection reactions (see Appendix 4.3.1), a diagnosis (if known) should be recorded in the AE section of the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the AE section of the eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Appendix 4.3.3 Adverse Events Occurring Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all 3 events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately in the AE section of the eCRF if it is unclear as to whether the events are associated.

Appendix 4.3.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once in the AE section of the eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded in the AE section of the eCRF. If the event becomes

serious, it should be reported to the MAH immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 8.1.3.1 for reporting instructions). The AE section of the eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between patient evaluation timepoints and recurs subsequently. Each recurrence of an AE should be recorded separately in the AE section of the eCRF.

Appendix 4.3.5 Abnormal Laboratory Values

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

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

It is the physician’s responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded in the AE section of the eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., “elevated potassium,” as opposed to “abnormal potassium”). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once in the AE section of the eCRF (see Appendix 4.3.4 for details on recording persistent AEs).

Appendix 4.3.6 Abnormal Vital Sign Values

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

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

- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the physician's judgment

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once in the AE section of the eCRF (see Appendix 4.3.4 for details on recording persistent AEs).

Appendix 4.3.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × the ULN) in combination with either an elevated total bilirubin (> 2 × the ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, physicians must report the occurrence of either of the following as an AE:

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded in the AE section of the eCRF (see Appendix 4.3.5) and reported to the MAH immediately (i.e., no more than 24 hours after learning of the event) either as an SAE or a non-serious AE of special interest (see Section 8.1.3.1).

Appendix 4.3.8 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 8.1.2.1), regardless of relationship to study medicine, must be recorded in the AE section of the eCRF and immediately reported to the MAH (see Section 8.1.3.1).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE section of the eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the AE section of the eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Appendix 4.3.9 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at baseline for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions in the eCRF.

A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events in the AE section of the eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

Appendix 4.3.10 Lack of Therapeutic Efficacy

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on review of optical coherence tomography (OCT) results (spectral-domain optical coherence tomography angiography (SD-OCT) or swept-source optical coherence tomography (SS-OCT)). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE. This exception from reporting includes events of disease progression with a fatal outcome which are clearly attributable to disease progression.

Appendix 4.3.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 8.1.1.2.1), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care
- Hospitalization for a pre-existing condition provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
    - The patient has not suffered an AE
    - Additional conditions
- Hospitalization solely due to progression of the underlying cancer.

The following hospitalization scenarios are not considered to be SAEs but should be reported as AEs instead:

Hospitalization that was necessary because of the patient’s requirement for outpatient care outside of the normal outpatient clinic operating hours.

Appendix 4.3.12 Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error

Any overdose, misuse, abuse, off-label use, occupational exposure, medication error (including intercepted or potential), or any other incorrect administration of medicine under observation should be noted in the Drug Administration section of the eCRF. Any overdose, abuse, misuse, inadvertent/erroneous administration, medication error (including intercepted or potential), or occupational exposure reports must be forwarded to the MAH with or without an AE.

Reports with or without an AE should be forwarded to the MAH as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the MAH immediately (i.e., no more than 24 hours after learning of the event, see Section 8.1.3.1).

For the purpose of reporting cases of suspected adverse reactions, an occupational exposure to a medicine means an exposure to a medicine as a result of one's professional or non-professional occupation.

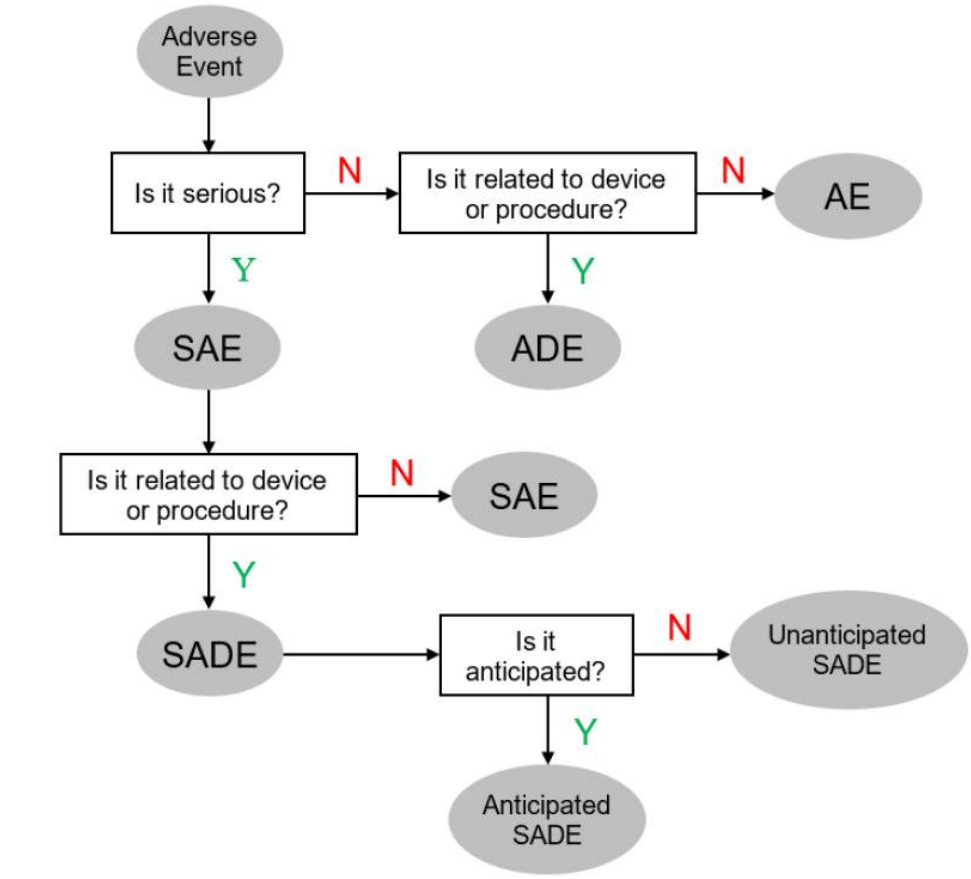
Appendix 4.3.13 Quality Defects, Falsified Products and Products Complaints

Reports of suspected or confirmed falsified product or quality defect of a product, with or without an associated AE, should be forwarded to the MAH as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the MAH immediately (i.e., no more than 24 hours after learning of the event, see Section 8.1.3.1).

Appendix 4.3.14 Drug Interactions

Reports of suspected or confirmed drug interactions, including drug/drug, drug/food, drug/device, and drug/alcohol, should be forwarded to the MAH as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the MAH immediately (i.e., no more than 24 hours after learning of the event, see Section 8.1.3.1).

Appendix 4.3.15 International Organization for Standardization (ISO) Adverse Event Categorization Guidelines



ADE = adverse device effect; AE = adverse event; N = no; SADE = serious adverse device effect; SAE = serious adverse event; Y = yes.

Reference: International Organization for Standardization. (2020). Clinical investigation of medical devices for human subjects – Good clinical practice (ISO Standard No. 14155:2020). https://www.iso.org/standard/71690.html

Appendix 5 Definition of Different Types of Treatment Regimens

- Fixed regimens - patients are treated in prespecified treatment regimen the whole duration of the treatment. (1,2)

- PRN-type regimens - patients are only treated on disease reactivation. The need for retreatment is typically determined at monthly assessment visits.(1,2) (Lanzetta et al., 2017; Mantel et al., 2015)

- Treat-and-Extend (T&E) regimens - patients usually begin the treatment with prespecified loading/initiation phase (in faricimab it refers to 4 monthly initiation doses). Subsequently patients are treated at intervals based on disease activity (in nAMD for faricimab the intervals range from every 8 weeks to every 16 weeks based on disease activity assessments at weeks 20 and 24). The length of fixed intervals can change during the treatment according to disease activity. (Khanani et al., 2021)

- Personalized Treatment interval (PTI) regimens - patients usually begin the treatment with prespecified loading/initiation phase (in faricimab it refers to 4 monthly initiation doses). Subsequently patients are treated at intervals based on disease activity (in DME for faricimab the intervals can be adjusted by 4-week intervals up to every 16 weeks based on disease activity assessments). The length of intervals can change during the treatment according to disease activity. (Eter et al., 2022)

- Observe and Plan (O&P) regimens - the regimen starts with treatment initiation, then measures the individual injection-recurrence interval, and finally applies a slightly shorter interval in a planned series of injections without intermediate monitoring visits. Over time, the interval is adjusted according to the results in periodical monitoring visits. (Parvin et al., 2017)