NOVARTIS

Clinical Development

RTH258/Brolucizumab

CRTH258C2301/ NCT03802630

CRTH258C2302 / NCT03810313

An Eighteen-Month, Two-Arm, Randomized, Double-Masked, Multi-center, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Macular Edema secondary to Branch Retinal Vein Occlusion (*RAPTOR)* and to Central Retinal Vein Occlusion (*RAVEN*)

Statistical Analysis Plan (SAP)

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List of abbreviations

ADA	Anti-drug antibody
AE	Adverse Event
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Classification
ATE	Arterial Thromboembolic Event
BCVA	Best Corrected Visual Acuity
BLQ	Below the Limit of Quantification
BRVO	Branch retinal vein occlusion
CF	Color Fundus photography
CFT	Central foveal thickness
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRVO	Central retinal vein occlusion
CSFT	Central subfield thickness (average thickness of circular 1mm area centered around fovea measured from RPE to ILM, inclusively)
CSR	Clinical Study Report
DBL	Database lock
DMC	Data Monitoring Committee
DSA	Disease stability assessment
eCRS	Electronic case retrieval strategy
EoS	End of Study
EoT	End of Treatment
ETDRS	Early treatment diabetic retinopathy study
FA	Fluorescein angiography
FAS	Full analysis set
HRVO	Hemiretinal vein occlusion
IFT	Individualized flexible treatment
IOP	Intraocular Pressure
IRT	Interactive Response Technology
IRF	Intraretinal fluid
ISFT	Inner subfield thickness
IVT	Intravitreal
KM	Kaplan Meier
LLOQ	Lower Limit of Quantification
LOCF	Last observation carried forward
MAR	Missing at random
ME	Macular Edema
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MH	Medical History
mL	Millilitres

MMRM	Mixed model for repeated measures
[redacted]	[redacted]
NEI	National Eye Institute
OCT	Optical Coherence Tomography
PD	Protocol Deviation
PPS	Per protocol set
PT	Preferred Term
q4w	Every 4 weeks
RAS	Randomized analysis set
RoW	Rest of World
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical analysis system
SD	Standard deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Standard Error
SOC	System Organ Class
SRF	Subretinal fluid
TEAE	Treatment-Emergent Adverse Event
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VFQ-25	Visual Functioning Questionnaire-25
WCF	Wide-field color fundus photography
WFA	Wide-field fluorescein angiography
WHO	World Health Organization

1 Introduction

Study CRTH258C2301 and CRTH258C2302 are terminated following the DMC recommendation on May 26, 2021 based on safety imbalance for adverse events. All the ongoing patients are discontinued from the study on the next scheduled visit. A database lock will be done once the clinical database is complete and cleaned. The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analyses planned in the protocol for study CRTH258C2301 (referred to as RAPTOR in this document), and CRTH258C2302 (referred to as RAVEN in this document) where applicable as well as new analyses deemed appropriate for early discontinued study.

A full clinical study report (CSR) will be created based on the analyses specified on this SAP including all data up to the end of the study visit (when a patient completed the study or discontinued from the study).

[redacted]

1.1 Study design

The study RAPTOR is an 18-month, randomized, double-masked, multi-center, active-controlled, non-inferiority, 2-arm study in subjects with visual impairment due to ME secondary to branch retinal vein occlusion (BRVO). The study RAVEN is an 18-month, randomized, double-masked, multi-center, active-controlled, non-inferiority, 2-arm study in subjects with visual impairment due to ME secondary to central retinal vein occlusion (CRVO).

In both studies, subjects who consent will undergo screening assessments to determine their eligibility. Subjects who meet all the predefined inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio to one of 2 treatment arms:

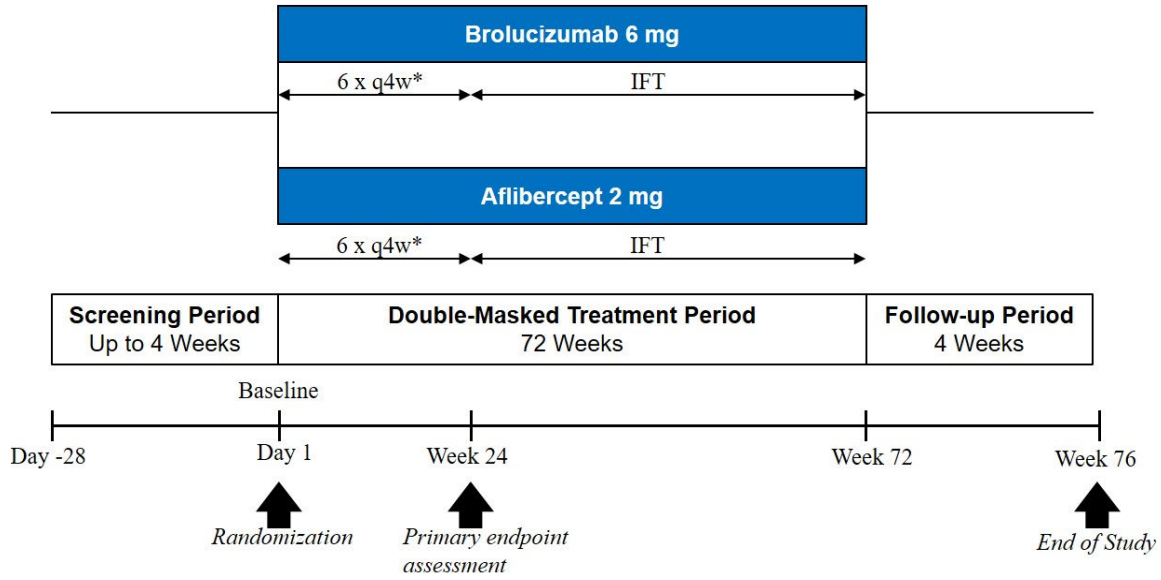
- Brolucizumab 6 mg: 6 x q4w followed by 48 weeks of individualized flexible treatment (IFT) from Week 24 onwards
- Aflibercept 2 mg: 6 x q4w followed by 48 weeks of IFT from Week 24 onwards

The randomization will be stratified by the following demographic groups: Japanese region, Chinese region (including Taiwan and Hong Kong), and rest of world (RoW) region for both studies. The maximum study duration for each subject is 80 weeks, including screening and safety follow-up.

In RAPTOR, approximately 625 adult subjects are planned to be screened (20% screening failure rate expected) so that approximately 500 subjects (250 per arm, 10% dropout rate expected) will be randomized in a 1:1 ratio in approximately 110 centers worldwide.

For the RAVEN study, approximately 938 adult patients are planned to be screened (20% screening failure rate expected) so that approximately 750 patients (375 per arm, 10% dropout rate expected) will be randomized in a 1:1 ratio in approximately 160 centers worldwide.

Figure 1-1 Study design



*Loading phase; IFT: Individualized flexible treatment

1.2 Study objectives and endpoints

The primary endpoint is at Week 24. The primary, secondary, [redacted] objectives and the corresponding endpoints planned on the protocol are listed in Table 1-1. A subset of the secondary objectives are considered in the testing strategy and details will be provided in section 2.6.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the change in best-corrected visual acuity (BCVA) from baseline up to Month 6	• Change from baseline in BCVA at Week 24
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the effect of brolucizumab as compared to aflibercept on best-corrected visual acuity (BCVA)	• Change from baseline in BCVA averaged over Week 40 to Week 52 and Week 64 to Week 76 • Change from baseline in BCVA by visit up to Week 76 • Proportion of study eyes with a gain ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline • Proportion of study eyes with a loss ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline
• To evaluate the anatomical outcome with brolucizumab relative to aflibercept	• Change from baseline in central subfield thickness (CSFT) averaged over Week 40 to Week 52 and Week 64 to Week 76 • Change from baseline in CSFT by visit up to Week 76 • Proportion of study eyes with presence of retinal fluid (intra- and/or subretinal fluid) by visit up to Week 76

Objective(s)	Endpoint(s)
	• Proportion of study eyes with a CSFT < 300 µm by visit up to Week 76
• To evaluate the treatment frequency with brolucizumab during the individualized flexible treatment (IFT) period relative to aflibercept	• Number of injections between Week 24 and Week 52 and between Week 24 and Week 72 • Time to recurrence after Week 20 and up to Week 76
• To assess the safety and tolerability of brolucizumab relative to aflibercept	• Incidence of ocular and non-ocular AEs up to [redacted] Week 76
• To evaluate the effect of brolucizumab relative to aflibercept on patient-reported vision-related quality of life	• Change from baseline in patient reported outcomes (NEI VFQ-25) at Week 24, Week 52 and Week 76
• To assess the immunogenicity of brolucizumab	• Anti-drug antibody status at screening and Week 4, Week 12, Week 24, Week 36, Week 52 and Week 76
[redacted]	

2 Statistical methods

2.1 Data analysis general information

[redacted]

Unless otherwise stated, all tables/figures/listings will be on all patients in the respective analysis sets. Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), standard errors (SE), median, quartiles, minimum and maximum values. Categorical variables will be summarized including n, frequencies and percentages.

The regions of Chinese, Japanese, and RoW are used as randomization factor to support local submission in China and Japan but is not expected to be a predictor for treatment effect. Therefore, statistical models will not be adjusted by region.

2.1.1 General definitions

Study treatment

Study treatment, or Investigational Product (IP) or study drug, refers to both Brolucizumab 6mg and Aflibercept 2mg intravitreal (IVT) injections.

Study day

Day 1 is defined as the date of first dose of study treatment (Brolucizumab or Aflibercept). Study day is defined as the number of days since the date of first dose of study treatment (Day 1).

Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the date of first administration of study treatment:

  Study day = Assessment date – Date of first dose of study treatment + 1;

- for dates prior to the date of first administration of study treatment:

  Study day = Assessment date – Date of first dose of study treatment.

Baseline

The baseline value is defined as the last assessment performed prior to administration of the first dose of study treatment.

All data collected after first study treatment are defined as post-baseline.

End of study/end of treatment day mapping

The EoS date is the date when a patient completes or discontinues the study, i.e., the "Disposition Event Date" from the "disposition" case report form (CRF) for study disposition.

The end of treatment (EoT) date is the date when a patient completes or discontinues the study treatment, i.e., the "Disposition Event Date" from the "disposition" CRF for treatment disposition.

The "Date of Last Exposure" (from "Study treatment" CRF form) is the date of the last study treatment or sham injection on or prior to the EoT date.

For reporting data by visit in outputs, the EoS/EoT date will be allocated to the actual (reported) visit number. If EoS/EoT date is not on a scheduled visit, then the EoS/EoT date will be allocated, based on study day, to the future unattended study visit. The target day for Week X visit is calculated as 7X+1.

Unscheduled visits

Data collected at unscheduled visits will not be used in 'by-visit' tabulations or graphs, but will be included in analyses based on all post-baseline values such as last observation carried forward (LOCF) imputation, and summary of maximum decrease/increase from baseline or abnormal findings during the study for pre-specified endpoints. These data will not be used in analyses with mixed model for repeated measures (MMRM).

All data collected at unscheduled visits will be included in listings.

Missing and imputable dates

The general approach to handling missing dates is described in Section 5.1.

OCT reading result for "Cannot Grade"

For subgroup definition or model factors based on the endpoints related to presence of fluids at baseline, if baseline visit is reported as "Cannot Grade", then it will be considered as "Absent".

If post-baseline visit is reported as "Cannot Grade", then it will be considered as missing where the endpoint is treated as a binary variable.

Prohibited therapy, Rescue therapy, and Alternative treatment for ME secondary to RVO

The prohibited medication/procedures are defined in the protocol ([section 6.2.2]). The application of such medications captured as PD (i.e., COMD01, prohibited medication and/or procedure with impact on efficacy and/or safety) during the study treatment period will be considered as an intercurrent event for efficacy analysis.

The rescue therapy is the application of macular laser photocoagulation on or after Week 24 and before the EoT.

The alternative treatment for ME secondary to RVO refers to the application of the treatments specified on the table below to the study eye. It is only applicable to treatment started on or after the discontinuation from study treatment date. The use of alternative treatment will not be captured as a PD but may be considered as an intercurrent event.

Table 2-1 Potential alternative treatment for ME secondary to RVO in the study eye

- Ranibizumab (Lucentis)
- Aflibercept (Eylea)
- Bevacizumab (Avastin, off-label use)
- Laser photocoagulation
- Steroids:
  - Dexamethasone (Ozurdex)
  - Fluocinolone acetonide (Iluvien)
  - Triamcinolone (off-label use)

2.2 Analysis sets

Subject exclusion rules for each analysis set based on the specific protocol deviations (PDs) will be specified in Section 5.6. Before the DBL, the relevant PDs will be identified and entered in the database.

All-Enrolled Analysis Set: The All-enrolled Analysis Set includes all subjects who signed informed consent and are assigned subject numbers.

Randomized Analysis Set (RAS) consists of all randomized subjects. Subjects are considered randomized when they have been given a randomization number, except for misrandomized subjects. An accidental or premature randomization of a subject without providing study medication is considered as a misrandomized subject. Subjects will be analyzed according to the treatment assigned to at randomization. The RAS will be used for the summaries of subject disposition, protocol deviation, demographics, baseline characteristics, and medical history data.

Full Analysis Set (FAS) includes all randomized subjects who receive at least one IVT injection of the study treatment. The full analysis set will serve as the primary analysis set for all efficacy analyses. Subjects in the FAS will be analyzed according to the treatment assigned to at randomization. The FAS will be used for all efficacy analyses, unless otherwise specified.

Per Protocol Set (PPS) is a subset of the FAS and will exclude subjects or data points with pre-specified PDs and other non-PD related criteria that are expected to majorly affect the validity of the assessment of the primary endpoint at Week 24. PPS will be used in supportive analyses of the primary endpoint.

Safety Analysis Set (SAF) includes all subjects who receive at least one IVT injection. Subjects in the SAF will be analyzed according to the actual treatment received during the study. If a subject received both study treatments accidentally during the study, he/she will be analyzed according to the treatment to which he/she was exposed for longer in duration during the study treatment period. The SAF will be used for all safety analyses, including concomitant medication/surgical and medical procedures, treatment exposure, as well as anti-drug antibody (ADA) status.

2.2.1 Subgroups of interest

Subgroup analyses are conducted to assess consistency of the treatment effect among the subgroups and will not apply multiplicity adjustments. The following subgroups will be evaluated for the primary endpoint of change from baseline in BCVA at Week 24:

- Age category (< 65, ≥ 65 years)
- Sex (male, female, undifferentiated, unknown)
- Baseline BCVA categories (≤ 34, ≥ 35 - ≤ 55, ≥ 56 letters)
- Duration of ME (≤ 3, > 3 months)
- Baseline CSFT (< 450, ≥ 450 - ≤ 650, > 650 μm)
- Baseline status of intraretinal fluid (IRF) (presence, absence)
- Baseline status of subretinal fluid (SRF) (presence, absence)
- Region (Japanese, Chinese, Rest of World)
- Impact to COVID-19 (with impact, without impact) up to Week 24 (defined in Section 5.8)

2.3 Subject disposition, demographics and other baseline characteristics

No inferential testing on the differences in subject disposition, demographics and other baseline characteristics between treatment arms will be performed.

2.3.1 Subject disposition

The number and percentage of subjects who were screened but not randomized will be summarized based on All-enrolled Analysis Set. The rescreened subjects will only be counted once and based on the final disposition status. The reasons for screen failures will also be listed.

The following disposition status will be summarized based on the RAS:

- The number and percentage of subjects who receive study treatment and who complete the study treatment
- The number and percentage of subjects who complete the study
- The number and percentage of subjects who discontinue from study treatment as well as the primary reason for discontinuation on or prior to Week 24, Week 52, and Week 72 (EoT)
- The number and percentage of subjects who discontinue from the study as well as the primary reason for discontinuation on or prior to Week 24, Week 52, and Week 76 (EoS)

In addition, listings of subjects who discontinue from the study and/or treatment along with the primary reason and the study day of discontinuation will be provided by treatment.

The number and percentage of subjects in each analysis set will be presented by treatment group for the RAS. In addition, PDs and non-PD events (if applicable) that lead to subject exclusion from PPS will be summarized by deviation category, deviation terms and treatment for the RAS. Number and percentage of subjects with PDs will be presented by deviation category and treatment. Due to the COVID-19 pandemic, higher number PDs are expected. To evaluate the PDs that occurred due to COVID-19, the number and percentage of subjects with PDs that occurred due to COVID-19 outbreak will also be provided by deviation category and treatment. A listing of all PDs will be provided by treatment and subject including the information if the PD leads to the subject exclusion from an analysis set and the relationship to COVID-19 if the PD is due to COVID-19.

2.3.2 Demographic characteristics

Demographic characteristics, including gender, race, ethnicity, age, age categories (<65 and ≥ 65 years) and region will be summarized with descriptive statistics for the RAS by treatment and overall.

Demographic characteristics will also be summarized by the following subgroups:

- COVID-19 impacted and non-impacted up to Week 24 (defined in Section 5.8)
- COVID-19 impacted and non-impacted up to Week 76

2.3.3 Ocular baseline characteristics

The summary of baseline ocular characteristics will be provided by treatment group using the RAS for the study eye and listed separately for the study eye and the fellow eye.

Ocular baseline characteristics include:

- The study eye selection (left eye, i.e., OS or right eye, i.e., OD)
- The number and percentage of patients with macular edema secondary to hemiretinal vein occlusion (HRVO) in the RAVEN study
- Time (months) since the primary diagnosis of macular edema secondary to BRVO or CRVO/HRVO as continuous variable and categories (≤ 3, > 3 months)

- Baseline best corrected visual acuity (BCVA) as continuous variable and categories (≤ 34, 35 - 55, ≥ 56 letters)
- Baseline anatomical and retinal pathology outcomes:
    - central subfield thickness (CSFT, µm) as continuous variable and categories (< 450, 450 - 650, > 650 µm)
    - The presence of IRF in the central subfield (present, absent, cannot grade)
    - The presence of SRF in the central subfield (present, absent, cannot grade)
    - The presence of IRF or SRF in the central subfield (present, absent, cannot grade)
    - The presence of macular capillary non-perfusion

Duration of macular edema secondary to BRVO or CRVO/HRVO since diagnosis (months) will be derived as [(first dose date – diagnosis date + 1)/365.25X12]. In case of partial dates, the imputation rule is specified in Section 5.1.4.

Baseline disease characteristics will also be summarized by the following subgroups:

- COVID-19 impacted and non-impacted up to Week 24 (defined in Section 5.8)
- COVID-19 impacted and non-impacted up to Week 76

2.3.4 Medical history

Any condition entered on the Medical History (MH) CRF, and any surgical and medical procedures taken and stopped prior to first dose of study treatment entered on the Therapies and Procedures (PR) CRF, will be coded using the MedDRA dictionary. Relevant medical history and current medical conditions will be summarized for ocular (study eye) and non-ocular events for the RAS. Listing will also be provided.

2.4 Treatments (study treatment concomitant therapies, compliance)

2.4.1 Study treatment/compliance

For each subject, the extent of exposure to study treatment is estimated as the total number of intravitreal (IVT) injections of study treatment received. The summary of the total number of IVT injections will be provided by treatment and time period as follows: from first dose up to the end of the loading phase (i.e., Week 20), from first dose up to Week 52, and from first dose up to the EoT for the Safety Set.

Exposure data and disease stability assessment (DSA) will be listed by visit for both treatment arms.

2.4.2 Prior, concomitant medications or surgical/medical procedures

Prior medications are defined as therapies taken and stopped prior to first dose of study treatment. Concomitant medications/surgical and medical procedures are defined as therapies received after the start of study treatment including those already started prior to the initiation of the study treatment. Medications/surgical and medical procedures will be categorized into

one (and only one) of the above classes based on recorded or imputed start and end dates. When incomplete or missing, dates will be imputed according to Section 5.1.3.

Prior and concomitant medication will be coded according to the WHO Drug Reference List dictionary, with Anatomical Therapeutic Classification (ATC) class 4 (i.e., Therapeutic/Pharmacological subgroup), if missing, the next higher level of ATC class will be used, and preferred term (PT). Ocular on the study eye and non-ocular prior and concomitant medications will be summarized by ATC class and PT for each treatment arm.

Concomitant surgical and medical procedures will be coded using the MedDRA dictionary and summarized by system organ class (SOC) and PT for the study eye.

The following listings will be provided for prior and concomitant medications as well as surgical and medical procedures for the Safety Set:

- Ocular and non-ocular prior and concomitant medications, concomitant surgical and medical procedures
- Alternative treatment for ME secondary to RVO on the study eye

Concomitant anti-VEGF medications will be summarized for the Safety Set by ATC class and preferred term for non-ocular route, the study eye and the fellow eye separately. Alternative treatment for ME secondary to RVO on the study eye on/after treatment discontinuation will be summarized by preferred term.

2.5 Analysis of the primary endpoint

This is a non-inferiority study. Non-inferiority will be considered established if the lower limit of the corresponding 95% CI for the estimated between group difference (brolucizumab vs. aflibercept) on change from baseline in BCVA at Week 24 is greater than -4 letters. Two-sided P-value for treatment comparison and one-sided p-value for non-inferiority testing will be provided.

2.5.1 Primary Estimand

The primary estimand for the primary endpoint includes the following components:

Population: Subjects with visual impairment due to ME secondary to BRVO/CRVO.

Endpoint: The primary endpoint is the change from baseline in BCVA at Week 24. BCVA will be assessed by the masked investigator using ETDRS-like charts at an initial distance of 4 meters.

Treatment of interest: The randomized study treatment (brolucizumab or aflibercept).

The handling of the remaining intercurrent events:

- Treatment discontinuation for any reason: ignore (treatment policy strategy)
- Data after the start of PD COMD01 (prohibited medication and/or procedure with impact on efficacy and/or safety) or alternative medication will be censored

Summary measure: Difference in the change from baseline in BCVA at Week 24 between brolucizumab and aflibercept treatment groups.

2.5.2 Statistical hypothesis, model, and method of analysis

The objective related to the primary endpoint is to demonstrate non-inferiority of brolucizumab versus aflibercept with respect to the change from baseline in BCVA at Week 24, assuming a non-inferiority margin of 4 ETDRS letters.

Let:

B = Brolucizumab 6 mg - 6 x q4w loading

A = Aflibercept 2 mg - 6 x q4w loading

Consider the following non-inferiority hypotheses related to a non-inferiority margin of 4 letters:

H_0: $\mu_B - \mu_A \leq$ -4 letters versus H_A: $\mu_B - \mu_A >$ -4 letters

where μ_B and μ_A are the corresponding unknown true mean changes from baseline in BCVA at Week 24 in the brolucizumab and aflibercept arms, respectively.

The primary hypothesis will be tested via an analysis of variance (ANOVA) model based on the FAS. The ANOVA model will include treatment, baseline BCVA ($\leq$ 34, 35 - 55, $\geq$ 56 letters) and age category (< 65, $\geq$ 65 years) as factors. The least square mean and two-sided 95% confidence interval (CI) for change from baseline in BCVA at Week 24 for each treatment arm as well as the difference (brolucizumab vs. aflibercept) will be presented. Descriptive analyses based on observed data will be provided for the FAS population.

2.5.3 Handling of missing values/censoring/discontinuations

The handling of the intercurrent events for the primary estimand is as below:

- Treatment discontinuation for any reason: ignore (treatment policy strategy)
- Data after the start of PD COMD01 (prohibited medication and/or procedure with impact on efficacy and/or safety) or alternative medication will be censored

As stated in Table 2-2, missing and censored BCVA values will be imputed by LOCF as the primary approach for the primary estimand. Observed values from both scheduled and unscheduled post-baseline visits will be used for the LOCF imputation. For subjects with no post-baseline BCVA value, the baseline value will be carried forward.

From an estimand perspective, the main focus on defining the primary estimand is to adequately reflect in the analysis unfavorable study outcomes related to the treatment (e.g., lack of efficacy, safety events). Data after the application of prohibited medications/procedures or alternative treatment for ME secondary to RVO will be censored. LOCF will then be based on the last value prior to the start of such treatment, expecting that this value would reflect the negative BCVA outcome under study treatment. The LOCF approach is expected to be sensitive to an early study termination due to lack of efficacy, assuming that such lack of efficacy is reflected in the last observed BCVA measurement before or at the time of the early study termination. In case of early study termination due to lack of safety/tolerability with impairment of the function of the study eye, the LOCF method would also provide a sensitive approach to capture such an unfavorable outcome.

LOCF is an established method within the assessment of efficacy of anti-VEGF treatments in terms of BCVA outcome. It is important to note that, in order to facilitate a meaningful treatment effect assessment, non-inferiority studies should follow the main design features (primary variables, the dose of the active comparator, eligibility criteria, etc.) as the previously conducted superiority trials in which the active comparator demonstrated clinically relevant efficacy. In the aflibercept Phase III studies COPERNICUS and GALILEO (CRVO) and VIBRANT (BRVO) missing BCVA data was imputed based on LOCF.

The major reason for missing BCVA assessment at Week 24 is discontinuation from study due to early study termination and this will result in data missing completely at random. The BCVA change from baseline is increasing very fast in the first several months then stabilized without much change. The application of LOCF is assuming the treatment effect at Week 24 is the same as the time when a patient discontinued from the study before Week 24, which may introduce an under- or overestimate of the between group difference if the BCVA improvement is responding slower or faster for brolucizumab compared to aflibercept early in the study. To consider the trajectory of the BCVA response to study treatment up to Week 24, the sensitivity analyses using Mixed Model Repeated Measure (MMRM) specified in Section 2.5.4.1 will be evaluated along with the primary method.

2.5.4 Supportive analyses

Sensitivity and supportive analyses for the primary endpoint, i.e., change from baseline in BCVA at Week 24, are planned and specified in Table 2-2.

The same approach for non-inferiority assessment in change from baseline in BCVA at Week 24 will be applied to sensitivity analysis and supplementary estimand. When assessing the robustness of the non-inferiority conclusions, considerations will be given to the analysis based on the primary estimand using FAS and the analysis based on the supplementary estimand using PPS, i.e., similar conclusions on non-inferiority based on both estimands are expected. Inconsistencies in the results will be examined and discussed in the CSR.

Table 2-2 Primary and supplementary estimands

Estimand	Analysis set	Analysis	Statistical methods (including missing/censored data strategy)
Primary	FAS	Primary analysis	ANOVA model including terms for treatment, baseline BCVA ≤ 34, 35 - 55, ≥ 56 letters) and age category (< 65, ≥ 65 years). Using LOCF imputation for missing/censored data.
		Sensitivity analysis	MMRM including fixed effect terms for treatment, visit, visit by treatment interaction, baseline BCVA (≤ 34, 35 - 55, ≥ 56 letters) and age category (< 65, ≥ 65 years) assuming an unstructured covariance matrix, no imputation on missing/censored data.
Supplementary	PPS	Supportive analysis	ANOVA model including terms for treatment, baseline BCVA ≤ 34, 35 - 55, ≥ 56 letters) and age category (< 65, ≥ 65 years). Using LOCF imputation for missing/censored data.

2.5.4.1 Sensitivity analyses on the primary estimand

The primary analysis on the primary estimand using LOCF to impute missing/censored data based on the assumption that the effect of the initially randomized treatment at the intake of the prohibited medications/procedures or alternative treatment for ME secondary to RVO remains constant to the end of the loading phase.

The sensitivity analysis to the LOCF/ANOVA method on the primary estimand is using MMRM, a model-based method assuming data missing at random (MAR). It is assessing the treatment effect of the initially randomized treatments assuming all subjects remained on the randomized treatment throughout the study. The MMRM will include treatment, visit (treated as a categorical variable), baseline BCVA category, age category and treatment by visit interaction as fixed-effect terms, and visit as a repeated measure. An unstructured covariance matrix will be used to model the within-subject error. If the MMRM model assuming unstructured covariance matrix does not converge, a more restricted covariance matrix can be considered in the following order until convergence is reached: compound symmetry (CS), Toeplitz (TOEP), and first-order autoregressive (AR).

Other methods for data imputation may be explored if the proportion of subjects with missing or censored data is deemed large enough so as to potentially impact the results from the primary analysis.

2.5.4.2 Supportive analysis using a supplementary estimand

The primary endpoint, the treatment of interest and the summary measure of the supplementary estimand are the same as for the primary estimand. Different from the primary estimand, the target population includes subjects with visual impairment due to ME secondary to BRVO/CRVO, and with no major protocol deviation or with low treatment compliance during loading phase. The details for subject exclusion from PPS can be found in section 5.6 for the PPS population. The handling of the intercurrent events for the supplementary estimand is as below:

- Treatment discontinuation due to lack of efficacy or safety: ignore
- Data after the treatment discontinuation due to other reasons will be censored
- Data after the start of PD COMD01 (prohibited medication and/or procedure with impact on efficacy and/or safety) or alternative medication will be censored
- Data collected on/after the start of PD of OTH01 (Any other protocol deviation with impact on efficacy and/or safety) will be censored

The supportive analysis on the supplementary estimand will apply the same LOCF/ANOVA method as for the primary estimand.

2.5.4.3 Subgroup analysis

The subgroup analyses (subgroups defined in Section 2.2.1) will be explored using the FAS and the same ANOVA model as described for the primary endpoint fitted by category of each subgroup. Subgroup variables that are used as fixed effects in the model will be removed from the model statement for subgroup analysis.

In case of analyses on subgroups with extremely imbalanced sample sizes, the subgroup levels can either be combined, if appropriate, or the extremely small subgroup will be excluded while fitting the analysis model. The point estimate and 95% CI for the between treatment difference for each subgroup will be presented using forest plots.

The COVID-19 related subgroups based on the impact from first treatment up to Week 24 will be included for the analysis of the primary endpoint (subgroups defined in Section 5.8).

2.6 Analysis of selected secondary endpoints

The inferential testing on selected secondary endpoints specified in this section will be performed if the null hypothesis of the primary endpoint is rejected.

2.6.1 Selected secondary endpoint

The selected secondary endpoints are:

1. Proportion of subjects with confirmed disease stability at Week 24
2. Proportion of subjects with retinal fluid in the central subfield (i.e., with IRF and/or SRF) at Week 24
3. CSFT change from baseline at Week 24
4. Time to recurrence after Week 20 and up to Week 76

2.6.2 Statistical hypothesis, model, and method of analysis

The hypotheses on the selected secondary endpoints will be tested hierarchically in the order specified in Section 2.6.1. Within this hierarchical testing approach the testing of a given hypothesis requires rejection of all preceding null hypothesis with a significance level of 0.05. This testing procedure controls the overall two-sided type-I error rate to less than 0.05 within study.

2.6.2.1 Disease stability at Week 24

The null hypothesis is that there is no difference in the proportion of subjects who achieved disease stability at Week 24. Superiority of brolucizumab over aflibercept will be concluded if there is an increase in proportion of subjects (i.e., rate difference>0) achieving disease stability at Week 24 in the brolucizumab arm compared with the aflibercept arm and the two-sided p-value for the between-treatment comparison is less than 0.05. The confirmatory analysis will be conducted on FAS population.

The confirmatory analysis of the proportion of subjects with disease stability at Week 24 will be done based on the FAS using a logistic regression model for response rate (95% CI) in each treatment group. The model will be adjusted by treatment, baseline BCVA categories, baseline CSFT categories and age categories as fixed effects. The rate difference (95% CI) and p-value for between group comparison will be provided using the marginal standardization method.

2.6.2.2 Subjects with IRF and/or SRF in the central subfield at Week 24

The null hypothesis is that there is no difference in the proportion of subjects free of retinal fluid (i.e., no IRF or SRF) in the central subfield at Week 24. Superiority of brolucizumab over

aflibercept will be concluded if higher proportion of subjects are free of retinal fluid at Week 24 in the brolucizumab arm compared with the aflibercept arm and the two-sided p-value for the between-treatment comparison is less than 0.05. The confirmatory analysis will be conducted on FAS population.

The confirmatory analysis of the proportion of subjects free of retinal fluid at Week 24 will be done based on the FAS using a logistic regression model for the mean response rate and 95% CI in each treatment group. The model will be adjusted by treatment, baseline fluid status, and age categories as fixed effects. Marginal standardization method will be used to calculate the rate difference (95% CI) and p-value for between group comparison.

2.6.2.3 CSFT change from baseline at Week 24

The null hypothesis is that there is no difference in the mean CSFT change from baseline at Week 24. Superiority of brolucizumab over aflibercept will be concluded if the reduction at Week 24 is higher in the brolucizumab arm compared with the aflibercept arm and the two-sided p-value for the between-treatment comparison is less than 0.05. The confirmatory analysis will be conducted on FAS population.

The confirmatory analysis of CSFT change from baseline at Week 24 will be done on the FAS using ANOVA model. The model will be adjusted by treatment, baseline CSFT categories, and age categories as fixed effects. The least square mean by treatment and two-sided 95% CI in each treatment group, their difference (95% CI) and p-value for between group comparison will be presented.

2.6.2.4 Time to recurrence after Week 20 and up to Week 76

The null hypothesis is that there is no difference in the time to recurrence after Week 20 and up to Week 76. Superiority of brolucizumab over aflibercept will be concluded if there is a reduction in risk (estimated hazard ratio from Cox-model < 1) between the brolucizumab arm and the aflibercept arm, and the two-sided p-value for the between-treatment comparison is less than 0.05. The confirmatory analysis will be conducted on FAS population.

A recurrence is defined as the need for injection according to the DSA. A subject is considered to have recurrence if showing the lack of disease stability after Week 20 and up to Week 76. For subjects with recurrence after the Week 20 visit, time-to-event is calculated as (first time with the lack of disease stability – the injection date on Week 20 visit + 1). For subjects without recurrence after Week 20, the censoring time will be calculated as (last visit with DSA assessment – the injection date on Week 20 visit + 1). If a subject had a missed injection at Week 20 visit, the visit date of Week 20 will be used for time calculation. If a subject had a missing Week 20 visit, the targeted visit day, i.e. day 141, will be used for time calculation. If a subject did not have any DSA after Week 20 then the subject will be censored at Week 20 visit.

The confirmatory analysis of the time to recurrence will be analyzed for FAS subjects excluding those who discontinue from study treatment on or before Week 20. Kaplan Meier (KM) estimates on percent of subjects with recurrence, together with 95% CI, will be presented for Week 52 and Week 76 visits. The median time (and 95% CI) to recurrence will also be constructed by treatment arm. KM curves presenting the cumulative probability of first injection

on or after Week 20 will be provided by treatment arm. A cox proportional hazards model adjusted for treatment, baseline BCVA categories, baseline CSFT categories, and age categories will be used for the hazard ratio (95% CI) estimate and the p-value for the between-treatment comparison.

2.6.3 Handling of missing values/censoring/discontinuations

2.6.3.1 Disease stability at Week 24

The handling of the intercurrent events for this endpoint is as below:

- With no disease stability at Week 24 if with PD COMD01 (prohibited medication and/or procedure with impact on efficacy and/or safety) on or before Week 24
- With no disease stability at Week 24 if treatment discontinuation due to lack of efficacy or safety on or before Week 24

No data imputation will be applied.

2.6.3.2 Subjects with IRF and/or SRF at Week 24

The handling of the intercurrent events for this endpoint is as below:

- Treatment discontinuation for any reason: ignore (treatment policy strategy)
- Data after the start of PD COMD01 (prohibited medication and/or procedure with impact on efficacy and/or safety) or alternative medication will be censored

Same as for the primary endpoint, missing and censored IRF and/or SRF values will be imputed by LOCF.

2.6.3.3 CSFT change from baseline at Week 24

The handling of the intercurrent events for this endpoint is as below:

- Treatment discontinuation for any reason: ignore (treatment policy strategy)
- Data after the start of PD COMD01 (prohibited medication and/or procedure with impact on efficacy and/or safety) or alternative medication will be censored

Missing and censored CSFT values will be imputed by LOCF.

2.6.3.4 Time to recurrence after Week 20 and up to Week 76

The handling of the intercurrent events for this endpoint is as below:

- Showing the lack of disease stability at the time of treatment discontinuation due to lack of efficacy or safety
- Showing the lack of disease stability at the start of PD COMD01, or rescue therapy

No data imputation will be applied.

2.7 Analysis of secondary efficacy endpoints

2.7.1 Secondary endpoints

Secondary efficacy endpoints based on BCVA:

- Change from baseline in BCVA averaged over Week 40 to Week 52 and Week 64 to Week 76
- Change from baseline in BCVA by visit up to Week 76
- Proportion of study eyes with a gain ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline.
  Note: Subjects with BCVA value of 84 letters or more at a postbaseline visit will be considered as responders for the corresponding endpoint. This is to account for a ceiling effect, e.g. for the' ≥15-letter gain' endpoint, for those subjects with BCVA values at baseline >=70 letters
- Proportion of study eyes with a loss ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline

Secondary efficacy endpoints related to anatomy:

- Change from baseline in central subfield thickness (CSFT) averaged over Week 40 to Week 52 and Week 64 to Week 76
- Change from baseline in CSFT by visit up to Week 76
- Proportion of study eyes with presence of retinal fluid (intraretinal fluid, subretinal fluid, intra- or subretinal fluid) by visit up to Week 76
- Proportion of study eyes with a CSFT < 300 µm by visit up to Week 76

Secondary efficacy endpoints related to treatment frequency:

- Number of injections between Week 24 and Week 52 and between Week 24 and Week 72

Secondary efficacy endpoints related to patient reported outcomes:

- Change from baseline in patient reported outcomes (NEI VFQ-25) at Week 24, Week 52 and Week 76

2.7.2 Statistical hypothesis, model, and method of analysis

No hypotheses will be tested for the secondary efficacy endpoints listed in 2.7.1. Between group difference may be estimated along with the corresponding 95% CI and nominal p-value. Unless otherwise specified, all the analyses will be based on the FAS.

Continuous endpoints:

The following continuous endpoints will be analyzed using ANOVA models on data with LOCF imputation up to Week 24. The estimates of least square means for each treatment arm and for the treatment differences, including 95% CIs, as well as nominal p-value will be presented. The line plot on LSMean (±SE) by visit up to Week 24 will also be provided for each

treatment arm. Summary statistics will also be provided by visit up to end of study based on observed data without data imputation

- BCVA change from baseline: ANOVA models similar to the one specified for the primary endpoint will be used.
- CSFT change from baseline: the ANOVA model will be adjusted by treatment, age category, and baseline CSFT category.

For other continuous endpoints, summary statistics will be provided by visit up to end of study based on observed data without data imputation.

Categorical variables:

For binary endpoints, frequency tables (count and proportion) will be provided by time point based on observed data in FAS. The following categorical endpoint will be analyzed using logistic regression with LOCF imputation by visit up to Week 24. The model will be adjusted by treatment, baseline fluid status, and age categories as fixed effects to calculate the mean response rate and 95% CI in each treatment group. The rate difference (95% CI) and p-value for between group comparison will be provided using the marginal standardization method.

- Proportion of study eyes with presence of retinal fluid (intraretinal fluid, subretinal fluid, intra- or subretinal fluid)

Count variables:

For endpoints on number of injections, the distribution of total number of injections observed between Week 24 and Week 52 and between Week 24 and Week 72 will be summarized in the subset of patients who are on study treatment at Week 52 and the subset of patients who completed the study treatment, respectively. No data censoring will be applied for this endpoints.

2.7.3 Handling of missing values/censoring/discontinuations

Where not specified, the same data censoring rules applied for the primary (Section 2.5) and selected secondary endpoints (Section 2.6) will be followed for the secondary endpoints with similar data type.

2.8 Safety analyses

Safety endpoints are based on the variables from safety assessments which include:

- Extent of exposure (see Section 2.4.1)
- Adverse events
- Ophthalmic examinations
- Vital signs
- Laboratory results

There are no formal safety hypotheses in this study. All safety analyses will be descriptive and performed based on observed data using the SAF. According to the definition of the SAF, subjects will be grouped by the actual treatment received.

The safety analyses will include all treatment-emergent data, i.e., data from first dose of study treatment until the EoS. Sensitivity analyses including all data from first dose of study treatment until the start of an alternative treatment for ME secondary to RVO will also be conducted if specified in the section for the relevant endpoint analysis.

2.8.1 Adverse events (AEs)

A treatment-emergent adverse event (TEAE) is defined as any adverse event that develops or any event already present that worsens on or after the first study treatment date

Adverse events will be coded using the MedDRA dictionary and presented by system organ class (SOC) and preferred term (PT). The MedDRA version used for reporting the study will be described in a footnote on AE related outputs.

The number (and percentage) of subjects with TEAE will be summarized by treatment and presented by the SOCs in alphabetical order and the PTs in descending incidence in the brolucizumab treatment arm and then in the aflibercept treatment arm. A subject with multiple adverse events within a given category is only counted once for summary purposes. Ocular and non-ocular (systemic) AEs will be presented separately; ocular AEs will be presented by study eye and fellow eye separately. AE summaries specified in the table below will be provided. Subject listings of all adverse events will be provided. Deaths and SAE (i.e., other serious or clinically significant non-fatal adverse events) will be listed separately.

Table 2-3 AE summary

TEAE summary	AE categories		
	Ocular AE in the study eye	Ocular AE in the fellow eye	Non-ocular AE
AEs by SOC and PT	Y#	Y	Y#
AEs by SOC and PT (excluding data after the use of alternative treatment for ME secondary to RVO on the study eye after discontinuation from study treatment)	Y		Y
Frequent AEs by PT†	Y		Y
AEs by maximum severity, SOC and PT	Y		Y
AEs related to study treatment by SOC and PT	Y		Y
AEs related to injection procedure by SOC and PT	Y		
AEs leading to permanent discontinuation of study treatment by SOC and PT	Y		Y
AEs leading to temporary interruption of study treatment by SOC and PT	Y		Y
AEs leading to discontinuation from the study by SOC and PT	Y		Y

TEAE summary	AE categories		
	Ocular AE in the study eye	Ocular AE in the fellow eye	Non-ocular AE
SAEs by SOC and PT	Y#	Y	Y#
SAEs by SOC and PT (excluding data after the use of alternative treatment for ME secondary to RVO on the study eye after discontinuation from study treatment)	Y		Y
SAEs related to study treatment by SOC and PT	Y		Y
SAEs related to injection procedure by SOC and PT	Y		
†≥ 2 % (or other cutting point as appropriate) in any treatment group for a given PT. #Including separate summary tables for impacted/non-impacted subjects to COVID-19 by end of the study as defined in Section 5.8.			

2.8.1.1 Adverse events of special interest/grouping of AEs

An adverse event of special interest (AESI) is the one of scientific and medical interest. The AESI for analysis includes, but not limited to:

- Endophthalmitis
- Intraocular Inflammation (excluding infective or viral nature and including retinal vasculitis)
- Retinal vascular occlusion

Incidence of AESI in the study eye will be tabulated by treatment arm. Listing for AESIs will also be provided.

AESIs will be identified via the RTH258 electronic case retrieval strategy (eCRS). The eCRS that is current at the time of the database lock will be used and AESIs will be identified where the flag Core Safety Topic Risk (SP) = 'Y'.

2.8.1.2 Other safety topics of interest

Other safety topics of interest includes, but not limited to, the following Ocular AEs in the study eye or non-ocular AEs:

- Arterial thromboembolic events
- Hypertension
- Intraocular pressure increased transient
- Non-ocular haemorrhage
- Retinal detachment and retinal tear
- Venous thromboembolic events

Incidence of other safety topics of interest will be tabulated by treatment arm. Listing will also be provided. Other safety topics of interest will be identified via the RTH258 eCRS where the flag Core Safety Topic Risk (SP) = 'Y'.

2.8.1.3 Adverse event reporting for clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on TEAEs (pooled with ocular and non-ocular AEs) which are not serious adverse events with an incidence greater than 5%, and on TEAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT based on the SAF.

If, for the same subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE (resp. non SAE) has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 Deaths

A summary of treatment-emergent deaths will be presented by primary SOC and PT.

All deaths recorded in the clinical database will be listed.

2.8.3 Laboratory data

Chemistry and hematology laboratory parameters will be presented graphically using boxplots of change from baseline values by treatment arm and visit. No summary by visit tables will be provided.

A summary on counts and percentages of subjects with laboratory assessment meeting the pre-specified clinically relevant abnormality criteria (Section 5.3) at any post-treatment visit will be presented. A listing of laboratory assessments for subjects meeting at least one abnormal criterion will also be provided.

2.8.4 Other safety data

2.8.4.1 Ophthalmic Examinations

The ophthalmic examinations will be summarized for the study eye only.

Descriptive summaries of change from baseline in pre-injection IOP values will be presented graphically by visit and treatment, considering line plots of the mean change in IOP values with

error bars representing ± SE. The x-axis will be the study visit and the y-axis will be the change from baseline value. No summary by visit tables will be provided.

The counts and percentages of the following findings will be summarized:

- Subjects with treatment-emergent pre-injection IOP >30 mmHg at any visit
- Subjects with post-injection IOP >30 mmHg at any visit
- Subjects with an increase of ≥10, ≥20 mmHg from pre-injection to post-injection IOP at any visit.
- Subjects with treatment-emergent pre-injection IOP ≥21 mmHg in 3 consecutive scheduled visits. A scheduled visit with missing pre-injection IOP is considered to meet the ≥21 mmHg criterion if the preceding and the following scheduled visits have pre-injection IOP ≥21 mmHg. For example, if scheduled visit X has missing pre-injection IOP and pre-injection IOP ≥21 mmHg for both scheduled visits X-1 and X+1, the subject is considered to meet the criteria.

A listing of all IOP assessments for subjects with at least one of the above findings on the study eye will be provided.

The abnormal findings via slit-lamp and indirect fundus examinations deemed as clinically significant by the investigator and reported as AE/SAE will be included in the safety analysis on AE/SAE.

Imaging parameters related to intraocular inflammation including retinal vasculitis and retinal vascular occlusion except for retinal vein occlusion in the study eye will be summarized by baseline, up to visit 7, after visit 7 to end of study, and for post-baseline up to end of study. When more than one grading result is available for a subject within a time period, the maximum level of sign will be used. These imaging parameters will be summarized by AESI status for baseline and post-baseline up to end of study. The parameters will be listed for subjects with AESI and subjects with imaging parameter present at any study visit.

2.8.4.2 Vital signs

A line plot of mean change from baseline with error bars representing ± SE for each vital sign parameter will be provided by visit and treatment.

The number and percentage of subjects with at least one assessment meeting the abnormal criteria specified on Section 5.4 will be presented. A listing of all vital sign assessments for subjects with at least one abnormal finding will also be presented.

2.8.4.3 Vision loss

A listing of subjects with BCVA loss of 15 letters or more from baseline will be provided for the SAF.

2.9 Pharmacokinetic endpoints

No pharmacokinetic parameters will be assessed.

2.10 Anti-drug antibody

ADA assessment will be done for subjects from the brolucizumab arm at screening, Week 4, 12, 24, 36, 52 and 76 (or premature EoS) visits prior to the injection/sham.

[redacted]

Subject listing of all ADA titer values and [redacted] will be presented for all subjects from the brolucizumab arm. Samples collected at unscheduled visits will not be part of the analysis.

[redacted]

Systemic exposure of brolucizumab will be measured concomitantly with ADA levels for interpretation purposes and no pharmacokinetic parameters will be determined from brolucizumab systemic exposure. Systemic exposure data will be summarized and listed.

2.11 Subject-reported outcomes

The VFQ-25 questionnaires will be scored (composite and sub-scale scores) at Baseline and Weeks 24, 52 and 76 visits.

The statistical analysis method is provided in section 2.7.2. Absolute scores and the changes from baseline will be calculated and summarized descriptively based on observed data using the FAS.

The details on the scoring algorithm and analysis are provided in this section. Each sub-scale score has a range of 0 to 100 inclusive and will be calculated from the re-scaled raw data as described in Table 2-4. A missing response will not be re-scaled (except for the response to question 15c, see below, which will be re-set to 0 if the response to question 15b is 1).

The answers to questions will be re-scaled as follows to calculate the total and subscale scores.

Table 2-4 Rescaling of VFQ-25 questions

Answer to question	Rescaling for questions 1, 3, 4 and 15c	Rescaling for question 2	Rescaling for questions 5-14, 16 and 16a	Rescaling for questions 17-25
1	100	100	100	0
2	75	80	75	25
3	50	60	50	50
4	25	40	25	75
5	0	20	0	100
6	N/A	0	N/A*	N/A
*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". Subscales will be calculated where at least one of the (re-scaled) questions contributing to that subscale is non-missing, otherwise set to missing.				

Note that the answer to question 15c will subsequently be adjusted based on the answer to question 15b:

- If the answer to 15b is 1 then the answer to 15c will be re-set to 0.
- If the answer to 15b is 2 or 3 then the answer to 15c will be re-set to missing

The general health rating is the re-scaled answer to question 1.

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". Subscales will be calculated where at least one of the (re-scaled) questions contributing to that subscale is non-missing, otherwise set to missing.

The sub-scales (excluding the general health question) and corresponding questions are shown in Table 2-5.

Table 2-5 Questions by sub-scales contributing to VFQ composite score

Sub-scale	Questions
General vision	2
Ocular pain	4 and 19
Near activities	5, 6 and 7
Distance activities	8, 9 and 14
Social functioning	11 and 13
Mental health	3, 21, 22 and 25
Role difficulties	17 and 18
Dependency	20, 23 and 24
Driving	15c, 16 and 16a
Color vision	12
Peripheral vision	10

The composite score is the average of the 11 sub-scales shown in Table 2-5. It will be set to missing if at least six of the subscales are missing. The change from baseline of rescaled composite score and sub-scale scores will be derived based on the changes in the individual items scores and then averaged for the sub-scale score.

2.13 Interim analysis

The study is terminated before the interim analysis at Week 52 DBL planned according to the protocol. Therefore, no interim analysis is conducted.

3 Sample size calculation

The sample size calculation is based on the primary endpoint, i.e., change from baseline in BCVA at Week 24.

For RAPTOR, a sample size of 230 subjects per arm will allow assessment of non-inferiority (using a non-inferiority margin, NIM, of 4 ETDRS letters) of brolucizumab 6 mg versus aflibercept 2 mg with respect to the change from baseline in BCVA at Week 24. Assuming equal means and a common standard deviation of 12 letters, for a NIM of 4 letters and a one-sided alpha level of 0.025, there is 94% power to reject the null hypothesis that brolucizumab 6 mg is inferior to aflibercept 2 mg. To account for a drop-out rate of 10%, a total of approximately 500 (250 per arm) subjects will need to be randomized.

For RAVEN, a sample size of 340 patients per arm will allow assessment of non-inferiority (using a non-inferiority margin, NIM, of 4 ETDRS letters) of brolucizumab 6 mg versus aflibercept 2 mg with respect to the change from baseline in BCVA at Week 24. Assuming equal means and a common standard deviation of 14 letters, for a NIM of 4 letters and a one-sided alpha level of 0.025, there is 96% power to reject the null hypothesis that brolucizumab 6 mg is inferior to aflibercept 2 mg. To account for a drop-out rate of 10%, a total of approximately 750 (375 per arm) patients will need to be randomized.

The RAPTOR study was terminated when 450 patients were randomized and RAVEN study was terminated when 493 patients were randomized.

4 Change to protocol specified analyses

The following table is a summary of the changes compared to the analyses specified in the protocol. [redacted]

Protocol section	Protocol wording	Change in the SAP	[redacted]
12.2	Demographics and baseline characteristics will be summarized with descriptive statistics for the FAS by treatment group and overall.	Demographic characteristics and baseline ocular characteristics for the study eye will be summarized with descriptive statistics for the RAS by treatment and overall.	
12.2	Relevant medical history and current medical conditions will be tabulated	Medical history and current medical conditions will be listed for ocular (study eye) and non-ocular events for	

Protocol section	Protocol wording	Change in the SAP
		RAS. No summary table will be produced.
12.3	Descriptive summary statistics for exposure to study treatment will be provided for the SAF, FAS and PPS	Descriptive statistics for exposure to study treatment will be provided for the SAF.
12.3	The number and percentage of subjects taking prior medication or concomitant therapies will be summarized using the SAF and FAS (in case there are differences between those two).	Ocular and non-ocular prior and concomitant medications will be listed. Anti-VEGF medications will be summarized for the safety set. No other summary table will be produced.
12.4.4	The categories for subgroups of: Sex: male, female Baseline BCVA: ≤34, 34-55,≥55 letters Baseline CSFT: <450, 450-650, ≥650 µm	The categories for subgroups of: Sex: male, female, Baseline BCVA: ≤34, 35-55, ≥ 56 letters Baseline CSFT: <450, 450-650, >650 µm
12.5.1	Secondary efficacy endpoints related to treatment frequency: • Number of injections between Week 24 and Week 76 • Time to first re-treatment between Week 24 and Week 76	Secondary efficacy endpoints related to treatment frequency: • Number of injections between Week 24 and Week 72 • Time to recurrence after Week 20 and up to Week 76
General	Analysis restriction is used to specify how the intercurrent event is handled	Analysis restriction is not used and the handling of intercurrent event will be specified under the Estimand framework
12.5.2		AESI is updated

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Missing or partial dates are not allowed, therefore, no imputation will be made to the start date and end date of study treatment.

5.1.2 AE date imputation

For the start and end dates of the adverse event records, when incomplete or missing, dates will be imputed according to Novartis standards as described below.

5.1.2.1 AE end date imputation

Incomplete or missing AE end date will be dealt with in the following way:

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.
4. If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

5.1.2.2 AE start date imputation

The following table explains the notation used in the logic matrix. Please note that completely missing start dates will not be imputed.

	Day	**Month**	**Year**
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	**MON < TRTM**	**MON = TRTM**	**MON > TRTM**
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.

2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:

a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment start date year value:
a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication and therapies and procedures date imputation

For the start and end dates of the concomitant medication records, when incomplete or missing, dates will be imputed according to Novartis standards as described below. The same data imputation rules will be applied for therapies and procedures.

5.1.3.1 Concomitant medication end date imputation

Incomplete or missing end date will be dealt with in the following way
1. If the CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date is set to NULL.
2. Else, if the CM end date month is missing, the imputed end date should be set to the last day of the year or set to the end of study date if it falls in the same year.
3. If the CM end date day is missing, the imputed end date should be set to the last day of the month or set to the end of study date if it falls in the same year and month.

If the imputed CM end date is less than the existing CM start date, use the CM start date as the imputed CM end date.

5.1.3.2 Concomitant medication start date imputation

Completely missing start dates will be set to one day prior to treatment start date. As a conservative approach, such treatments will be classified as prior and concomitant (and summarized for each output).

Concomitant treatments with partial start dates will have the date or dates imputed.

The following table explains the notation used in the logic matrix

	Day	**Month**	**Year**
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	**MON < TRTM**	**MON = TRTM**	**MON > TRTM**
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.a) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).

3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior to treatment start date.
    b. Else if the CM month is less than the treatment start date month, the imputed CM start

date is set to the mid-month point (15MONYYYY).

c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.4 Medical history date of Primary diagnosis imputation

Completely missing dates and partially missing end dates will not be imputed. Partial dates of diagnosis will be compared to the treatment start date.

- If DIAG year < treatment start date year and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY)
- else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY)
- If DIAG year = treatment start date year
- and (DIAG month is missing OR DIAG month is equal to treatment start month), the imputed DIAG date is set to one day before treatment start date
- else if DIAG month < treatment start month, the imputed DIAG date is set to the midmonth point (15MON YYYY)
- else if DIAG month > treatment start month => data error
- If DIAG year > treatment start date year => data error

5.1.5 Concomitant therapies and procedures date imputation

The missing dates will be imputed using the same rule as for the concomitant medication.

5.2 AEs coding/grading

AEs are coded using the MedDRA terminology. The latest version of MedDRA will be used and will be specified on the footnote of relevant output.

AEs severity are assessed by investigators and captured on the AE CRF based on three levels: mild, moderate, and severe.

5.3 Laboratory parameters derivations

No laboratory parameters need to be derived. All laboratory parameters will be analyzed directly based on the assessments provided by central lab. For observations below the limit of quantification (BLQ), a value of one half of the lower limit of quantification (LLOQ) will be used for summary.

The clinically notable laboratory values to be used for the two studies are listed below.

Table 5-1 Clinically notable laboratory values

Test	Conventional Units	Critical Low	Critical High	Standard Units	Critical Low	Critical High	Non-numeric
Calcium	mg/dL	< 6.0	> 13.0	mmol/L	< 1.50	> 3.25	
Creatinine	mg/dL	NA	>5.0	umol/L	NA	>442	

Test	Conventional Units	Critical Low	Critical High	Standard Units	Critical Low	Critical High	Non-numeric
Glucose	mg/dL	< 40	> 500	mmol/L	< 2.22	> 27.75	
Magnesium	mg/dL	< 0.7	> 6.1	mmol/L	< 0.30	> 2.50	
Magnesium	mEq/L	< 0.6	> 5.0	mmol/L	< 0.30	> 2.50	
Phosphate (Phosphorus)	mg/dL	< 1.0	N/A	mmol/L	< 0.32	N/A	
Potassium	mEq/L	< 2.8	> 6.5	mmol/L	< 2.8	> 6.5	
Sodium	mEq/L	< 120	> 160	mmol/L	< 120	> 160	
HCG							Positive
Hematocrit	%	< 20	> 60	V/V	< 0.20	> 0.60	
Hemoglobin	g/dL	< 6.0	> 20.0	g/L	< 60	> 200	
Platelet	X10E3/uL	< 50	> 999	X10E9/L	< 50	> 999	
WBC	X10E3/uL	< 2.00	NA	X10E9/L	< 2.00	NA	

5.4 Clinically notable vital signs

Clinically notable vital sign values to be used for the two studies are listed below.

Table 5-2 Clinically notable vital signs

Variable	Category	Critical values
Systolic blood pressure (mmHg)	High	Either >180 with an increase from baseline >30 or >200 absolute
	Low	Either <90 with a decrease from baseline >30 or <75 absolute
Diastolic blood pressure (mmHg)	High	Either >105 with an increase from baseline >20 or >115 absolute
	Low	Either <50 with a decrease from baseline > 20 or <40 absolute
Pulse rate (bpm)	High	Either >120 with an increase from baseline of >25 or > 130 absolute
	Low	Either <50 with a decrease from baseline >30 or <40 absolute

5.5 Statistical models

5.5.1 Primary analysis

The primary endpoint (change from baseline in BCVA at Week 24) will be analyzed using ANOVA model on data with LOCF as the primary method. The MMRM on observed data will be used as the sensitivity analysis.

Analysis of Variance (ANOVA)

The following ANOVA model will be used for the primary endpoint.
change from Baseline in BCVA at Week 24= intercept + treatment + Baseline BCVA category + age category + error.

The SAS procedure MIXED will be used to perform the ANOVA. The LSmean and two-sided 95% CI for Change from baseline in BCVA within each treatment arms will be estimated using the LSMEAN statement; the LSmean, two-sided 95% CI, and the two-sided p-value on the between group difference will be obtained by adding the DIFF option under the LSMEAN statement. The one-sided p-value for non-inferiority is calculated as the probability on observing the between group difference when the between group difference is less than -4 and can be calculated under the assumption of T-distribution:
P_{NI}=(1-probt((between group difference+4)/stderr,df))

For the above analysis, the data structure is one record per subject.

Mixed Model Repeated Measures (MMRM)
The following MMRM model will be used for the supportive analysis of the primary endpoint:
*change from Baseline in BCVA= intercept + treatment + Baseline BCVA category + age category + visit + treatment*visit + error.*

The SAS procedure MIXED will be used to perform the MMRM. For the MMRM analysis, the data structure is one record per FAS subject per scheduled visit. The data will include all subjects and have records for all scheduled visits, regardless of whether the assessment was missed or not at a given visit. Missing values will NOT be imputed using LOCF. Instead, the value will be passed to the model as missing.

5.5.2 Other analysis

5.5.2.1 Logistic regression for proportion variables

The binary efficacy variables will be analyzed using the logistic regression model adjusted for treatment, age category, corresponding baseline variables, and other corresponding covariates if necessary.

Logistic regression is a model for prediction of the probability of occurrence of an event. It can be used to analyze the dichotomous response data while adjusting for one or more covariates. Usually, Logistic regression analyzes binomially distributed data of form

$Y_i \sim B(n_i, p_i)$, for i=1,…,n.

The logits of the unknown binomial probabilities (i.e., the logarithms of the odds) are modeled as a linear function of the Xi. $\log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1 x_{1,i} + \cdots + \beta_k x_{k,i}$

The LOGISTIC procedure in SAS will be used. The data structure is one record per subject. The estimated difference in proportions, the corresponding 95% CIs, and p-value will be obtained based on the marginal standardization method. This method uses the same fitted logistic model, but involves using the model to predict, for each subject in the study, the mean outcome assuming assignment to each particular treatment group in turn, assuming each subject's observed values for the baseline CSFT categories and age categories. Averaging these predictions for each treatment group provides the estimate of the mean response rate for each treatment group. Then the difference will be derived based on the estimated mean response rates comparing brolucizumab arm vs. aflibercept arm.

The method will be implemented using SAS macro %margins.

5.5.2.2 Survival analysis for time to event variables

Log-rank test will be used to compare the survival distributions of two treatment groups for variable of time to recurrence.

The log-rank test statistic compares estimates of the hazard functions of the two groups at each observed event time. It is constructed by computing the observed and expected number of events in one of the groups at each observed event time and then adding these to obtain an overall summary across all time points where there is an event. The lifetest procedure in SAS will be used. The data structure is one record per subject.

Cox proportional hazards model is to estimate the effect parameter(s) without any consideration of the hazard function assuming the proportional hazards assumption holds. The proportional hazards assumption is the assumption that effect parameters multiply hazard at any time. The effect parameter(s) estimated by any proportional hazards model can be reported as hazard ratios. The phreg procedure in SAS will be used.

Estimation of 95% confidence intervals

Approximate 95% CIs will be generated at selected time-points, the (Kaplan and Meier 1958) estimates of the proportion of subjects experiencing a specific event. Details of such confidence intervals are displayed in Table 5-3.

Table 5-3 Confidence Interval calculations

Approximate Confidence Interval (CI)	Lower Limit	Upper Limit
x% CI for the Kaplan-Meier estimate KM	$KM - c_x * SE$	$KM + c_x * SE$
Notation: SE = estimated standard error of KM; estimation of standard error uses Greenwood's formula, $c_x = \Phi^{-1}(½ + x/200)$, where Φ is the normal distribution function.		
Examples: for $x = 95$, $c_x = \Phi^{-1}(0.975) = 1.95996$; for $x = 97.5$, $c_x = \Phi^{-1}(0.9875) = 2.24140$		

5.6 Rule of exclusion criteria of analysis sets

Subject exclusion and data censoring from the analysis sets is based on protocol deviation and non-protocol deviation criteria including analysis restrictions.

The important PDs that will lead to exclusion of a subject from a corresponding analysis set is provided in the following table

Table 5-4 Important protocol deviations leading to exclusion from analysis sets

Deviation ID	Description of Deviation	Exclusion in Analysis sets
INCL01	Written informed consent not obtained	Excluded from all analysis sets
INCL03	Patients without visual impairment due to macular edema secondary to RVO diagnosed <6 months prior to screening (study eye)	Excluded from PPS

Deviation ID	Description of Deviation	Exclusion in Analysis sets
INCL04	Study Eye: BCVA score outside limits defined in protocol, at screening and baseline	Excluded from PPS
EXCL01	Study eye: confounding ocular concomitant conditions or ocular disorders with impact on efficacy and/or safety	Excluded from PPS
EXCL03	Study Eye: Confounding concomitant medications or procedures	Excluded from PPS
EXCL04	Systemic: Confounding systemic conditions or systemic treatments with impact on efficacy and/or safety	Excluded from PPS

The following table is the summary on the subject classification for each analysis set based on the presence of PDs and non-PD criteria.

Table 5-5 Subject Classification

Analysis Set	PD ID that causes subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RAS	INCL01	Not randomized, misrandomized
FAS	INCL01	Not in RAS
		Subjects without any study treatment
PPS	As listed in Table 5-4	Not in FAS;
		Under treatment (missing >1 injections) up to Week 20 (no injection due to adverse event or discontinuation from study due to lack of efficacy/safety is not considered as missed dose)
		No valid BCVA assessment (after all data censoring rules are applied) at Week 16, 20, or 24
SAF	INCL01	Subjects without any study treatment

5.7 Definition for discontinuation from treatment due to lack of efficacy or safety

Discontinuation from study treatment due to lack of efficacy/safety will be identified if the primary reason for discontinuation is “Progressive disease” or “Adverse event”. As discontinuation due to lack of efficacy is handled the same as lack of safety, no additional rule will be used to separate lack of efficacy versus lack of safety.

5.8 Subgroup analysis to evaluate the impact of COVID-19 pandemic

Based on the internal guidance, sensitivity analysis related to the impact of subjects to COVID-19 will be conducted.

Impacted subjects to COVID-19 up to Week X (X can be 24 or 76) are defined as subjects who:

- were exposed to COVID-19 as per the definition below,
- and missed at least one study treatment or visit up to and including Week X due to COVID-19.

Non-impacted subjects to COVID-19 up to Week X are defined as subjects who:

- were not exposed to COVID-19 as per the below definition,
- or were exposed to COVID-19 but did not miss any study treatment or visit up to and including Week X due to COVID-19.

The exposure to COVID-19 are based on start and end dates by geographical areas:

Region/Country	**Start Date**	**End Date**
China	01-Jan-2020	End date has not yet been defined
South Korea	20-Feb-2020	End date has not yet been defined
Japan	21-Feb-2020	End date has not yet been defined
Italy	23-Feb-2020	End date has not yet been defined
Rest of the World	01-Mar-2020	End date has not yet been defined

Non-exposed subjects to COVID-19 up to Week X (X can be 24 or 76) are defined as subjects who:

- completed Week X visit prior to the pandemic start date,
- or withdrew study prior to the pandemic start date,

Exposed subjects to COVID-19 up to Week X are defined as subjects who:

- did not complete Week X visit prior to the pandemic start date (while remaining in the study at the time of the pandemic start date),
- or withdrew the study on or after the pandemic start date,

6 Reference

Brown DM, Heier JS, et al (2013) Intravitreal Aflibercept Injection for Macular Edema Secondary to Central Retinal Vein Occlusion: 1-Year Results From the Phase 3 COPERNICUS Study. Am J Ophthalmol 2013;155:429–437.

Clark WL, Boyer DS, et al (2013) Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion: 52-week Results of the VIBRANT Study. Ophthalmology 2016;123:330-336.

Korobelnik JF, Holz FG, et al (2014) Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology 2014;121:202-208