Clinical Development

RTH258/Brolucizumab

CRTH258B2304 / NCT04058067

A One-Year, Randomized, Double-Masked, Multicenter, Phase III, Two-Arm Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Chinese Patients with Visual Impairment Due to Diabetic Macular Edema (KINGLET)

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

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17-Jan-2020	Prior to DB lock	Creation of first version	N/A	NA
16-Feb-2023	Prior to DB lock	Creation of amendment 1	Clarify primary and supplementary estimands and analyses based on estimands	Sections 2.1, 2.5.1, 2.5.2, 2.5.4
			Add analyses of impact of the COVID-19 pandemic	Sections 2.2.1, 2.3.1, 2.5.4.3, 2.6.4, 2.7.2.1, 2.8.1
			Modify table of alternative DME treatment	Section 2.5.3
			[redacted]	
			Update DRSS original scale definition and analysis method	Section 2.7.2.2
			Add confirmatory testing related to additional secondary efficacy endpoints	Section 2.7.2.3
			Add SRF/IRF status classification	Section 2.7.3
			Add listing for imaging parameters	Section 2.8.4.4
			Combine outputs of PK endpoints with ADA endpoints	Sections 2.9, 2.10
			Modify titer value threshold, and add analyses of ADA endpoints	Section 2.10
			Update listing of “change to protocol specified analyses”	Section 4
			Update statistical methods for proportion variables	Section 5.4.2.2
			Update rules of exclusion and censoring of analysis	Sections 5.5, 5.6

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List of abbreviations

ADA	Anti-drug antibody
AE	Adverse Event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AR	Analysis restrictions
ATC	Anatomical Therapeutic Classification
BCVA	Best Corrected Visual Acuity
CI	Confidence interval
CM	Concomitant Medication
cm	Centimeter
CF	Color Fundus
CSFT	Central subfield thickness (average thickness of circular 1mm area centered around fovea measured from RPE to ILM, inclusively)
[redacted]	[redacted]
CSR	Clinical Study Report
CRC	Central Reading Center
DBL	Database lock
DMC	Data Monitoring Committee
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
DRSS	Diabetic Retinopathy Severity Scale
eCRF	Electronic Case Report Form
EDTRS	Early Treatment Diabetic Retinopathy Study
IOP	Intraocular Pressure
IRT	Interactive Response Technology
IRF	Intraretinal fluid
IVT	Intravitreal
KM	Kaplan Meier
LLOQ	Lower Limit of Quantification
LSM	Least Square Means
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliters
NPDR	Non-Proliferative Diabetic Retinopathy
OCT	Optical Coherence Tomography
PD	Protocol Deviation
PDR	Proliferative Diabetic Retinopathy
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Standard Error
SOC	System Organ Class

SRF	Subretinal fluid
ULN	Upper Limit of Normal
q1	25th percentile
q3	75th percentile
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
q12w	Every 12 weeks
SRF	Subretinal fluid
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures, Listings
VA	Visual acuity
VFQ-25	Visual Functioning Questionnaire-25
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of statistical analysis planned in the study protocol, and to provide detailed statistical methods that will be used for the Clinical Study Report (CSR) of study CRTH258B2304.

Data will be analyzed according to the data analysis Section 12 of the study protocol which will be available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details will be provided, as applicable, in Appendix 16.1.9 of the CSR.

The SAP will be finalized before the database lock (DBL). Any changes to the SAP after approval will be documented.

The following document archived in CREDI was referenced while writing this SAP:

CRTH258B2304-v02--protocol dated 14-Oct-2021

1.1 Study design

This is a randomized, double-masked, multi-center, active-controlled, 2-armed study in patients with diabetic macular edema (DME) to evaluate the safety and efficacy of brolucizumab 6 mg against the active control aflibercept 2 mg.

Approximately 335 Chinese patients will be screened (20% screening failure rate expected) and approximately 268 patients will be randomized in a 1:1 ratio in one of the following treatment arms:

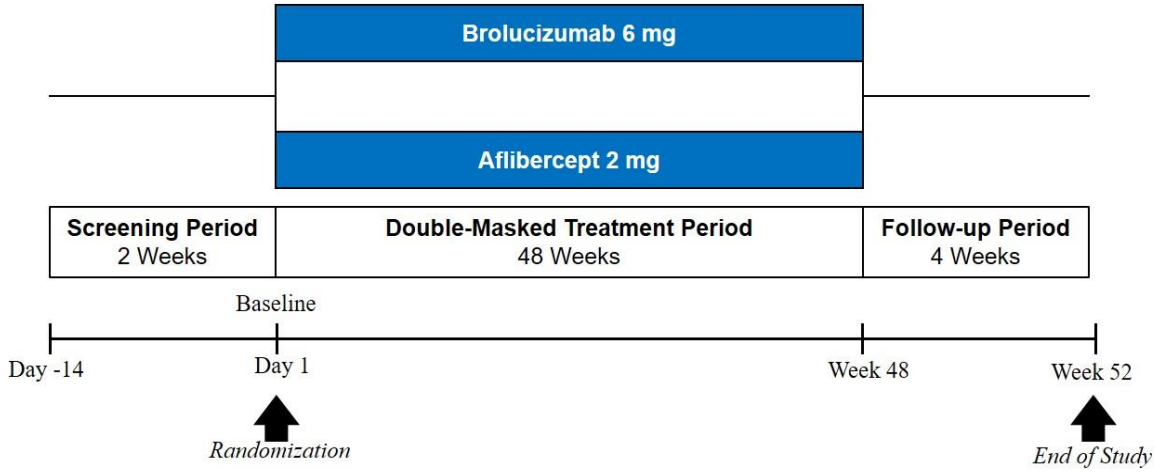
- Brolucizumab 6mg: 5 × q6w loading then q12w/q8w maintenance
- Aflibercept 2mg: 5 × q4w loading then q8w maintenance

At baseline visit, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms, stratified by systemic exposure sampling status (serum PK sample consented vs. not consented). This stratification is only for the purpose of ensuring approximately half of PK sample consented patients would be randomized to Brolucizumab 6 mg treatment arm.

Since the treatment schedule is different for each arm the following will be applied to ensure masking:

- In addition to every 4-week visits for all patients, extra visits are scheduled at Weeks 6 and 18 for both treatment arms
- The patients will receive active/sham injection at each protocol visit except weeks 20, 28 and 52 visits (no scheduled treatment for either arm)
- Disease activity assessment will be performed for both arms.
- To fulfil the double-masking requirement, the investigational site will have masked and unmasked staff.

Figure 1-1 Study design



There will be two treatment phases for intravitreal (IVT) injections with different timing for brolucizumab and aflibercept treatment arms:

Loading Phase:

Brolucizumab 6 mg: In the loading phase, treatment with brolucizumab will occur every 6 weeks for five (5) consecutive injections (Baseline, Weeks 6, 12, 18 and 24). To preserve the masking, the patients assigned to this regimen will receive sham injection on Weeks 4, 8 and 16.

Aflibercept 2 mg: In the loading phase, treatment with aflibercept will occur every 4 weeks for five (5) consecutive injections (Baseline, Weeks 4, 8, 12 and 16). To preserve the masking, the patients assigned to this regimen will receive sham injection on Weeks 6 and 18.

Maintenance Phase:

Brolucizumab 6 mg: From Week 24 onwards, patients will be scheduled to receive one injection of brolucizumab 6 mg every 12 weeks. If, however, disease activity is identified by the evaluating/masked investigator at Weeks 32 or 36, the patient will be assigned to receive injection of brolucizumab 6 mg every 8 weeks (please refer to protocol for 'Evaluation of Disease Activity'). A disease activity assessment will also be performed at Week 48 but will not be entered into IRT and will have no effect on the subject's treatment schedule.

Aflibercept 2 mg: From Week 16 onwards, patients will receive one injection of aflibercept 2 mg every 8 weeks (first injection after Week 16 to be given at Week 24) until Week 48 visit. Disease activity assessments will be conducted by the evaluating/masked investigator for masking purposes and will not influence the treatment interval.

The primary safety and efficacy analysis will be based on the data up to and including Week 52.

1.2 Study objectives and endpoints

Study objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that brolucizumab 6 mg is non-inferior to aflibercept 2 mg with respect to the visual outcome after up to one year of treatment	• Change from baseline in BCVA at Week 52 • Change from baseline in BCVA averaged over a 3 month period (from Week 40 to Week 52)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To estimate the proportion of patients treated at q12w frequency with brolucizumab	• Proportion of patients maintained at q12w up to Week 52
• To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab	• Proportion of patients maintained at q12w up to Week 52, within those patients that qualified for q12w at Week 36
• To evaluate the functional and anatomical outcome with brolucizumab relative to aflibercept	• Change from baseline by visit up to Week 52 in BCVA and in parameters derived from SD-OCT, Color fundus photography and Fluorescein angiography
• To evaluate the effect of brolucizumab relative to aflibercept on the Diabetic Retinopathy status	• Change in ETDRS Diabetic Retinopathy Severity Scale (DRSS) score up to Week 52
• To assess the safety of brolucizumab relative to aflibercept	• Incidence of Ocular and Non-ocular AEs, vital signs and laboratory values up to Week 52
• To evaluate the effect of brolucizumab relative to aflibercept on patient-reported outcomes (VFQ-25)	• Change in patient reported outcomes (VFQ-25) total and subscale scores from baseline up to Week 52
• To confirm the systemic brolucizumab exposure in a subset of patients	• Systemic brolucizumab concentration approximately 24 hours after initial and final loading phase doses in a subset of patients
• To assess the immunogenicity of brolucizumab over one year of treatment	• Anti-drug antibody status at screening and up to Week 52 in brolucizumab arm
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The primary safety and efficacy analysis will be based on the data up to and including Week 52, once all subjects completed or discontinued from the study.

The statistical analysis will be performed by Novartis using SAS Version 9.4 or above.

Continuous variables will be summarized using the number of observations, mean, standard deviation, standard errors (SE), median, quartiles, minimum and maximum values. Categorical variables will be summarized with number of observations, the number of observations for each category and the corresponding percent. Where appropriate, 2-sided 95% confidence intervals (CIs) for point estimates of the mean or proportion will be provided unless otherwise specified.

Point estimates, 95% CIs of treatment differences will be provided as appropriate unless otherwise specified.

2.1.1 General definitions

Study drug and study treatment

Study drug refers to both Brolucizumab 6 mg and Aflibercept 2 mg IVT injections.

Study treatment refers to study drug or sham injections.

Study day

Day 1 is defined as the date of first administration of study treatment. 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 day mapping

The end of study date is the date when a subject completes or discontinues the study.

For reporting data by visit in outputs, the end of study visit will be allocated to the actual (reported) visit. If end of study date is not on a scheduled visit, then the end of study visit will be allocated, based on study day, to the closest future scheduled study visit.

End of treatment day mapping

The end of treatment day/date of last exposure is the date of the last study treatment.

For reporting data by visit in outputs, the end of treatment date will be allocated to the actual (reported) visit number. If end of treatment date is not on a scheduled visit, then the end of treatment date will be allocated, based on study day, to the closest future scheduled study visit.

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 letter loss in BCVA from baseline. These data will not be used in analyses with mixed model for repeated measures (MMRM). Moreover, given unscheduled visits will not be active treatment visits, IOP measurements at unscheduled visits will not be considered as pre-injection IOP measurements, hence will not be used to identify subjects with pre-injection IOP >30 mmHg.

Missing and implausible dates

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

2.2 Analysis sets

The **All Enrolled set** includes all subjects who signed informed consent. This analysis set will be used to summarize subject disposition.

The **Randomized Set** will consist of all randomized subjects. Subjects are considered randomized when they had been deemed eligible for randomization by the investigator and given a randomization number. Subjects will be analyzed according to the treatment assigned to at randomization.

The **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. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization.

Supportive analyses of the primary and key secondary endpoints will include analysis using the **Per Protocol Set** (PPS). PPS is a subset of the FAS and will exclude subjects with important protocol deviations (PDs) and analysis restrictions (ARs) that are expected to majorly affect the validity of the assessment of efficacy and/or safety at Week 52, e.g. lack of compliance (including missed treatments and treatment misallocation), missing data, prohibited concomitant medication and deviation from inclusion/exclusion criteria. Confounded data or discontinuation from treatment due to lack of efficacy and/or safety do not constitute a reason for exclusion from the PPS.

Before the database lock the relevant important protocol deviations will be identified at the subject level in the database. After the database lock, analysis restrictions will be derived in the analysis database.

The FAS will be the analysis set for the primary estimand as defined in Table 2-1. However, when assessing the robustness of the overall efficacy conclusions, considerations will be given to the analysis based on the primary estimand using FAS and the supplementary estimand (see Table 2-1) using PPS. Inconsistencies in key efficacy study results between the FAS and PPS will be examined and discussed in the clinical study report (CSR).

The **Safety Analysis Set** (SAF) will include all subjects who receive at least one study drug IVT injection. Subjects in the safety analysis set will be analyzed according to the treatment arm from which they received majority of study treatments.

Before the database lock, the relevant important protocol deviations will be identified as specified in Section 5.6. The corresponding identifications at the subject level including data exclusion from PPS and censoring will be captured in the database. Analysis Restrictions (non-protocol deviations) will be identified by programming (as specified in the programming specification document) independently to the treatment arm.

Rules of exclusion criteria of analysis sets are in Appendix Section 5.5.

2.2.1 Subgroups of interest

The subgroups of interest are specified below:

- Age category (<65, ≥65 years)
- Gender (male, female)
- Diabetes type (Type 1, Type 2)
- Baseline HbA1c (<7.5, ≥7.5%)
- Baseline BCVA categories (≤65, >65 letters)
- Duration of DME since the primary diagnosis (≤ 3, >3 - <12, ≥12 months)
- DME type (focal, diffuse) as per central reading center (CRC)
- Baseline central subfield thickness (CSFT) (<450, ≥450 - <650, ≥650 µm)
- Baseline status of intraretinal fluid (IRF) in the central subfield 1 mm area (presence, absence)
- Baseline status of subretinal fluid (SRF) in the central subfield 1 mm area (presence, absence)

Subgroup analysis will be performed for the primary and key secondary efficacy endpoints only, (as defined in Section 2.5.1 and Section 2.6.1), using the primary analysis approach. More details can be found in Section 2.5.4 and Section 2.6.2.

Additionally, analyses of the impact of COVID-19 pandemic in subjects will be conducted.

Impacted subjects are defined as subjects who:

- Miss at least one visit due to COVID-19
- Or discontinue study/study treatment due to COVID-19
- Or report COVID-19 infection (including suspected as per PTs in the PDS)

Subgroup analyses will be conducted using the same model described for the primary endpoint and selective secondary endpoints in the impacted and non-impacted subgroups. Details can be found in Section 2.5.4, Section 2.6.4, Section 2.7.2 and Section 2.8.1. Demographics and baseline characteristics will be summarized for impacted and non-impacted subjects.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

The following summaries will be included in the disposition table considering all enrolled subjects: Number and percent of subjects who are enrolled into the study, treated, complete the study, discontinue the study prior to Week 52 (including reasons for discontinuation) and discontinue from study treatment prior to Week 48 (including reasons for discontinuation).

The number and percent of subjects who discontinue the study and who discontinue study treatment will be presented by study visit. The number and percent of subjects treated by site will be presented.

A listing of subjects who discontinue from the study and/or treatment early will be provided by treatment arm. The listing will identify the visits completed and when the study or treatment was discontinued including the corresponding reasons.

Subjects who sign an informed consent form and who are subsequently found to be ineligible prior to randomization will be considered a screen failure. Screen failure information will not be summarized and only listed.

Number and percent of subjects who were excluded (i.e. not evaluable) from each of the SAF, FAS, and PPS will be presented using the randomized analysis set. A listing of subjects along with the analysis set that they were excluded from and the corresponding reasons will also be presented.

Number and percent of subjects with important PDs and ARs will be presented by treatment arm and deviation/restriction category. Due to the COVID-19 pandemic, higher number of PDs are expected. To evaluate the PDs that occur due to COVID-19, the number and percentage of subjects with PDs that occur due to COVID-19 will also be provided by deviation category, relationship to COVID-19 and treatment arm. A listing of all ARs and PDs will be provided by treatment arm and subject, including the information if the AR/PD leads to the subject exclusion from an analysis set and the relationship to COVID-19.

2.3.2 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics for the FAS by treatment arm and overall. Demographics characteristics will include age, age category (< 65, ≥ 65 years), gender and race. The summary of baseline ocular characteristics will be presented for the study eye only and listed separately for the study eye and the fellow eye.
Ocular baseline characteristics include:

- Study eye selection (left eye OS or right eye OD),
- Duration of DME since the primary diagnosis as continuous variable and using categories (≤ 3, >3 - <12, ≥12 months),
- Macular edema type (focal, diffuse) as per CRC,
- Baseline BCVA as continuous variable and using categories (≤65, >65 letters, and ≤60, ≥61 - ≤69, ≥70 letters),
- Baseline CSFT (<450, ≥450 - <650, ≥650 µm),
- Baseline status of IRF in the central subfield 1 mm area (presence, absence),
- Baseline status of SRF in the central subfield 1mm area (presence, absence),
- Baseline ETDRS DRSS 12-point scale using categories (as defined in Table 2-4).

Other baseline characteristics include:

- Diabetes type (type 1, type 2),
- Baseline HbA1c as continuous variable and using categories (<7.5, ≥7.5%),

Duration of DME since diagnosis (months) will be derived as [(first dose date –diagnosis start date + 1)/(365.25/12)]. In case of partial dates, the imputation rule is specified in Section 5.1.4.

Other relevant baseline information will be listed and summarized with descriptive statistics as appropriate.

No tests for differences in demographics and baseline characteristics between treatment arms will be performed. Potential related differences will be assessed based on clinical relevance.

2.3.3 Medical history

Medical history and current medical conditions will be summarized and listed for ocular (study eye) and non-ocular events.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment exposure

Extent of exposure to study treatment is calculated as the number of study treatment injections received.

Descriptive statistics for exposure to study treatment will be provided for the Safety Set.

The following summaries will be presented:

- Overall number of treatments for baseline to Week 48/end of treatment including separate analysis for the loading phases, i.e. up to Week 16 (last treatment of the 5xq4w loading of aflibercept) and up to Week 24 (last treatment of 5xq6w loading of brolucizumab), and maintenance phase, using the following categories: active and sham IVT injections, active only, sham only
- Treatment exposure by visit: The number and percent of subjects who received active IVT injections, sham injections, missed a treatment (active and sham) and missed visits will be presented by treatment arm and visit
- Frequency of all observed dosing patterns from baseline to Week 52, differentiating between active and sham treatments, missed study treatments and wrong study treatments
- Brolucizumab q12w/q8w allocation by visit from Week 32 onwards: Number and percent of subjects on q12w and q8w at each visit, including number of subjects who switched from q12w to q8w

Exposure data will be listed for each treatment arm.

2.4.2 Prior medication and concomitant therapies

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Concomitant medications are defined as medications received after the start of study treatment including those already started prior to the start of the study treatment.

Prior and concomitant medications will be coded according to the WHO Drug Reference List dictionary, with Anatomical Therapeutic Classification (ATC) class and preferred term.

Ocular and non-ocular prior and concomitant medications will be summarized and listed by ATC class and preferred term for each treatment arm. Ocular medications will be listed for the study eye and the fellow eye separately. Anti-VEGF medications will be summarized by ATC class and preferred term for systemic route, for the study eye and the fellow eye separately by treatment arm.

Ocular concomitant non-drug therapies and procedures will be summarized for the study eye only. Both ocular and non-ocular concomitant significant non-drug therapies and procedures will be listed.

In the summary tables, data collected after the subject discontinued study treatment and started alternative DME treatment in the study eye will be censored (from the day the subject started alternative DME treatment onwards).

2.5 Analysis of the primary objective

2.5.1 Primary and first key secondary endpoints

The primary endpoint is the change from baseline in BCVA at Week 52 in the study eye.

The first key secondary endpoint is average change in BCVA from baseline over the period Week 40 through Week 52 in the study eye. For each subject, this endpoint is defined as the average of the changes from baseline to Weeks 40, 44, 48 and 52.

The motivation for the choice of this endpoint is that averaging the BCVA values over Week 40 to Week 52 will account for both random fluctuations and potential trough and peak values during the different treatment cycles.

The primary analysis of the primary and first key secondary endpoints will be based on the FAS with last observation carried forward (LOCF) imputation of missing or censored BCVA values.

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

- Population: Subjects with visual impairment due to DME as per the inclusion/exclusion criteria
- Endpoint: The primary endpoint is the change from baseline in BCVA at Week 52. BCVA will be assessed by the masked assessor 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 intercurrent events as follows:
    - Study discontinuation due to any reason: data imputed with LOCF
    - Treatment discontinuation due to any reason: use all the data
    - Data after the start of alternative DME treatment will be censored and replaced using LOCF
- Summary measure: Difference in the change from baseline in BCVA at Week 52 between brolucizumab and aflibercept treatment arms.

2.5.2 Statistical hypothesis, model, and method of analysis

The objective related to the primary and first key secondary endpoints is to demonstrate non-inferiority of brolucizumab to aflibercept with respect to change from baseline in BCVA, considering a margin of 4 ETDRS letters.

Let:

B = Brolucizumab 6 mg - 5 x q6w loading then q12w/q8w maintenance

A = Aflibercept 2 mg - 5 x q4w loading then q8w maintenance

The following non-inferiority hypotheses are related to a non-inferiority margin of 4 letters:

$\mathbf{H0_1}$: $\mu_B - \mu_A \leq$ -4 letters vs. $\mathbf{HA_1}$: $\mu_B - \mu_A >$ -4 letters

$\mathbf{H0_2}$: $\varphi_B - \varphi_A \leq$ -4 letters vs. $\mathbf{HA_2}$: $\varphi_B - \varphi_A >$ -4 letters

where μ_B and μ_A are the corresponding unknown true mean changes from baseline in BCVA at Week 52; φ_B and φ_A are the corresponding unknown true mean changes from baseline in BCVA averaged over the period Week 40 to Week 52;

Based on the FAS, the above hypotheses will be tested via an analysis of variance (ANOVA) model. The model will include treatment, baseline BCVA (≤65, >65 letters) and age category (<65, ≥65 years) as factors. Two-sided 95% confidence interval (CI) for the least square means (LSM) difference (brolucizumab - aflibercept) will be presented. Non-inferiority will be considered established if the lower limit of the corresponding 95% CI is greater than -4 letters. P-value for treatment comparison (2-sided) and p-value for non-inferiority (4 letter margin) (1-sided) will be presented.

The two hypotheses will be tested sequentially (H_{An}, n=1, 2), i.e. confirmatory testing of the second hypothesis requires rejection of the first null hypothesis.

In this setting, each hypothesis will be assessed at a one-sided significance level of 0.025, while keeping the global type I error rate at 0.025.

The primary estimand and other supplementary estimands of interest are described in Table 2-1 below, together with their key attributes. The same approach for non-inferiority assessment in change from baseline in BCVA at Week 52 and average change from baseline in BCVA over the period Week 40 through Week 52 will be applied to any supplementary estimand.

Table 2-1 Primary and supplementary estimands

Estimand	Estimand definition	Analysis set	Use of data after discontinuation of study treatment due to[1]: use of alternative DME treatment	Use of data after discontinuation of study treatment due to[1]: any other reason	Statistical methods (Including missing data strategy)
Primary estimand	Difference in change from baseline in BCVA at Week 52 excluding the effect of switching to alternative DME medication in the study eye	FAS	Not included; treated as missing	Included	Analysis of variance (ANOVA) model assessed at a two-sided significance level of 0.05, and including terms for treatment, baseline BCVA (≤ 65, > 65 letters) and age category (< 65, ≥ 65), and using LOCF imputation/replacement for missing/censored data.
Supplementary Estimand A	Difference in change from baseline in BCVA at Week 52 for subjects adhering to the protocol as per the PPS definition	PPS	Not included; treated as missing	Not Included; treated as missing at subject level	ANOVA model as per the primary estimand. LOCF imputation/replacement for missing/censored data

Estimand	Estimand definition	Analysis set	Use of data after discontinuation of study treatment due to[1]: use of alternative DME treatment	Use of data after discontinuation of study treatment due to[1]: any other reason	Statistical methods (Including missing data strategy)
Supplementary estimand B	Difference in change from baseline in BCVA at Week 52 including the effect of switching to alternative DME medication in the study eye	FAS	Included	Included	ANOVA model as per the primary estimand. LOCF imputation for missing data. No censoring of data after start of alternative DME treatment for the study eye

1 Note that, for all estimands as applicable, all data captured until the start of alternative DME treatment will be included in the analysis;

2 For additional information on data handling related to intercurrent events, see Section 5.5 and Section 5.6.

2.5.3 Handling of missing values/censoring/discontinuations

Missing BCVA values will be imputed by LOCF as a primary approach. Observed values from both scheduled and unscheduled visits will be used for the LOCF imputation. For subjects with no post-baseline BCVA value, the baseline value will be carried forward.

For subjects who discontinue treatment but continue in the study, data collected after switching to alternative DME treatment in the study eye (see Table 2-2) will be censored for the primary analysis. Censored data will be replaced using LOCF by the last observation collected prior to the start of alternative DME treatment in the study eye. Detailed alternative DME treatments will be listed in the Programming Data Specifications (PDS) documentation.

Table 2-2 Alternative DME treatment in the study eye

- Ranibizumab
- Aflibercept
- Bevacizumab (off-label use)
- Conbercept
- Laser photocoagulation, previous standard of care still being used as mono- or combination therapy with anti-VEGF;
- Intraocularly/periocularly administered steroids:
  - Dexamethasone
  - Fluocinolone acetonide
  - Triamcinolone acetonide
  - Other intraocular/periocular steroids

From an estimand perspective, the main focus is to adequately reflect in the analysis unfavorable study outcome related to the treatment (e.g. lack of efficacy, safety problems).

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. In case of the use of alternative treatment for the underlying disease (DME), data collected after the start of such a treatment would be censored. LOCF will then be based on the last value prior to the start of this treatment, again expecting that this value would reflect the unfavorable BCVA outcome under study treatment. In case of missing data 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.

In case of missing data occurring independently of the response to study treatment, the LOCF approach assumes stability which seems to be adequate based on historical data both for the maintenance treatment phase (i.e. stabilization of BCVA) and also in case of the absence of any treatment effect with an average natural disease progression in terms of BCVA loss of only 1-2 letters over 1 year. In case of an early study termination during the loading phase, the LOCF method will result in a conservative estimate potentially underestimating the true outcome.

LOCF is an established method within the assessment of efficacy of anti-VEGF treatments in terms of BCVA outcome. 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. The primary endpoint in aflibercept Phase III studies VIVID and VISTA was the BCVA change from Baseline at Week 52 with missing data imputed based on LOCF. Based on those studies, the percentage of missing data regarding BCVA is not considered critical (<10%), which limits the impact of the missing data imputation method.

2.5.4 Sensitivity and Supportive analyses

2.5.4.1 Sensitivity analyses on the primary estimand

Sensitivity to the statistical model and imputation assumptions from the primary estimand will be considered, using the primary analysis set (FAS) only.

An alternative method of handling missing values such as below will be considered to assess the robustness of the hypothesis testing resulting from the primary analysis:

Mixed model for repeated measures (MMRM) assuming missing at random (MAR) with observed data (including censoring of BCVA values collected after the start of alternative DME treatment). The MMRM will include treatment, visit, 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. For the MMRM analysis:

- The treatment difference brolucizumab - aflibercept at Week 52 will be estimated using the LSM and 95% CI.
- For the endpoint of average change from Baseline over the period Week 40 through Week 52, a SAS code using the ESTIMATE statement in PROC MIXED will be provided in the programming specification document to obtain the LS mean estimate and 95% CI for the corresponding treatment difference.
- If an MMRM model with 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), first-order autoregressive (AR) and Toeplitz (TOEP), and variance components (VC).

In this analysis, data collected after the switch to alternative DME treatment in the study eye will be censored.

Other sensitivity analyses on the primary estimand might be considered, such as tipping point analysis or multiple imputation by chained equations (MICE) method.

2.5.4.2 Supportive analysis using a supplementary estimand

Supplementary estimand on the PPS:

The target population, 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 handling of the intercurrent events for the supplementary estimand can be found in Table 5-6 for the PPS population.

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

Supplementary estimand on the FAS:

The target population, the primary endpoint, the treatment of interest and the summary measure of the supplementary estimand are the same as for the primary estimand. However, data after start of alternative DME treatment in the study eye will be included in the analysis (see Table 2-1).

2.5.4.3 Summary statistics and subgroup analysis

Summary statistics:

- Descriptive statistics of BCVA primary and first key secondary endpoints will use observed data and primary analysis set (FAS), with and without censoring data after use of alternative DME treatment in the study eye.

Subgroup analyses will be conducted to assess the consistency of treatment effect across various subgroups described in Section 2.2.1, including in the impacted and non-impacted subgroups defined in Section 2.2.1. They will be conducted using the framework for the primary estimand only (FAS with censoring of data collected after use of alternative DME treatment in the study eye, and missing/censored values imputed using LOCF):

- Subgroup analyses will be conducted using the same model and analysis strategies described for the primary and first key secondary analyses but fitted by category of each of the subgroups. Subgroup variables that are used as fixed effects in the model will be removed from the model statement for the 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.

2.6 Analysis of the additional key secondary objectives

2.6.1 Additional key secondary endpoints

Additional key secondary endpoints are:

- Proportion of subjects maintained at q12w up to Week 52 (for brolucizumab treatment arm only)
- Proportion of subjects maintained at q12w up to Week 52, within those subjects that qualified for q12w at Week 36 (for brolucizumab treatment arm only)

2.6.2 Statistical hypothesis, model, and method of analysis

No hypothesis will be tested for the additional key secondary efficacy endpoints.

The primary analysis approach described below (**efficacy/safety approach**) will be conducted using the FAS.

The estimate for the proportion of subjects with a positive q12w treatment status will be derived from Kaplan Meier (KM) time-to-event analyses for the event 'first q8w-need' imputing a 'q8w-need' allocation in case of missing or confounded data attributable to lack of efficacy and/or lack of safety.

The proportion of subjects with a positive q12w treatment status will be derived as follows requiring 'sufficient duration of effect' (as assessed by q8w-need) together with 'sufficient efficacy and safety':

- For the 'sufficient duration of effect' requirement, subjects will need to have the status of 'q8w-need = no' at Weeks 32, 36 and 48 unless the 'q8w-need = yes' is confounded by reasons other than lack of efficacy and/or safety (see censoring details below)
- The requirement regarding 'sufficient efficacy and safety' will be addressed by considering subjects – even without an explicit 'q8w-need = yes' – as having a negative q12w status in case any of the following confounding factors is attributable to lack of efficacy and/or lack of safety of the study treatment: early treatment/study discontinuation, missed DAA. The q8w-need assessment will be imputed as "Yes" at the DAA visit following early treatment/study discontinuation due to lack of efficacy and/or lack of safety of the study treatment (applies to both missing and non-missing DAAs)

In case missing or confounded data regarding the q12w treatment status are attributable to reasons other than lack of efficacy and/or safety, the subject is censored within the q12w treatment status analysis according to the following specifications:

- Early treatment/study discontinuation: censoring at the last valid DAA visit on or prior to treatment/study discontinuation
- Single missed visit with a relevant DAA: censoring at the last valid DAA prior to the missed visit.
- Prohibited concomitant medications/procedures: censoring at the last valid DAA prior to the corresponding application

- Discrepancy between DAA by investigator and the actual treatment received: censoring at the corresponding visit
- Other treatment allocations/applications deviating from the concept of 'treatment allocation according to disease activity': censoring at the last valid DAA at or prior to the deviating visit.

Censoring rules related to the q12w treatment status analysis are described in Section 5.5.

The proportion of subjects with a positive q12w treatment status at Week 52 will be presented together with a two-sided 95% confidence interval (see Section 5.4.2.3).

The outcome of the Kaplan Meier analyses will be presented graphically by the estimated q12w-probability over time, i.e. at each DAA-visit.

While for the analysis of the overall q12w proportion, all subjects in the FAS will be considered, the analysis of the proportion of subjects maintained at q12w up to Week 52, within those subjects that qualified for q12w at Week 36 is based on the subset of FAS subjects with no identified q8w-need at Week 32 and Week 36. For this subset of subjects a valid Week 36 DAA is required, while missing the Week 32 assessment is considered as no q8w-need.

2.6.3 Handling of missing values/censoring/discontinuations

The details regarding handling of missing values and discontinuations, including the timing of censoring for the time-to-event analyses of 'first q8w-need', are specified in the previous section.

Remark: Subjects without any valid DAA are considered censored at baseline for the overall q12w-proportion and for the analysis of the predictive value of the first q12w cycle.

From an estimand perspective, the assessment of failing study completion according to protocol due to lack of efficacy/safety is considered adequately represented by a negative q12w-status.

2.6.4 Supportive analyses

Supportive analysis will be performed on the FAS using alternative methods of handling missing or confounded data:

- **'Efficacy only' approach**: approach with 'q8w-need' allocation only in case the reason for a missing or confounded q12w status was attributable to lack of efficacy of the study treatment. In case of a corresponding safety reason the subject was censored at the last valid DAA.
- **'As observed' approach:** analysis without 'q8w-need' allocation.

Additionally, analysis described in Section 2.6.2 conducted on FAS will be repeated on PPS to assess the consistency of the assessments of the q12w proportions when looking only at those subjects who adhere to the protocol.

Subgroup analyses will be conducted as well to assess the consistency of the assessment of the q12w proportions across various subgroups described in Section 2.2.1, considering the FAS only and the efficacy/safety approach only.

In addition, subgroup analyses will be conducted for the additional key secondary endpoints in the impacted and non-impacted subgroups defined in Section 2.2.1.

2.7 Analysis of secondary efficacy objectives

2.7.1 Secondary efficacy endpoints

Secondary efficacy endpoints related to BCVA, dosing regimen, anatomy or status of diabetic retinopathy are listed below.

[redacted]

Secondary efficacy endpoints based on BCVA:

- Change from baseline in BCVA at each visit up to Week 52
- Average change from baseline in BCVA over the period Week 4 to Week 52. For each subject this endpoint is derived as the average of the changes from baseline at each post-baseline visit between Week 4 and Week 52.
- Average change from baseline in BCVA over the period Week 20 to Week 52 and Week 28 to Week 52. For each subject those endpoints are derived as the average of the changes from baseline at each post-baseline visit between Week 20 and Week 52, and between Week 28 and Week 52.
- Number and percentage of subjects with a gain in BCVA of ≥5, ≥10 and ≥15 ETDRS letters from baseline to each post-baseline visit

  Note: Subjects with BCVA value of 84 letters or more at a post-baseline 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.
- Time to achieve gain of ≥5, ≥10 and ≥15 ETDRS letters from baseline (or reaching a score of 84 or more)
- Number and percentage of subjects with a loss in BCVA of ≥5, ≥10 and ≥15 ETDRS letters from baseline to each post-baseline visit
- Number and percentage of subjects with an absolute BCVA ≥73 ETDRS letters at each post-baseline visit

Secondary efficacy endpoints related to dosing regimen:

- Number and percent of subjects with q8w treatment need status assessed at Week 32
- Treatment status at Week 52

Secondary efficacy endpoints related to anatomy:

- Change from baseline in central subfield thickness (CSFT, as determined by SD-OCT from the central reading center) at each assessment visit
- Average change in CSFT from baseline over the period Week 40 through Week 52. For each subject this endpoint is derived as the average of the changes from baseline at Weeks 40, 44, 48, 52.
- Average change in CSFT from baseline over the period Week 4 to Week 52
- Subject status regarding normal CSFT (<280 microns) at each assessment visit

- Proportion of subjects with presence of SRF, IRF and proportion of subjects with presence of SRF and/or IRF in the central subfield 1 mm area at each assessment visit
- Proportion of subjects with presence of leakage on fluorescein angiography (FA) at Week 52

Secondary efficacy endpoints related to the status of Diabetic Retinopathy (see Section 2.7.2.1):

- Proportion of subjects with ≥2- and ≥3-step improvement or worsening from baseline in the ETDRS DRSS at each assessment visit
- Incidence of progression to proliferative diabetic retinopathy (PDR) as assessed by ETDRS DRSS original scale ≥61 by Week 52 among non-PDR subjects at screening

2.7.2 Statistical hypothesis, model, and method of analysis

2.7.2.1 General analysis specifications for secondary efficacy endpoints

No hypothesis will be tested for the secondary efficacy endpoints listed in the above Section 2.7.1 besides testings specified in Section 2.7.2.3.

These endpoints will be summarized and presented descriptively, based on the FAS with LOCF imputation for missing or censored data if not otherwise specified. Details on data handling such as missing values are described in Section 2.7.3.

Continuous endpoints:

The continuous secondary endpoints related to BCVA and CSFT will be analyzed using ANOVA models. The LSM estimates for each treatment and for the treatment difference (brolucizumab – aflibercept), including 95% CIs for treatment difference, will be presented.

For the ANOVA analysis of BCVA-related endpoints, baseline BCVA categories (≤65, >65 letters) and age categories (<65, ≥65 years) will be considered as class variables. For the ANOVA analysis of CSFT, baseline CSFT categories (<450, ≥450 - <650, ≥650 µm) will be used instead of baseline BCVA categories as a class variable.

The line plot on LSM (±SE) by visit will also be provided for each treatment arm.

Binary endpoints:

For binary endpoints, frequency tables (count and percentage) will be provided by visit. In addition, proportions and treatment differences in proportions along with 95% CIs will be presented for each time point using a logistic regression with treatment, the corresponding baseline status (similar to the ones specified for the ANOVA models) and age category as fixed effects.

Bar chart will be plotted by visit and treatment arm.

Time-to-event endpoints:

The time to achieve gain of ≥5, (respectively ≥10 and ≥15) ETDRS letters from baseline (or reaching a score of 84 or more) will be analyzed using KM analysis. KM estimates on percent of subjects who achieve gain will be presented together with 95% CI by treatment and visit. The median time (95% CI) to gain will also be constructed by treatment arm. KM curves

presenting the cumulative probability of subjects with gain of ≥5, (respectively ≥10 and ≥15) ETDRS letters from baseline will be provided by treatment arm.

The impact of COVID-19 pandemic on the following secondary endpoints will be assessed with subgroup analysis of impacted and non-impacted subjects defined in Section 2.2.1:

- Average change in CSFT from baseline over the period Week 40 through Week 52
- Change from baseline in CSFT at each assessment visit
- Proportion of subjects with ≥2-step improvement or worsening from baseline in the ETDRS DRSS 12-point scale at each assessment visit
- Treatment status at Week 52

2.7.2.2 ETDRS DRSS

Definition of Endpoints

The following categories of change from baseline in diabetic retinopathy (DR) status will be analyzed:

- Subject status regarding a ≥2- and ≥3-step improvement or worsening from baseline in the ETDRS DRSS at each assessment visit
- Incidence of progression to PDR as assessed by ETDRS-DRSS of at least 61 by Week 52 (among non-PDR subjects at screening)

Those endpoints will be derived from the ETDRS-DRSS assessed by the central reading center based on color fundus (CF) photography images in the study eye at screening, Week 28, and end of study visit or premature discontinuation visit.

When the ETDRS-DR severities are evaluable, they will be categorized using the following scores:

Table 2-3 Definition of DRSS: original scale

DRSS scale	Definition
10	DR absent
20	Microaneurysms only
35	Mild non-proliferative diabetic retinopathy (NPDR)
43	Moderate NPDR
47	Moderately severe NPDR
53	Severe NPDR
61	Mild PDR
65	Moderate PDR
71	High-Risk PDR
75	Very high risk PDR
81	Advanced PDR
85	Very advanced PDR

Other recorded DRSS values (code 98: Indeterminable due to missing images, 99: Indeterminable due to upgradable images, 00: NA, No images received) that are not related to an evaluable DR severity level will be handled as missing.

All DRSS values will be converted into a 12-point scale as defined in Table 2-4.

Table 2-4 Definition of DRSS: 12-point scale

12-point scale	Definition	Original DRSS
1	DR absent	10
2	Microaneurysms only	20
3	Mild NPDR	35
4	Moderate NPDR	43
5	Moderately severe NPDR	47
6	Severe NPDR	53
7	Mild PDR	61
8	Moderate PDR	65
9	High-Risk PDR	71
10	Very high-Risk PDR	75
11	Advanced PDR	81
12	Very advanced PDR	85

DR= diabetic retinopathy, DRSS= diabetic retinopathy severity score, NPDR= non-proliferative diabetic retinopathy, PDR= proliferative diabetic retinopathy.

Table 2-5 and Table 2-6 describe the definition of a 2-step and a 3-step change, respectively, for each (non-missing) baseline and post-baseline ETDRS based on the 12-point scale, as defined below:

- ≥2-step improvement: DRSS (12-point scale) at the visit – DRSS (12-point scale) at baseline ≤-2
- ≥3-step improvement: DRSS (12-point scale) at the visit – DRSS (12-point scale) at baseline ≤-3
- ≥2-step worsening: DRSS (12-point scale) at the visit – DRSS (12-point scale) at baseline ≥2
- ≥3-step worsening: DRSS (12-point scale) at the visit – DRSS (12-point scale) at baseline ≥3

Table 2-5 Definition of 2-step change in DRSS on the 12-point scale

Baseline	Post-baseline		
	≥2-step improvement	No change or change <2 steps	≥2-step worsening
1	-	1, 2	3 or higher
2	-	1, 2 or 3	4 or higher
3	1	2, 3, or 4	5 or higher
4	1 or 2	3, 4, or 5	6 or higher
5	3 or lower	4, 5, or 6	7 or higher
6	4 or lower	5, 6, or 7	8 or higher
7	5 or lower	6, 7, or 8	9 or higher
8	6 or lower	7, 8, or 9	10 or higher
9	7 or lower	8, 9, or 10	11 or 12
10	8 or lower	9, 10, or 11	12
11	9 or lower	10, 11, or 12	-
12	10 or lower	11, 12	-

Table 2-6 Definition of 3-step change in DRSS on the 12-point scale

Baseline	Post-baseline		
	≥3-step improvement	No change or change <3 steps	≥3-step worsening
1	-	1, 2 or 3	4 or higher
2	-	1, 2, 3 or 4	5 or higher
3	-	1, 2, 3, 4 or 5	6 or higher
4	1	2, 3, 4, 5 or 6	7 or higher
5	1 or 2	3, 4, 5, 6 or 7	8 or higher
6	3 or lower	4, 5, 6, 7 or 8	9 or higher
7	4 or lower	5, 6, 7, 8 or 9	10 or higher
8	5 or lower	6, 7, 8, 9 or 10	11 or 12
9	6 or lower	7, 8, 9, 10 or 11	12
10	7 or lower	8 or higher	-
11	8 or lower	9 or higher	-
12	9 or lower	10 or higher	-

Analysis method

All DRSS analyses will be based on the 12-point scale shown in Table 2-4.

Proportions of subjects with ≥2- and ≥3-step improvement or worsening from baseline will be summarized using the FAS by assessment visit. Bar chart will be plotted by assessment visit and treatment arm.

For the proportions of subjects with ≥ 2-step change from baseline at Week 52 (and similarly for ≥ 3-step change), the 95% CIs for the proportions in each treatment arm, the difference in proportions between treatment arms and the 95% CI for the difference will be calculated using a logistic regression with treatment, the corresponding baseline DRSS (score ≤43, ≥47 from the

original scale or ≤4, ≥5 from the 12-level scale) and age categories (<65, ≥65 years) as fixed effects.

The proportion of subjects who progress to PDR, as assessed by DRSS 12-point scale ≥7 by Week 52, will be summarized among the subset of non-PDR subjects at screening (DRSS 12-point scale < 7).

2.7.2.3 Confirmatory testing related to additional secondary efficacy endpoints

Confirmatory hypothesis testing for additional secondary endpoints will be performed in case non-inferiority related to BCVA is claimed for the hypotheses of primary endpoint and first key secondary endpoint specified in section 2.5.1 (corresponding to H1 and H2 in Figure 2-1).

The additional hypotheses are linked to the endpoints below:

- H3. Proportion of subjects with ETDRS DRSS ≥ 2-step improvement in the study eye from baseline by Week 52 (non-inferior for proportion of subjects in brolucizumab 6 mg vs aflibercept 2 mg with non-inferior margin 10%)
- H4. Proportion of subjects with presence of fluid (SRF and/or IRF) in the study eye at Week 52 (superior in proportion of subjects with absence of SRF and IRF in brolucizumab 6 mg vs aflibercept 2 mg)
- H5. Average change in CSFT from baseline over the period Week 40 through Week 52 in the study eye (superior in reduction of the CSFT change from baseline in brolucizumab 6 mg vs aflibercept 2 mg)

Figure 2-1 Multiple testing strategy

- Hypotheses H_1,..., H_5 are represented by circles with initial proportion of significance level assigned. The arrow represents the direction in which the significance level is propagated throughout the graph and the number in the square box represents the proportion of the propagated significance level.

All the tests are performed at the level resulting from the graphical procedure. If a tested null hypothesis is rejected at the local significance level assigned to this null hypothesis, the alpha is passed on to other null hypotheses as per the graph.

As described in Section 2.5.2, the primary hypothesis and first key secondary hypothesis will be tested sequentially.

If the primary hypothesis (H1) and first key secondary hypothesis (H2) are rejected sequentially at a one-sided significance level of 0.025, then H3, H4 and H5 will be tested sequentially in the order of their numbering, i.e., confirmatory testing of the third, fourth, or fifth hypothesis requires rejection of the preceding null hypothesis, at a one-sided significance level of 0.025.

The family-wise type I error rate will be controlled at the one-sided 2.5% level.

The basis for these tests will be the FAS.

2.7.3 Handling of missing values/censoring/discontinuations

Missing data for all the secondary efficacy endpoints will be imputed using the LOCF method unless specified otherwise.

For the LOCF method, missing data will be imputed by the value of the last available non-missing post-baseline observation. For subjects who discontinue treatment but continue in the study, data collected after start of alternative DME treatment in the study eye will be censored for the analysis. Censored data will be imputed by the last available observation prior to the start of alternative DME treatment in the study eye.

Missing baseline values will not be imputed. For subjects with no post-baseline values (scheduled or unscheduled), the baseline value will be carried forward, as a conservative approach.

Table 2-7 describes definition of presence of SRF/IRF:

Table 2-7 Definition of presence/absence status of SRF and IRF

IRF/SRF presence in 6mm field	IRF/SRF presence within 1mm central subfield	Presence/absence status of SRF/IRF
Definite	Yes	Present
Definite	No	Absent
Absent	Not Applicable	Absent
Cannot Grade	Not Applicable	Baseline: Absent Post-baseline: Missing
Not Applicable		Missing

For endpoints related to presence of SRF and/or IRF, if post-baseline visit is reported as “Missing”, LOCF method for imputation will be applied.

For the presence of leakage on FA, if baseline visit is reported as “Cannot Grade” or “Not Applicable”, then it will be considered as missing; if post-baseline visit is reported as “Cannot Grade” or “Not Applicable”, then it will be considered as missing and LOCF method for imputation will be applied.

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
- Loss in BCVA

There are no formal safety hypotheses in this study. All safety analyses will be performed using the Safety Set.

Except for imputation of partial dates for AEs, no imputations will be performed for missing values in the safety analyses.

In all summary tables, unless otherwise specified, data collected after the subject discontinued study treatment and started alternative DME treatment in the study eye will be censored (data on the day the subject started alternative DME treatment will be included).

2.8.1 Adverse events (AEs)

A treatment-emergent adverse event (TEAE) is defined as any adverse event that develops after initiation of the study treatment or any event already present that worsens following exposure to the study treatment. Only TEAEs will be presented in the summary tables.

Adverse events will be coded using the MedDRA dictionary and presented by system organ class (SOC) and preferred term (PT). TEAEs will be analyzed based on the number and percentage of subjects with at least one AE in the category of interest.

The number (and proportion) of subjects with TEAEs will be summarized in the following ways:

Table 2-8 TEAE summary

TEAE summary	AE categories		
	Ocular AE in the study eye	Ocular AE in the fellow eye	Non-ocular AE
AEs by primary SOC and PT	Y#		Y#
AEs by primary SOC and PT (including events with onset date after start of alternative DME treatment)	Y	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		Y

TEAE summary	AE categories		
	Ocular AE in the study eye	Ocular AE in the fellow eye	Non-ocular AE
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
SAEs by SOC and PT	Y#		Y#
SAEs by SOC and PT (including events with onset date after start of alternative DME treatment)	Y	Y	Y
SAEs related to study treatment by SOC and PT	Y		Y
SAEs related to injection procedure by SOC and PT	Y		Y
┼≥2 % (or other cutting point as appropriate) in any treatment group for a given PT. # Including separate summary tables for impacted and non-impacted subjects to COVID-19 as defined in Section 2.2.1			

In all summary tables listed above, unless otherwise specified, data collected after the subject discontinued study treatment and started alternative DME treatment in the study eye will be censored. If an AE started on the same day as the start of alternative DME treatment for a subject, the AE will be excluded from the summary table, unless this AE led to study drug withdrawal (in such a case, the AE would be included in the analysis).

Subject listings of all adverse events will be provided. Deaths and SAEs will be listed separately.

The MedDRA version used for reporting the AEs will be described in a footnote.

2.8.1.1 Adverse events of special interest / grouping of AEs

Incidence of adverse events of special interest will be tabulated by treatment arm. AESIs and other safety topics of interest will be identified via the RTH258 electronic case retrieval strategy (eCRS). The eCRS that is current at the time of database lock will be used and AESIs and other safety topics of interest will be identified where the flag Core safety topic risk (SP) = 'Y'.

2.8.1.2 Adverse event reporting for clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov, two required tables on TEAEs which are not serious adverse events with an incidence greater than 2% and on treatment emergent AEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety set. Ocular TEAEs for study eye and fellow eye will be considered separately.

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 (respectively non-SAE) has to be checked in a block e.g., among AEs 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

Laboratory data will be presented graphically using boxplots of absolute change from baseline values by treatment arm and visit. No summary by visit tables will be provided.

A summary table with counts and percentage of subjects satisfying the criteria representing clinically relevant abnormality given in Section 5.3 at any visit will be presented. A listing for subjects satisfying at least one criterion in Table 5-1 at any visit will also be presented.

2.8.4 Other safety data

2.8.4.1 Ophthalmic examinations

Intraocular pressure (IOP) values summarized and listed in safety analyses refer to assessments for study eye. IOP assessed in fellow eye will only be presented if deemed by the investigator as adverse event.

Descriptive summaries of pre-injection IOP change from baseline will be presented graphically at each study visit by treatment arm, considering line plots of the mean change in IOP values with error bars representing ± SE. The x-axis will be study visit and the y-axis will be the change from baseline value. No summary by visit tables will be provided.

The number and percentage of subjects with pre-injection IOP >30 mmHg at any visit will be summarized.

Post-injection IOP will be assessed within 60 minutes after injection and if ≥25 mmHg, assessment should be repeated until back to normal. Summary tables with counts and percentage of subjects with an IOP increase of ≥10, ≥20 mmHg from pre-injection to post-injection at any visit for the study eye will be presented. A listing for subjects with post-injection IOP increase of ≥10 mmHg from pre-injection IOP at any visit will be presented.

A summary table with counts and percentages of subjects with observed pre-injection IOP ≥ 21mmHg in 3 consecutive scheduled visits will be presented.

A visit with missing pre-injection IOP is considered to meet the ≥ 21 mmHg criterion if the preceding and the following visits meet the criterion that pre-injection IOP ≥ 21 mmHg. For example, if scheduled visit X has missing pre-injection IOP and pre-injection IOP ≥ 21 mmHg is observed for both visits X-1 and X+1, the subject is considered to meet the criteria at visit X as well.
A listing of subjects with any IOP > 30 mmHg will be presented.

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.

2.8.4.2 Loss in BCVA

The number and percentage of subjects with a loss in BCVA ≥15, ≥30 letters (study eye) from baseline to the last visit, and maximum loss at any visit will be presented.

BCVA data (study eye) for subjects presenting loss in BCVA ≥15 letters from baseline at any post-baseline visit will be listed.

2.8.4.3 Vital signs

A summary table with counts and percentages of subjects satisfying the criteria given in Table 5-2 of the Section 5.3 at any visit will be presented. A listing for subjects satisfying at least one criterion in Table 5-2 will also be presented.

A line plot of mean change from baseline in each vital sign parameter by study visit and treatment with error bars representing ±SE will be presented. The x-axis will be study visit and the y-axis will be the mean change from baseline value.

2.8.4.4 Imaging parameters

Pre-defined imaging parameters in the study eye associated with intraocular inflammation and/or retinal vascular occlusion as assessed by the CRC will be listed.

2.9 Pharmacokinetic endpoints

Serum concentration of brolucizumab will be assessed in around 12 subjects in brolucizumab arm at Day 2 and Week 24, both approximately 24 hours after dosing.

At each time point, one-half the lower limit of quantification (LLOQ) will be used for analysis when a subject has a determined concentration value below the LLOQ. If a majority of subjects at any time point are below the LLOQ or if the calculated mean concentration value is below the nominal LLOQ then the resultant mean concentration will be reported as below the LLOQ instead.

2.10 Anti-drug antibodies

Collection of blood for ADA assessment for brolucizumab treatment arm will be done at Screening, Weeks 4, 12, 24 and 36 prior to the injection/sham, and at exit/premature discontinuation. [redacted]

[redacted]

In addition, tabulations will be presented for ADA titer values by ADA assessment visit for the brolucizumab arm.

[redacted]

The line plots showing the BCVA change from baseline up to Week 52 for the study eye by ADA status (pre-existing and integrated status up to Week 52) and NAb status (pre-existing and integrated status up to Week 52) will be generated.

The summary tables of the incidence of AESIs by ADA status (pre-existing, integrated status up to Week 52) will be presented.

Subject listings of all ADA titer values [redacted] will be presented for all subjects in the brolucizumab arm. Samples collected at unscheduled visits will not be part of the analysis. Systemic exposure of brolucizumab will be measured concomitantly with ADA levels for interpretation purposes, no pharmacokinetic parameters will be determined from brolucizumab systemic exposure. In addition, systemic brolucizumab exposure assessment will be performed in a subset of consented subjects at 2 time points, approximately 24 hours after the first dose and approximately 24 hours after the treatment at Week 24. Systemic exposure data will be summarized and listed.

2.11 Subject-reported outcomes

The Visual Function Questionnaires (VFQ-25) will be scored (total and subscale scores) at Baseline, Week 28 and Week 52 visits. Absolute scores and the absolute changes from baseline will be calculated and summarized descriptively using the FAS.

Further details on the scoring algorithm and analysis are provided below.

Each subscale score has a range of 0 to 100 inclusive and will be calculated from the re-scaled raw data as described in Table 2-9. 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 composite and subscale scores.

Table 2-9 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

Note: * 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, and 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 VFQ subscales and their corresponding questions are shown in Table 2-10.

Table 2-10 Questions contributing to VFQ subscales

Subscale	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

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

The composite score is the average of the 11 subscales shown in Table 2-10. It will be set to missing if at least six of the subscales are missing.

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

Descriptive summary statistics for change from baseline to post baseline VFQ assessments will be presented using the FAS for the composite and subscale scores. Mean changes from baseline to each post baseline VFQ assessments visits will be compared between the brolucizumab arm and the aflibercept arm. Appropriate statistical methods (e.g. ANCOVA model with treatment as a fixed effect factor and corresponding baseline value of the endpoint in the model) will be

used for treatment group comparison. Additionally, descriptive statistics will also be presented for the general health score.

The VFQ-25 composite score and subscale scores will not be listed.

2.13 Interim analysis

Not applicable.

3 Sample size calculation

A sample size of 120 subjects per arm will allow to demonstrate a non-inferiority (NIM of 4 ETDRS letters) of brolucizumab 6 mg vs. aflibercept 2 mg with respect to the BCVA change from baseline at Week 52, with 80% power at a one-sided alpha level of 0.025, assuming equal means and a common standard deviation of 11 letters. Assuming that averaging over the 4 time points will not lead to an increase in the standard deviation, a power of at least 80% can also be expected for its corresponding non-inferiority claim.

To account for a drop-out rate of 10%, a total of 268 (134 per arm) subjects will need to be randomized.

4 Change to protocol specified analyses

There is no change to the protocol specified analysis in terms of endpoints.

Some changes compared to the protocol specified analyses are made in the current statistical analysis plan:

Protocol section	Protocol wording	Change in the SAP
12.3	Descriptive statistics for exposure to study treatment will be provided for the safety set, FAS and PPS	Descriptive statistics for exposure to study treatment will be provided for the Safety set.
12.3	The number and percentage of patients taking prior medication or concomitant therapies will be summarized by preferred term according to the WHO Drug Reference List dictionary using the Safety Set and FAS (in case there are differences between those two).	Ocular and non-ocular prior and concomitant medications will be summarized and listed by ATC class and preferred term for the Safety set.
12.5.2	Laboratory data and vital signs will be summarized by presenting shift tables using extended normal ranges (as provided by the central laboratory) with thresholds representing clinical relevant abnormality and by presenting descriptive statistics of raw data and change from baseline. Values outside the extended normal range will be listed by patient and treatment arm and flagged in data listings.	No summary by visit tables will be provided. A summary table with counts and percentage of subjects satisfying the criteria representing clinically relevant abnormalities at any visit will be presented. A listing for subjects satisfying at least one criterion in Table 5-1 at any visit will also be presented.
[redacted]		

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

No imputation will be made to the start date and end date of study treatment.

5.1.2 AE date imputation

5.1.2.1 AE start date imputation

The following table explains the notation used in the logic matrix below. 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

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
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.

5.1.2.2 AE end date imputation

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.

5.1.3 Concomitant medication date imputation

5.1.3.1 Concomitant medication start date

In order to classify a medication as prior and prior/concomitant, it may be necessary to impute the start date.

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 concomitant medication (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.

5.1.3.2 Concomitant medication end date imputation

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 earliest of the (treatment end date, 31DECYYYY, date of death).

3. If the CM end date day is missing, the imputed end date should be set to the earliest of the (treatment end date, last day of the month, date of death).

4. 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.

5.1.4 Medical history date of 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.

1. If DIAG year < treatment start date year
    a. and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY)
    b. else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY)
2. If DIAG year = treatment start date year
    a. 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
    b. else if DIAG month < treatment start month, the imputed DIAG date is set to the midmonth point (15MON YYYY)
    c. else if DIAG month > treatment start month => data error
3. If DIAG year > treatment start date year => data error

5.2 AEs coding/severity

AEs are coded using the MedDRA terminology.

AEs severity is assessed by investigators according to the following:

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

5.3 Laboratory parameters and vital signs derivations

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		NA	>3xULN				
Glucose	mg/dL	< 40	> 450	mmol/L	< 2.2	> 25.0	
Potassium	mEq/L	< 2.8	> 6.2	mmol/L	< 2.8	> 6.2	
Sodium	mEq/L	< 120	> 160	mmol/L	< 120	> 160	
HCG							Negative, inconclusive
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	< 2.0	> 35.0	X10E9/L	< 2.0	> 35.0	

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

5.4 Statistical models

5.4.1 Primary and first key secondary analysis

The primary endpoint (change from baseline in BCVA at Week 52) and first key secondary endpoint (average change from baseline in BCVA over the period Week 40 through Week 52) will be analyzed using ANOVA models.

Analysis of Variance (ANOVA)

The following ANOVA model will be used for the primary and first key secondary efficacy endpoints:

<change from Baseline in BCVA at Week 52> <average change from Baseline in BCVA from Week 40 to Week 52> = intercept + treatment + Baseline BCVA category + age category + error.

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

The SAS Proc MIXED will be used to perform the ANOVA analyses.

Mixed Model Repeated Measures (MMRM)
The following MMRM model will be used for the supportive analysis of the primary and first key secondary efficacy variables:
*<change from Baseline in BCVA> = intercept + treatment + Baseline BCVA category + age category + visit + treatment*visit + error.*

The SAS Proc MIXED will be used to perform the MMRM analyses.
Note: For the above MMRM analysis, the data structure is one record per 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.

5.4.2 Other secondary efficacy analysis

5.4.2.1 ANCOVA model for continuous variables

The continuous efficacy variable (such as VQF-25 score change from baseline) will be analyzed using an ANCOVA model adjusted for treatment, age category, and the corresponding baseline VFQ-25 score.
The SAS Proc MIXED will be used to perform the ANCOVA analyses.

5.4.2.2 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 covariates if necessary.

The SAS Proc LOGISTIC will be used.
Note:

- For the above analyses, the data structure is one record per subject and visit. The least square mean estimates obtained from the above model are for the log-odds ratios.
- The estimated difference in proportions and the corresponding 95% confidence intervals will be obtained by applying the bootstrap method. The pseudo SAS code to derive the treatment difference and 95% CI from the least square mean output of the fitted model will be provided in the programming specification document.
- For superiority tests, p-values (if applicable) will be obtained from odds ratio test in logistic model. For non-inferiority tests, p-values (if applicable) will be obtained by applying the bootstrap method.

5.4.2.3 KM estimate for time to event variables

Within the brolucizumab treatment arm, the proportion of subjects maintained at q12w up to Week 52 will be estimated from Kaplan Meier time-to-event analyses for the event ‘ first q8w-need’ applying event allocations (in case of lack of efficacy and/or lack of safety) and censoring as described in Section 2.6.2.

A corresponding 95% CI will be derived from the LOGLOG transformation, using SAS Proc Lifetest, with CONFTYPE = LOGLOG.

5.5 Rule of exclusion criteria of analysis sets

Important protocol deviations are defined in the Protocol Deviations Requirements Document. Table 5-3 includes the important protocol deviations which lead to exclusion of a subject from one or more analysis sets.

Table 5-3 Important Protocol deviations leading to exclusion from analysis

Deviation ID	Description of Deviation	Exclusion in Analyses
M_INCL01_ICF not obtained	Written informed consent not obtained	Exclude from all analysis
P_INCL02_Age less than 18 yrs	Subject less than 18 years of age at screening	Exclude from PP analysis
M_INCL03_Diabetes eligibility criteria	Subjects without diabetes mellitus or HbA1c of more than 10% at screening or insufficient diabetes management at screening or baseline	Exclude from PP analysis
P_INCL04_No visual impairment (study eye)	Study Eye: no visual impairment due to DME as per BCVA or CSFT criteria	Exclude from PP analysis
M_EXCL01_Condition with impact study eye	Study Eye: Confounding ocular concomitant conditions or ocular disorders with impact on efficacy and/or safety	Exclude from PP analysis
M_EXCL03_Confounding treatment study eye with impact	Study Eye: Confounding concomitant medications or procedures with impact	Exclude from PP analysis
M_EXCL06_Systemic cond/trt with impact	Systemic: Confounding systemic conditions (including Blood Pressure) or systemic treatments with impact on efficacy and/or safety	Exclude from PP analysis
M_TRT01_Wrong IP administered	Wrong IP administered during the study	Exclude from PP analysis
M_TRT02_Under-treatment during loading phase	Under-treatment during loading phase; missed active treatment (not due to any safety event)	Exclude from PP analysis
M_TRT03_Over treatment	Over treatment, received active when schedule was for sham /no treatment	Exclude from PP analysis
M_TRT04_Under-treatment after loading phase	Under-treatment after loading phase; missed active treatment (not due to any safety event)	Exclude from PP analysis if any missed active treatment between W40 and W48 inclusive, or if at least 2 missed consecutive active doses (not due to safety); Otherwise include in all analysis
M_OTH01_Other PD with impact	Any other protocol deviation with impact on the efficacy assessments or safety of the subject	Exclude from PP analysis
M_COMD01_Prohibited trt with impact	Prohibited medication and/or procedure as per protocol with impact on efficacy and/or safety	Exclude from PP analysis
P_WITH01_Treatment but consent withdrawn	Subject withdrew consent but continued to receive study medication	Exclude from PP analysis

Table 5-4 lists the non-protocol deviations (analysis restrictions) that may lead to exclusion from per-protocol analysis. Analysis restrictions (ARs) address limitations in the evaluability which result from missing or confounded data with underlying background not qualifying as a

PD (e.g. early study terminations, early treatment discontinuations, missing DAA or BCVA assessments).

Rules of determination of ARs by programming will be specified in the Programming Data Specifications (PDS) documentation.

Table 5-4 Non-protocol deviations (analysis restrictions)

AR ID	Description of AR	Category of reason	Exclusion in Analyses
AR_EST_01	Early study termination due to lack of efficacy	1	Include in all analyses
AR_EST_02	Early study termination due to lack of safety	2	Include in all analyses
AR_EST_03	Early study termination due to reasons other than lack of efficacy/safety	0	Exclude from PP analysis if before week 40. Otherwise include in all analyses
AR_ETD_01	Early study treatment termination due to lack of efficacy	1	Include in all analyses
AR_ETD_02	Early study treatment termination due to lack of safety	2	Include in all analyses
AR_ETD_03	Early treatment termination due to reasons other than lack of efficacy/safety	0	Exclude from PP analysis if before week 40. Otherwise include in all analyses
AR_MD_01	No valid BCVA assessment between W40 and W52	0	Exclude from PP analysis
AR_MD_02	Missing DAA due to lack of safety	2	Include in all analyses
AR_MD_03	Missing DAA due to reasons other than lack of safety	0	Include in all analyses

Subject evaluability is based on two components:

- Exclusion from an analysis set
- Censoring of specific data points from an analysis (see Section 5.6).

The consequence of an AR on the evaluability depends on the underlying reason, while three different categories of reason are considered:

- Lack of efficacy of the study treatment (=1)
- Lack of safety / tolerability of the study treatment (=2)
- Other (=0)

Remark: Based on the concept of PD's, their underlying reason will always be '0'.

As a general rule, ARs with a reason of 1 or 2 do not lead to an exclusion from any analysis set, as a potential link between exclusion reason and treatment would constitute a source for systematic bias.

Table 5-5 describes subject classification with regards to analysis sets:

Table 5-5 Subject classification

Analysis Set	PD ID that may cause subjects to be excluded	Non-PD (AR) ID that cause subjects to be excluded
RAN	M_INCL01_ICF not obtained	Not Randomized;
FAS	M_INCL01_ICF not obtained	Not in the RAN; Did not receive at least one study injection

Analysis Set	PD ID that may cause subjects to be excluded	Non-PD (AR) ID that cause subjects to be excluded
SAF	M_INCL01_ICF not obtained	Did not receive at least one study injection
PPS	M_INCL01_ICF not obtained, P_INCL02_Age less than 18 yrs, M_INCL03_Diabetes eligibility criteria, P_INCL04_No visual impairment (study eye), M_EXCL01_Condition with impact study eye, M_EXCL03_Confounding treatment study eye with impact, M_EXCL06_Systemic cond/trt with impact, M_TRT01_Wrong IP administered, M_TRT02_Under-treatment during loading phase, M_TRT03_Over treatment, M_TRT04_Under-treatment after loading phase, M_OTH01_Other PD with impact, M_COMD01_Prohibited trt with impact, P_WITH01_Treatment but consent withdrawn	Not in the FAS AR_EST_03, AR_ETD_03, AR_MD_01

5.6 Censoring rules for analysis

PDs and ARs that are considered to be critical for the subject evaluability regarding the primary and key secondary endpoints are described in Section 5.5.

The focus of the ARs is the identification of censoring related to the analysis of BCVA and q12w proportion as derived from DAA and described in Section 2.6.2. Censoring is only applied in case the underlying reason for a confounded DAA is assessed as '0'. Censoring of BCVA and DAA applies both to FAS and PPS.

Table 5-6 summarizes the concepts of censoring for the key parameters BCVA and q12w-status/ DAA applied to the two efficacy analysis sets, FAS and PPS, as well as the details for the timing of censoring for BCVA and DAA.

In case a subject has multiple PDs/ARs with impact on subject's evaluability the following rules are applied:

- A subject is excluded from an analysis set if at least one PD or AR with this consequence was identified (see Table 5-5). This rule is built on the concept of the medical assessment of the 'reason' which considers the reason of an earlier event to potentially also be the reason for following PDs or ARs.
- In case of multiple censoring time points censoring will be performed at the earliest.

Table 5-6 Censoring concepts for BCVA and DAA

Analysis Set	Censoring concept for BCVA	Censoring concept for DAA
FAS	Censoring of BCVA data after switch to alternative DME treatment in the study eye: imputation using the last observation collected prior to the start of alternative DME treatment (see section 2.5.3) No other censoring related to PDs or ARs.	M_TRT01_Wrong_IP_administered: censoring at the last valid DAA visit at or prior to the PD visit M_TRT02_Under-treatment during loading phase: censoring at baseline M_TRT03_Over treatment: censoring at the last valid DAA visit at or prior to the PD visit

		M_TRT04_Under-treatment after loading phase: censoring at the last valid DAA visit at or prior to the PD visit M_COMD01_Prohibited trt with impact: censoring at the last valid DAA prior to the start of the prohibited medication or procedure AR_ETD_03: censoring at the last valid DAA visit at or prior to the PD visit AR_EST_03: censoring at the last valid DAA visit at or prior to the PD visit AR_MD_03: censoring at the last valid DAA prior to the missed visit Remark: The primary analysis of the q12w proportion as derived from DAA and described in section 2.6.2 applies censoring in case the underlying DAA is considered to be confounded by reasons other than lack of efficacy and/or safety. Based on the underlying time-to-'first-q8w-need' analysis, all information up to and including the censoring time-point contribute to the evaluation of the q12w status. **Censoring: subjects are considered to no longer be under risk for a q8w-need identification at later visits.** Censoring at baseline if above PD/AR occurred prior to Week 32. Censoring at Week 52 visit if subjects completed Week 52 without above PD/AR
PPS	Censoring of BCVA data after switch to alternative DME treatment in the study eye: imputation using the last observation collected prior to the start of alternative DME treatment (see section 2.5.3)	Similar to FAS