Document Type:	Statistical Analysis Plan
Official Title:	Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of Aflibercept 8 mg in Macular Edema Secondary to Retinal Vein Occlusion
NCT Number:	NCT05850520
Document Date:	21 NOV 2024

Title Page

Protocol Title: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of Aflibercept 8 mg in Macular Edema Secondary to Retinal Vein Occlusion

Protocol Number: 22153

Compound Number: BAY 86-5321/aflibercept

Short Title: Efficacy and Safety of High Dose Aflibercept in Macular Edema Secondary to Retinal Vein Occlusion

Acronym: QUASAR

Sponsor Name: Bayer AG

Legal Registered Address: Bayer AG, 51368 Leverkusen, Germany

Regulatory Agency Identifier Number(s):

Investigational New Drug (IND): 12462 (Regeneron Pharmaceuticals, Inc.)

EU-CT number: 2022-502174-16-00

Date: 21 NOV 2024

Version: 2.0

Statistical Analysis Plan template version: 4.0

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.
The approval of the Statistical Analysis Plan is documented in a separate signature document.

Table of Contents

Tables of Tables

Tables of Figures

Version History

This Statistical Analysis Plan (SAP) for study 22153 is based on the protocol Version 1.0 dated 07 FEB 2023.

SAP Version	Date	Change	Rationale
1	15 01 2024	Not Applicable	Original version
2	21 11 2024	- Section 1.1: updated population attribute definition of both estimands. - Section 1.1: updated table with inclusion of column including supplementary estimand 2 - Section 4.1: minor editorial updates - Section 4.1.2.1: Handling of missing data and rules for imputing partial or missing start and end dates for medications and adverse events updated.	More details and improvements added; Updates made to align after

		- Section 4.1.3: Corrective stratification in analysis included to account for stratification errors and adjustments based on correct stratification categories, including the use of reading center data for RVO type - Section 4.1.7: Minor edits made to the prohibited therapies list. - Section 4.1.8: Update of the evaluation and classification of the imaging data, with specific rules for evaluating intraretinal fluid, subretinal fluid, retinal thickness, and fluorescein angiography assessments. - Section 4.2.2: Added description that least-square mean change will be calculated with categorical covariates weighted as observed; minor updates to the description of the descriptive summary tables. - Table 4.2 Updated to change days from +10 to +5. - Section 4.2.3.1: Editorial updates in the description of the analysis as well as the SAS code; update of the estimation approach: single linear regression model including the treatment group variable with three levels instead of two pairwise regression models; added expression for the population-level summary. - Section 4.3.2.: Minor edits for description of summary statistics. - Section 4.3.2.1: Added clarification on handling the composite strategy for the ICE "premature discontinuation of study intervention due to treatment-related AEs," where the number of injections will be set to 9. - Section 4.3.2.7: Updated the covariate description - Section 4.3.2.8: Updated the statistical model used to account for the correct data collected. - Sections 4.3.2.9/10/11: Minor editorial changes to reflects tables are provided already in Section 6.1.3. - Section 4.3.2.12: Update definition for race subgroup analysis. - Section 4.4: Minor editorial changes. - Section 4.4.4: Added clarification regarding the exclusion of participants with no fluid at baseline, missing baseline information, or "undetermined" baseline fluid status from the analysis. - Section 4.5.1: Minor editorial changes. - Section 4.5.2.2: Minor editorial changes and removal of shift tables from the text.	review of TLF shells

		- Section 4.6.1: Added Baseline CST as subgroup and updated definition of the Race subgroup. - Section 4.6.2: Added clarification for pooling the two 8mg arms and updated the analysis for subgroup by RVO type to include descriptive summary statistics for additional secondary endpoints. - Section 4.8: Added clarification about the change for the population attribute in the estimand definition from "participants" to "patients" for alignment with the target population - Section 6.1: Minor editorial changes. - Section 6.1.1: Minor editorial changes. - Section 6.1.3.2: Minor editorial changes. - Section 6.1.4: Removed the section on Kaplan-Meier analyses for time-to-treatment discontinuation and intake of prohibited medication and additional minor editorial changes - Section 6.5: Minor editorial changes and removed the reference to the secondary estimand strategy and deleted the associated Table 6-13. - Section 6.6: Added new section on identification of prohibited medication.	

List of Abbreviations

Abbreviation	Description
ADE	adverse device effect
AE	adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
APAC	Asia-Pacific
APTC	anti-platelet trialists' collaboration
ATE	arterial thromboembolic events
AxMP	auxiliary medicinal product
BCVA	best-corrected visual acuity
BMI	body mass index
BRVO	branch retinal vein occlusion
CE	conformité européenne
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CRVO	central retinal vein occlusion
CST	central subfield thickness
DL-AAA	DL-α-aminoadipic acid
DMC	data monitoring committee
DME	diabetic macular edema
DRM	dose regimen modification
eCRF	electronic case report form
ECG	electrocardiogram
EoS	end of study
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiography
FAS	Full analysis set
FBR	future biomedical research
FDA	Food and Drug Administration
FP	fundus photography
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormonal replacement therapy
HRVO	hemiretinal vein occlusion
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IOP	intraocular pressure
IRF	intraretinal fluid
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine hormone releasing system
IVT	Intravitreal(ly)

Abbreviation	Description
LLOQ	Lower Limit of Quantification
MAR	Missing at Random
MDR	Medical Device Regulation
MMRM	mixed model for repeated measurements
nAMD	neovascular age-related macular degeneration
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
NI	non-inferiority
NVD	Neovascularization of the optic disc
OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography
PCR	polymerase chain reaction
PCSV	potentially clinically significant value
PlGF	placental growth factor
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
PT	preferred term
QoL	quality of life
Q4W	every 4 weeks
Q8W	every 8 weeks
RVO	retinal vein occlusion
SADE	serious adverse device effects
SAE	serious adverse event
SAF	Safety analysis set
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD-OCT	spectral domain optical coherence tomography
SDLL	Source Data Location List
SoA	schedule of activities
SOC	system organ class
SRF	sub-retinal fluid
SUSAR	suspected unexpected serious adverse reactions
T&E	treat and extend
TEAE	treatment-emergent adverse event
TMF	trial master file
ULOQ	Upper Limit of Quantification
US	United States
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WOCBP	woman (women) of childbearing potential
YAG	yttrium-aluminum-garnet

1. Introduction

Retinal vein occlusion (RVO) is one of the most frequent causes of visual loss from diseases affecting the retinal vessels of the eye (Rogers_2010). The 2 major RVO categories are central RVO (CRVO), with blockage of the single, central vein draining blood from the retina, and branch RVO (BRVO), where one or more of the branches of the central retinal vein are occluded. A less frequent subtype is hemiretinal vein occlusion (HRVO), where branches from the superior or inferior hemisphere are occluded, sharing characteristics with both CRVO and BRVO. RVO results in impaired venous drainage from the eye and retinal non-perfusion, leading to increased vascular endothelial growth factor (VEGF) expression. High VEGF levels can lead to macular edema, retinal hemorrhage, and neovascularization. Patients with central macular edema secondary to RVO lose visual acuity, and the visual prognosis, if untreated, is often poor (Holz_2013).

Intravitreal (IVT) anti-VEGF agents, including aflibercept 2 mg, have become the standard of care for the treatment of macular edema secondary to RVO, with a recommended dose of once every 4 weeks (Q4W). The goal of the current study is to test a IVT formulation with a higher concentration of aflibercept, aiming to increase the total amount of anti-VEGF therapeutic protein administered. This increased concentration has the potential to increase the drug's biological duration of action and provide greater efficacy. Additionally, it could reduce patient burden by extending the interval between IVT injections and reducing the overall number of doses. This reduction in treatment burden is particularly important for this population, many of whom are still working (United States Prescribing Information - USPI). The development candidate, aflibercept 8 mg (with a concentration of 114.3 mg/mL), targets IVT delivery of increased molar concentrations of VEGF inhibitors relative to the formulation currently approved for Eylea® 2 mg (USPI).

Aflibercept 8 mg has been proven to be effective and safe in adult patients with DME and nAMD in Phase 2/3 PHOTON and Phase 3 PULSAR studies, respectively. In DME, 91% to 89% of patients were able to maintain 12-16 week treatment intervals with the 8 mg formulation while achieving similar visual acuity results as the 2 mg formulation through Week 48. In nAMD, 79% to 77% of patients were able to maintain 12-16 week treatment intervals with the 8 mg formulation and achieved similar visual acuity results as the 2 mg formulation through Week 48. The safety profile of aflibercept 8 mg in both studies was consistent with the known safety profile of aflibercept 2 mg and no new safety signals were observed.

Study 22153 will investigate the efficacy and safety of aflibercept 8 mg in patients with RVO with the intent of achieving non-inferior BCVA gains from baseline, while extending the dosing interval to reduce the number of injections and potentially improving visual and/or anatomic outcomes for aflibercept 8 mg vs. the currently approved aflibercept 2 mg dose regimen as well as maintaining the same safety profile as aflibercept 2 mg.

This Statistical Analysis Plan (SAP) outlines the specific details of the required statistical analyses to be conducted at Week 36 and at Week 64, which corresponds to the end-of-study (EOS). No interim statistical analysis in the sense of a group-sequential or adaptive design will be performed. However, once all participants have completed Week 36 or discontinued prematurely, an analysis of all available data up to and including Week 36, including the primary estimand analysis, will be conducted using the database that has been locked after all subjects have completed the Week 36 visit (or discontinued). Subsequently, a final analysis of

all data, including the secondary estimand analysis, will be conducted after all participants have completed the study at Week 64 (or prematurely discontinued). The Week 36 endpoints will not be formally re-analyzed at the timepoint of the Week 64 analysis. The summary tables, figures, and listings (TFLs) that will be included in the Clinical Study Report (CSR) will be defined in a separate document. This SAP is based on the clinical study protocol version 1.0, dated February 7, 2023. All references to the study protocol henceforth refer to that version of the protocol.

1.1 Objectives, Endpoints, and Estimands

Table 1-1: Objectives and endpoints

Objectives	Endpoints
Primary objective: • To determine if treatment with aflibercept 8 mg Q8W provides non-inferior BCVA change compared to aflibercept 2 mg Q4W	**Primary Endpoint:** • Change from baseline in BCVA measured by the ETDRS letter score at Week 36
Secondary objectives – Efficacy	
• To determine if treatment with aflibercept 8 mg Q8W requires less injections compared to aflibercept 2 mg Q4W	**Key Secondary Endpoint** • Number of active injections from baseline to Week 64[1] **Secondary Endpoint** • Number of active injections from baseline to Week 36
• To determine the effect of aflibercept 8 mg Q8W compared to aflibercept 2 mg Q4W on other visual and anatomic measures of response	**Secondary Endpoints:** • Change from baseline in BCVA measured by the ETDRS letter score at Week 44[2] • Change from baseline in BCVA measured by the ETDRS letter score at Week 64 • Participant gaining at least 15 letters in BCVA from baseline at Weeks 36 and 64 • Participant achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Weeks 36 and 64 • Participant having no IRF and no SRF in the center subfield at Weeks 36 and 64 • Change from baseline in CST at Weeks 36 and 64
• To assess the efficacy of aflibercept 8 mg Q8W compared to aflibercept 2 mg aflibercept Q4W on vision-related QoL	• Change from baseline in NEI-VFQ-25 total score at Weeks 36 and 64
Secondary objective - Safety	
• To evaluate the safety of aflibercept 8 mg Q8W compared to aflibercept 2 mg aflibercept Q4W	• Occurrence of TEAEs and SAEs through Weeks 36 and 64
Secondary objectives - Other	
• To evaluate duration of effect of aflibercept 8 mg Q8W compared to aflibercept 2 mg aflibercept Q4W	• Participants dosed only Q8W through Week 36 in the 8 mg Q8W group • Participant having last treatment interval ≥12 or of 16 weeks at Week 64 • Participant having next intended interval ≥12, ≥16 or of 20 weeks at Week 64

Objectives	Endpoints
• To evaluate the PK of aflibercept 8 mg Q8W compared to aflibercept 2 mg aflibercept Q4W	• Systemic exposure to aflibercept as assessed by plasma concentrations of free, adjusted bound and total aflibercept from baseline through Weeks 36 and 64
Exploratory objectives	
• To determine the effect of aflibercept 8 mg Q8W compared to aflibercept 2 mg Q4W on further visual and anatomic measures of response	• Change from baseline in BCVA measured by the ETDRS letter score at each visit • Participant with vision changes of at least 5, 10, or 15 letters in BCVA from baseline at each visit • Participant with no IRF and no SRF in the center subfield at each visit • Time to fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield) • Participant having sustained fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield) • Change in area of retinal ischemia at Weeks 36 and 64 • Change in the area of fluorescein leakage at Weeks 36 and 64
• To study molecular drivers of RVO or related diseases, clinical efficacy of aflibercept, and affected molecular pathways	• Evaluation of clinical efficacy parameters by repertoire or frequency of genetic alterations (genomics substudy) • Treatment related changes in circulating biomarkers (FBR)

AE=adverse event, BCVA=best-corrected visual acuity, CST=central subfield thickness, ETDRS=early treatment diabetic retinopathy study, FBR=future biomedical research, IRF=intraretinal fluid, NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25, PK=pharmacokinetics, QoL=quality of life, Q4W=every 4 weeks, Q8W=every 8 weeks, RVO=retinal vein occlusion, SAE=serious adverse event, SRF=sub-retinal fluid, TEAE=treatment-emergent adverse event

[1] Where premature treatment discontinue due to treatment related AE is considered as treatment-failure and the number of active injections from baseline to Week 64 is set to an unfavorable outcome (equal to 16, the maximum value).

[2] For the 8mg/5 and 2 mg groups only.

Primary Estimand

The primary estimand for the primary objective is described by the following attributes:

- Population: Adult patients with treatment-naïve macular edema secondary to RVO
- Endpoint: Change from baseline in BCVA measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 36
- Treatment condition:
  - Aflibercept 8 mg administered with 3 initial every 4 weeks (Q4W) initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response (8mg/3)
  - Aflibercept 8 mg administered with 5 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response (8mg/5)
  - Aflibercept 2 mg administered Q4W until Week 32, followed by adjustment of treatment intervals according to treatment response (2mg)

A delayed active injection resulting in an injection interval up to 4 weeks longer than planned is considered to be in line with the treatment regimen of interest.

- Intercurrent events and strategies:
  - Premature treatment discontinuation – addressed by the hypothetical strategy (had participants continued treatment until Week 36)
  - Use of prohibited medication – addressed by the hypothetical strategy (had prohibited medications not been taken)
  - Missed study intervention:
    - Missed active injection resulting in an injection interval up to 4 weeks longer than planned: treatment policy strategy (the effect of a missed active injection will be included in the estimate of the treatment effect)
    - Missed active injection resulting in an injection interval more than 4 weeks longer than planned: hypothetical strategy (had injection not been missed or delayed by less than 4 weeks)
- Population-level summary: Difference in mean change from baseline to Week 36 in BCVA between each aflibercept 8 mg group and the aflibercept 2 mg group

Rationale for estimand: A hypothetical strategy is mainly used to address intercurrent events (especially premature treatment discontinuation) since the aim is to show non-inferiority (NI) of aflibercept 8 mg vs. aflibercept 2 mg and using a hypothetical strategy would be a conservative approach since it prevents the treatment arms from appearing more similar. See Table 4-2 for details on the analysis approach for hypothetical strategy. For the intercurrent event "missed study intervention", a missed sham injection has no impact on the endpoint as no active treatment was missed and thus it is not considered as additional intercurrent event. The impact of other potential intercurrent events is expected to be negligible.

Supplementary Estimand for the primary estimand.

The supplementary estimands for the primary objective is defined in Table 1-2 in addition to the primary estimand.

Table 1-2: Supplementary Estimand for the Primary Objective

Primary Objective: To determine if treatment with aflibercept 8 mg Q8W provides non-inferior BCVA change compared to aflibercept 2 mg Q4W			
	Primary Estimand	**Supplementary Estimand 1**	**Supplementary Estimand 2**
Population	Adult patients with treatment-naïve macular edema secondary to RVO.	Same as primary	Same as primary
Treatment condition	• Aflibercept 8 mg administered with 3 initial every 4 weeks (Q4W) initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response • Aflibercept 8 mg administered with 5 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response • Aflibercept 2 mg administered Q4W until Week 32, followed by adjustment of treatment intervals according to treatment response	Same as primary	Same as primary
Variable (endpoint)	Change from baseline in BCVA measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 36	Same as primary	Same as primary
Population-level summary	Difference in mean change from baseline to Week 36 in BCVA between each aflibercept 8 mg group and the aflibercept 2 mg group	Same as primary	Same as primary
Intercurrent events and strategies	• Premature treatment discontinuation – addressed by the hypothetical strategy (had participants continued treatment until Week 36)	• Premature treatment discontinuation – addressed by the treatment policy strategy (the estimated treatment effect	• Premature treatment discontinuation o Due to death: composite strategy (treatment

Primary Objective: To determine if treatment with aflibercept 8 mg Q8W provides non-inferior BCVA change compared to aflibercept 2 mg Q4W			
	Primary Estimand	**Supplementary Estimand 1**	**Supplementary Estimand 2**
	• Use of prohibited medication – addressed by the <u>hypothetical strategy</u> (had prohibited medications not been taken) • Missed study intervention: ○ Missed active injection resulting in an injection interval up to 4 weeks longer than planned: <u>treatment policy strategy</u> (the effect of a missed active injection will be included in the estimate of the treatment effect) ○ Missed active injection resulting in an injection interval more than 4 weeks longer than planned: <u>hypothetical strategy</u> (had injection not been missed or delayed by less than 4 weeks)	will consider the impact of early discontinuation of treatment) • Use of prohibited medication – addressed by the <u>treatment policy strategy</u> (effect of prohibited medications will be included in the estimate of the treatment effect) • Missed study intervention: ○ Missed active injection resulting in an injection interval up to 4 weeks longer than planned: <u>treatment policy strategy</u> ○ Missed active injection resulting in an injection interval more than 4 weeks longer than planned: <u>treatment policy strategy</u> (the effect of missed active injection will be included in the estimate of the treatment effect)	discontinuation due to death is indicative of non-response) ○ For any other reason than death: <u>treatment policy strategy</u> • Use of prohibited medication – addressed by the <u>composite strategy</u> (intake of prohibited medication is indicative of non-response) • Missed study intervention: ○ Same as Supplementary Estimand 1

Secondary Estimand

The secondary estimand for the secondary objective "To determine if treatment with aflibercept 8 mg Q8W requires less injections compared to aflibercept 2 mg Q4W" is described by the following attributes:

- Population: Adult patients with treatment-naïve macular edema secondary to RVO
- Endpoint: Number of active injections from baseline to Week 64 where premature treatment discontinuations due to treatment related AE is considered as treatment-failure and the number of injections is set to an unfavorable outcome (equal to 16, the maximum value)
- Treatment condition:
  - Aflibercept 8 mg administered with 3 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response
  - Aflibercept 8 mg administered with 5 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response
  - Aflibercept 2 mg administered Q4W until Week 32, followed by adjustment of treatment intervals according to treatment response

  The minimum treatment interval is 4 weeks while the study duration allows the maximum treatment interval to be 16 weeks. Imperfect adherence other than premature treatment discontinuation is considered as part of the treatment.
- Intercurrent events and strategies:
  - Premature treatment discontinuation
    - Due to lack-of-efficacy: Hypothetical strategy (had participants continued treatment until Week 64)
    - Due to treatment related AEs: Composite strategy (addressed in the endpoint definition)
    - Due to treatment unrelated AEs and other reasons: Hypothetical strategy (had participants continued treatment until Week 64)
  - Missed study intervention – addressed by treatment policy strategy (the effect of a missed active injection will be included in the estimate of the treatment effect)
- Population-level summary: Difference in mean number of active injections up to Week 64 between each aflibercept 8 mg group and the aflibercept 2 mg group

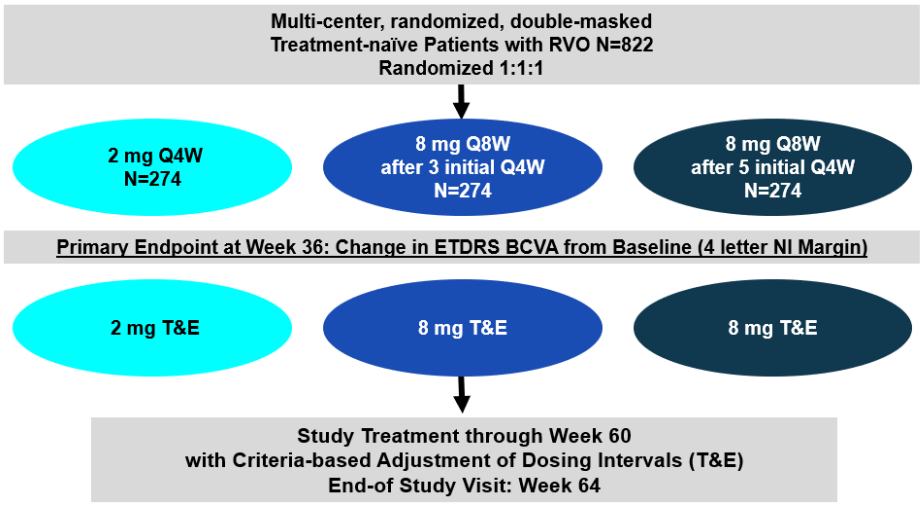
Rationale for estimand: Premature discontinuation due to treatment related AE; usually these participants would stop treatment. However, this would make it appear as if these participants had a reduced burden with respect to the number of injections. To mitigate this and to assign a penalty (since this is regarded as treatment failure) an unfavorable outcome equal to the maximum possible (i.e., 16 injections) is assigned using the composite strategy. Premature discontinuation due to lack-of-efficacy is handled by the hypothetical strategy , as describe in Section 4.3.1.3, assuming that these participants would have continued study treatment with the maximum number of active injections possible with shortening of treatment interval in 4-week decrements (i.e., assuming they would meet the dose regimen modification (DRM) criteria for shortening at every dosing visit. For treatment unrelated AEs it is assumed that those participants could have continued in the study otherwise and behave similar to other

participants in the study arm and hence addressed by the hypothetical strategy. Missed study intervention is regarded as part of clinical practice and hence addressed by the treatment policy strategy. The impact of other potential intercurrent events is expected to be negligible.

1.2 Study Design

As show in Figure 1–1, this is a Phase 3, multi-center, randomized, double-masked, active-controlled clinical study to assess the efficacy and safety of high dose (8 mg) aflibercept compared to 2 mg aflibercept (both administered IVT) in participants with treatment-naïve macular edema secondary to RVO.

Figure 1–1: Study Design



BCVA=Best-corrected Visual Acuity, ETDRS=Early Treatment of Diabetic Retinopathy Study, NI=non-inferiority, Q4W=every 4 weeks, Q8W=every 8 weeks, RVO=retinal vein occlusion, T&E=treat and extend

Participants will be randomized in a 1:1:1 ratio to:

- Aflibercept 8 mg every 8 weeks (Q8W) after 3 initial Q4W initiation doses group (8 mg/3)
- Aflibercept 8 mg Q8W after 5 initial Q4W initiation doses group (8 mg/5)
- Aflibercept 2 mg Q4W group (2 mg)

The study consists of a screening/baseline period, a treatment period with a duration of 60 weeks, and an end of study (EoS) visit at Week 64. Details of the dosing schedule are shown in Figure 1–2. No study intervention will be administered at the end of study visit at Week 64.

The primary analysis will be performed at Week 36 once all participants have either completed this timepoint or discontinued prematurely. This analysis will not be repeated at Week 64. The final analysis will be conducted at Week 64, once all participants have either completed the study or discontinued prematurely. The analysis of the Week 36 efficacy endpoints will not be repeated at Week 64. The databases and analyses at Week 36 will only include study intervention information up to the visit prior to Week 36. For the Week 36

analysis, only data assessed prior to the study intervention will be part of the database/analyses. Further details are provided in a separate document "Data Cut-Off Specifications".

Figure 1–2: Dosing Schedule

Year 1	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36 PE	Wk 40	Wk 44 SE[1]	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64 KSE
AFL 2 mg	X	X	X	X	X	X	X	X	X	T&E →							
AFL 8 mg/3	X	X	X	O	X	O[2]	X	O[2]	X	T&E →							
AFL 8 mg/5	X	X	X	X	X	O	X	O[2]	X	O[2]	X	T&E →					

DRM Criteria

Shortening Criteria:
- BCVA loss >5 letters from reference visit, AND
- >50 µm increase in CST from reference visit

Interval shortening possible from W16 for 8 mg/3, W24 for 8 mg/5, and W40 for 2mg

Reference is W12 for 8 mg/3, W20 for 8 mg/5 and 2 mg

Extension Criteria:
- BCVA loss <5 letters from reference visit, AND
- CST thickness <320 µm including Bruch's membrane / <300 µm excluding Bruch's membrane

Interval extension possible from W32 for 8 mg/3, W40 for 8 mg/5 and W32 for 2 mg

Reference is W12 for 8 mg/3, W20 for 8 mg/5 and 2 mg

AFL=aflibercept, BCVA=best-corrected visual acuity, CST=central subfield thickness, DRM=dose regimen modification, KSE=key secondary endpoint, O=sham injection visit, PE=primary endpoint, SE=secondary endpoint, SD-OCT=spectral domain optical coherence tomography, T&E=treat and extend, Wk=week, X=active injection visit, -=no injection, 8 mg/3=8 mg Q8W after 3 initial Q4W doses, 8 mg/5=8 mg Q8W after 5 initial Q4W doses.
[1]=Secondary endpoint BCVA change from baseline to Week 44 for 2 mg and 8 mg/5 groups.
[2]=Participants meeting interval shortening criteria at any dosing visit starting from Week 16 for 8 mg/3, Week 24 for 8 mg/5 or Week 40 for 2 mg have their dosing interval shortened by 4 weeks. Interval extension is possible from Week 32 for 8 mg/3, from Week 40 for 8 mg/5, and from Week 32 for 2 mg depending on DRM.

2. Statistical Hypotheses

The one-sided test hypotheses in relation to the primary and two-sided test hypotheses in relation to the secondary estimands, are described according to the fixed hierarchical order planned for their testing.

1. The first test problem (related to the primary estimand) involves the non-inferiority testing of 8 mg 5 loads vs 2mg:

   Null hypothesis H_{01}: $\mu_{1.5} \leq \mu_0 - 4$ vs. alternative hypothesis H_{11}: $\mu_{1.5} > \mu_0 - 4$

   Where $\mu_{1.5}$ and μ_0 represent the group means for the change from baseline in BCVA at Week 36 for the 8 mg/5 group and the 2 mg group, respectively.

   Note that larger values measured for the change from baseline in BCVA are better. The aim is to show that the 8 mg/5 group is no less effective than the existing the 2 mg group, using a NI margin of 4 letters for the difference of the means.

2. The second test problem (related to the primary estimand) involves the non-inferiority testing of 8 mg 3 loads vs 2mg:

   Null hypothesis H_{02}: $\mu_{1.3} \leq \mu_0 - 4$ vs. alternative hypothesis H_{12}: $\mu_{1.3} > \mu_0 - 4$

   Where $\mu_{1.3}$ and μ_0 represent the group means for the change from baseline in BCVA at Week 36 for the 8 mg/3 group and the 2 mg group, respectively.

   Note that larger values measured for the change from baseline in BCVA are better. The aim is to show that the 8 mg/3 group is no less effective than the existing the 2 mg group, using a NI margin of 4 letters for the difference of the means.

3. The third test problem (related to the secondary estimand) focuses on comparing the conditional distributions for the number of active injections between the 8 mg 3 loads and 2 mg groups:

   Null hypothesis H_{03}: $f_3(Y_1|X) = g(Y_2|X)$ vs. alternative hypothesis H_{13}: $f_3(Y_1|X) \neq g(Y_2|X)$

   Where $f_3(Y_1|X)$ and $g(Y_2|X)$ represent the conditional distributions for the number of active injections Y conditional on the data X from baseline to Week 64 for the 8 mg/3 group and the 2 mg group, respectively.

   Note that smaller values for the number of active injections are better. The aim is to show that the 8 mg/3 group is superior to the existing the 2 mg group in that it leads to fewer injections. Thus, the null hypothesis should be rejected in favor of the alternative hypothesis and the estimate of the treatment effect based on a linear regression model adjusted for the stratification variables should favor the 8 mg/3 group.

4. The fourth test problem (related to the secondary estimand) focuses on comparing the conditional distributions for the number of active injections between the 8 mg 5 loads and 2 mg groups:

   Null hypothesis H_{04}: $f_5(Y_1|X) = g(Y_2|X)$ vs. alternative hypothesis H_{14}: $f_5(Y_1|X) \neq g(Y_2|X)$

   Where $f_5(Y_1|X)$ and $g(Y_2|X)$ represent the conditional distributions for the number of active injections Y conditional on the data X from baseline to Week 64 for the 8 mg/5 group and the 2 mg group, respectively.

Note that smaller values for the number of active injections are better. The aim is to show that the 8 mg/5 group is superior to the existing the 2 mg group in that it leads to fewer injections. Thus, the null hypothesis should be rejected in favor of the alternative hypothesis and the estimate of the treatment effect based on a linear regression model adjusted for the stratification variables should favor the 8 mg/5 group.

5. The fifth test problem (related to the primary estimand) involves the superiority testing of 8 mg 5 loads vs 2mg:

   Null hypothesis H_{05}: $\mu_{1.5} \leq \mu_0$ vs. alternative hypothesis H_{15}: $\mu_{1.5} > \mu_0$

   Where $\mu_{1.5}$ and μ_0 represent the group means for the change from baseline in BCVA at Week 36 for the 8 mg/5 group and the 2 mg group, respectively.

   Note that larger values measured for the change from baseline in BCVA are better. The aim is to show that the 8 mg/5 group is superior to the existing the 2 mg group.

6. The sixth test problem (related to the primary estimand) involves the superiority testing of 8 mg 3 loads vs 2mg:

   Null hypothesis H_{06}: $\mu_{1.3} \leq \mu_0$ vs. alternative hypothesis H_{16}: $\mu_{1.3} > \mu_0$

   Where $\mu_{1.3}$ and μ_0 represent the group means for the change from baseline in BCVA at Week 36 for the 8 mg/3 group and the 2 mg group, respectively.

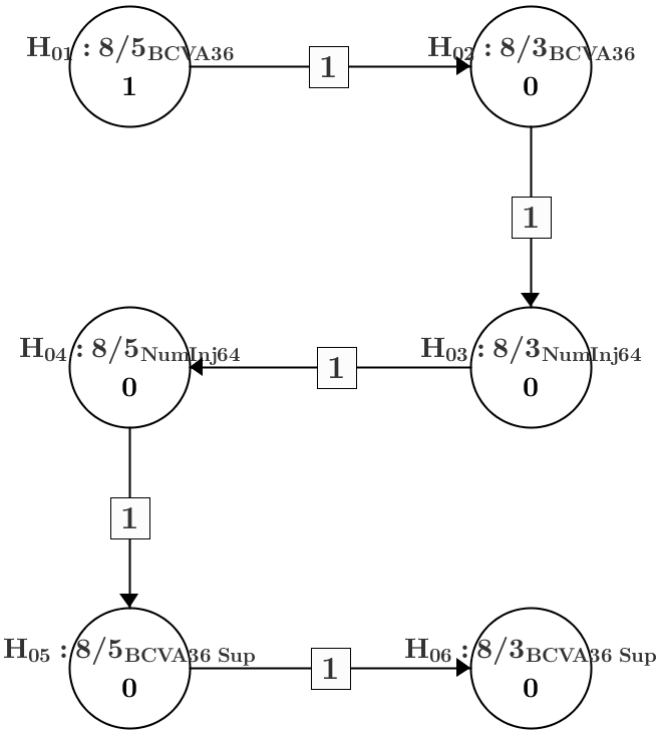
   Note that larger values measured for the change from baseline in BCVA are better. The aim is to show that the 8 mg/3 group is superior to the existing the 2 mg group.

Justification for the NI margin can be found in Section 9.1 of the study protocol.

2.1 Multiplicity Adjustment

As shown in Figure 2–1 and described in Section 2 a hierarchical testing procedure will be used to control the overall family-wise type I error in the strong sense. The statistical comparisons will be carried out in the hierarchical order as defined for the hypotheses in Section 2. Consequently, the second, third, fourth, fifth, and sixth null hypotheses will only be tested if the previous comparisons were in favor of the 8 mg/5 group or 8 mg/3 group in that the previous null hypotheses were rejected and, for two-sided null hypotheses only, the related estimate supported a superiority of the corresponding 8 mg arm. Operationally the non-inferiority and superiority hypotheses will be evaluated by one-sided tests with a significance level of 0.025, and the hypotheses for comparing number of active injections will be evaluated by two-sided tests with a significance level of 0.05. Two-sided 95% CIs for the treatment difference will be reported corresponding to all hypotheses.

Figure 2–1: Hierarchical Hypothesis Testing



8/5 BCVA36 = Group means for the change from baseline in BCVA at Week 36 for the 8 mg/5 group and the 2 mg group. Testing Non-inferiority of 8 mg/5 vs 2mg.
8/3 BCVA36 = Group means for the change from baseline in BCVA at Week 36 for the 8 mg/3 group and the 2 mg group. Testing Non-inferiority of 8 mg/3 vs 2mg.
8/3 NumInj64= Conditional distributions for the number of active injections from baseline to Week 64 for the 8 mg/3 group and the 2 mg group.
8/5 NumInj64= Conditional distributions for the number of active injections from baseline to Week 64 for the 8 mg/5 group and the 2 mg group.
8/5 BCVA36 Sup= Group means for the change from baseline in BCVA at Week 36 for the 8 mg/5 group and the 2 mg group. Testing Superiority of 8 mg/5 vs 2mg.
8/3 BCVA36 Sup= Group means for the change from baseline in BCVA at Week 36 for the 8 mg/3 group and the 2 mg group. Testing Superiority of 8 mg/3 vs 2mg.

3. Analysis Sets

For the purpose of analysis, the following analysis sets are defined:

Table 3-1: Analysis Sets

Participant Analysis Set	Description
Full analysis set (FAS)	All participants randomly assigned to study intervention who were exposed to study intervention at least once.
Safety analysis set (SAF)	All participants randomly assigned to study intervention who were exposed to study intervention at least once.
Pharmacokinetic analysis set (PKS)	All participants randomly assigned to study intervention with at least one non missing PK result after the first dose of study intervention.

PK=pharmacokinetic

Full analysis set (FAS)

The Full Analysis Set (FAS) will consist of all participants who have been randomly assigned to the study intervention and who were exposed to study intervention at least once. The participants will be analyzed based on their original randomized group. This approach ensures that the analysis accurately reflects the participants' original randomization status, thereby maintaining the integrity of the study results. The FAS will be used to analyze endpoints related to efficacy.

Safety analysis set (SAF)

The Safety analysis set (SAF) will consist of all participants who have been randomly assigned to the study intervention and who have received at least one dose of the study intervention. The analysis of the SAF will be based on the actual treatment the participant received during the study (as treated). This means that the participant's exposure to the study intervention will be accounted for and considered in the analysis, regardless of any deviations from the planned intervention. The SAF will be used to analyze the endpoints and assessments related to safety.

Pharmacokinetic analysis set (PKS)

The Pharmacokinetic analysis set (PKS) will consist of all participants who have been randomly assigned to study interventions and have recorded at least one non-missing PK measurement after the first dose of the study intervention. The analysis of the PKS will be based on the treatment that the participant actually received, not necessarily on the treatment that they were initially assigned to receive (as treated analysis).

As randomized versus as treated

The only systematic deviation from the randomized treatment that may occur is due to a systematic error in the IXRS system set up. Therefore, it is assumed that participants are generally treated as randomized, meaning the randomized treatment group is considered the actual treatment group, unless the participant did not receive any treatment after randomization. However, isolated instances of incorrect treatment at specific timepoints will not change the "as treated" assignment. Any participant whose "as treated" assignment differs from their "as randomized" assignment will be specifically listed.

Final decisions regarding the assignment of participants to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s).

4. Statistical Analyses

4.1 General Considerations

The testing of the primary and secondary endpoints is performed at an overall significance level of 0.025 for one-sided tests and 0.05 for two-sided tests, along with reporting of two-sided 95% CIs for these tests. The testing strategy is defined in Section 2.1. For descriptive purposes of other endpoints, 95% two-sided CIs will be provided where applicable.

The summary of continuous data will include the number of observations, mean, standard deviation (SD), median, quartiles, minimum, and maximum.

For categorical data, the summary will include the number of participants who provided data at the relevant time point (n), frequency counts, and percentages. The percentages will be presented to one decimal place but will not be reported for zero counts. The calculation of percentages will use n (the number of observations with non-missing values) as the denominator, unless otherwise specified in the output.

Number of decimal places for summary statistics will be the following:

Table 4-1: Number of decimal places for summary statistics

Statistic	Number of digits
Minimum, maximum	Same as original data
Mean, median	1 more than in original data
SD	1 more than in original data
Frequencies (%)	1 digit
Quartiles	1 more than in original data
Confidence Intervals (CI)	1 more than in original data
p-values	4 digits

Additionally, where applicable, descriptive summary tables for efficacy endpoints will be provided by treatment group and visit for and based on:

- All observed cases regardless of the occurrence of an ICE in the FAS population
- All observed cases until the occurrence of an ICE in line with the primary estimand strategy in the FAS population (see Table 6-11 in Section 6.5),
- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF in the FAS population (see Table 6-12 in Section 6.5)

The statistical evaluation will be performed by using the software SAS (release 9.4 or higher; SAS Institute Inc., Cary, NC, USA) and/or R (R Core Team 2013, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/).

The exclusion of participants from the primary analysis will be determined during the Data Review Meeting (on masked data) that will be held in accordance with ICH E9 prior to the database freeze on Week 36 data. Only participants who have completed Week 36 will be included in the analysis.

4.1.1 Definition of Dropouts

In the context of this study, dropouts will be defined as participants who withdraw or prematurely discontinue both their participation in the study and the study intervention, regardless of the reason. This definition also encompasses participants who are lost to follow-up, meaning their status cannot be determined or they are unable to be contacted. The primary reasons for withdrawing will be collected in the eCRF and tabulated accordingly.

4.1.2 Handling of Missing Data

All missing or incomplete data will be displayed in the participant data listing exactly as it is recorded in the eCRF.

4.1.2.1 General Rules

The following rules will be applied where applicable to ensure that participants are not excluded from statistical analysis due to missing or incomplete data:

- **Efficacy Variables**

  The statistical methods for handling missing data resulting from participant discontinuing the study will be dealt with in line with the corresponding estimand strategies and are outlined in Section 4.2.2 and in Section 4.3.1.2., as applicable.

- **Concomitant medication and adverse events**

  For Adverse Events (AEs) and prior/concomitant medications, complete start and stop dates must be recorded to determine if the AE occurred during the study intervention period (i.e. treatment-emergent) or the medication was taken during the study intervention period (i.e. concomitant). In case of partial dates, the following rules will be applied

  For partial/missing start dates of medications and AEs, impute as follows to determine whether concomitant and treatment-emergent, respectively:

  - If only the month and year of the start date is available and the end date is after (or unclear due to missingness) the date of the first study intervention:
    - If the month/year of the start date equals the month/year of first study intervention, then impute as the date of first study intervention.
    - If the month/year of the start date is before the month/year of first study intervention, then impute as the last day of that month/year.
    - If the month/year of the start date is after the month/year of first study intervention, then impute as the first day of that month/year.
  - If only the year of the start date is available, and the end date is after (or unclear due to missingness) the date of the first study intervention:
    - If the year of the start date equals the year of first study intervention, then impute as the date of first study intervention.
    - If the year of the start date is before the year of first study intervention, then impute as the last day and month of that year.
    - If the year of the start date is after the year of first study intervention, then impute as the first day and month of that year.

- If the start date is entirely missing and the end date is after (or unclear due to missingness) the date of the first study intervention, then impute as the date of first study intervention.

For partial/missing end dates of medications, impute as follows to determine whether concomitant:

- If only the month and year of the end date is available, and the start date is before (or unclear due to missingness) the date of the last study intervention:
  - If the month/year of the end date equals the month/year of last study intervention, then impute as the date of last study intervention.
  - If the month/year of the end date is before the month/year of last study intervention, then impute as the last day of that month/year.
  - If the month/year of the end date is after the month/year of last study intervention, then impute as the first day of that month/year.
- If only the year of the end date is available, and the start date is before (or unclear due to missingness) the date of the last study intervention:
  - If the year of the end date equals the year of last study intervention, then impute as the date of last study intervention.
  - If the year of the end date is before the year of last study intervention, then impute as the last day of that year.
  - If the year of the end date is after the year of last study intervention, then impute as the first day of that year.
- If the end date is entirely missing and the start date is before (or unclear due to missingness) the date of the last study intervention, then impute as the date of last study intervention.

Imputed dates will only be used for summary tables. Original (partial) entries will be retained in listings.

4.1.3 Data Rules

Definition of baseline: The latest available valid measurement at or before the start of study intervention will be used as baseline value for all assessments, unless specified otherwise. These measurements may be taken either at the screening visit (Visit 1) or the baseline visit (Visit 2), depending on the study's planned procedure timeline. The detailed timing of study procedures can be found in the study protocol.

For systolic and diastolic blood pressure, the baseline value is determined by averaging all of the measurements taken at or prior to randomization. It is important to note that any measurements taken during the initial screening visit will not be included in the calculation if the participant failed to meet the screening criteria.

Change from baseline: The absolute change from baseline will be calculated by subtracting the baseline value from the value obtained during treatment/follow-up. The formula for this calculation is:

Absolute Change = post-baseline value – baseline value.

Additionally, some parameters may also be analyzed as relative change, which is calculated as the percentage change from the baseline value. This calculation is defined as:

Relative change = 100 * [(post-baseline value – baseline value) / baseline value].

Laboratory values < LLOQ or > ULOQ : For laboratory values which are given as < LLOQ, half the value of the LLOQ will be used for analysis. Differences between two values < LLOQ will be assigned values of 0, and ratios between two values < LLOQ will be assigned a value of 1. For PK values, those under < LLOQ will be set to LLOQ/2 for geometric mean statistics in PK analysis but set to 0 for arithmetic statistics (mean, SD, CV). For values > ULOQ, the value of ULOQ will be used for analysis.

Repeated measurements at the same visit after start of treatment: If more than one post-randomization measurement is available for a given visit, the first valid observation will be used in the data summaries and all observations will be presented in the data listings.

Corrective Stratification in Analysis: in the event of stratification errors with respect to the stratification variables (geographic region [Japan vs. APAC vs Europe vs America], categorized baseline BCVA [<60 vs. ≥60], and RVO type [CRVO/HRVO vs BRVO]) at the time of randomization, analyses will be conducted based on participants' correct stratification category. Additionally, for RVO type the category will be derived from the reading center data. In case of missing reading center data, the RVO type category based on the investigator assessment as used for the randomization will be used.

4.1.4 Unscheduled Assessments

To provide an accurate representation of the data collected, measurements taken at unscheduled visits will be displayed in individual subject data listings. However, these measurements will not be incorporated into the general summary tables for the data. Should multiple measurements of the same variable be taken during an unscheduled visit, all the measurements will be displayed in the relevant subject data listing.

4.1.5 End of Study / Early Discontinuation Visit

Participants are allowed to discontinue the study intervention prematurely. This can happen at any point during the study. However, regardless of when the premature discontinuation occurs, all required assessments must be completed according to the protocol for the end-of-study (EOS) or early-discontinuation (ED) visit.

If participants discontinue study prematurely, the visit-based information recorded in the EOS/ED visit folder will be re-mapped to the relevant regular study visit, provided the EOS/ED visit falls within the appropriate visit window and the corresponding regular visit has not taken place. If any visit-based information cannot be re-mapped to a regular visit, it will be treated as an unscheduled assessment and managed accordingly as described in Section 4.1.4.

For participants who complete the study and intervention, no re-mapping is necessary, but the visit-based information in the EOS/ED visit folder will be assigned to "Week 64" and presented in the summary tables as such.

It is important to note that for some variables, data may be collected at visits where this variable was not scheduled to be collected. However, this data will still be used in last observation carried forward (LOCF) analyses when applicable. Descriptive by-visit summary tables and repeated measurement analyses should only include data from pre-planned, visits for which the respective variable was scheduled to be collected.

Mapping of selected assessments to regular study visits

The following assessments will be mapped:

- BCVA (ETDRS) and Refraction
- IOP
- Slit Lamp Examination
- Indirect Ophthalmoscopy
- SD-OCT
- Vital signs
- Pregnancy test

The following rule will be used:

- If EOS/ED visit performed within visit window of a regular study visit (as specified in the "Schedule of Activities" in the protocol), then re-mapping to regular study visit

For example, if a participant discontinued prematurely (study and/or study intervention) at the timing of Visit 3 / Week 4 (i.e. EOS/ED visit date = study day 29±5 days), then any of the assessments listed above recorded in the EOS/ED visit folder will be re-mapped to regular study Visit 3, unless a regular study Visit 3 was already performed.

4.1.6 Definition of Fellow-Eye Treatment

The treatment of the fellow eye will be documented on the Concomitant Medication page in the eCRF by specifying the fellow eye that was treated.

Any medication given prior to the first dose of the study intervention will be considered prior treatment for the fellow eye, while any medication given after the first dose of the study intervention will be considered concomitant bilateral treatment. The rules for partially missing dates will apply as described in section 4.1.2.1.

4.1.7 Definition of Prohibited Medications

The following medications are prohibited, as identified on the prior and concomitant medication page:

- Any of the following anti-VEGF medications administered in the study eye:
    - Aflibercept (trade name: Eylea), unless administered as study intervention
    - Bevacizumab (trade name: Avastin)
    - Brolucizumab (trade name: Beovu)
    - Ranibizumab (trade name: Lucentis)
    - Faricimab (trade name: Vabysmo)

- Conbercept (trade name Lumitin)
- Pegaptanib sodium (trade name: Macugen)

- Treatment with intraocular or periocular implant in the study eye.
- Administration of systemic anti-angiogenic medications for any condition.
- Use of intraocular or periocular steroids for the treatment of RVO, or steroid implants in the study eye.
- Treatment with ocriplasmin in the study eye.
- Gene therapy, or cell therapy in the study eye or fellow eye.

Additionally, the following surgical procedures are prohibited:

- Treatment with retinal laser photocoagulation for the treatment of RVO in the study eye.
- Treatment with vitrectomy surgery in the study eye.

The investigator may administer any medication that is deemed necessary for the participant's well-being and is not expected to affect the evaluation of the study intervention.

Both the prohibited medications and the prohibited procedures outlined above count towards the intercurrent event "Use of prohibited medication" that is used in the definition of the primary estimand (see Section 1.1).

Please refer to Section 6.6 on details how to identify intake of prohibited medications and cases of prohibited procedures during the study.

4.1.8 Imaging data assessed by the reading center

If imaging data have been assessed by the reading center, but were also captured in the eCRF, only the data assessed by the reading center will be used for the analysis unless otherwise stated.

In summary tables the following parameters will be evaluated and classified as follows:

From spectral domain optical coherence tomography (SD-OCT) assessment:

- Intraretinal fluid (IRF) in central subfield (Reading center variables: Intraretinal fluid (IRF: cystoid edema) present and IRF in the central 1mm affected):
    - IRF = No (if any of them is ticked):
        - IRF presence = No
        - IRF presence = Yes AND IRF in the central 1mm = No or QT
        - IRF presence = QT
    - IRF = Yes:
        - IRF presence = Yes AND IRF in the central 1mm = Yes
    - IRF = Undetermined (if any of them is ticked):
        - IRF presence = CG

        - IRF presence = Yes AND IRF in the central 1mm = CG

- Subretinal fluid (SRF) in central subfield (Reading center variables: Subretinal fluid (SRF) present and SRF in the central 1mm involved):
    - SRF = No (if any of them is ticked):
        - SRF presence = No
        - SRF presence = Yes AND SRF in the central 1mm = No or QT
        - SRF presence = QT
    - SRF = Yes:
        - SRF presence = Yes AND SRF in the central 1mm = Yes
    - SRF = Undetermined (if any of them is ticked):
        - SRF presence = CG
        - SRF presence = Yes AND SRF in the central 1mm = CG

- Central subfield thickness (CST)
    - Retinal thickness in central subfield
        - CST = reported value in µm
        - If CG, set to missing

From fluorescein angiography (FA) assessment:

- Area of retinal ischemia (Reading center variables: 'Presence of perifoveal and parafoveal ischemia' and 'total area of macular ischemia (not considering the FAZ)')
    - If Yes
        - Area = reported value in mm^2
    - If No
        - Area = 0
    - If QT
        - Area = 0
    - If CG
        - Set to missing
- Area of fluorescein leakage (Reading center variables: 'Presence of macular leakage' and 'area of macular leakage')
    - If Yes
        - Area = reported value in mm^2
    - If No

- Area = 0

- If QT
  - Area = 0
- If CG
  - Set to missing

4.2 Primary Endpoint Analysis

The testing of the primary and key secondary endpoints is performed at an overall significance level of 0.025 for the one-sided tests and 0.05 for the two-sided tests. The testing strategy is defined in Section 2.1. The 95% two-sided CIs will also be provided as applicable.

4.2.1 Definition of Endpoint

The primary endpoint is the change from baseline in BCVA (as measured by ETDRS letter score) at Week 36.

4.2.2 Main Analytical Approach

For the primary analysis of the primary efficacy variable, a mixed model for repeated measurements (MMRM) will be used with baseline BCVA measurement as a covariate and treatment group (2q4 vs 8q8/3 vs 8q8/5), visit (up to Week 36), and the stratification variables (geographic region [Japan vs. APAC vs Europe vs America], categorized baseline BCVA [<60 vs. ≥60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors as well as terms for the interaction between baseline and visit (up to Week 36) and for the interaction between treatment and visit (up to Week 36). Only data up to Week 36 will be included for this analysis. A Kenward-Roger approximation will be used for the denominator degrees of freedom. Further, an unstructured covariance structure will be used to model the within-subject error, assuming different covariance parameters per treatment group. The unstructured covariance structure will be used since it avoids making any assumptions on the correlations between repeated measures. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: Toeplitz with heterogeneity, autoregressive with heterogeneity, Toeplitz, autoregressive and compound symmetry.

$$Y_{ijk} = \beta_0 + x_i \times \beta_{base} + \beta_{type}^{(t)} + \beta_{reg}^{(l)} + \beta_{base\_cat}^{(m)} + \beta_{treat}^{(k)} + \beta_{visit}^{(j)} + x_i \times \beta_{base*visit}^{(j)} + \beta_{treat*visit}^{(k,j)} + \epsilon_{ijk}$$

with

- Y_{ijk} being the change from baseline to visit j for the participant i receiving treatment k
- β_0 being the intercept
- x_i being the baseline BCVA measurement of participant i
- β_{base} the fixed effect of the baseline BCVA measurement
- $\beta_{type}^{(t)}$ the fixed effect of RVO type t
- $\beta_{reg}^{(l)}$ the fixed effect of region l (as recorded on the eCRF),
- $\beta_{base\_cat}^{(m)}$ the fixed effect of categorized baseline BCVA measurement m

- $\beta_{treat}^{(k)}$ the fixed effect of treatment k
- $\beta_{visit}^{(j)}$ the fixed effect of visit j
- $\beta_{base*visit}^{(j)}$ the interaction between baseline BCVA and visit j
- $\beta_{treat*visit}^{(k,j)}$ the interaction between treatment k and visit j
- ϵ_{ijk} the residual error with $\epsilon_{ijk} \sim N(0, \sigma_{jk}^2)$ and $corr(\epsilon_{ijk}, \epsilon_{ij'k}) = \rho^k\_\{j, j'\}$

In terms of the model parameters the population-level summary for the primary estimand (i.e., the treatment effect at Week 36) can then be expressed as

$$D_{8/3} = \left[\beta_{treat}^{(8mg/3)} + \beta_{treat*visit}^{(8mg/3,w36)}\right] - \left[\beta_{treat}^{(2mg)} + \beta_{treat*visit}^{(2mg,w36)}\right]$$

for the comparison of 8mg/3 vs 2 mg and

$$D_{8/5} = \left[\beta_{treat}^{(8mg/5)} + \beta_{treat*visit}^{(8mg/5,w36)}\right] - \left[\beta_{treat}^{(2mg)} + \beta_{treat*visit}^{(2mg,w36)}\right]$$

for the comparison of 8mg/5 vs 2 mg.

The primary analysis will be conducted using the FAS. Participants will be analyzed within their original randomized intervention group, regardless of any modifications in their dose interval as per DRM criteria.

In accordance with the primary estimand and approach to intercurrent events of premature treatment discontinuation, no explicit imputation will be performed for missing BCVA measurements. Instead, missing BCVA measurements will be assumed to be missing at random (MAR) and will be handled by the MMRM model. This model will account for the missing data and provide a more robust estimate of the treatment effect.

Summary tables will include number of participants, least-square mean (LSmean) change (with categorical covariates weighted as observed), (unadjusted) mean change and SD and baseline means of each treatment group. For non-inferiority and superiority testing the estimates expressed as LSmean change, the test statistics, the degrees of freedom and corresponding p-values will be presented. Two-sided 95% confidence intervals will be provided as well.

An overview of the implementation strategies for handling of intercurrent events is described in Section 4.2.2.1.

Descriptive summary tables will be provided by treatment group and visit as described in Section 4.1 for:

- all observed cases regardless of the occurrence on an ICE,
- all observed cases until the occurrence of an ICE in line with the estimand strategy,
- all observed cases until the occurrence of an ICE with imputation of missing values using LOCF.

4.2.2.1 Strategies for occurrence of intercurrent events

Analysis strategies for intercurrent events for the primary estimand occurring through Week 36 are described in Table 4-2 below.

Table 4-2: Implementation strategies for the handling of intercurrent events (ICEs) for analysis at Week 36 for the Primary Estimand

ICE Strategies for the Primary Estimand			
Intercurrent event	**Strategy**	**Main Analysis**	**Sensitivity Analysis**
Premature discontinuation of study intervention for any reason before Week 36	Hypothetical	and discontinuation of study: non-observed data beyond discontinuation of study intervention will be covered implicitly in the MMRM	Non-observed data beyond discontinuation of study intervention will be imputed by LOCF
		and continuation of study: observed data beyond last active injection (that was administered before the premature discontinuation of study intervention) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be covered implicitly in the MMRM	Observed data beyond last active injection (that was administered before the premature discontinuation of study intervention) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be imputed by LOCF
Use of a prohibited medication (as per section 4.1.7) before Week 36	Hypothetical	Observed data beyond first administration of the prohibited medication in study eye will be excluded from analysis and resulting missing data will be covered implicitly in the MMRM	Observed data beyond first administration of the prohibited medication in study eye will be excluded from analysis and resulting missing data will be imputed by LOCF
Missed active injection resulting in an actual injection interval up to 4 weeks longer than planned	Treatment policy	All observed data will be included in the analysis and the MMRM	All observed data will be included in the analysis
Missed active injection resulting in an actual injection interval more than 4 weeks longer than planned	Hypothetical	Observed data beyond last active injection (that was administered before the first missed active injection) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be covered implicitly in the MMRM	Observed data beyond last active injection (that was administered before the first missed active injection) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be imputed by LOCF

4.2.3 Sensitivity Analyses

In addition to the MMRM approach described above, we will conduct three additional sensitivity analyses.

Firstly, we will use the Last Observation Carried Forward (LOCF) method until Week 36 to impute missing post-baseline BCVA values of participants who have at least one post-baseline value.

Secondly, we will apply Multiple Imputation (MI) assuming Missing at Random (MAR) to impute missing post-baseline BCVA values. For both LOCF and MI, we will use ANCOVA to analyze the change from baseline in BCVA at Week 36.

Thirdly, we will assess the sensitivity of the MI results in the second sensitivity analyses to deviations from the MAR assumption. To do this, we will conduct a tipping point analysis.

4.2.3.1 ANCOVA using LOCF

The sensitivity analysis of the primary efficacy endpoint using an ANCOVA with LOCF follows the same estimand strategy as the primary analysis. Observed data after occurrence of ICE will be handled as described in Table 4-2.

Baseline BCVA measurement will be included as a covariate, while treatment group (2q4 vs 8q8/3 vs 8q8/5) and stratification variables (geographic region [Japan vs. APAC vs Europe vs America], baseline BCVA [<60 vs. ≥60]), and RVO type ([CRVO or HRVO] vs BRVO) will be treated as fixed factors. Variance terms will be estimated separately for each of the three treatment groups.

The observation at Week 36 of participant i receiving treatment t can be written as follows:

$$Y_{itrb} = \mu_t + \gamma_r + \eta_b + \omega_p + x_i\beta + \epsilon_{itrb}$$

with

- Y_{itrb} being the change from baseline to Week 36 for the ith participant,
- μ_t being the treatment effect,
- γ_r being the geographic region effect (as recorded on the eCRF),
- η_b being the categorical baseline BCVA (<60 vs. ≥60; as recorded on the eCRF),
- ω_p being the RVO type effect,
- x_i being the baseline BCVA measurement of participant i,
- ϵ_{itrb} the residual error with $\epsilon_{itrb} \sim N(0, \sigma_t^2)$ being the residual error for treatment arm *t*.

In terms of the model parameters the population-level summary for the primary estimand (i.e., the treatment effect at Week 36) can then be expressed as

$$D_{8/3} = \left[\beta_{treat}^{(8mg/3)}\right] - \left[\beta_{treat}^{(2mg)}\right]$$

for the comparison of 8mg/3 with 2 mg and

$$D_{8/5} = \left[\beta_{treat}^{(8mg/5)}\right] - \left[\beta_{treat}^{(2mg)}\right]$$

for the comparison of 8mg/5 with 2 mg.

For this analysis, missing Week 36 BCVA data will be imputed using the Last Observation Carried Forward (LOCF) method. This means that the last non-missing post-baseline BCVA measurement will be carried forward up to Week 36. The summary tables will include the number of participants, least-square mean (LSmean) change (with categorical covariates weighted as observed), unadjusted mean change and standard deviation (SD), as well as the baseline means of each treatment group. For non-inferiority testing, a one-sided alpha of 0.025 will be used for the population-level estimates comparing 2mg Aflibercept Q4 vs (8mg Aflibercept 3xQ4 then Q8) vs (8mg Aflibercept 5xQ4 then Q8).

The results will be presented as LSmean change, the test statistics, degrees of freedom, and corresponding p-values. Additionally, two-sided 95% confidence intervals will be provided. This sensitivity analysis will be performed for the Full Analysis Set (FAS).

4.2.3.2 ANCOVA with Multiple Imputation

This sensitivity analysis for the primary efficacy endpoint uses ANCOVA after applying multiple imputation to impute missing data (instead of using an LOCF approach). The method follows the same estimand strategy as the primary analysis. The process of multiple imputation involves three steps:

I. Imputation: Imputation involves generating multiple copies of the original dataset by replacing missing values with appropriate stochastic models. The missing data will be imputed using the Fully Conditional Specification (FCS) method. This method employs an iterative algorithm, where linear regression models are used for prediction and imputation. 10 imputations will be performed using a seed of 22153. The imputation model will include treatment groups, RVO type (CRVO/HRVO vs. BRVO), geographic region (Japan, APAC, Europe, America), categorical baseline BCVA (<60, ≥60), baseline BCVA, and BCVA at each previous post-baseline visit. Imputed values exceeding the normal 0 to 100 range will be truncated to 0 or 100 accordingly.
II. Analysis: Each of the imputed datasets will be analyzed using ANCOVA, as specified in Section 4.2.3.1. No missing data will be present in the imputed datasets.
III. Pooling: Pooling combines the different parameter estimates across the imputed datasets based on Rubin's rules (Rubin, 1987) to produce a single point estimate and standard error that takes into account the uncertainty of the imputation process.

This sensitivity analysis will be performed on the Full Analysis Set (FAS).

4.2.3.3 Tipping-point analysis

To evaluate the robustness of the results with regards to departure from the MAR assumption, a tipping-point analysis will be performed based on the results of the multiple imputation analysis described in Section 4.2.3.2. The tipping-point analysis will only be conducted if the multiple imputation analysis demonstrates non-inferiority of the 8 mg groups relative to the 2 mg group.

If non-inferiority can be established, additional tipping-point analyses will be carried out by reducing the imputed BCVA values in the 8mg arms by a series of ascending natural numbers (delta = 1, 2, 3, etc.) with the goal of finding the "tipping point" for each 8mg treatment group that would significantly change the results of the analysis. The smallest delta for which non-inferiority cannot be established will be the "tipping point".

For each delta value, summary tables will include the number of participants, least-square mean change, unadjusted mean change and standard deviation, as well as the baseline means of each treatment group. The estimates will also be expressed as least-square mean change with two-sided confidence intervals at a 5% alpha level, the test statistics, degrees of freedom, and corresponding p-values. This sensitivity analysis will be performed for the FAS.

4.2.3.4 Additional Sensitivity Analysis

It has been stated in the CSP Section 9.3.2.3 that an additional sensitivity analysis will be performed to account for important protocol deviations that may potentially affect efficacy for the main analysis of the primary endpoint as described in Section 4.2.2. However, considering the estimand strategy described in Section 1.1, this analysis is deemed obsolete, since relevant ICEs that may potentially affect efficacy are already covered in the estimand definition. Therefore, the sensitivity analysis as described in Section 9.3.2.3 of the CSP will not be performed.

4.2.4 Supplementary Analysis

Two supplementary analyses will be conducted based on the supplementary estimands for the primary objective described in Table 1-2.

Analysis based on Supplementary Estimand 1:

A treatment policy strategy will be applied to handle all the ICEs, as presented in Table 1-2, whereby all collected data will be used in the analysis regardless of the occurrence of the ICEs.

For the supplementary estimand, analysis strategies for intercurrent events occurring through Week 36 are described in Table 4-3.

A similar MMRM model as described for the main analysis (Section 4.2.2) will be used to analyze the data. No imputation of missing data will be performed. Missing BCVA measurements will be assumed to be missing at random and will be handled by the MMRM model. No sensitivity analyses will be performed for the supplementary analysis.

Table 4-3: Strategies for occurrence of intercurrent events (ICEs) for analysis at Week 36 for the Supplementary Estimand

ICE Strategies for the Supplementary Estimand 1		
Intercurrent event	**Strategy**	**Analysis**
Premature discontinuation of study intervention for any reason before Week 36	Treatment policy	and discontinuation of study: all observed data will be included in the analysis and the MMRM. Non-observed data beyond discontinuation of study intervention will be assumed to be MAR and will be handled by the MMRM. and continuation of study: all observed data will be included in the analysis and the MMRM.
Use of a prohibited medication (as defined in section 4.1.7) before Week 36	Treatment policy	All observed data will be included in the analysis and the MMRM.
Missed active injection resulting in an injection interval up to 4 weeks longer than planned	Treatment policy	All observed data will be included in the analysis and the MMRM.
Missed active injection resulting in an injection interval more than 4 weeks longer than planned	Treatment policy	All observed data will be included in the analysis and the MMRM.

Analysis based on Supplementary Estimand 2:

A mixture of treatment policy and composite strategy will be used to handle ICEs, as presented in Table 1-2. Analysis strategies for the occurrence of ICEs are described in Table 4-4.

Table 4-4: Strategies for occurrence of intercurrent events (ICEs) for analysis at Week 36 for the Supplementary Estimand 2

ICE Strategies for the Supplementary Estimand 2		
Intercurrent event	**Strategy**	**Analysis**
Premature discontinuation of study intervention due to death before Week 36	Composite	The change from baseline in BCVA at the visit prior to death will be set to 0. Non-observed data beyond death will be assumed to be MAR and will be handled by the MMRM.
Premature discontinuation of study intervention for any other reason than death before Week 36	Treatment policy	and discontinuation of study: all observed data will be included in the analysis and the MMRM. Non-observed data beyond discontinuation of study intervention will be assumed to be MAR and will be handled by the MMRM. and continuation of study: all observed data will be included in the analysis and the MMRM.
Use of prohibited medication (as defined in section 4.1.7) before Week 36	Composite	The change from baseline in BCVA at all visits beyond the first use of prohibited medication through Week 36 will be set to 0.
Missed active injection resulting in an injection interval up to 4 weeks longer than planned	Treatment policy	All observed data will be included in the analysis and the MMRM.
Missed active injection resulting in an injection interval more than 4 weeks longer than planned	Treatment policy	All observed data will be included in the analysis and the MMRM.

For participants that experience the intercurrent event "use of prohibited medication" first and discontinue subsequently, the following data rules apply:

- Discontinuation due to death: The change from baseline in BCVA at all visits beyond the first use of prohibited medication through the last visit prior to death will be set to 0 and non-observed data beyond death will not be imputed.
- Discontinuation due to any other reason than death (regardless of whether the participant remained in the study or not): The change from baseline in BCVA at all visits beyond the first use of prohibited medication through Week 36 will be set to 0.

For scenarios where a participant experiences an intercurrent event handled by treatment policy strategy first followed by an intercurrent event handled by composite strategy, the corresponding composite strategy will be applied from the timepoint of the intercurrent event handled by composite strategy as described in the table above.

A similar MMRM model as described for the main analysis (Section 4.2.2) will be used to analyze the data. No imputation of missing data other than the described above will be

performed. Remaining missing BCVA measurements will be assumed to be missing at random and will be handled by the MMRM model. No sensitivity analyses will be performed for the supplementary analysis.

4.3 Secondary Endpoints Analysis

4.3.1 Key Secondary Endpoint

4.3.1.1 Definition of Endpoint(s)

The key secondary efficacy endpoint in this study is the number of active injections from baseline to Week 64. Active injections refer to the number of injections that were actually administered, as opposed to the number of planned injections.

In addition to the number of injections that were actually administered, the endpoint value will also reflect the occurrence of certain intercurrent events: premature discontinuation of study intervention due to a treatment-related adverse event or lack of efficacy, which will be addressed using a composite and a hypothetical strategy, respectively. Participants experiencing these types of intercurrent events will have their endpoint value calculated in a way that reflects an unfavorable outcome (under the composite strategy) or an injection schedule under a hypothetical scenario. See Section 4.3.1.3 for details.

4.3.1.2 Main Analytical Approach

The analysis will be conducted in a pairwise manner, i.e., comparing the 8 mg/3 treatment group vs the 2 mg treatment group and the 8 mg/5 treatment group vs the 2 mg treatment group in two separate analyses. For simplicity, in the following the secondary analysis will be formulated in a general manner and applied to both pairwise comparisons of 8 mg/3 treatment group vs the 2 mg treatment group and 8 mg/5 treatment group vs the 2 mg treatment group.

The key secondary endpoint, the number of active injections from baseline to Week 64, will be analyzed using a non-parametric rank analysis of covariance (non-parametric rank ANCOVA). This analysis will adjust for covariates when comparing treatment groups. Additionally, treatment effects will be estimated using a linear regression model adjusted for the same covariates.

Endpoint values will be unobservable (missing) for participants who prematurely discontinue the study intervention due to reasons other than treatment-related adverse events or lack of efficacy. Their treatment schedule will be modeled under a hypothetical scenario as discussed in Section 4.3.1.3. No other type of missing data is expected for this endpoint.

To impute hypothetical values, a MI model (Rubin, 1987) will be employed. The process involves creating multiple imputed datasets, and each dataset will be subjected to the same analysis procedures using the non-parametric rank ANCOVA and linear regression. The results from multiple imputed datasets will then be combined for overall inference using the Rubin's rule. Each of the steps mentioned above is described in more detail below.

Missing endpoint values (total number of active injections) for participants with afore-mentioned intercurrent events will be imputed in alignment with the hypothetical scenario, namely that these participants would receive a similar number of active injections as other participants without such intercurrent events with similar baseline characteristics within their treatment arm. The imputation model will include as predictors the same baseline covariates as those included in the analysis models described below, i.e., baseline BCVA, baseline CST, and the stratification factors for region, BCVA score (greater equal than or less than 60), and

RVO type. The stratification variable 'region' will be collapsed into three categories (Japan+APAC, Europe, and America) by combining the two smaller strata Japan and APAC. This adjustment is made because the rank ANCOVA is a randomization-based method with variance estimation under the null hypothesis of no treatment difference in all strata. The asymptotic statistical properties of this approach rely on the central limit theory, which conventionally requires approximately 30 samples in each stratum (Gasparyan, 2021) to support its statistical properties. The Predictive Mean Matching imputation method (Heitjan and Little 1991; Schenker and Taylor 1996) will be used, which will ensure that the imputed values are integer and in the range of allowed number of injections within each treatment arm. The number of donor observations, a user-specified parameter of the Predictive Mean Matching imputation method, will be set to 5 (default in SAS Proc MI).

To ensure robustness, a total of 500 multiple imputation steps will be conducted.

The MI model will be implemented as follows, using the SAS pseudo code given below as an example. Alternatively, R may be used for the actual analysis. The random seed (22153) will be specified in the corresponding option of Proc MI in SAS or its equivalent in R.

```
/* Step 1: Perform multiple imputation */
proc mi data=my_data out=multiple_imputed_data seed=22153 nimpute=500;
 class treatment region_RVO_BCVA;
  var baseline_BCVA baseline_CST treatment region_RVO_BCVA active_injections;
  monotone regpmm (active_injections / k=5);
run;
```

where "`region_RVO_BCVA`" is a categorical variable with 12 levels, representing a cross of the three original stratification factors baseline BCVA score, region (collapsed into three categories as described above), and RVO type.

For the non-parametric ANCOVA, the Cochran-Mantel-Haenszel score test will be applied to residuals of a regression model on rank-transformed data as described in Stokes et al. (2012). Baseline BCVA, baseline CST, and the stratification factors region (collapsed to three categories as describe above), BCVA score (greater equal than or less than 60), and RVO type will be adjusted for.

The methodology described by Stokes et al. (2012) will be applied as follows (and exemplified based on the SAS pseudo code provided below). First, the endpoint values (total number of injections) and continuous baseline covariates baseline BCVA and baseline CST will be transformed to standardized ranks by stratum using fractional ranks and the mean method for ties will be implemented as:

```
/* Step 2: Transform to standardized ranks */
proc rank data=multiple_imputed_data nplus1 ties=mean out=ranks;
        by _Imputation_ region BCVA_score RVO_type;
        var baselineBCVA baselineCST active_injections;
run;
```

Subsequently, separate regression models will be fit within each stratum defined by the stratification factors, using the standardized rank values of the endpoint as dependent and of

the baseline BCVA and CST values as independent variables, respectively. Residuals from these models will be captured for further testing of differences between treatment groups:

```
/* Step 3: Conduct separate regression models */
proc reg data=ranks;
      by _Imputation_ region BCVA_score RVO_type;
      model active_injections = baselineBCVA baselineCST;
      output out=residuals r=resid;
run;
```

Finally, the stratified Cochran-Mantel-Haenszel (CMH) mean score test, using the residuals as scores, will be used to compare the two treatment groups as:

```
/* Step 4: Implement the Cochran-Mantel-Haenszel (CMH) test */
proc freq data=residuals;
  by _Imputation_;
  tables region*BCVA_score*RVO_type*treatment*resid / CMH2;
  ods output cmh=cmhstat;
run;
```

The non-parametric rank ANCOVA described above will be applied to each imputation dataset within the multiple imputation procedure. Before combining the results of the CMH test using Rubin's rule, a normalizing transformation using the Wilson-Hilferty transformation, as described in Ratitch et al. (2013), will be applied. The CMH statistic computed for each imputed dataset ($cmh^{(m)}$) will be standardized using its corresponding degrees of freedom (df) to obtain the standardized test statistic $st\_cmh^{(m)}$ as:

$$st\_cmh^{(m)} = \frac{\sqrt[3]{\frac{cmh^{(m)}}{df}} - \left(1 - \frac{2}{9 \times df}\right)}{\sqrt{\frac{2}{9 \times df}}}$$

```
/* Step 5: Standardize the CMH statistic for each imputed dataset */
data cmh_stat;
  set cmhstat;
  std_cmh = ((cmh/df)**(1/3) - (1-2/(9*df))) / sqrt(2/(9*df));
  std_cmh_stderr = 1;
run;
```

The standardized statistic, along with its standard error of 1, will be used to perform a combined CMH test using Rubin's rule as:

```
/* Step 6: Perform the combined CMH test using Rubin's rule */
proc mianalyze data=cmh_stat;
  modeleffects std_cmh;
```

```
   stderr std_cmh_stderr;
run;
```

Along with evaluating the treatment effect based on the non-parametric rank ANCOVA for each pairwise comparison (i.e., 8mg/3 vs 2mg and 8mg/5 vs 2mg), a single linear regression model including the treatment group variable with three levels (2mg vs 8mg/3 vs 8mg/5) and adjusted for baseline BCVA, baseline CST, and the stratification factors region (collapsed to three categories Japan+APAC, Europe, and America as described above), BCVA score (greater equal than or less than 60), and RVO type will be used to estimate the treatment effects. The linear regression model can be represented by the following formula:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \varepsilon \quad (1)$$

Where:

- y is the response variable (i.e. number of active injections from baseline to Week 64),
- β_0 is the intercept,
- $x_1, x_2,$ and x_3 are the region, BCVA score, and RVO type variables.
- $x_4,$ and x_5 are the baseline variables (Baseline BCVA and Baseline CST)
- x_6 is the treatment group variable (i.e. 2mg vs 8mg/3 vs 8mg/5),
- $\beta_1, \beta_2, \beta_3, \beta_4$ and β_5 are the corresponding regression coefficients for the stratification factors and baseline variables,
- β_6 represents the regression coefficient for the treatment group variable, and
- ε is the error term.

In terms of the model parameters the population-level summary for the secondary estimand (i.e., the number of injections at week 64) can then be expressed as

$$D_{8/3} = \left[\beta_{6_{treat}}^{(8mg/3)}\right] - \left[\beta_{6_{treat}}^{(2mg)}\right]$$

for the comparison of 8mg/3 with 2 mg and

$$D_{8/5} = \left[\beta_{treat}^{(8mg/5)}\right] - \left[\beta_{6_{treat}}^{(2mg)}\right]$$

for the comparison of 8mg/5 with 2 mg.

Please note that this formulation is intended as a general framework. For each categorical variable (Region, BCVA score, and RVO type), the model will include p-1 coefficient estimates, where p corresponds to the number of categories within the variable. Furthermore, a separate variance term will be estimated for each treatment group. The linear regression model will be fit to each of the imputation data sets created in the previous step. The treatment effect estimate across the imputation datasets will be then combined using Rubin's rule and the corresponding 95% confidence interval will also be created.

For cases where the baseline CST measurement is not available from the reading center, the investigator assessment of the baseline CST will be used in the analysis of the number of active injections described in this section.

The two-sided p-value based on the non-parametric rank ANCOVA, as well as the linear regression treatment estimates (with categorical covariates weighted as observed) together with the corresponding standard error and 95 % confidence interval, will be reported.

Descriptive summary tables will be provided by treatment group for:

- All observed cases regardless of the occurrence of an ICE in the FAS population

4.3.1.3 Strategies for occurrence of intercurrent events

Analysis strategies for intercurrent events for the secondary estimand occurring before week 64 are described in Table 4-6 below.

For the intercurrent event "Premature discontinuation of study intervention due to lack of efficacy", a hypothetical strategy will be applied assuming that the patient would have continued in the study and would have met the DRM criteria for shortening at each active injection visit. The number of injections administered until the occurrence of the intercurrent event will be counted. After the occurrence, it will be assumed that the patients would have continued to be treated as often as possible according to the DRM criteria, i.e., meeting the shortening criteria at every visit with an active injection after the occurrence of the ICE. For example, as shown in Table 4-5, if a participant discontinues due to LoE while on an 8-week interval, for example, his/her next injection would be as scheduled, but then the interval will be shortened to 4 weeks, and the participant will be treated every 4 weeks thereafter. Specifically, as shown in Table 4-5, if Patient 1 discontinues due to LoE at week 20, it will be assumed that his/her following dosing intervals will be shortened to 4 weeks, thus receiving additional active doses at Week 28 and remaining on 4-week intervals until the end of the study. Similarly, if Patient 2 discontinues due to LoE while on a 12-week interval at week 44, it will be assumed that his/her following dosing interval will be shortened to 8 weeks, thus receiving additional active doses at Week 52 and then shortened again to 4-week intervals and subsequently remaining on 4-week intervals until the end of the study.

Table 4-5: Shortening Criteria

	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	number of injections
Patient 1	x	x	x		x		x	x	x	x	x	x	x	x	x	x	x	15
Patient 2	x	x	x		x		x		x			x		x	x	x	x	11
Patient 3	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	16
								treatment discontinuation due to LoE										
								assumed path forward if they had continued to be treated										

This approach would ensure that none of the affected participants can have missing data and reflects what could have happened if the participant had remained in the study.

Table 4-6: Strategies for occurrence of intercurrent events for analysis at week 64 for the Secondary Estimand

ICE Strategies for Secondary Estimand		
Intercurrent event	**Strategy**	**Secondary Analysis**
Premature discontinuation of study intervention due to lack-of-efficacy	Hypothetical	See details in text above.
Premature discontinuation of study intervention due to treatment related AEs	Composite	Discontinuations due to treatment related AE is considered as treatment-failure and the number of injections will be set to 16 to represent an unfavorable outcome
Premature discontinuation of study intervention due to treatment unrelated AEs and other reasons	Hypothetical	Non-observed data beyond discontinuation of study intervention due to treatment unrelated AEs and other reasons will be imputed using multiple imputation technique as described in Section 4.3.1.2.
Missed injection	Treatment policy	The observed number of injections will be used in the analysis.

4.3.1.4 Supplementary Analyses

The analysis presented in Section 4.3.1.2 will be repeated for the subgroup of participants who completed the study intervention period, that is, for the participants that did not prematurely discontinue study intervention (for any reason) prior to the end of study at week 64. In this particular subgroup, the intercurrent event strategies for premature discontinuation of study intervention as outlined in Table 4-6 will not be applicable. Moreover, complete data on the number of injections at Week 64 will be accessible for all participants. Consequently, there won't be any missing data issues related to the number of injections, and the multiple imputation method detailed in Section 4.3.1.2 will not be used.

The nonparametric rank ANCOVA and the linear regression model for estimating the treatment effect, as described in Section 4.3.1.2, will be applied to this subgroup. A 95% CI based on the linear regression model will be provided along with a 95 % CI based on bootstrapping. The bootstrap confidence interval will be constructed generating B=1000 bootstrap samples by fitting the linear regression model to each bootstrap sample and obtaining B treatment effect estimates. The final bootstrap confidence interval will be constructed using the basic percentile method where the 2.5^{th} and 97.5^{th} percentiles of the B treatment effect estimates defining the limits of the confidence interval (Efron and Tibshirani 1993). Bootstrap samples will be drawn with replacement from the observed data of the subgroup.

4.3.2 Supportive Secondary Endpoints

The following additional secondary efficacy endpoints will be evaluated:

- Number of active injections from baseline to Week 36
- Change from baseline in BCVA measured by the ETDRS letter score at Week 44 for the 8mg/5 and 2 mg groups only.
- Change from baseline in BCVA measured by the ETDRS letter score at Week 64.
- Participant gaining at least 15 letters in BCVA from baseline at Weeks 36 and 64.
- Participant achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Weeks 36 and 64.
- Participant having no IRF and no SRF in the center subfield at Weeks 36 and 64.
- Change from baseline in CST at Weeks 36 and 64.
- Change from baseline in NEI-VFQ-25 total score at Weeks 36 and 64.
- Participants dosed only Q8W through Week 36 in the 8 mg Q8W group.
- Participant having last treatment interval ≥12 or of 16 weeks at Week 64.
- Participant having next intended interval ≥12, ≥16 or of 20 weeks at Week 64.

All analyses will be conducted on the FAS. Unless specified otherwise, summary statistics (see also Section 4.1) will be provided by treatment group and visit for:

- for all observed cases regardless of the occurrence of an ICE
- for all observed cases until the occurrence of an ICE in line with the primary estimand strategy.

Unless otherwise stated, the main evaluation of the binary secondary endpoints will be based on the summary statistics in line with the primary estimand strategy.

4.3.2.1 Number of active injections from baseline to Week 36

The number of active injections from baseline to Week 36 will be analyzed descriptively by treatment group and by using the analysis described for the key-secondary endpoint in Section 4.3.1. Intercurrent events will be handled similarly as described in Table 4-6. However, for the composite strategy for the ICE “premature discontinuation of study intervention due to treatment related AEs” the value for the number of injections will be set to 9 (the maximum possibly by Week 36). This analysis will be performed once all participants have completed Week 36 or have discontinued the study prematurely. Summary statistics will be presented by treatment group in line with the key-secondary endpoint described in Section 4.3.1.2.

4.3.2.2 Change from baseline in BCVA measured by the ETDRS letter score at Week 44 for the 8mg/5 and 2 mg groups only

The endpoint of "Change from baseline in BCVA measured by the ETDRS letter score at Week 44 for the 8mg/5 and 2 mg groups only" will be analyzed descriptively by treatment group and using the mixed model for repeated measurements (MMRM) as described in Section 4.2.2. The MMRM analysis will include baseline BCVA measurement as a covariate and treatment group, visit, and stratification variables (geographic region, categorized baseline BCVA, and RVO type) as fixed factors. Additionally, terms for the interaction between baseline and visit and for the interaction between treatment (8mg/5 and 2 mg groups only) and visit (up to week 44) will also be included in the analysis.

4.3.2.3 Change from baseline in BCVA measured by the ETDRS letter score at Week 64.

The endpoint of "Change from baseline in BCVA measured by the ETDRS letter score at Week 64" will be analyzed descriptively by treatment group and using the mixed model for repeated measurements (MMRM) as described in Section 4.2.2. The MMRM analysis will include baseline BCVA measurement as a covariate and treatment group, visit, and stratification variables (geographic region, categorized baseline BCVA, and RVO type) as fixed factors. Additionally, terms for the interaction between baseline and visit and for the interaction between treatment and visit (up to week 64) will also be included in the analysis.

4.3.2.4 Participant gaining at least 15 letters in BCVA from baseline at Weeks 36 and 64.

The proportion of participant gaining at least 15 letters in BCVA from baseline at Weeks 36 and 64 will be analyzed descriptively. Missing cases will not be included in the denominator when calculating proportions.

4.3.2.5 Participant achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Weeks 36 and 64.

The proportion of participants achieving an ETDRS letter score of at least 69 at Week 36 and 64 will be analyzed descriptively. Missing cases will not be included in the denominator when calculating proportions.

4.3.2.6 Participant having no IRF and no SRF in the center subfield at Weeks 36 and 64.

The proportion of participants having no IRF and no SRF in the center subfield at Weeks 36 and 64 will be analyzed descriptively. Missing cases will not be included in the denominator when calculating proportions.

4.3.2.7 Change from baseline in CST at Weeks 36 and 64.

The endpoints "Change from baseline in CST measured at Week 36" and "Change from baseline in CST measured at Week 64" will be analyzed both descriptively by treatment group and using the mixed model for repeated measurements (MMRM) as described in Section 4.2.2. The MMRM analysis will include baseline CST measurement as a covariate and visit, treatment group and stratification variables (geographic region, categorized baseline BCVA, and RVO type) as fixed factors. Additionally, terms for the interaction between baseline and visit and for the interaction between treatment and visit (up to Week 36 and Week 64) will also be included in the analysis.

4.3.2.8 Change from baseline in NEI-VFQ-25 total score at Weeks 36 and 64.

The change from baseline in NEI-VFQ-25 total score at Weeks 36 and 64 will be analyzed both descriptively by treatment group and using the ANCOVA using LOCF approach as described in Section 4.2.3.1 based on the sensitivity analysis strategy for the primary estimand. The ANCOVA analysis will include baseline NEI-VFQ-25 total score measurement as a covariate and treatment group, visit, and stratification variables (geographic region, categorized baseline BCVA, and RVO type) as fixed factors.

4.3.2.9 Participants dosed only Q8W through Week 36 in the 8 mg Q8W group.

The number participants dosed only Q8W through Week 36 in the 8 mg Q8W group will be provided as part of the exposure analysis as described in Section 6.1.3.

4.3.2.10 Participant having last treatment interval ≥12 or of 16 weeks at Week 64.

The proportion of participants having last treatment interval ≥12 or of 16 weeks at Week 64 will be provided as part of the exposure analysis as described in Section 6.1.3.

4.3.2.11 Participant having next intended interval ≥12, ≥16 or of 20 weeks at Week 64.

The proportion of participants having next intended interval ≥12, ≥16 or of 20 weeks at Week 64 will be provided as part of the exposure analysis as described in Section 6.1.3.

4.3.2.12 Pharmacokinetics

Endpoint: Systemic exposure to aflibercept as assessed by plasma concentrations of free, adjusted bound and total aflibercept from baseline through Weeks 36 and 64.

All the analyses performed for PK samples will be carried out by treatment group on the PKS analysis set. This study does not evaluate any pharmacodynamic parameters.

PK samples are collected at baseline (Visit 2), Week 4 (Visit 3), Week 12 (Visit 5), Week 16 (Visit 6), Week 24 (Visit 8), Week 36 (Visit 11) and Week 64 (Visit 18) for all participants. The individual concentrations of free, adjusted bound, and total aflibercept over time will be summarized and listed by descriptive statistics by visit.

Individual concentrations of adjusted bound aflibercept will be calculated as 0.717 x individual concentrations of bound aflibercept.

Individual concentrations of total aflibercept will be calculated as the sum of individual concentrations of free and adjusted bound aflibercept.

The following LLOQs are used by the laboratory:

- For free aflibercept assay: LLOQ = 15.6ng/mL
- For bound aflibercept assay: LLOQ = 31.3ng/mL

Drug concentrations will be further grouped by the following baseline factors:

- age categories as defined in Section 6.1.1,
- medical history of renal impairment as determined by baseline serum creatinine values as defined in Section 6.3.6,
- hepatic impairment based on medical history as defined in Section 6.3.7,
- BMI categories as defined in Section 6.1.1,
- ethnicity as defined in Section 6.1.1,
- race grouped as White, Asian, Black or African American, and Other/Not Reported,

and evaluated by means of descriptive statistics.

No formal statistical hypothesis testing will be performed.

4.4 Exploratory Endpoints Analysis

The following exploratory endpoints will be analyzed using descriptive statistical methods by treatment group.

Unless specified otherwise, summary statistics (see also Section 4.1) will be provided by treatment group and visit for:

- for all observed cases regardless of the occurrence of an ICE
- for all observed cases until the occurrence of an ICE in line with the primary estimand strategy.

The exploratory endpoints are:

4.4.1 Change from baseline in BCVA measured by the ETDRS letter score at each visit

The exploratory endpoint of "Change from baseline in BCVA measured by the ETDRS letter score at each visit" will be analyzed descriptively by treatment group.

4.4.2 Participant with vision changes of at least 5, 10, or 15 letters in BCVA from baseline at each visit

The proportion of participants with vision changes of at least 5, 10, or 15 letters in BCVA from baseline at each visit will be analyzed descriptively. Missing cases will not be included in the denominator when calculating proportions.

4.4.3 Participant with no IRF and no SRF in the center subfield at each visit

The proportion of participants with no IRF and no SRF in the center subfield at each visit will be analyzed descriptively. Missing cases will not be included in the denominator when calculating proportions.

4.4.4 Time to fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield)

Total fluid-free retina (no IRF and no SRF in central subfield) is defined as the absence of total fluid, i.e. no IRF and no SRF in the central subfield as found in the SD-OCT, regardless of whether any retinal fluid was found again after that.

Time to total fluid-free retina (no IRF and no SRF in central subfield) will be analyzed by Kaplan-Meier analysis and shown in Kaplan-Meier plots and descriptive summaries. Estimated event rates at Week 36 and Week 64 will be provided along with the Hazard Ratios (HRs) and p-values. Time to total fluid-free retina is defined as the duration from randomization to the timepoint when total fluid was absent for the first time whereas intercurrent events are handled according to Table 6-11. The analysis will be performed using the study visits (i.e. multiples of 4 weeks) and not the calendar time as unit. Participants without total fluid-free retina will be censored at the time of their last SD-OCT assessment.

HRs will be calculated using a stratified Cox proportional hazards model, including treatment group as a factor and stratification variables. The p-value will be calculated by a stratified log-rank test to compare the 8mg groups vs. the 2mg group.

Time to IRF-free retina (no IRF in central subfield) and time to SRF-free retina (no SRF in central subfield) will be analyzed in the similar way.

Participants with no fluid at baseline are considered to not be “at risk” and are thus excluded from the analysis. Similarly, participants with missing baseline information or with baseline category “undetermined” for the fluid status (see Section 4.1.6) are also excluded. If both IRF status and SRF status are undetermined, then the total fluid-free retina status is also undetermined.

4.4.5 Participant having sustained fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield)

Sustained total fluid-free retina (no IRF and no SRF in central subfield) is defined as the absence of total fluid for at least 2 consecutive visits and all subsequent visits, i.e. no IRF and no SRF in the central subfield as found in the SD-OCT. The proportion participants having sustained fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield) will be analyzed descriptively. Missing cases will not be included in the denominator when calculating proportions.

4.4.6 Change in area of retinal ischemia at Weeks 36 and 64

The change in area of retinal ischemia at Weeks 36 and 64 will be analyzed descriptively by treatment group.

4.4.7 Change in the area of fluorescein leakage at Weeks 36 and 64.

The change in the area of fluorescein leakage at Weeks 36 and 64 will be analyzed descriptively by treatment group.

4.5 Safety Analyses

The analysis of safety variables will be performed descriptively on the SAF population at Weeks 36 and 64. The data collected at these timepoints will be used to generate descriptive statistics as described in Section 4.1 for continuous and categorical data. The purpose of this analysis is to provide an overview of the safety data, including the occurrence of adverse events, serious adverse events, and other safety-related variables. This may involve transforming the data or utilizing categorical cut-points for safety scales to enhance our understanding of safety trends.

4.5.1 Adverse Events

The analysis of adverse events (AEs) will be conducted according to the following procedures:

- An AE is defined as any adverse medical event in a study participant that is associated with the use of study intervention, regardless of its relation to the study intervention.
- All reported AEs will be coded using the latest version of MedDRA at the time of database lock. Coding will be done at the lowest level of specificity according to Bayer's global standards.
- AEs will be recorded from the time of informed consent signature until the end of the study. If a participant withdraws from the study during the screening process, AEs will

be recorded up until their withdrawal. If a participant is withdrawn after receiving the first dose of study medication, AEs will be recorded up until 30 days after their last dose of study intervention or the termination visit, whichever is later.

- A Treatment-emergent adverse events (TEAE) are defined as AEs that occurred in the time frame from first injection (active or sham) to the last injection (active or sham) plus 30 days. For the participants who have not discontinued study treatment prematurely (i.e., are “ongoing”) at the Week 36 analysis, all AEs that started at first injection or later will be considered treatment-emergent.

The data cut-off rules for Week 36 and Week 64 AE reporting are described in a separate document (“Data Cut-Off Specifications”).

The proportions of participants experiencing AEs will be used as safety variables for AE summary. Other variables used for AE description and analysis will include AE Verbatim Term, AE start date/time and end date/time/ongoing, corresponding study day, AE Duration, relationship of AE to study drug, relationship of AE to commercial aflibercept (2 mg), relationship of AE to intravitreal injection, relationship of AE to protocol-required procedure, seriousness, intensity, action due to AE, treatment of AE, and outcome. Summaries that include frequencies and proportions of participants reporting AEs will include the Preferred Terms (PTs) and the System Organ Classes (SOCs).

Evaluations for TEAEs will mainly be conducted for the following categories, which will be identified from the information in the Case Report Form (CRF):

- Ocular TEAEs in the treated study eye
- Ocular TEAEs in the fellow eye
- Non-ocular TEAEs

AE summaries will be provided, displaying AEs within each SOC in alphabetical order. For an overall characterization of the AE profile for aflibercept in this study, an AE summary will include AEs within each SOC listed in alphabetical order, with columns for treatment groups, including a column "All 8mg" for the pooled 8mg group.

TEAEs in the study eye assessed by the investigator as being related to the injection procedure, related to protocol-required procedures, and those related to the study medication will be summarized separately. TEAEs in the fellow eye assessed by the investigator as being related to the injection procedure, related to protocol-required procedures, related to the study medication, and those related to commercial aflibercept (2 mg) will also be summarized separately.

A listing will be constructed that includes the participant identification, treatment group, category of AE (ocular study eye, non-ocular), AE, MedDRA term, seriousness, severity, causality, elapsed time to onset since first dose of aflibercept and since last does of aflibercept, duration, and outcome.

Serious Adverse Events (SAEs) will be summarized in the same way as described for TEAEs.

A frequency table of TEAEs of **intraocular inflammation of study eye** terms, cross-tabulated with related MedDRA PT and SOC, will be displayed by treatment arm (see Section 6.3.2 for the definition of terms).

A frequency table of adjudicated treatment-emergent Anti-Platelet Trialists Collaboration (APTC) events terms, cross-tabulated with related MedDRA PT and SOC, will also be displayed by treatment arms. The adjudication of AE is described in the "APTC adjudication committee charter".

Additionally, frequency tables of TEAEs of **hypertension** terms and **nasal mucosal finding** terms, cross-tabulated with related MedDRA PT and SOC, will be displayed by treatment arm (see Section 6.3 for the definition of terms).

Adverse Event of Special Interest (AESI) as defined in the study protocol are arterial thromboembolic events including cerebrovascular ischemic events and cardiovascular ischemic events and will be summarized in the same way as described for TEAEs.

4.5.1.1 Subgroup Analyses

Subgroup analyses for TEAEs will be performed for the safety analysis subgroups described in Section 4.6.1 and by RVO type as describe in Section 4.6.2 for each of the following types of TEAE:

Number of participants with

- ocular TEAEs in the study eye
- non-ocular TEAEs
- Serious ocular TEAEs in the study eye
- Serious non-ocular TEAEs

4.5.2 Additional Safety Assessments

4.5.2.1 Surgeries

All surgeries after informed consent will be collected on the CRF, and a listing of all surgeries and diagnostic procedures will be provided.

4.5.2.2 Clinical Laboratory Variables

Chemistry, hematology, and urinalysis will be collected at screening (Visit 1), Week 36 (Visit 11), and Week 64 (EOS) or ED. Pregnancy testing will be performed at each visit. The tests detailed in Table 4-7 will be conducted by the central laboratory.

Table 4-7: Pre-defined laboratory abnormalities

Laboratory Assessments	Parameters	
Hematology	Platelet count	WBC count
	RBC count	Differential:
	Hemoglobin	Neutrophils
	Hematocrit	Lymphocytes
	RBC Indices	Monocytes
		Eosinophils
		Basophils
Clinical Chemistry	Sodium	Total and direct bilirubin
	Potassium	Urea (or BUN)
	Chloride	LDH
	Carbon dioxide	Total protein, serum
	Calcium	Total cholesterol
	Creatinine	Triglycerides
	Glucose (non-fasting)	LDL
	Albumin	HDL
	AST/SGOT	Uric acid
	ALT/SGPT	CPK
	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity, color, clarity, crystals • pH, glucose (non-fasting), protein, blood, ketones, bilirubin, nitrite, leukocyte esterase by dipstick • WBC, RBC, hyaline and other casts, bacteria, epithelial cells, yeast • Creatinine • UPCR	
Other Screening Tests	• Follicle stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Highly sensitive serum hCG pregnancy test (as needed for WOCBP)[a]	

ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CPK=creatine phosphokinase, eCRF=electronic Case Report Form, hCG=human chorionic gonadotropin, HDL=high density lipoprotein, LDH=lactate dehydrogenase, LDL=low density lipoprotein, RBC=red blood cell, SGOT=serum glutamic-oxaloacetic transaminase, SGPT=serum glutamic-pyruvic transaminase, UPCR=urine protein: creatinine ratio, WBC=white blood cell, WOCBP=women of childbearing potential

[a] For WOCBP, a negative serum pregnancy test at screening is required for eligibility.

Number and percentage of participants with a treatment-emergent potentially clinically significant value (PCSV, any value fulfilling pre-defined criteria for abnormal laboratory parameters as described in Table 6-1 in the Appendix 6.2) at any time point will be summarized for selected clinical laboratory test for all participants.

Laboratory values out of normal range will be summarized in tables and also flagged in laboratory value listings.

4.5.2.3 Electrocardiogram

A standard digital 12-lead Electrocardiogram (ECG) will be performed at screening (Visit 1), Week 36 (Visit 11), and Week 64 (EOS) or ED. ECG variables, including heart rate, PR interval, QRS duration, RR interval, QT interval, and overall interpretation of ECG (normal/abnormal), will be analyzed for the SAF using appropriate descriptive methods.

Change from baseline or frequency tables and/or cross-tabulation of baseline vs. post-baseline status for categorical variables (overall interpretation of ECG normal/abnormal) will be presented by visit and treatment arms. QTc with Bazett and Fridericia correction will be used.

4.5.2.4 Vital Signs

Vital signs, including heart rate, systolic blood pressure, and diastolic blood pressure, will be collected pre-injection and before any blood draws at each visit during the study. The timing of blood pressure assessments should be within ±2 hours of the clock time of dosing at the baseline visit, if possible. Vital signs will be summarized by baseline and change from baseline to each scheduled visit by treatment group for the SAF.

Additionally, summaries will be provided for participants with at least one treatment-emergent PCSV of systolic blood pressure:

- ≤ 95 mmHg and decrease from baseline ≥ 20 mmHg
- ≥160 mmHg and increase from baseline ≥ 20 mmHg

As well as for participants with diastolic blood pressure treatment emergent PCSV of

- ≤ 45 mmHg and decrease from baseline ≥ 10 mmHg
- ≥110 mmHg and increase from baseline ≥ 10 mmHg.

Heart rate and blood pressure assessments will also be displayed as figures with mean change from baseline for SAF.

4.5.2.5 Other Safety Measures

Variables of analysis for ocular safety measures include:

- Proportion of participants with increased IOP
    - ≥ 10 mmHg increase in IOP measurement from baseline to any pre-dose measurement
    - > 21 mmHg for any pre-dose measurement at any time during the study
    - ≥ 25 mmHg for any pre-dose measurement at any time during the study
    - ≥ 35 mmHg for any pre-dose or post-dose measurement at any time during the study,

where the post-dose IOP measurement will be the final measurement before the participant leaves the site.

Summary statistics will also be displayed by visit for:

- change from baseline for pre-dose IOP values
- Proportion of participants with Anterior Chamber Cells (only pre-dose assessment for study eye)
    - 0: no cells
    - Trace: less than 5 cells
    - 1+: 5 to 10 cells
    - 2+: 10 to 20 cells

- 3+: 20 to 30 cells
- 4+: cells too numerous to count.

- Proportion of participants with Anterior Chamber Flare (only pre-dose assessment for study eye)
  - 0: no protein
  - Trace: trace amount of protein
  - 1+: mild amount of protein
  - 2+ and 3+: moderate amount of protein (continuum)
  - 4+: severe amount of protein.

Frequency tables will be provided for each of the above categories at each visit where data is available. Shift tables will be provided for the gradings (only pre-dose assessment for study eye).

- Portion of participants with retinal ischemia (perifoveal and parafoveal ischemia, non-perfusion outside the macula) by FA
- Portion of participants with macular leakage by FA

Frequency tables will be provided for each of the above categories at each visit where data is available.

4.6 Other Analyses

4.6.1 Subgroup Analyses

Exploratory subgroup analyses will be performed, using descriptive summary statistics for the following subgroups:

1. Age at enrollment: < 55 years, ≥ 55 to < 65 years, ≥ 65 years to < 75 years, ≥ 75 years
2. Sex: male, female
3. Geographic region:
   - Japan vs. APAC vs Europe vs America
   - USA vs Rest of the world
   - Asia (Japan and APAC) vs ROW
4. Ethnicity: Not Hispanic or Latino, Hispanic or Latino
5. Race (only categories with sufficient sample size): Asian, White
6. Baseline BCVA: < 60 letters, ≥ 60 letters
7. Baseline CST: ≤ observed median, > observed median
8. Medical history of hypertension: No, Yes (see section 6.3.1)
9. Medical history of diabetes: No, Yes
10. Medical history of cerebrovascular disease: No, Yes (see section 6.3.4)
11. Medical history of ischaemic heart disease: No, Yes (see section 6.3.5)

12. Medical history of renal impairment: Normal, Mild, Moderate, Severe (see section 6.3.6)
13. Medical history of hepatic impairment: No, Yes (see section 6.3.7)

Subgroups 1 to 7 will be analyzed for the primary and key secondary endpoints. For subgroup analysis based on geographic regions and categorized baseline BCVA, the corresponding variable will be excluded from the statistical models. These subgroup analyses are exclusively descriptive, and tables will present 95% confidence intervals. For the primary endpoint, subgroups will be analyzed using the MMRM without imputing missing values (see Section 4.2.2), for the key-secondary endpoint, subgroups will be analyzed using the non-parametric rank ANCOVA (see Section 4.3.1.2). In the subgroup analyses of the key-secondary endpoint, the stratification factor "region" will be excluded from the analysis and imputation model to mitigate issues associated with small sample sizes within strata. Subgroups 1 to 13 will be analyzed for the safety analyses mentioned in Section 4.5.1.1.

If the number of participants in a subgroup is less than 10%, the subgroup categories may be redefined prior to unmasking.

4.6.2 Subgroup Analysis by RVO type

To conduct a supportive exploratory subgroup analysis for BRVO and CRVO/HRVO, we plan to randomize a minimum of 40% of participants (i.e., 329 participants) per RVO type ([CRVO or HRVO] vs BRVO).

The primary efficacy endpoint will be analyzed for the FAS, as described in Section 4.2.2, by RVO type (CRVO/HRVO or BRVO) and by:

- individual arm (2q4 vs 8q8/3 vs 8q8/5)
- pooling the two 8mg arms (8q8/3 and 8q8/5).

The corresponding RVO type variable will be excluded from the MRMM statistical model, and for the analysis with pooled 8mg arms the treatment group variable will only consist of two categories (8mg vs 2mg).

Furthermore, summary statistics for the subgroup analysis by RVO type (CRVO/HRVO or BRVO) will be presented.

Furthermore, the secondary endpoint “Number of active injections from baseline to Week 36” will also by analyzed as described in Section 4.3.2.1 by RVO type (individual arms). For the secondary endpoints “Change from baseline in CST at Weeks 36 and 64”, descriptive summary statistics by RVO type will be provided.

Additionally, summary statistics for the safety analysis described in Section 4.5.1 will be summarized by RVO type (BRVO and CRVO/HRVO). This includes AEs, TEAEs, SAEs, including ocular TEAEs in the study eye and non-ocular TEAEs, as well as serious ocular TEAEs in the study eye and serious non-ocular TEAEs.

4.7 Interim Analyses and Data Monitoring Committee

No interim analyses in the sense of a group-sequential or adaptive design are planned.

An analysis of all data up to and including Week 36, including the primary efficacy analysis, will be performed once all participants have completed Week 36 or have discontinued the study prematurely.

A final analysis of all data, including the key-secondary analysis, will be conducted after all participants have completed the study at Week 64 or have discontinued prematurely.

A Data Monitoring Committee (DMC) that operates independently will convene periodically to assess the ongoing masked and unmasked safety data of study participants and make recommendations regarding continuation or termination of the study based on these evaluations. The DMC's operations are governed by a charter that outlines the frequency of meetings, procedures for monitoring safety (among other things), and reporting requirements to the sponsor. No adjustments to the alpha level will be made in regard to the DMC's analyses as there is no expectation of early stopping for overwhelming efficacy.

A Steering Committee will maintain close communication with the DMC, however, only masked data will be shared or discussed. Additional information about this can be found in the study protocol.

4.8 Changes to Protocol-planned Analyses

Since the population attribute in the estimand definition should be in reference to the target population, the population attribute in the primary and secondary estimand definition was revised from

- Adult **participants** with treatment-naïve macular edema secondary to RVO

to

- Adult **patients** with treatment-naïve macular edema secondary to RVO.

It has been stated in the CSP Section 9.3.2.3 that an additional sensitivity analysis will be performed to account for important protocol deviations that may potentially affect efficacy for the main analysis of the primary endpoint as described in Section 4.2.2. However, it should be noted that additional ICEs may only be considered for the primary analysis, as stated in Section 4.1.8. Therefore, the sensitivity analysis will not be performed, as it is deemed obsolete in light of any additional ICEs considered for the primary analysis.

Furthermore, the definition of the FAS, as specified in the CSP Section 9.2, has been revised, as described in Section 3.

5. Sample Size Determination

The sample size calculation is based on the primary efficacy estimand and its endpoints, change from baseline in BCVA measured by the ETDRS letter score at Week 36.

The details of the sample size calculations can be found in Section 9.5 of the study protocol.

6. Supporting Documentation

6.1 Appendix 1: Population characteristics

In general, variables defined in this section will have descriptive statistics presented by treatment group and overall. For continuous variables, presentation will include number of observations, mean, standard deviation, minimum, median, and maximum. For categorical variables, presentation will include number and percentage of subjects. Listings will be provided as appropriate.

6.1.1 Demographics and baseline characteristics

All demographic and baseline characteristics will be summarized by treatment group and overall. The descriptive statistics will be presented for the FAS and SAF.

Demographic and baseline assessments to be summarized will include:

- Age at enrollment
- Categorized age: < 55 years, ≥ 55 to < 65 years, ≥ 65 years to < 75 years, ≥ 75 years
- Sex: male, female
- Geographic region: Japan vs. APAC vs Europe vs America
- Ethnicity: Not Hispanic or Latino, Hispanic or Latino
- Race (only subgroups with sufficient sample size)
- Weight (kg)
- Height (cm)
- Body mass index (BMI in kg/m^2)
- BMI (≤ 25 kg/m^2, 25 $kg/m^2 < BMI \leq 30$ kg/m^2, 30 $kg/m^2 < BMI \leq 35$ kg/m^2, $BMI > 35$ kg/m^2)
- Systolic blood pressure
- Diastolic blood pressure
- Baseline BCVA (ETDRS letters score)
- Baseline BCVA: < 60 letters, ≥ 60 letters
- Medical history of hypertension: No, Yes
- Medical history of cerebrovascular disease: No, Yes
- Medical history of ischaemic heart disease: No, Yes
- Medical history of renal impairment: Normal, Mild, Moderate, Severe
- Medical history of hepatic impairment: No, Yes
- Baseline intraocular pressure (IOP in mmHg)
- Baseline CST (in µm)

- Baseline National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25, total score)
- Baseline presence of perifoveal and parafoveal ischemia by FA
- Baseline total area of macular ischemia by FA
- Baseline presence of retinal areas of non-perfusion outside the macula by FA

6.1.2 Medical History

The medical history will be coded according to the version of Medical Dictionary for Regulatory Activities (MedDRA) available at database lock. An evaluation of medical history will be conducted through a frequency table, which will show the number of participants with medical history findings by primary system organ class (SOC) and preferred term (PT). The ocular medical or surgical history of the study eye, ocular medical or surgical history of the fellow eye, and non-ocular medical or surgical history will be summarized, respectively. All summaries will be presented for the SAF. Furthermore, a listing that includes medical history records will be provided.

6.1.3 Exposure and Compliance to Study Intervention

Compliance and exposure to the study intervention will be analyzed for SAF using descriptive statistics. Specifically, data up to Week 36 will be utilized for the analysis at Week 36, and data up to Week 64 will be used for the analysis at Week 64.

6.1.3.1 Compliance

The compliance with the study intervention will be assessed at different time points, including the first 36 weeks, and 64 weeks, or until premature discontinuation. The calculation of compliance per participant will be as follows:

Compliance = (Number of actual study interventions received during the specified period) / (Number of planned study interventions during the specified period) x 100%.

For example, if a participant discontinues the study after Week 20 but before or at Week 24, the denominator will be 6, representing the number of planned injections until before Week 24. In the calculation of compliance, all injections, regardless of being sham or active and whether they were scheduled or unscheduled study interventions, will be considered.

The compliance data will be summarized for all periods, and a listing will be prepared to provide an overview of the compliance levels.

6.1.3.2 Exposure

For each participant, the following variables will be used to summarize the exposure to the study intervention in the study eye, including both scheduled and unscheduled interventions:

Based on actual injections:

- Total number of active injections
- Total number of sham injections
- Total amount of active study treatment (mg)

- Duration of study intervention calculated in weeks as: [(date of last study intervention prior to Week 36/ Week 64) – (date of first study intervention) +28]/7; 28 days are added because of the minimum 4-week dosing interval in the study

Based on assigned intervals as determined through IVRS based on the DRM criteria:

- Proportion of participants with specific treatment intervals (analyses up to Week 36 will only be performed for the Week 36 analysis, while analyses up to Week 64 will only be performed for the Week 64 analysis.)
    - For the 2mg group, the proportion of participants with 8 week or longer treatment interval from W32 through Week 64 (i.e., all participants extended to 8 week interval at the W32 visit for whom it was not planned to have their interval shortened to 4 week interval [according to DRM criteria] prior to Week 64).
    - For the 8mg/3 and 8mg/5 groups, the proportion of participants with 8 week or longer treatment interval through Week 36 and Week 64 (i.e. all participants on 8 week interval for whom it was not planned to have their interval shortened to 4 week interval [according to DRM criteria] prior to Week 36 and prior to Week 64, respectively).
    - Proportion of participants with 8 week or longer treatment interval as the last intended treatment interval at Week 36 and Week 64 in 8mg/3 and 8mg/5 groups, respectively (based on DRM criteria assessed at the last visit with active injection before Week 36 and Week 64, respectively).
    - Proportion of participants with 8 week or longer treatment interval as the last intended treatment interval at Week 36 and Week 64 in the 2mg group, (based on DRM criteria assessed at the Week 32 visit and the last visit with active injection before Week 64, respectively).
- Proportion of participants shortening treatment intervals.
- Proportion of participants extending treatment intervals (only for Week 64 analysis).
- Proportion of participants with q4, q8, q12, or q16, as the last intended treatment interval (only for Week 64 analysis)
- Proportion of participants with q4, q8, q12, or q16, as the last completed treatment interval (only for Week 64 analysis)
- Proportion of participants shortening treatment interval at W16, W24, W32 (only for 8/3 arm)
- Proportion of participants shortening treatment interval at W24, W32 (only for 8/5 arm)
- Proportion of participants never extending treatment interval (only for Week 64 analysis)

It's important to note that these exposure variables do not consider temporary interruptions in the study intervention.

Exposure to the study intervention will be summarized for the following periods:

- From Baseline to Week 36 (excluding intervention data at Week 36) - summary to be included for the Week 36 analysis
- From Baseline to Week 36 (excluding intervention data at Week 36, only participants considered as completers for Week 36) - summary to be included for the Week 36 analysis
- From Baseline to Week 64 (only participants considered as completers for Week 64) – summary to be displayed for the Week 64 analysis
- From Baseline to end of the study (Week 64) – summary to be displayed for the Week 64 analysis
- From Week 36 to the end of the study (Week 64) – summary to be displayed for the Week 64 analysis

For each participant who received concomitant fellow eye treatment (as defined in Section 4.1.6), the following variables will be shown for SAF only:

- Total number of injections in fellow eye
- Participants without concomitant fellow eye treatment
- Participants with concomitant fellow eye treatment
    - Aflibercept (trade name: Eylea)
    - Bevacizumab (trade name: Avastin)
    - Brolucizumab (trade name: Beovu)
    - Ranibizumab (trade name: Lucentis)
    - Faricimab (trade name: Vabysmo)
    - Conbercept (trade name: Lumitin)
    - Pegaptanib sodium (trade name: Macugen)

Listings will provide information on the participants' exposure duration, the number of sham and active injections, and participants who met DRM criteria will be listed separately.

6.1.4 Disposition of Study Participants

The disposition of participants will be descriptively summarized in the following categories:

- The total number of participants who signed informed consent, were randomized, treated, completed study intervention and completed study for the respective analysis (Week 36 and Week 64). The summary will include all participants who gave informed consent. Participants who prematurely discontinued the study/study intervention will be summarized by reason for discontinuation.
- A summary table will include the total number and percentage of participants who qualified as FAS, SAF, and PKS (as defined in Section 3), including the reasons for exclusion from the respective analysis set.
- The disposition of participants who signed the informed consent will be summarized overall and by study site, including the date of first consent, date of last visit, and the number of participants with informed consent and in each analysis set.

- The disposition of participants and the number of sites in regions and countries will be presented for all randomized patients. Totals of all regions and within a country will be added.
- The number of participants with important protocol deviations will be presented by country and study site for all participants with signed informed consent. The number of screen failures will also be included. A second summary will show the number and percentage of participants in each protocol deviation category for the FAS. The important protocol deviations will be listed for the FAS.
- The distribution of observed ICE for the primary and key secondary estimands will be summarized by treatment group.

6.1.5 Prior and Concomitant Medication

Prior and concomitant medication or therapy will be coded to Anatomical Therapeutic Chemical (ATC) classification codes according to the version of World Health Organization Drug Dictionary (WHO Drug Dictionary) available at database lock. The number and percentage of participants who took at least one prior and (new) concomitant medication and by ATC class (level 1) and subclass (level 2) will be presented for the SAF. Prior medication refers to medication taken before the start of the study drug intake, regardless of when it ended, while concomitant medication refers to medication taken during the treatment phase, between the first and last study drug intake, regardless of when it started or ended. Prior and concomitant medication for all medications will be summarized. A listing including reason for use, start and end dates and dosage information will be provided for the SAF. Participants with prior and concomitant medication will be summarized for all medications. The treatment of the fellow eye (as defined in Section 4.1.6) will be collected as concomitant medication. A listing of all prior and concomitant medication will be provided. The definitions of concomitant medications and prior medications will be used as defined above.

6.2 Appendix 2: Pre-defined Laboratory Abnormalities

Table 6-1: Pre-defined laboratory abnormalities

Parameter	Pre-defined laboratory abnormalities for phase 2/3 studies
Clinical chemistry	
ALT	> 3 ULN
AST	> 3 ULN
Alkaline Phosphatase	> 1.5 ULN
Total Bilirubin	> 1.5 ULN
Conjugated bilirubin	> 35% total bilirubin (when total bilirubin >1.5 ULN)
ALT and Total Bilirubin	ALT > 3 ULN and Total Bilirubin > 2 ULN
CPK	> 3 ULN
Creatinine	>= 150 umol/L (1.7 mg/dL) (Adults) ≥ 30% from baseline
Uric Acid	Hyperuricemia: > 408 umol/L (6.86 mg/dL) Hypouricemia: < 120 umol/L (2.02 mg/dL)
Blood Urea Nitrogen	> 1.5 ULN
Chloride	< 80 mmol/L > 115 mmol/L
Sodium	≤ 129 mmol/L ≥ 160 mmol/L
Potassium	< 3 mmol/L ≥ 5.5 mmol/L
Total Cholesterol	>= 7.74 mmol/L (299.3 mg/dL)
Triglycerides	>= 4.6 mmol/L (407.3 mg/dL)
Glucose	
- Hypoglycaemia	Hypoglycaemia: <= 3.9 mmol/L (70.3 mg/dL) and < LLN
- Hyperglycaemia	>= 11.1 mmol/L (200 mg/dL, unfasted), >= 7 mmol/L (126.1 mg/dL, fasted)
Albumin	<= 2.5 g/dL
Hematology	
WBC	< 3.0 GIGA/L (non-Black), < 2.0 GIGA/L (Black), ≥ 16.0 GIGA/L
Lymphocytes	> 4.0 GIGA/L
Neutrophils	< 1.5 GIGA/L (non-Black) < 1.0 GIGA/L (Black)
Monocytes	> 0.7 GIGA/L
Basophils	> 0.1 GIGA/L
Eosinophils	> 0.5 GIGA/L or > ULN if ULN ≥ 0.5 GIGA /L
Hemoglobin	Males: <= 11.5 g/dL (7.14 mmol/L), Females: <= 9.5 g/dL (5.9 mmol/L) Decrease from baseline >= 2.0 g/dL (1.24 mmol/L) Males: >= 18.5 g/dL (11.48 mmol/L), Females: >= 16.5 g/dL (10.24 mmol/L)
Hematocrit	Males: <= 37 %, Females: <= 32 % Males: >= 55 %, Females: >= 50 %
RBC	≥ 6 TERA/L
Platelets	< 100 GIGA/L

LLN: lower limit of normal, ULN: upper limit of normal

6.3 Appendix 3: Definition of safety subgroups

In the following the definitions for subgroups based on medical history and adverse events are given.

6.3.1 Hypertension

Hypertension will be selected based on the PTs as described in Table 6-2 below, following the PBMQ 1275. All PTs given are based on MedDRA version 26.0 and might be subject to change in future MedDRA version.

Table 6-2: PTs for selection of "Hypertension"

Preferred term (MedDRA version 26.0)
Accelerated hypertension
Blood pressure ambulatory increased
Blood pressure diastolic increased
Blood pressure inadequately controlled
Blood pressure increased
Blood pressure systolic increased
Diastolic hypertension
Endocrine hypertension
Essential hypertension
Hypertension
Hypertension neonatal
Hypertensive angiopathy
Hypertensive cardiomegaly
Hypertensive cardiomyopathy
Hypertensive cerebrovascular disease
Hypertensive crisis
Hypertensive emergency
Hypertensive encephalopathy
Hypertensive end-organ damage
Hypertensive heart disease
Hypertensive nephropathy
Hypertensive urgency
Labile hypertension
Malignant hypertension
Malignant hypertensive heart disease
Malignant renal hypertension
Maternal hypertension affecting foetus
Mean arterial pressure increased
Neurogenic hypertension
Nocturnal hypertension
Orthostatic hypertension
Page kidney
Prehypertension
Renal hypertension
Renovascular hypertension
Retinopathy hypertensive
Supine hypertension
Systolic hypertension
White coat hypertension

6.3.2 Intraocular inflammation

Intraocular inflammation will be defined as either PBMQ 1854 Infectious Intraocular Inflammations (Eylea) or PBMQ 1855 Non-Infectious Intraocular Inflammation (Eylea), as described in Table 6-3 below. All PTs given are based on MedDRA version 26.0 and might be subject to change in future MedDRA version.

Table 6-3: PTs for selection of "Intraocular Inflammation"

Preferred term (MedDRA version 26.0)
Anterior chamber fibrin
Anterior chamber cell
Anterior chamber flare
Anterior chamber inflammation
Aqueous fibrin
Autoimmune uveitis
Candida endophthalmitis
Chorioretinitis
Choroiditis
Cyclitis
Endophthalmitis
Eye infection bacterial
Eye infection chlamydial
Eye infection fungal
Eye infection intraocular
Eye infection staphylococcal
Eye infection
Eye inflammation
Hypopyon
Infectious iridocyclitis
Infective iritis
Infective uveitis
Iridocyclitis
Iritis
Mycotic endophthalmitis
Necrotising retinitis
Non-infectious endophthalmitis
Noninfective chorioretinitis
Pseudoendophthalmitis
Uveitis
Vitreal cells
Vitreous fibrin
Vitritis

6.3.3 Nasal mucosal events

Nasal mucosal events will be defined as PBMQ - SMQ_90001902 Nasal Mucosal Events (Eylea), as described in Table 6-4 below. All PTs given are based on MedDRA version 26.0 and might be subject to change in future MedDRA version.

Table 6-4: PTs for selection of "Nasal mucosal events"

Preferred term (MedDRA version 26.0)
Epistaxis
Nasal inflammation
Nasal mucosal erosion
Nasal mucosal ulcer
Nasal ulcer

6.3.4 Medical history of cerebrovascular disease (e.g. CVA / Stroke)

Defined by MSSO SMQ 20000060 'Central nervous system vascular disorders as described in Table 6-5 below. All PTs given are based on MedDRA version 26.0 and might be subject to change in future MedDRA version.

Table 6-5: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 26.0)
Agnosia
Amaurosis fugax
Amyloid related imaging abnormalities
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits
Amyloid related imaging abnormality-oedema/effusion
Angiogram cerebral abnormal
Aphasia
Balint's syndrome
Basal ganglia haematoma
Basal ganglia haemorrhage
Basal ganglia infarction
Basal ganglia stroke
Basilar artery aneurysm
Basilar artery occlusion
Basilar artery perforation
Basilar artery stenosis
Basilar artery thrombosis
Benedikt's syndrome
Blood brain barrier defect
Brachiocephalic arteriosclerosis
Brachiocephalic artery occlusion
Brachiocephalic artery stenosis
Brain hypoxia
Brain injury
Brain stem embolism
Brain stem haematoma
Brain stem haemorrhage
Brain stem infarction

Table 6-5: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 26.0)
Brain stem ischaemia
Brain stem microhaemorrhage
Brain stem stroke
Brain stem thrombosis
Brain stent insertion
CADASIL
CARASIL syndrome
CSF bilirubin positive
CSF red blood cell count positive
Capsular warning syndrome
Carotid aneurysm rupture
Carotid angioplasty
Carotid arterial embolus
Carotid arteriosclerosis
Carotid artery aneurysm
Carotid artery bypass
Carotid artery disease
Carotid artery dissection
Carotid artery dolichoectasia
Carotid artery insufficiency
Carotid artery occlusion
Carotid artery perforation
Carotid artery restenosis
Carotid artery stenosis
Carotid artery stent insertion
Carotid artery stent removal
Carotid artery thrombosis
Carotid endarterectomy
Carotid revascularisation
Central nervous system haemorrhage
Central nervous system vasculitis
Central pain syndrome
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebellar atherosclerosis
Cerebellar embolism
Cerebellar haematoma
Cerebellar haemorrhage
Cerebellar infarction
Cerebellar ischaemia
Cerebellar microhaemorrhage

Table 6-5: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 26.0)
Cerebellar stroke
Cerebral amyloid angiopathy
Cerebral aneurysm perforation
Cerebral aneurysm ruptured syphilitic
Cerebral arteriosclerosis
Cerebral arteriovenous malformation haemorrhagic
Cerebral arteritis
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery perforation
Cerebral artery restenosis
Cerebral artery stenosis
Cerebral artery stent insertion
Cerebral artery thrombosis
Cerebral capillary telangiectasia
Cerebral cavernous malformation
Cerebral circulatory failure
Cerebral congestion
Cerebral cyst haemorrhage
Cerebral endovascular aneurysm repair
Cerebral gas embolism
Cerebral haematoma
Cerebral haemorrhage
Cerebral haemorrhage foetal
Cerebral haemorrhage neonatal
Cerebral haemosiderin deposition
Cerebral hypoperfusion
Cerebral infarction
Cerebral infarction foetal
Cerebral ischaemia
Cerebral microangiopathy
Cerebral microembolism
Cerebral microhaemorrhage
Cerebral microinfarction
Cerebral reperfusion injury
Cerebral revascularisation
Cerebral septic infarct
Cerebral small vessel ischaemic disease
Cerebral thrombosis
Cerebral vascular occlusion
Cerebral vasoconstriction

Table 6-5: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 26.0)
Cerebral venous sinus thrombosis
Cerebral venous thrombosis
Cerebral ventricular rupture
Cerebrovascular accident
Cerebrovascular accident prophylaxis
Cerebrovascular arteriovenous malformation
Cerebrovascular disorder
Cerebrovascular insufficiency
Cerebrovascular pseudoaneurysm
Cerebrovascular stenosis
Charcot-Bouchard microaneurysms
Chronic cerebrospinal venous insufficiency
Claude's syndrome
Congenital cerebrovascular anomaly
Congenital hemiparesis
Delayed ischaemic neurological deficit
Diplegia
Dural arteriovenous fistula
Dysarthria
Embolic cerebellar infarction
Embolic cerebral infarction
Embolic stroke
Epidural haemorrhage
Extra-axial haemorrhage
Extradural haematoma
Extradural haematoma evacuation
Extraischaemic cerebral haematoma
Foetal cerebrovascular disorder
Foville syndrome
Haemorrhage intracranial
Haemorrhagic cerebellar infarction
Haemorrhagic cerebral infarction
Haemorrhagic stroke
Haemorrhagic transformation stroke
Heidelberg classification
Hemianaesthesia
Hemiasomatognosia
Hemiataxia
Hemidysaesthesia
Hemihyperaesthesia
Hemihypoaesthesia

Table 6-5: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 26.0)
Hemiparaesthesia
Hemiparesis
Hemiplegia
Hunt and Hess scale
Hypertensive cerebrovascular disease
Hypoxic-ischaemic encephalopathy
Inner ear infarction
Internal capsule infarction
Internal carotid artery deformity
Intra-cerebral aneurysm operation
Intracerebral haematoma evacuation
Intracranial aneurysm
Intracranial artery dissection
Intracranial haematoma
Intracranial haemorrhage neonatal
Intracranial tumour haemorrhage
Intraventricular haemorrhage
Intraventricular haemorrhage neonatal
Ischaemic cerebral infarction
Ischaemic stroke
Lacunar infarction
Lacunar stroke
Lateral medullary syndrome
Lateropulsion
Malignant middle cerebral artery syndrome
Medullary compression syndrome
Meningorrhagia
Metabolic stroke
Migrainous infarction
Millard-Gubler syndrome
Modified Rankin score decreased
Modified Rankin score increased
Monoparesis
Monoplegia
Moyamoya disease
NIH stroke scale abnormal
NIH stroke scale score decreased
NIH stroke scale score increased
Paralysis
Paraparesis
Paraplegia

Table 6-5: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 26.0)
Paresis
Perinatal stroke
Periventricular haemorrhage neonatal
Pituitary apoplexy
Pituitary haemorrhage
Post cardiac arrest syndrome
Post procedural stroke
Post stroke depression
Posthaemorrhagic hydrocephalus
Precerebral arteriosclerosis
Precerebral artery aneurysm
Precerebral artery dissection
Precerebral artery embolism
Precerebral artery occlusion
Precerebral artery thrombosis
Primary familial brain calcification
Pseudo-occlusion of internal carotid artery
Putamen haemorrhage
Quadriparesis
Quadriplegia
Reversible cerebral vasoconstriction syndrome
Reversible ischaemic neurological deficit
Right hemisphere deficit syndrome
Ruptured cerebral aneurysm
Septic cerebral embolism
Sigmoid sinus thrombosis
Sneddon's syndrome
Spinal artery embolism
Spinal artery thrombosis
Spinal cord haematoma
Spinal cord haemorrhage
Spinal cord infarction
Spinal cord ischaemia
Spinal epidural haematoma
Spinal epidural haemorrhage
Spinal stroke
Spinal subarachnoid haemorrhage
Spinal subdural haematoma
Spinal subdural haemorrhage
Spinal vascular disorder
Spinal vessel congenital anomaly

Table 6-5: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 26.0)
Stroke in evolution
Subarachnoid haematoma
Subarachnoid haemorrhage
Subarachnoid haemorrhage neonatal
Subclavian steal syndrome
Subdural haematoma
Subdural haematoma evacuation
Subdural haemorrhage
Subdural haemorrhage neonatal
Superficial siderosis of central nervous system
Superior sagittal sinus thrombosis
Susac's syndrome
Thalamic infarction
Thalamus haemorrhage
Thrombotic cerebral infarction
Thrombotic stroke
Transient ischaemic attack
Transverse sinus thrombosis
Vascular encephalopathy
Vascular stent occlusion
Vascular stent stenosis
Vein of Galen aneurysmal malformation
Vertebral artery aneurysm
Vertebral artery arteriosclerosis
Vertebral artery dissection
Vertebral artery occlusion
Vertebral artery perforation
Vertebral artery stenosis
Vertebral artery thrombosis
Vertebrobasilar dolichoectasia
Vertebrobasilar insufficiency
Vertebrobasilar stroke
Visual agnosia
Visual midline shift syndrome
Weber's syndrome

6.3.5 Medical history of ischaemic heart disease (e.g., myocardial infarction)

PBMQ SMQ_90001278 'Medical history of myocardial infarction (VEGF Trap-Eye)' is defined by selected PTs only (from MSSO SMQs below):

- 20000043: Ischaemic heart disease (MSSO SMQ)

- 20000047: Myocardial infarction (MSSO SMQ)

as described in Table 6-6 below. All PTs given are based on MedDRA version 26.0 and might be subject to change in future MedDRA version.

Table 6-6: PTs for selection of medical history of "Ischaemic Heart Disease"

Preferred Term (MedDRA version 26.0)
Acute coronary syndrome
Acute myocardial infarction
Angina pectoris
Angina unstable
Anginal equivalent
Arterial revascularisation
Arteriogram coronary abnormal
Arteriosclerosis coronary artery
Arteriospasm coronary
Cardiac perfusion defect
Cardiac ventricular scarring
Chronic coronary syndrome
Computerised tomogram coronary artery abnormal
Coronary angioplasty
Coronary arterial stent insertion
Coronary artery bypass
Coronary artery compression
Coronary artery disease
Coronary artery dissection
Coronary artery embolism
Coronary artery insufficiency
Coronary artery occlusion
Coronary artery reocclusion
Coronary artery restenosis
Coronary artery stenosis
Coronary artery surgery
Coronary artery thrombosis
Coronary brachytherapy
Coronary bypass stenosis
Coronary bypass thrombosis
Coronary endarterectomy
Coronary no-reflow phenomenon
Coronary ostial stenosis
Coronary revascularisation
Coronary steal syndrome
Coronary vascular graft occlusion
Coronary vascular graft stenosis
ECG electrically inactive area

Table 6-6: PTs for selection of medical history of "Ischaemic Heart Disease"

Preferred Term (MedDRA version 26.0)
ECG signs of myocardial infarction
ECG signs of myocardial ischaemia
Electrocardiogram PR segment depression
Electrocardiogram PR segment elevation
Electrocardiogram ST segment abnormal
Electrocardiogram ST segment depression
Electrocardiogram ST segment elevation
Electrocardiogram ST-T segment abnormal
Electrocardiogram ST-T segment depression
Electrocardiogram ST-T segment elevation
External counterpulsation
Haemorrhage coronary artery
Infarction
Ischaemic cardiomyopathy
Ischaemic contracture of the left ventricle
Kounis syndrome
Myocardial hypoperfusion
Myocardial hypoxia
Myocardial infarction
Myocardial ischaemia
Myocardial necrosis
Myocardial reperfusion injury
Myocardial stunning
Papillary muscle infarction
Percutaneous coronary intervention
Periprocedural myocardial infarction
Positive vessel remodelling
Post angioplasty restenosis
Post procedural myocardial infarction
Postinfarction angina
Prinzmetal angina
Scan myocardial perfusion abnormal
Silent myocardial infarction
Stent patency maintenance
Stress cardiomyopathy
Subclavian coronary steal syndrome
Subendocardial ischaemia
Vascular device occlusion
Vascular graft occlusion
Vascular graft restenosis
Vascular graft stenosis

Table 6-6: PTs for selection of medical history of "Ischaemic Heart Disease"

Preferred Term (MedDRA version 26.0)
Vascular graft thrombosis
Vascular stent occlusion
Vascular stent stenosis
Ventricular compliance decreased
Wellens' syndrome

6.3.6 Medical history of renal impairment

Renal impairment is defined by creatinine clearance (CrCl) values.

Categories for renal impairment:

- CLCR >80ml/min (normal),
- CLCR >50-80ml/min (mild),
- CLCR >30-50 ml/min (moderate),
- CLCR <=30ml/min or 'requiring dialysis' (severe).

CLCR will be calculated using baseline values (creatinine, age, weight, sex) using the Cockcroft-Gault equation:

Males: CLCR = (140-age)*body weight / (72*creatinine)

Females: CLCR = (140-age)*body weight*0.85 / (72*creatinine)

PBMQ SMQ_90001274 'Medical History of renal impairment requiring dialysis (VEGF Trap-Eye)' is defined by PT from Table 6-7. All PTs given are based on MedDRA version 26.0 and might be subject to change in future MedDRA version.

Table 6-7: PTs for selection of medical history of renal impairment requiring dialysis

Preferred Term (MedDRA version 26.0)
Continuous haemodiafiltration
Dialysis
Dialysis device insertion
Haemodialysis
Haemofiltration
Peritoneal dialysis
Removal of renal transplant
Renal replacement therapy
Renal transplant

6.3.7 Medical history of hepatic impairment

Defined by MSSO SMQ: Hepatic disorders 20000005 excluding sub-SMQ 20000018: Pregnancy-related hepatic disorders as described in Table 6-8 below. All PTs given are based on MedDRA version 26.0 and might be subject to change in future MedDRA version.

Table 6-8: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 26.0)
5'nucleotidase increased
AST to platelet ratio index increased
AST/ALT ratio abnormal
Accessory liver lobe
Acquired antithrombin III deficiency
Acquired factor IX deficiency
Acquired factor V deficiency
Acquired factor VIII deficiency
Acquired factor XI deficiency
Acquired hepatocerebral degeneration
Acquired protein S deficiency
Acute graft versus host disease in liver
Acute hepatic failure
Acute hepatitis B
Acute hepatitis C
Acute on chronic liver failure
Acute yellow liver atrophy
Adenoviral hepatitis
Alagille syndrome
Alanine aminotransferase abnormal
Alanine aminotransferase increased
Alcoholic encephalopathy
Alcoholic liver disease
Allergic hepatitis
Alloimmune hepatitis
Ammonia abnormal
Ammonia increased
Anorectal varices
Anorectal varices haemorrhage
Anti factor X activity abnormal
Anti factor X activity decreased
Anti factor X activity increased
Anti-liver cytosol antibody type 1 positive
Antithrombin III decreased
Ascites
Aspartate aminotransferase abnormal
Aspartate aminotransferase increased

Table 6-8: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 26.0)
Asterixis
Asymptomatic viral hepatitis
Autoimmune hepatitis
Bacterascites
Benign hepatic neoplasm
Benign hepatobiliary neoplasm
Benign recurrent intrahepatic cholestasis
Bile output abnormal
Bile output decreased
Biliary ascites
Biliary cirrhosis
Biliary fibrosis
Bilirubin conjugated abnormal
Bilirubin conjugated increased
Bilirubin excretion disorder
Bilirubin urine present
Biopsy liver abnormal
Blood alkaline phosphatase abnormal
Blood alkaline phosphatase increased
Blood bilirubin abnormal
Blood bilirubin increased
Blood bilirubin unconjugated increased
Blood cholinesterase abnormal
Blood cholinesterase decreased
Blood fibrinogen abnormal
Blood fibrinogen decreased
Blood thrombin abnormal
Blood thrombin decreased
Blood thromboplastin abnormal
Blood thromboplastin decreased
Bromosulphthalein test abnormal
Cardiohepatic syndrome
Cerebrohepatorenal syndrome
Child-Pugh-Turcotte score abnormal
Child-Pugh-Turcotte score increased
Cholaemia
Cholangiosarcoma
Cholestasis
Cholestatic liver injury
Cholestatic pruritus
Chronic graft versus host disease in liver
Chronic hepatic failure

Table 6-8: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 26.0)
Chronic hepatitis
Chronic hepatitis B
Chronic hepatitis C
Cirrhosis alcoholic
Coagulation factor IX level abnormal
Coagulation factor IX level decreased
Coagulation factor V level abnormal
Coagulation factor V level decreased
Coagulation factor VII level abnormal
Coagulation factor VII level decreased
Coagulation factor X level abnormal
Coagulation factor X level decreased
Coagulation factor decreased
Coma hepatic
Complications of transplanted liver
Computerised tomogram liver abnormal
Congenital absence of bile ducts
Congenital hepatic fibrosis
Congenital hepatitis B infection
Congenital hepatitis C infection
Congenital hepatobiliary anomaly
Congenital hepatomegaly
Congenital viral hepatitis
Congestive hepatopathy
Cryptogenic cirrhosis
Cystic fibrosis hepatic disease
Cytokeratin 18 increased
Cytomegalovirus hepatitis
Deficiency of bile secretion
Diabetic hepatopathy
Dilatation intrahepatic duct congenital
Drug-induced liver injury
Duodenal varices
Fatty liver alcoholic
Flood syndrome
Focal nodular hyperplasia
Foetor hepaticus
Galactose elimination capacity test abnormal
Galactose elimination capacity test decreased
Gallbladder varices
Gamma-glutamyltransferase abnormal
Gamma-glutamyltransferase increased

Table 6-8: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 26.0)
Gastric variceal injection
Gastric variceal ligation
Gastric varices
Gastric varices haemorrhage
Gastrooesophageal variceal haemorrhage prophylaxis
Gianotti-Crosti syndrome
Glutamate dehydrogenase increased
Glycocholic acid increased
Glycogen storage disease type I
Glycogen storage disease type III
Glycogen storage disease type IV
Glycogen storage disease type VI
Graft versus host disease in liver
Granulomatous liver disease
Guanase increased
HBV-DNA polymerase increased
Haemangioma of liver
Haemorrhagic ascites
Haemorrhagic hepatic cyst
Hepaplastin abnormal
Hepaplastin decreased
Hepatectomy
Hepatic adenoma
Hepatic amoebiasis
Hepatic angiosarcoma
Hepatic artery flow decreased
Hepatic atrophy
Hepatic calcification
Hepatic cancer
Hepatic cancer metastatic
Hepatic cancer recurrent
Hepatic cancer stage I
Hepatic cancer stage II
Hepatic cancer stage III
Hepatic cancer stage IV
Hepatic candidiasis
Hepatic cirrhosis
Hepatic cyst
Hepatic cyst infection
Hepatic cyst ruptured
Hepatic cytolysis
Hepatic echinococciasis

Table 6-8: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 26.0)
Hepatic encephalopathy
Hepatic encephalopathy prophylaxis
Hepatic enzyme abnormal
Hepatic enzyme decreased
Hepatic enzyme increased
Hepatic failure
Hepatic fibrosis
Hepatic fibrosis marker abnormal
Hepatic fibrosis marker increased
Hepatic function abnormal
Hepatic gas gangrene
Hepatic haemangioma rupture
Hepatic hamartoma
Hepatic hydrothorax
Hepatic hypertrophy
Hepatic hypoperfusion
Hepatic infection
Hepatic infection bacterial
Hepatic infection fungal
Hepatic infection helminthic
Hepatic infiltration eosinophilic
Hepatic lesion
Hepatic lipoma
Hepatic lymphocytic infiltration
Hepatic mass
Hepatic necrosis
Hepatic neoplasm
Hepatic neuroendocrine tumour
Hepatic pain
Hepatic perfusion disorder
Hepatic sarcoma
Hepatic sequestration
Hepatic steato-fibrosis
Hepatic steatosis
Hepatic vascular resistance increased
Hepatic venous pressure gradient abnormal
Hepatic venous pressure gradient increased
Hepatitis
Hepatitis A
Hepatitis A antibody abnormal
Hepatitis A antibody positive
Hepatitis A antigen positive

Table 6-8: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 26.0)
Hepatitis A immunity confirmed
Hepatitis A virus test positive
Hepatitis B
Hepatitis B DNA assay positive
Hepatitis B DNA increased
Hepatitis B antibody abnormal
Hepatitis B antibody positive
Hepatitis B antigen positive
Hepatitis B core antibody positive
Hepatitis B core antigen positive
Hepatitis B e antibody positive
Hepatitis B e antigen positive
Hepatitis B immunity confirmed
Hepatitis B reactivation
Hepatitis B surface antibody positive
Hepatitis B surface antigen positive
Hepatitis B virus test positive
Hepatitis C
Hepatitis C RNA increased
Hepatitis C RNA positive
Hepatitis C antibody positive
Hepatitis C core antibody positive
Hepatitis C virus test positive
Hepatitis D
Hepatitis D RNA positive
Hepatitis D antibody positive
Hepatitis D antigen positive
Hepatitis D virus test positive
Hepatitis E
Hepatitis E RNA positive
Hepatitis E antibody abnormal
Hepatitis E antibody positive
Hepatitis E antigen positive
Hepatitis E immunity confirmed
Hepatitis E virus test positive
Hepatitis F
Hepatitis G
Hepatitis H
Hepatitis acute
Hepatitis alcoholic
Hepatitis cholestatic
Hepatitis chronic active

Table 6-8: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 26.0)
Hepatitis chronic persistent
Hepatitis fulminant
Hepatitis infectious mononucleosis
Hepatitis mumps
Hepatitis neonatal
Hepatitis non-A non-B
Hepatitis non-A non-B non-C
Hepatitis post transfusion
Hepatitis syphilitic
Hepatitis toxic
Hepatitis toxoplasmal
Hepatitis viral
Hepatitis viral test positive
Hepato-lenticular degeneration
Hepatobiliary cancer
Hepatobiliary cancer in situ
Hepatobiliary cyst
Hepatobiliary disease
Hepatobiliary infection
Hepatobiliary neoplasm
Hepatobiliary scan abnormal
Hepatoblastoma
Hepatoblastoma recurrent
Hepatocellular carcinoma
Hepatocellular damage neonatal
Hepatocellular foamy cell syndrome
Hepatocellular injury
Hepatomegaly
Hepatopulmonary syndrome
Hepatorenal failure
Hepatorenal syndrome
Hepatosplenic abscess
Hepatosplenic candidiasis
Hepatosplenomegaly
Hepatosplenomegaly neonatal
Hepatotoxicity
Hereditary haemochromatosis
Herpes simplex hepatitis
Hyperammonaemia
Hyperbilirubinaemia
Hyperbilirubinaemia neonatal
Hypercholia

Table 6-8: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 26.0)
Hyperfibrinolysis
Hypertransaminasaemia
Hypoalbuminaemia
Hypocoagulable state
Hypofibrinogenaemia
Hypoprothrombinaemia
Hypothrombinaemia
Hypothromboplastinaemia
Icterus index increased
Immune-mediated cholangitis
Immune-mediated hepatic disorder
Immune-mediated hepatitis
Increased liver stiffness
International normalised ratio abnormal
International normalised ratio increased
Intestinal varices
Intestinal varices haemorrhage
Intrahepatic portal hepatic venous fistula
Ischaemic hepatitis
Jaundice
Jaundice cholestatic
Jaundice hepatocellular
Jaundice neonatal
Kayser-Fleischer ring
Kernicterus
Leucine aminopeptidase increased
Liver abscess
Liver and pancreas transplant rejection
Liver carcinoma ruptured
Liver dialysis
Liver disorder
Liver function test abnormal
Liver function test decreased
Liver function test increased
Liver induration
Liver injury
Liver iron concentration abnormal
Liver iron concentration increased
Liver opacity
Liver operation
Liver palpable
Liver sarcoidosis

Table 6-8: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 26.0)
Liver scan abnormal
Liver tenderness
Liver transplant
Liver transplant failure
Liver transplant rejection
Liver-kidney microsomal antibody positive
Lupoid hepatic cirrhosis
Lupus hepatitis
Magnetic resonance imaging hepatobiliary abnormal
Magnetic resonance proton density fat fraction measurement
Mitochondrial aspartate aminotransferase increased
Mixed hepatocellular cholangiocarcinoma
Mixed liver injury
Model for end stage liver disease score abnormal
Model for end stage liver disease score increased
Molar ratio of total branched-chain amino acid to tyrosine
Multivisceral transplantation
Necrolytic acral erythema
Neonatal cholestasis
Neonatal hepatomegaly
Nodular regenerative hyperplasia
Non-alcoholic fatty liver
Non-alcoholic steatohepatitis
Non-cirrhotic portal hypertension
Ocular icterus
Oedema due to hepatic disease
Oesophageal varices haemorrhage
Omental oedema
Osteopontin increased
Parenteral nutrition associated liver disease
Perihepatic discomfort
Perinatal HBV infection
Peripancreatic varices
Periportal oedema
Peritoneal fluid protein abnormal
Peritoneal fluid protein decreased
Peritoneal fluid protein increased
Peritoneovenous shunt
Pneumobilia
Polycystic liver disease
Porphyria acute
Porphyria non-acute

Table 6-8: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 26.0)
Portal fibrosis
Portal hypertension
Portal hypertensive colopathy
Portal hypertensive enteropathy
Portal hypertensive gastropathy
Portal pyaemia
Portal shunt
Portal shunt procedure
Portal tract inflammation
Portal vein cavernous transformation
Portal vein dilatation
Portal vein flow decreased
Portal vein pressure increased
Portal venous system anomaly
Portopulmonary hypertension
Primary biliary cholangitis
Progressive familial intrahepatic cholestasis
Protein C decreased
Protein S abnormal
Protein S decreased
Prothrombin level abnormal
Prothrombin level decreased
Prothrombin time abnormal
Prothrombin time prolonged
Prothrombin time ratio abnormal
Prothrombin time ratio increased
Radiation hepatitis
Regenerative siderotic hepatic nodule
Renal and liver transplant
Retinol binding protein decreased
Retrograde portal vein flow
Reye's syndrome
Reynold's syndrome
Schistosomiasis liver
Small-for-size liver syndrome
Spider naevus
Splenic artery embolisation
Splenic varices
Splenic varices haemorrhage
Splenorenal shunt
Splenorenal shunt procedure
Spontaneous bacterial peritonitis

Table 6-8: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 26.0)
Spontaneous intrahepatic portosystemic venous shunt
Steatohepatitis
Stomal varices
Subacute hepatic failure
Sugiura procedure
Sustained viral response
Thrombin time abnormal
Thrombin time prolonged
Total bile acids increased
Transaminases abnormal
Transaminases increased
Ultrasound liver abnormal
Urine bilirubin increased
Urobilinogen urine decreased
Urobilinogen urine increased
Varices oesophageal
Varicose veins of abdominal wall
Viral hepatitis carrier
Weil's disease
White nipple sign
Withdrawal hepatitis
X-ray hepatobiliary abnormal
Yellow skin
Zieve syndrome

6.4 Appendix 4: Handling of Questionnaires

6.4.1 NEI-VFQ-25 Sub-scale Scores and Total Score

The calculation for NEI-VFQ-25 sub-scale scores and total score will be performed according to The National Eye Institute (2000). The algorithm is then: As a preparation of the VFQ-25 calculation, the items of the questionnaire will be recoded according to Table 6-9. In the further calculations, only the recoded item values will be used. For the recoded values, they generally represent the best possible result as "100" and the worst possible result as "0".

Table 6-9: Recoding of NEI-VFQ 25 items

Item no.	Original response to	Recoded item
1, 3, 4, 15c[(a)]	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 16a	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
17, 18, 19, 20, 21, 22, 23, 24, 25	1	0
	2	25
	3	50
	4	75
	5	100

[(a)] Item 15c has four-response levels but is expanded to a five-levels using item 15b: if 15b="1", then 15c="0" / if 15b=("2" or "3"), then 15c="missing"

* Here, Response choice "6" indicates that the person does not perform the activity because of non-vision-related problems. If this choice is selected, the item is coded as "missing".

For the VFQ questionnaire, 12 sub-scales will be evaluated (see Table 6-10), and 11 of these sub-scales will be included in the total VFQ score.

Table 6-10: Sub-scales of the NEI-VFQ 25 score

Sub-scale no.	Sub-scale	Number of items	(Recoded) items to be averaged	Sub-scale included in total scale
1	General Health	1	1	No
2	General Vision	1	2	Yes
3	Ocular Pain	2	4, 19	Yes
4	Near Activities	3	5, 6, 7	Yes
5	Distance Activities	3	8, 9, 14	Yes
	Vision specific:			
6	Social Functioning	2	11, 13	Yes
7	Mental Health	4	3, 21, 22, 25	Yes
8	Role Difficulties	2	17, 18	Yes
9	Dependency	3	20, 23, 24	Yes
10	Driving	3	15c, 16, 16a	Yes
11	Color vision	1	12	Yes
12	Peripheral Vision	1	10	Yes

For a single sub-scale, the value will be determined as the average of the non-missing recoded item values assigned to this sub-scale. A sub-scale value will only be assessed as missing if all items for this sub-scale have "missing" as a result.

The total score is calculated as the arithmetic mean of all non-missing sub-scales (except General Health):

$$total\ result = \frac{(sum\ of\ non\ -missing\ sub-\ scale\ values)}{Total\ number\ of\ sub-\ scales\ with\ non\ -missing\ result}$$

Due to this calculation approach, the total result will be non-missing if at least one sub-scale result is non-missing.

6.5 Appendix 5: Strategies for displaying Summary Statistics

The strategies for displaying summary statistics based on the primary estimand and for utilizing imputation of missing data with LOCF are presented in Table 6-11 and Table 6-12, respectively.

Table 6-11: Strategies for displaying Summary Statistics in line with the primary estimand

Intercurrent event	Analysis
Premature discontinuation of study intervention for any reason before Week 36	and discontinuation of study: non-observed data beyond discontinuation of study intervention will not be included in the summary statistics and continuation of study: observed data beyond last active injection (that was administered before the premature discontinuation of study intervention) + current treatment interval +5 days will be excluded from summary statistics
Use of a prohibited medication (as per section 4.1.7) before Week 36	Observed data beyond first administration of the prohibited medication in study eye will be excluded from the summary statistics
Missed active injection resulting in an actual injection interval up to 4 weeks longer than planned	All observed data will be included in the summary statistics
Missed active injection resulting in an actual injection interval more than 4 weeks longer than planned	Observed data beyond last active injection (that was administered before the first missed active injection) + current treatment interval +5 days will be excluded from the summary statistics

Table 6-12: Strategies for displaying Summary Statistic using imputation of missing values with LOCF.

Intercurrent event	Analysis
Premature discontinuation of study intervention for any reason before Week 36	and discontinuation of study: non-observed data beyond discontinuation of study intervention will be imputed using LOCF and continuation of study: observed data beyond last active injection (that was administered before the premature discontinuation of study intervention) + current treatment interval +5 days will be excluded from summary statistics and imputed by LOCF
Use of a prohibited medication (as per section 4.1.7) before Week 36	Observed data beyond first administration of the prohibited medication in study eye will be excluded from the summary statistics and resulting missing data will be imputed by LOCF.
Missed active injection resulting in an actual injection interval up to 4 weeks longer than planned	All observed data will be included in the summary statistics
Missed active injection resulting in an actual injection interval more than 4 weeks longer than planned	Observed data beyond last active injection (that was administered before the first missed active injection) + current treatment interval +5 days will be excluded from summary statistics and imputed by LOCF

6.6 Appendix 6: Identification of intake of prohibited medications and cases of prohibited procedures

To identify any intake of prohibited medications (see Section 4.1.7), Table 6-13 provides a list of corresponding WHO drug names and record numbers. The list is based on the specific medications mentioned in Section 4.1.7 and additionally on observed concomitant medications during study conduct meeting the definition in Section 4.1.7 as of finalization of this statistical analysis plan. The list may be updated before unmasking and this would be documented in a separate document.

Table 6-13: Preliminary list of prohibited medication by drug names (may be updated before unmasking of the data)

WHO Drug Name	WHO Drug Record Number	WHO Drug Sequence Number 1	WHO Drug Sequence Number 2
Aflibercept	062254	01	any
Bevacizumab	015552	01	any
Brolucizumab	088687	01	any
Conbercept	073395	01	any

Faricimab	156766	01	any
Pegaptanib sodium	022285	02	any
Ranibizumab	020889	01	any
Ocriplasmin	079085	01	001
Dexamethasone (Ozurdex)	000160	01	404

As for prohibited procedures (also see Section 4.1.7), cases of vitrectomy surgery will be identified from the Surgical, Diagnostic and Therapeutic Procedure(s) page using the standardized procedure name “Vitrectomy”. Cases of retinal laser photocoagulation for the treatment of RVO will be identified based on a dedicated protocol deviation (PD) category (PD Term: Subject received laser therapy for treatment of their macular edema secondary to RVO in the study eye.).

7. References

1. Gasparyan SB, Folkvaljon F, Bengtsson O, Buenconsejo J, Koch GG. Adjusted win ratio with stratification: Calculation methods and interpretation. *Statistical Methods in Medical Research*. 2021;30(2):580-611. doi:10.1177/0962280220942558
2. Efron, B., and Tibshirani, R. J. (1993). An Introduction to the Bootstrap. New York, NY: Chapman and Hall. doi: 10.1007/978-1-4899-4541-9
3. Heitjan, F., and Little, R. J. A. (1991). “Multiple Imputation for the Fatal Accident Reporting System.” Journal of the Royal Statistical Society, Series C 40:13–29
4. Holz FG, Roider J, Ogura Y, Korobelnik JF, Simader C, Groetzbach G, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. Br J Ophthalmol. 2013;97(3):278-84.
5. Ratitch B, Lipkovich I, O’Kelly M. Combining Analysis Results from Multiply Imputed Categorical Data. PharmaSUG 2013 - Paper SP0.
6. Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, Mitchell P, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. Ophthalmology. 2010;117(2):313-9.e1.
7. Rubin D E. Multiple Imputation for Nonresponse in Surveys. Wiley. 1987
8. Schenker, N., and Taylor, J. M. G. (1996). “Partially Parametric Techniques for Multiple Imputation.” Computational Statistics and Data Analysis 22:425–446.
9. Stokes ME, Davis CS, Koch GG. Categorical Data Analysis Using SAS, Third Edition. SAS Institute, 2012