NOVARTIS

Clinical Development

RTH258/Brolucizumab/Beovu®

CRTH258A2307 / NCT04047472

A Twelve-Month, Randomized, Double-Masked, Multicenter, Phase III, Two-Arm Study Comparing the Efficacy and Safety of Brolucizumab 6 mg versus Aflibercept in Chinese Patients with Neovascular Age-Related Macular Degeneration (HOBBY)

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Amendment V2
Release date:	25-Mar-2024
Number of pages:	45

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
13-Apr-2021	Prior to DB lock	Creation of final version	N/A - First version	NA
25-Mar-2024	Prior to DB lock	Creation of amendment 1	Update the list of abbreviations	
			Update the version of protocol	Section 1
			Population sample size and significance level alpha for data analysis are updated	Section 1.1, Section 2.1, Section 2.5.4.1, Section 3
			Add footnote in Table 1-1	Section 1.2
			Clarify the study drug and study treatment	Section 2.1.1
			Update unscheduled visits	Section 2.1.1
			Modify the definition of PK set	Section 2.2
			Add other subgroups of interest	Section 2.2.1
			[redacted]	[redacted]
			Update disposition tables	Section 2.3.1
			Update demographics and baseline characteristics	Section 2.3.2
			Specify CNV, fibrosis, foveal involvement	Section 2.3.2, 2.7.1,2.8
			Add medical history	Section 2.3.3
			[redacted]	[redacted]
			Update the alternative nAMD treatment list	Section 2.5.3

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Add listing for imaging parameters	Section 2.8.4.4
			[redacted]	[redacted]
			Clarify primary and supplementary estimands and analyses based on estimands	Sections 2.5.1, 2.5.2, 2.5.4
			Modify table of nAMD treatments	Section 2.5.3
			Delete “as observed” approach	Section 2.6.4
			[redacted]	[redacted]
			Specify AESIs and AE reporting for safety disclosure	Section 2.8.1.1 and Section 2.8.1.2
			Add shift tables of laboratory data	Section 2.8.3
			Add analyses on presence of fibrosis	Section 2.8.4.2
			Move up the imaging parameters section	Section 2.8.4.5
			Specify tables and plots of PK endpoints	Section 2.9
			Modify titer value threshold of ADA	Section 2.10
			Specify tables, plots and listings of ADA endpoints	Section 2.10
			Update listing of “change to protocol specified analyses”	Section 4

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Modify concomitant medication/procedure imputation	Section 5.1.3
			Update the important PD table	Section 5.5

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List of abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
AMD	Age-Related Macular Degeneration
ANCOVA	Analysis of covariance
ANOVA	Analysis of Variance
AR	Analysis restriction
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BCVA	Best Corrected Visual Acuity
BID	Bis in diem/twice a day
BLQ	Below the Quantization Limit
CI	Confidence interval
Cmax	Maximum concentration
CNV	Choroidal neovascularization
COVID-19	Coronavirus disease 2019
CS	Compound symmetry
CSFT	Central Subfield Thickness
CSFTns	Central Subfield Thickness-neurosensory retina
CSFTtot	Central Subfield Thickness Total
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAA	Disease activity assessment
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
eCRS	Electronic case retrieval strategy
EOS	End of Study
EOT	End of Treatment
ESI	Event of Special Interest
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FP	Fundus Photography (FP)
ICF	Informed consent form
IOP	Intraocular pressure
IRF	Intraretinal fluid
IVR	Interactive Voice Response
IVT	Intravitreal
IWR	Interactive Web Response
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
LOCF	Last Observation Carried Forward

LSM	Least square means
MAR	Missing at random
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed model repeated measures
nAMD	Neovascular Age-related Macular Degeneration
NCI	National Cancer Institute
OCT	Optical coherent tomography
o.d.	Once Daily
OS	Overall Survival
[redacted]	[redacted]
PD	Protocol deviation
PDS	Programming Data Specifications
PDT	Photodynamic therapy
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PT	Preferred term
q4w	Every 4 weeks
q8w	Every 8 weeks
q12w	Every 12 weeks
QoL	Quality of Life
RAP	Report and Analysis Process
RAS	Randomized analysis set
RECIST	Response Evaluation Criteria in Solid Tumors
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SOC	System Organ Class
SRF	Subretinal fluid
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, Listings
TOEP	Toeplitz
UWF-C	Ultra-wide field Color Fundus Photography
VC	Variance components
VEGF	Vascular endothelial growth factor
VFQ-25	Visual Function Questionnaire-25
WBC	White blood cell(s)
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 CRTH258A2307.

Data will be analyzed according to the data analysis Section 12 of the study protocol (Clinical Trial Protocol CRTH258A2307 v04 dated 14-Jun-2022) 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 treatment unmasking. Any changes to the SAP after approval will be documented in CREDI.

1.1 Study design

This is a randomized, double-masked, multicenter, parallel-group, active-controlled study. The study includes 14 scheduled visits over 48 weeks. A screening period of 2 weeks will be used to assess eligibility.

After confirmation of eligibility at baseline, approximately 390 subjects will be randomized in a 1:1 ratio to one of the two treatment arms (approximately 195 subjects per arm):

- Brolucizumab 6 mg: three monthly intravitreal injections of brolucizumab 6 mg during the loading treatment period (q4w regimen) up to Week 8 followed by injections every 12 weeks (q12w regimen) or 8 weeks (q8w regimen) up to Week 40 or Week 44, depending on the status of disease activity.
- Aflibercept 2 mg: three monthly intravitreal injections of aflibercept 2 mg during the loading treatment period (q4w regimen) up to Week 8 followed by injections every 8 weeks (q8w regimen) up to Week 40.

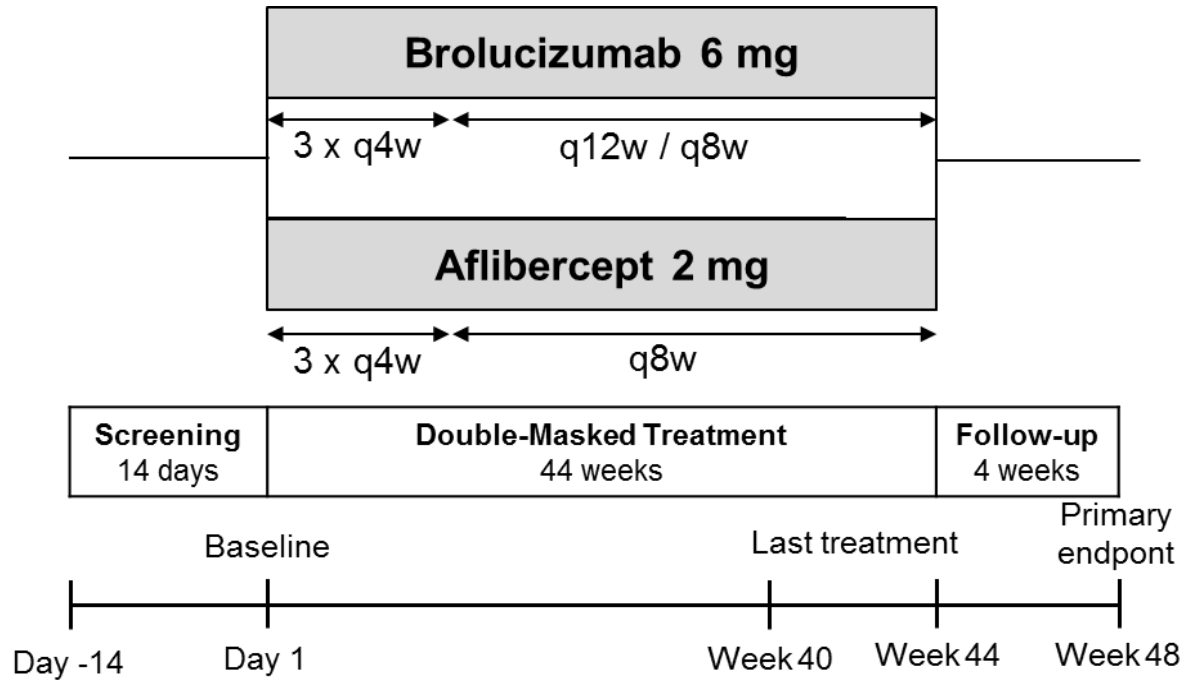
Only one eye fulfilling all eligibility criteria will be selected/ treated and will be defined as the study eye.

Novartis Interactive Response Technology will be used for randomization.

There are no stratification factors in this study.

There are no interim analyses in this study.

Figure 1-1 Study design



q4w - injection every 4 weeks; q8w - injection every 8 weeks; q12w - injection every 12 weeks

1.2 Study objectives and endpoints

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 not inferior to aflibercept 2 mg with respect to the change in BCVA after 48 weeks of treatment	• Change in BCVA from Baseline to Week 48+ • Average change in BCVA from Baseline over the period Week 36 to Week 48#
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To estimate the proportion of q12w subjects (1 injection every 12 weeks) up to Week 48 in the brolucizumab 6 mg treatment arm	• q12w treatment status at Week 48 (for subjects randomized to brolucizumab 6 mg only)
• To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment up to Week 48 in the brolucizumab 6 mg treatment arm	• q12w treatment status at Week 48 within the subjects with no q8w need during the first q12w cycle (Week 16 and Week 20) (for subjects randomized to brolucizumab 6 mg only)
• To evaluate the efficacy of brolucizumab 6 mg relative to aflibercept 2 mg over the time period up to Week 48 by assessing changes in BCVA	• Change in BCVA from Baseline to each postbaseline visit • Average change in BCVA from Baseline over the period Week 4 to Week 48 • Average change in BCVA from Baseline over the period Week 12 to Week 48 • Gain in BCVA of 15/10/5 letters or more from Baseline at each postbaseline visit

Objective(s)	Endpoint(s)
• To evaluate the efficacy of brolucizumab 6 mg relative to aflibercept 2 mg over the time period up to Week 48 by assessing changes in anatomical parameters of disease activity	• Number and percentage of subjects with BCVA of 73 letters or more at each visit • Loss in BCVA of 15/10/5 letters or more from Baseline at each postbaseline visit • Change in CSFTtot from Baseline to each postbaseline visit • Average change in CSFTtot from Baseline over the period Week 36 through Week 48 • Average change in CSFTtot from Baseline over the period Week 4 to Week 48 • Change in CSFTns from Baseline to each postbaseline visit • Change in area of CNV lesion from Baseline at Weeks 12 and 48 • Presence of subretinal and/or intraretinal fluid (central subfield) at each postbaseline visit (and specifically Week 16 and Week 48) • Number of visits with simultaneous absence of subretinal and intraretinal fluid (central subfield) during Week 36 to Week 48 • Presence of subretinal fluid (central subfield) at each postbaseline visit • Presence of intraretinal fluid (central subfield) at each postbaseline visit • Presence of sub RPE fluid (central subfield) at each postbaseline visit
• To evaluate the efficacy of brolucizumab 6 mg relative to aflibercept 2 mg at the end of the matched treatment phase	• Change in CSFTtot from Baseline at Week 16 • Presence of subretinal and/or intraretinal fluid (central subfield) at Week 16 • q8w treatment need identified at Week 16
• To assess the safety and tolerability of brolucizumab 6 mg relative to aflibercept 2 mg	• Incidence and characteristics of treatment-emergent adverse events • Treatment-emergent changes in ocular and systemic parameters • Presence of fibrosis from color fundus photography by assessment visit
• To assess visual function-related subject reported outcomes following treatment with brolucizumab 6 mg relative to aflibercept 2 mg	• Change in subject reported outcomes (VFQ-25) total and subscale scores from Baseline to Weeks 24 and 48
• To assess immunogenicity of brolucizumab 6 mg	• ADA status at Baseline (enrollment), Weeks 4, 12, 24, 36, and 48 (End of Study)
• To assess systemic PK of brolucizumab at 6 mg following a single IVT injection	• PK parameters after first brolucizumab 6 mg dose in a subset of subjects

Objective(s)	Endpoint(s)
[redacted]	

† Change in BCVA from Baseline to Week 48 in the study eye is the primary endpoint, corresponding to the primary objective, which is consistent with pivotal studies (HAWK & HARRIER).

Average change in BCVA from Baseline over the period Week 36 to Week 48 in the study eye is the first key secondary endpoint, considered also of clinical importance and therefore corresponds to the primary objective of the study.

2 Statistical methods

2.1 Data analysis general information

The primary analysis will be performed after all subjects completed or discontinued the study by Novartis using SAS 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 90% confidence intervals (CIs) for point estimates of the mean or proportion will be provided. For the treatment difference brolucizumab – aflibercept, point estimates with 90% CIs will be provided as appropriate unless otherwise specified.

[redacted]

2.1.1 General definitions

Study drug and study treatment

Study drug refers to both Brolucizumab 6 mg and Aflibercept 2 mg via intravitreal (IVT) injections.

Study treatment refers to study drug or sham injections.

Study day

Day 1 is defined as the date of the first 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 study treatment + 1;

- for dates prior to the date of first administration of study treatment:
  Study day = Assessment date – Date of first 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 the first study treatment are defined as post-baseline.

End of study day mapping

The end of the study day 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 number. If the 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.

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 postbaseline values such as last observation carried forward (LOCF) imputation, and summary of maximum letter loss in BCVA from baseline. Only values at scheduled visits (observed or imputed by LOCF) will be considered to average BCVA change from baseline over a given period. 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 and are assigned with subject numbers. This analysis set will be used to summarize subject disposition.

The **Randomized Set** (RAN) will consist of all randomized subjects. Subjects are considered randomized when they have 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, i.e. non-protocol deviations) that are

expected to majorly affect the validity of the assessment of efficacy and/or safety at the end of study. Confounded data or discontinuation from treatment due to lack of efficacy and/or safety do not constitute a reason for exclusion from the PPS.

PDs that may lead to exclusion from PPS are specified in Table 5-3. ARs that may lead to exclusion from PPS are specified in Table 5-4. Before the database locks, the relevant protocol deviations will be identified at the subject level in the database. After the database locks, analysis restrictions will be derived in the analysis database. Subject evaluability based on pre-specified PDs and/or ARs and their impact on analysis sets will be determined prior to the database lock. Censoring applied in relation to the specific PDs/ARs will be specified as well. Details are specified in Section 5.5 and Section 5.6.

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 the majority of treatments.

2.2.1 Subgroup of interest

The subgroups of interest are specified below:

- Age category (< 75 years and ≥ 75 years)
- Gender (male and female)
- Baseline BCVA categories (≤ 55, ≥56-≤70, ≥ 71 letters)
- Baseline CSFT category (< 400, ≥ 400 µm)
- Baseline type of CNV (predominantly classic, minimally classic, pure occult)

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

[redacted]

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

The number of subjects enrolled in the study and with screen failures will be presented in the subject disposition table. The number and percentage of subjects who are randomized, are treated, complete the study, discontinue from the treatment prior to Week 44, and discontinue from study prior to Week 48 will be summarized by the treatment arm randomized, based on the all enrolled set. The reasons for discontinuation (from the study and/or treatment) will also be summarized.

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

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

A subject is considered to have completed the study period if he/she does not discontinue from the study prior to Week 48.

Subjects who sign an informed consent form and who are subsequently found to be ineligible prior to randomization will be considered as screen failures. Appropriate table and listing of all screen failures with corresponding reason will be presented as necessary.

Number and percentage of subjects who are excluded (i.e. not evaluable) from any 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 are excluded from, and the corresponding reasons will also be presented.

Number and percentage of subjects with important PDs and ARs will be presented by treatment arm and deviation/restriction category, including corresponding listings.

Subjects who discontinue from the study and/or treatment early related to COVID-19 will be identified. To evaluate the PDs that occur related to COVID-19, the number and percentage of subjects with PDs that occur related 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

Demographic and baseline characteristics will be summarized with descriptive statistics by treatment arm and overall based on FAS. The demographic characteristics include age, age category (50 to 64, 65 to 74, 75 to 84, and ≥ 85 years), gender and race.

Baseline characteristics table will include:

- Study eye selection (left eye/OS or right eye/OD)
- Time since diagnosis of nAMD category (< 1 month, 1-3 months, >3 months)
- Whether neovascular AMD is unilateral or bilateral

- BCVA (letters)
- BCVA category (≤55, ≥56-≤70, ≥71 letters)
- Type of CNV (predominantly classic, minimally classic, pure occult) from Color Fundus Photography (FP) / Ultra-wide field Color Fundus Photography (UWF-C)
- Foveal involvement (subfoveal, juxtafoveal, extrafoveal) from FP/UWF-C
- CNV lesion size from FP/UWF-C
- Presence of subretinal fluid (central subfield)
- Presence of intraretinal fluid/cyst
- Presence of sub RPE fluid
- Neurosensory retinal thickness (CSFTns)
- CSFTtot
- CSFTtot category (< 400, ≥ 400 µm)

Pure occult in type of CNV is considered present if at least one of the 3 subtypes (Fibrovascular PED, Serous PED and Late Leakage) is present. "Predominantly classic" category in type of CNV includes both "Predominantly classic" and "Classic" subcategories.

With regard to eye-level assessments, the baseline characteristics table will be presented for the study eye only and a corresponding listing will be provided separately for the study eye and the fellow eye. Other relevant baseline information will be listed and summarized with descriptive statistics as appropriate.

Time since diagnosis of nAMD (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.

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

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

2.4.1 Study treatment exposure

Extent of exposure to study drug is calculated as the number of IVT injections received. Descriptive statistics for exposure to study treatment will be provided for the Safety Analysis Set.

The following summaries will be presented based on the Safety analysis set:

- Number of injections will be presented separately (active and sham, active only, sham only) in the following time periods:
  - Baseline to Week 8
  - Week 12 to Week 44

- Baseline to Week 44

- Treatment exposure by visit: The number and percentage of subjects who received active, sham injections, missed a treatment (active or sham) and missed visits will be presented separately by arm and visit.
- Frequency of all observed dosing patterns up to and including Week 44 will be presented by treatment group, differentiating between active and sham treatments, missed treatments and wrong treatments.
- Brolucizumab q12w/q8w allocation by visit: Number and percentage of subjects on q12w and q8w treatment regimen including the number of subjects switched from q12w to q8w with the reasons based on FAS.

Dose administration records will be listed by each treatment arm.

2.4.2 Prior medications and concomitant therapies

The Safety analysis set will be used for the analyses below.

Prior medications are defined as treatments taken and stopped prior to the 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 or concomitant medications will be coded according to the WHO Drug Reference List dictionary, with Anatomical Therapeutic Classification (ATC) class and preferred term (PT).

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

Concomitant anti-VEGF medications will be summarized by ATC class and PT for the fellow eye by each treatment arm.

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

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

A listing of subjects who received alternative nAMD treatment in the study eye will be provided.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint and first key secondary endpoint

- The primary efficacy endpoint is change in BCVA from baseline to Week 48 in the study eye.
- The first key secondary endpoint is average change in BCVA from baseline over the period Week 36 through Week 48 in the study eye. For each subject, this endpoint is defined as the average of the changes from baseline to Weeks 36, 40, 44 and 48.

The primary efficacy analyses of these two endpoints will be based on the FAS with LOCF imputation or replacement of missing or censored BCVA values.

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

- Population: Chinese subjects with neovascular age-related macular degeneration as per the inclusion/exclusion criteria.
- Endpoint: The primary endpoint is the change from baseline in BCVA at Week 48. BCVA will be assessed by the masked assessor using ETDRS-like charts at an initial distance of 4 meters.
- Treatment of interest: brolucizumab or aflibercept
- The handling of the intercurrent events as follows:
  - Treatment discontinuation due to any reason: use the observed data, or impute using LOCF if missing
  - Data after the start of alternative nAMD treatment will be censored and replaced using LOCF
- Summary measure: Difference in the change from baseline in BCVA at Week 48 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 letters.

Let:

B = Brolucizumab 6 mg - 3 x q4w loading then q12w/q8w maintenance

A = Aflibercept 2 mg - 3 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 48; φ_B and φ_A are the corresponding unknown true mean changes from baseline in BCVA averaged over the period Week 36 to Week 48.

Based on the FAS, the above hypotheses will be tested via an analysis of variance (ANOVA) model. The model will include treatment, baseline BCVA ($\leq$ 55, $\geq$56-$\leq$70, $\geq$ 71 letters) and age category (<75, $\geq$75 years) as factors. Two-sided 90% 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 90% CI is greater than -4 letters. 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 0.05, while keeping the global type I error rate at 0.05.

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 48 and average change from baseline in BCVA over the period Week 36 through Week 48 will be applied to supplementary estimands.

Table 2-1 Primary and supplementary estimands

Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (Including missing data strategy)
Primary estimand	Difference in change from baseline in BCVA at Week 48 excluding the effect of switching to alternative nAMD medication (treatment) in the study eye	FAS	All data captured until the start of alternative nAMD treatment(s) will be included	Analysis of variance (ANOVA) model at one-sided significance level of 0.05, and including terms for treatment, baseline BCVA (≤ 55, ≥56-≤70, ≥ 71 letters) and age category (<75, ≥75 years), and using LOCF imputation/replacement for missing/censored data.
Supplementary estimand 1	Difference in change from baseline in BCVA at Week 48 for subjects adhering to the protocol as per the PPS definition	PPS	All data captured until the start of alternative nAMD treatment(s) or relevant PDs/Ars will be included	ANOVA model as per the primary estimand. LOCF imputation/replacement for missing/censored data

Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (Including missing data strategy)
[redacted]				

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

LOCF is an established method within the assessment of efficacy of anti-VEGF treatments in terms of BCVA 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 the nature of the disease progression and historical data. In case of missing data due to lack of efficacy or safety/tolerability with impairment of the function of the study eye, the LOCF method would be able to capture such an unfavorable outcomes as reflected in the last observed measurement.

For subjects who discontinue treatment but continue in the study, data collected after switching to the alternative nAMD treatment in the study eye (see Table 2-2) will be censored for the primary analysis. Censored or missing data will be replaced or imputed using LOCF by the last observation collected prior to the start of alternative nAMD treatment in the study eye. Detailed alternative nAMD treatments will be listed in the Programming Data Specifications (PDS) documentation. If there are newly approved nAMD treaments, they will be reflected in the PDS.

Table 2-2 Alternative nAMD treatment in the study eye that leads to censoring

- Ranibizumab
- Aflibercept
- Bevacizumab (off-label use)
- Conbercept
- Faricimab
- Visudyne/ photodynamic therapy (PDT)
- 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 the estimand perspective, the main purpose is to adequately reflect the unfavorable study outcome related to the treatment (e.g. lack of efficacy, safety problems) in the analysis.

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 FAS only.

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

- Mixed model for repeated measures (MMRM) assuming missing at random (MAR) using observed data only. 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-patient error. For the MMRM analysis:
  - The treatment difference brolucizumab - aflibercept at Week 48 will be estimated using the LSM and 90% CI.
  - If an MMRM model with an unstructured covariance matrix does not converge, a more restricted covariance matrix can be considered in the following order until convergence is reached: Toeplitz (TOEP), first-order autoregressive (AR), compound symmetry (CS), and variance components (VC).

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

For the endpoint of average change from baseline over the period Week 36 through Week 48, a SAS code using the ESTIMATE statement in PROC MIXED will be provided in the programming specification document to obtain the LSM estimate and 90% CI for the corresponding treatment difference. P-value for non-inferiority (1-sided) will be presented.

Other sensitivity analyses on the primary estimand might be considered.

2.5.4.2 Supportive analyses using different supplementary estimands

Supplementary estimand 1 on the PPS:

The target population, the primary endpoint, the treatment of interest and the summary measure of the supplementary estimand 1 are the same as for the primary estimand. Different from the primary estimand, the handling of the intercurrent events for the supplementary estimand 1 can be found in Table 5-6 for the PPS population. The supportive analysis on the supplementary estimand 1 will apply the same LOCF/ANOVA method as for the primary estimand.

[redacted]

[redacted]

2.5.4.3 Summary statistics and subgroup analysis

Summary statistics:

- Descriptive statistics of primary and first key secondary endpoints will use observed data and primary analysis set (FAS), with censoring data after use of alternative nAMD 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. They will be conducted using the framework for the primary estimand only (FAS with censoring of data collected after use of alternative nAMD treatment in the study eye, and missing/censored values imputed/replaced using LOCF).

- Subgroup analyses will be conducted using the same model and analysis strategies described for the primary and first key secondary endpoint 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 90% CI for the between treatment difference for each subgroup will be presented using forest plots.

2.6 Analysis of additional key secondary objectives

2.6.1 Additional key secondary endpoints

Additional key secondary efficacy endpoints related to dosing regimen:

- q12w treatment status at Week 48 for subjects randomized to brolucizumab 6 mg
- q12w treatment status at Week 48 within the subjects randomized to brolucizumab 6 mg and with no q8w need during the first q12w cycle (Week 16 and Week 20)

2.6.2 Statistical hypothesis, model, and method of analysis

No hypothesis will be tested for additional key secondary efficacy endpoints. The additional key secondary efficacy endpoints will be analyzed based on FAS in brolucizumab 6 mg group.

The analysis approach described below (**efficacy/safety approach**) will be conducted.

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’, applying a ‘q8w-need’ allocation in case of missing or confounded data attributable to lack of efficacy and/or lack of safety for the purpose of analysis.

The proportion of subjects with a positive q12w treatment status will be derived as follows according to the ‘sufficient efficacy and safety’ approach:

- The q8w-need assessment is 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).

Intercurrent events associated with missing or confounded data regarding the q12w treatment status that are attributable to reasons other than lack of efficacy and/or safety are described below, together with the corresponding data handling strategies:

- Early treatment/study discontinuation: censoring at the last valid DAA visit while on treatment/study
- 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 5.6.

The proportion of subjects with a positive q12w treatment status at Week 48 will be presented together with two-sided 90% confidence intervals.

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

The analysis of 'q12w treatment status at Week 48 within the subjects randomized to brolucizumab 6 mg and with no q8w need during the first q12w cycle' is based on the subset of FAS subjects randomized to brolucizumabe 6 mg with no identified q8w-need at Week 16 and Week 20. For this subset a valid Week 20 DAA is required while missing the Week 16 DAA 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 within the time-to-event analyses for the event 'first q8w-need', are specified in the previous Section 2.6.2.

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

2.6.4 Supportive analyses

Supportive analyses 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 is attributable to lack of efficacy of the study treatment. In case of a corresponding safety reason the subject is censored at the last valid DAA.

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

2.7 Analysis of secondary efficacy objectives

2.7.1 Secondary endpoints

Secondary efficacy endpoints are listed below.

Secondary efficacy endpoints based on BCVA:

- Change in BCVA from Baseline to each postbaseline visit
- Average change in BCVA from Baseline over the period Week 4 to Week 48
- Average change in BCVA from Baseline over the period Week 12 to Week 48
- Number and percentage of subjects with a gain in BCVA of 15/10/5 letters or more from Baseline to each postbaseline visit
  Note: Subjects with BCVA value of 84 letters or more at a postbaseline visit will be considered as responders for the corresponding endpoint. This is to account for a ceiling effect, e.g. for the' ≥15-letter gain' endpoint, for those subjects with BCVA values at Baseline ≥ 70 letters.
- Number and percentage of subjects with an absolute BCVA of 73 letters or more at each visit
- Number and percentage of subjects with a loss in BCVA of 15/10/5 letters or more from Baseline to each postbaseline visit

Secondary efficacy endpoints related to anatomical parameters of disease activity:

- Change in CSFTtot from Baseline to each postbaseline visit
- Average change in CSFTtot from Baseline over the period Week 36 through Week 48
- Average change in CSFTtot from Baseline over the period Week 4 to Week 48
- Change in CSFTns from Baseline to each postbaseline visit
- Change in area of CNV within the lesion from Baseline to Weeks 12 and 48 from FP/UWF-C
- Number and percentage of subjects with presence of subretinal and/or intraretinal fluid (central subfield) at each postbaseline visit (and specifically Week 16 and Week 48)
- Number of visits with simultaneous absence of subretinal and intraretinal fluid (central subfield) during Week 36 to Week 48
- Number and percentage of subjects with presence of subretinal fluid (central subfield) at each postbaseline visit
- Number and percentage of subjects with presence of intraretinal fluid (central subfield) at each postbaseline visit
- Number and percentage of subjects with presence of sub RPE fluid (central subfield) at each postbaseline visit

Secondary efficacy endpoints related to efficacy at the end of the matched treatment phase:

- Change in CSFTtot from Baseline at Week 16
- Number and percentage of subjects with presence of subretinal and/or intraretinal fluid (central subfield) at Week 16
- Number and percentage of subjects with q8w treatment need identified at Week 16

2.7.2 Statistical hypothesis, model, and method of analysis

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

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 will be analyzed using ANOVA models. The LSM estimates for each treatment and for the treatment difference (brolucizumab – aflibercept), including 90% CIs will be presented.

For the ANOVA analysis of BCVA-related endpoints, baseline BCVA category (≤55, ≥56-≤70, ≥71 letters) and age category (<75, ≥75 years) will be considered as a class variable. For the ANOVA analysis of CSFT-related endpoints, baseline CSFT category (<400, ≥400 µm) will be used instead of baseline BCVA as a class variable. For the ANOVA analysis of CSFTns-related endpoints, baseline CSFTns category (< overall median value, ≥ overall median value) will be used instead of baseline BCVA as a class variable. For the ANOVA analysis of CNV-related endpoints, baseline type of CNV (predominantly classic, minimally classic, pure occult) will be used instead of baseline BCVA as a class variable.

The line plot of change from baseline in CNV lesion size, CSFTtot and CSFTns 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 90% CIs will be presented for each time point using a logistic regression with treatment, the corresponding baseline status and age category (<75, ≥75 years) as fixed effects. Bar chart of the endpoints related to fluid will be plotted by visit and treatment arm.

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 with no postbaseline values (scheduled or unscheduled), the baseline value will be carried forward, as a conservative approach. For subjects who discontinue treatment but continue in the study, data collected after start of alternative nAMD treatment in the study eye will be censored for the analysis. Censored data

will be replaced by the last available observation prior to the start of alternative nAMDtreatment. Missing baseline values will not be imputed.

For endpoints related to presence of fluids, if baseline visit is reported as “Cannot Grade” or “Not Applicable”, then it will be considered as “Absent”; if postbaseline 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 include:

- Extent of exposure (see Section 2.4.1)
- Adverse events
- Deaths
- Laboratory evaluations
- Ophthalmic examinations
- Presence of fibrosis from color fundus photography / ultra-wide field color fundus photography
- Loss in BCVA
- Vital signs

There are no formal safety hypotheses in this study. All safety analyses will be performed using the Safety Analysis 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 nAMD treatment in the study eye will be censored (data on the day the subject started alternative nAMD 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 TEAE 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 by treatment arm:

Table 2-4 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 nAMD 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
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 nAMD 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. [redacted]			

In all summary tables listed above, unless otherwise specified, data collected after the subject discontinued study treatment and started alternative nAMD treatment in the study eye will be censored.

Subject listings of all adverse events will be provided. Deaths and other serious or clinically significant non-fatal adverse events 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

An adverse events of special interest (AESI) is one of scientific and medical interest to the sponsor and include the following:

- Endophthalmitis
- Intraocular Inflammation
- Retinal Vascular Occlusion

Incidence of adverse events of special interest will be tabulated by treatment arm. AESIs in study eye 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 X% and on treatment emergent AEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety analysis 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 evaluations

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 notable values given in Section 5.3 at any visit will be presented. A listing of 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.

Descriptive summaries of pre-injection change from baseline in intraocular pressure (IOP) values for the study eye will be presented 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 is to be assessed within 60 minutes after injection and if ≥25 mmHg, the 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 any post-injection IOP increase of ≥10 mmHg from pre-injection IOP at any visit for the study eye will be presented.

A summary table with counts and percentage of subjects with observed pre-injection IOP ≥ 21 mmHg at 3 consecutive scheduled visits will be presented. A visit with missing pre-injection IOP is considered to meet the ≥ 21mmHg criterion if the proceeding and the following visits meet the criterion that pre-injection IOP ≥ 21mmHg. For example, if schedule visit X has missing pre-injection IOP and pre-injection IOP ≥ 21mmHg is observed for both visit 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 Presence of fibrosis

A summary table with counts and percentage of subjects with presence of fibrosis (central subfield) in study eye from color fundus photography/ ultra-wide field color fundus photograph will be presented by visit. Fibrosis data will be presented in a subject listing.

2.8.4.3 Loss in BCVA

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

2.8.4.4 Vital signs

Vital signs include assessment of sitting blood pressure (systolic and diastolic pressure in mm Hg) and pulse (beats per minute).

A summary table with numbers and percentages of subjects satisfying the criteria given in Table 5-2 of Section 5.3 at any visit will be presented. A listing of 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.

2.8.4.5 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

PK parameters of brolucizumab in serum will be assessed in subgroup with approximately 12 PK consented subjects in brolucizumab arm.

A PK profile is considered evaluable if all the following conditions are satisfied:

- Subject receives the planned first dose of brolucizumab
- Subject provides at least one primary PK parameter of brolucizumab (e.g. Cmax or AUC)

Pharmacokinetic parameters including but not limited to those presented in Table 2-5 will be determined using Phoenix WinNonlin (Version 8.3 or higher) using non-compartmental method(s). Descriptive summary statistics for PK parameters will include n (number), mean (arithmetic and geometric), SD, SE (arithmetic and geometric), and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. In addition, half-life (T1/2) will be summarized using Harmonic mean along with the Jack-Knife estimate for standard deviation.
For PK consented group in brolucizumab arm, line plots showing the mean serum concentration ± standard error versus nominal sample collection time will be presented, and the individual line plots will also be presented.
Descriptive statistics will be presented for serum concentration levels for all the subjects with PK sample collection at each sampling time. Serum concentration values will also be listed by treatment subject and time point. Summary statistics will include n (number of values to be reported), arithmetic and geometric mean, median, SD, SE, CV, and geometric SE, geometric CV, minimum and maximumSamples collected outside of the protocol defined visit window will be excluded from that visit/timepoint for the purpose of presenting descriptive summaries by time point.At each time point, one-half the lower limit of quantitation (LLOQ) will be used for analysis when a subject has a determined concentration value below the LLOQ. For the purpose of calculating descriptive statistics for serum concentrations, post-injection concentrations below the LLOQ will be treated as half of LLOQ in summary statistics. If the mean was less than the LLOQ, it was reported as being Below the Limit of Quantitation (BLQ) within the summary tables.

Table 2-5 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUC0-t	The AUC calculated from time zero to the defined time point t (eg.648h)(massx time x volume^{-1})
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (lz) of a semi logarithmic concentration-time curve (time).

2.10 Anti-drug antibodies (ADA)

Collection of blood for ADA assessment will be done at screening, Weeks 4, 12, 24, 36, 48 and exit/premature discontinuation. Analyses will be performed only in brolucizumab treatment arm.

ADA status is defined using the following criteria. The pre-dose is referring to screening assessment and the post-dose is referring to postbaseline assessment in the following definition:

- ADA negative:
  - ADA negative at all time points (pre-dose and post-dose)
  - ADA negative at pre-dose and no titer values above 40 at all other time points
  - ADA titer of 40 at pre-dose but negative at all other time points
- ADA positive without boost:
  - ADA positive at pre-dose, post-dose titer values do not increase from pre-dose by more than 3-fold (1 dilution) at any time point
- Induced:
  - ADA negative at pre-dose, post-dose titer value of 120 or more increase
- Boosted:
  - ADA positive at pre-dose, post-dose titer values increase from pre-dose by more than 3-fold (1 dilution) at any time point

The number and percentage of subjects according to their integrated ADA status (ADA negative, ADA positive without boost, induced, boosted) will be presented. In addition, tabulations will be presented for ADA titer pattern.

The number and percentage of subjects with positive neutralizing antibody (NAb) will be summarized by ADA assessment visit for subjects with ADA titer values (ADA positive).

The line plots showing the BCVA change from baseline up to Week 48 for the study eye by ADA status (pre-existing and integrated status up to Week 48) and NAb status (pre-existing and integrated status up to Week 48) among all the subjects and the subjects without AESI in study eyewill be generated.

The summary tables of the incidence of AESIs in study eye by ADA status (pre-existing, pre-existing nAb, integrated ADA and integrated nAb status up to Week 48) will be presented.

Subject listings of all ADA titer values and NAb status 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.

2.11 Patient-reported outcomes

The Visual Function Questionnaires (VFQ-25) will be scored (total and subscale scores) at Baseline, Week 24 and EOS visits. Absolute scores and the absolute changes from baseline will be calculated and summarized descriptively using the FAS. PRO data at EOS which is different from Week 48 will be excluded.

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 2-6. 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 2-6 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 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 2-7.

Table 2-7 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 2-7. 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.

[redacted]

[redacted]

2.13 Interim analysis

Not applicable.

3 Sample size calculation

A sample size of 175 subjects per treatment arm is sufficient to demonstrate noninferiority (margin = 4 letters) of brolucizumab 6 mg versus aflibercept 2 mg with respect to the BCVA change from Baseline to Week 48 at a one-sided alpha level of 0.05 with a power of approximately 80% assuming equal efficacy and a common standard deviation of 15 letters. A power of at least 80% can be expected for the first key secondary endpoint assuming that averaging BCVA change from Baseline over the 4 time points will not lead to an increase in the standard deviation. To account for a drop-out rate of 10%, a total of 195 subjects will be randomized per treatment arm.

4 Change to protocol specified analyses

Protocol section	Protocol wording	Change in SAP
12.2	Demographic and Baseline characteristics will be summarized for all analysis sets.	Demographic based on FAS, but not on all analysis 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.	Section 2.8.3 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 notable values given in Section 5.3 at any visit will be presented. A listing of subjects with all laboratory data in Table 5-1 at any visit will also be presented. Section 2.8.4.4 A summary table with numbers and percentages of subjects satisfying the criteria given in Table 5-1 at any visit will be presented. A listing for subjects satisfying at least one criterion in Table 5-1 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.

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
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/procedure date imputation

5.1.3.1 Concomitant medication/procedure start date imputation

In order to classify a medication/procedure 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 CM/PR 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)/concomitant procedure (PR) start date year value is missing, the imputed CM/PR start date is set to one day prior to treatment start date.

2. If the CM/PR start date year value is less than the treatment start date year value, the CM/PR started before treatment. Therefore:
   a. If the CM/PR month is missing, the imputed CM/PR start date is set to the mid-year point (01JulYYYY).
   b. Else if the CM/PR month is not missing, the imputed CM/PR start date is set to the mid-month point (15MONYYYY).
3. If the CM/PR start date year value is greater than the treatment start date year value, the CM/PR started after treatment. Therefore:
   a. If the CM/PR month is missing, the imputed CM/PR start date is set to the year start point (01JanYYYY).
   b. Else if the CM/PR month is not missing, the imputed CM/PR start date is set to the month start point (01MONYYYY).
4. If the CM/PR start date year value is equal to the treatment start date year value:
   a. And the CM/PR month is missing or the CM/PR month is equal to the treatment start date month, then the imputed CM/PR start date is set to one day prior to treatment start date.
   b. Else if the CM/PR month is less than the treatment start date month, the imputed CM/PR start date is set to the mid-month point (15MONYYYY).
   c. Else if the CM/PR month is greater than the treatment start date month, the imputed CM/PR start date is set to the month start point (01MONYYYY).

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

5.1.3.2 Concomitant medication/procedure end date imputation

1. If the CM/PR end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM/PR end year value is missing or ongoing, the imputed CM/PR end date is set to NULL.
2. Else, if the CM/PR 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/PR 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/PR end date is less than the existing CM/PR start date, use the CM/PR start date as the imputed CM/PR 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/grading

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, Jaffe or Enzymatic	mg/dL	N/A	>5.0	umol/L	N/A	>442	
Glucose	mg/dL	< 40	> 500	mmol/L	< 2.22	> 27.75	
Sodium	mEq/L	< 120	> 160	mmol/L	< 120	> 160	
Hemoglobin	g/dL	< 6.0	> 20.0	g/L	< 60	> 200	
Magnesium	mg/dL	< 0.7	> 6.1	mmol/L	< 0.30	> 2.50	
Magnesium	mEq/L	< 0.6	> 5.0	mmol/L	< 0.30	> 2.50	
Phosphate (Phosphorus)	mg/dL	< 1.0	N/A	mmol/L	< 0.32	N/A	
Platelet	X10E3/uL	< 50	> 999	X10E9/L	< 50	> 999	
Potassium	mEq/L	< 2.8	> 6.5	mmol/L	< 2.8	> 6.5	
WBC	X10E3/uL	< 2.0	N/A	X10E9/L	< 2.0	N/A	

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

Variable	Category	Critical values
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 48) and first key secondary endpoint (average change from baseline in BCVA over the period Week 36 through Week 48) 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 48> <average change from Baseline in BCVA from Week 36 to Week 48> = 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 90% confidence intervals will be obtained by applying the bootstrap method. The pseudo SAS code to derive the treatment difference and 90% CI from the least square mean output of the fitted model will be provided in the programming specification document.

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 48 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 and Section 2.6.3.

A corresponding 90% CI will be derived from the LOGLOG transformation, using SAS Proc Lifetest, with CONFTYPE = LOGLOG.

[redacted]

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 from Analyses
M_INCL01_ICF not obtained	Written informed consent not obtained	Exclude from all analysis

Deviation ID	Description of Deviation	Exclusion from Analyses
P_INCL02_Age less than 50 yrs	Subject less than 50 years of age at screening	Exclude from PP analysis
M_INCL03_CNV eligibility criteria	Subject without active choroidal neovascularization (CNV) lesions secondary to AMD affecting central subfield or total area of CNV comprising less than 50% of the total lesion area at screening	Exclude from PP analysis
P_INCL04_BCVA score outside limits	Study Eye: Subject not meeting BCVA eligibility criteria between 78 and 23 letters, inclusive, at screening or baseline	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 W36 and W44 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 continue 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 36. 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 36. Otherwise include in all analyses
AR_MD_01	No valid BCVA assessment between W36 and W48	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
SAF	M_INCL01_ICF not obtained	Did not receive at least one study injection
PPS	M_INCL01_ICF not obtained,	Not in the FAS

Analysis Set	PD ID that may cause subjects to be excluded	Non-PD (AR) ID that cause subjects to be excluded
	P_INCL02_Age less than 50 yrs, M_INCL03_CNV eligibility criteria, P_INCL04_ BCVA score outside limits, 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, P_WITH01_Treatment but consent withdrawn	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 2.6.3. 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 nAMD treatment in the study eye: imputation using the last observation collected prior to the start of alternative nAMD 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 analysis of the q12w proportion as derived from DAA and described in section 2.6.3 applies censoring in case the underlying DAA is considered to be confounded by reasons other than lack of efficacy and/or safety. [redacted] Censoring: subjects are considered no longer to be under risk for a q8w-need identification at later visits. Censoring at baseline if above PD/AR occurred prior to Week 16. Censoring at Week 48 visit if subjects completed Week 48 without above PD/AR.
PPS	Censoring of BCVA data after switch to alternative nAMD treatment in the study eye: imputation using the last observation collected prior to the start of alternative nAMD treatment (see section 2.5.3)	Similar to FAS

6 Reference