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RTH258/Brolucizumab

CRTH258A2303 / NCT04005352

A 64-week, two-arm, randomized, double-masked, multi-center, phase IIIb study assessing the efficacy and safety of brolucizumab 6 mg compared to aflibercept 2 mg in a treat-to-control regimen in patients with neovascular age-related macular degeneration (TALON)

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Final Amendment 4
Release date:	20-OCT-2022
Number of pages:	49

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
24-Jun-2019	Prior to FPFV	Creation of first draft	N/A - First version	NA
14-Aug-2019	Prior to FPFV	Updated as per SAP reviewers' comments	Final v 1.0	
4-Apr-2021	Prior to DB lock	Creation of amendment 1	Add analyses of COVID-19 impact assessment	Sections 2.2.1, 2.3.1, 2.5.4, 2.7.1, 2.8.1
3-Nov-2021	Prior to DB lock	Creation of amendment 2	Add analyses in response to the urgent safety measures	Sections 2.2.1, 2.3.1, 2.5.4, 2.7.1, 2.8.1
			Revision of listings	Sections 2.3, 2.4.2, 2.7.1, 2.8.1, 2.8.3, 2.8.4.3, 2.11, 2.13
			Addition of secondary endpoints: Time to first dry retina, time to first sustained dry retina, BCVA/CSFT by visit	Sections: 1.2, 2.7.1, 2.8.1, 4
			Added description of exclusion criteria for the analyses	Section 5.5
			Added sensitivity estimand based on MMRM	Section 2.5.3, 2.5.4
23-Feb-2022	Prior to DB lock	Creation of amendment 3	Amended protocol version 03 as a reference	Section 1
			Revised the paragraph about masking to be as in Amended protocol v03	Section 1.1
			Time-to-first secondary endpoints are clarified to be defined at Week 64	Section 1.2
			SAS version added	Section 2.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Description of when Week 32 and Week 64 analyses are performed	Section 2.1
			Deleted paragraph repeated twice in further sections	Section 2.1
			FAS is defined to be the subset of randomized subjects who received at least one dose of the study treatment	Section 2.2
			Clarified the definition of exposed and non-exposed	Section 2.2.1
			Baseline characteristics to be described in FAS and edited IOP and BCVA description	Section 2.3
			Listing of BCVA loss of at least 15 letters moved from section 2.7.1 to 2.8.1	Sections 2.7.1 and 2.8.1
			Clarified that summaries of ocular AEs are not by system organ class but summaries of non-ocular AEs are by system organ class	Sections 2.8 and 2.8.1
			AEs are listed in Safety Sets	Section 2.8
			Listing of AESI to include an indication of BCVA loss of at least 15 letters	Section 2.8.1.1
			Added listing of AESIs related to the study treatment and/or procedure	Section 2.8.1.1
			Described changes relative to the protocol-specified analyses	Section 4

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			AR_MD_03 is not leading to exclusion	Section 5.5
			Added summaries for IRF, SRF, sub-RPE and CSFT by visit, for discontinued patients	Section 2.7.1
			Added summary of imaging variables for patients with adverse events of special interest	Section 2.8.1
			Laboratory data section is expanded	Section 2.8.3
4-March-2022	Prior to DB lock	Creation of amendment 3.1	Revised a paragraph about SAP for interim analyses being in a separate file, as the interim analysis is described in the current document	Section 2.14
			Revised a sentence about summary of imaging variables	Section 2.8.1.1
			Revised incorrect line in the summary of amendments	Document history file
20-OCT-2022	After interim (Week 32) DBL but prior to final (Week 64) DB lock. This amendment will not impact the preplanned analysis for Week 32	Creation of amendment 4	Added clarification for the on-treatment period for the Week 32 analysis, added clarification for unscheduled visit analysis	Section 2.1.1
			Updated disposition summary to be for all enrolled patients	Section 2.2.1
			corrected typo on BCVA categories and make it consistent with other sections, Updated subgroup definition for COVID impacted, specify secondary endpoints for which subgroup analysis for COVID and USM are needed for.	
			Change the Randomized set to Enrollment set for patient disposition	Section 2.3.1
			Clarified the definition of prior and comcomitant medication	Section 2.4.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Moved the analysis for the supplementary estimand for Week 64 to Section 2.7.1	Section 2.5.4
			Added clarification regarding the primary supportive estimand related to BCVA under Table 2-1, removed Week 60 and Week 62 reference from this section and moved it to Section 2.7.1	Section 2.7.1
			Deleted the secondary endpoint analysis for time from last loading injection to first visit with no DA Removed analysis of time to first sustained dry retina, Added analysis detail for the time to first dry retina analysis Added analysis details for the secondary endpoints related BCVA, CSFT, presence fluid Added clarification for handling of missing value in case of alternative treatment. Added clarification that observed data will be summarized for CSFT, SRF, IRF, and Sub-RPE at week 60 and 64.	
			Added a table summarizing AE planned analyses and updating text to refer to table, add sensitivity analyses for selected AE summaries by excluding events with onset date after start of alternative treatment	Section 2.8.1
			Added new safety analysis for BCVA loss of >=30 letters, Updated AESI to also include summaries for ‘other safety topics of interest’	Section 2.8.3
			Add new safety analysis for ‘sustained IOP elevation’	Section 2.8.5

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Updated Section 4 to match changes in previous sections.	Section 4

Table of contents

List of abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
CFP	Color Fundus Photography
CM	Concomitant Medication
CNV	Choroidal Neovascularization
COVID-19	Coronavirus disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRS	Case Retrieval Sheet
CSFT	Central Subfield Thickness
CSR	Clinical Study Report
DAA	Disease Activity Assessment
EOS	End-of-Study
EOT	End-of-Treatment
FA	Fluorescein Angiography
FAS	Full Analysis Set
FPFV	First Patient First Visit
iDBL	Interim Database Lock
IRF	Intraretinal Fluid
IOP	Intraocular Pressure
LOCF	Last Observation Carried Forward
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed effects model for repeated measures
nAMD	neovascular Age-related Macular Degeneration
OCT	Optical Coherence Tomography
PD	Protocol Deviation
PDS	Programming Datasets Specifications
PPS	Per-Protocol Set
PRO	Patient Reported Outcomes
RAS	Randomized Analysis Set
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SRF	Subretinal Fluid

SS	Safety Set
TFL	Tables, Figures and Listings
TtC	Treat-to-Control
VEGF	Vascular Endothelial Growth Factor
VFQ25	Visual Function Questionnaire 25

1 Introduction

This document describes the detailed statistical methodology to be used for the Clinical Study Report (CSR) of the TALON study CRTH258A2303, a 64-week, two-arm, randomized, double-masked, multi-center, phase IIIb study assessing the efficacy and safety of brolucizumab 6 mg compared to aflibercept 2 mg in a Treat-to-Control (TtC) regimen in patients with neovascular age-related macular degeneration (nAMD).

The content of this SAP is based on the amended protocol version 03. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock and unblinding of the study data.

CSR deliverables (shells for tables, figures, listings) and further programming specifications will be described in the Tables, Figures & Listings (TFL) shells and Programming Datasets Specifications (PDS), respectively.

1.1 Study design

The study is a 64-week randomized, double-masked, multi-center, active-controlled, two-arm study in patients with nAMD who have not previously received anti-VEGF treatment.

Approximately 692 patients will be randomized in a 1:1 ratio to one of two treatment arms:

- Brolucizumab 6 mg
- Aflibercept 2 mg

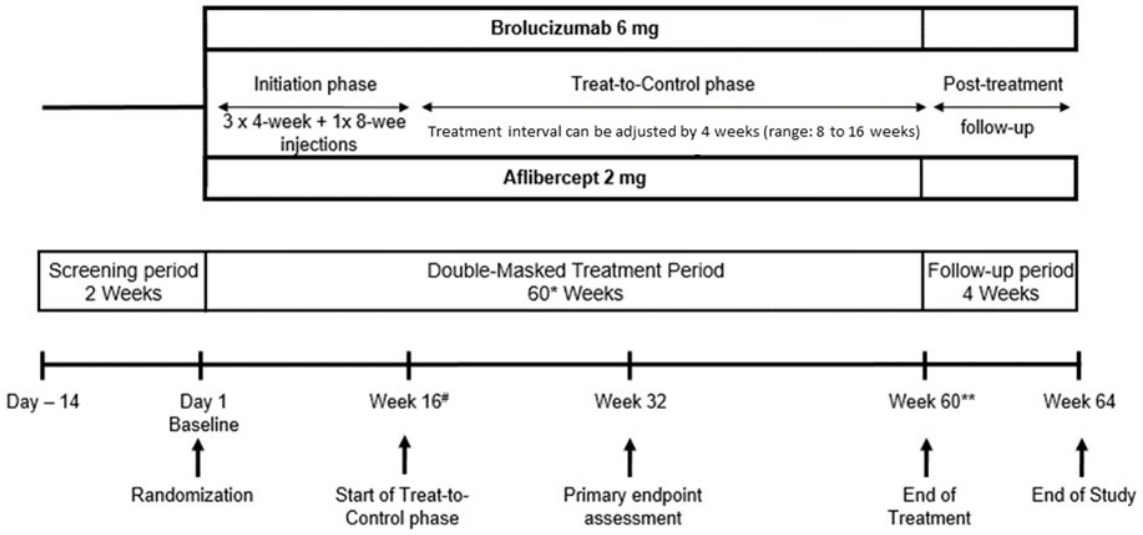
There will be no specific stratification.

The maximum study duration for one subject is 66 weeks, including screening and post-treatment follow-up.

There will be 3 periods in this study (see Figure 1-1):

- Screening period: from Day -14 to Baseline
- Double-masked treatment period: from Baseline (Day 1) to Week 60/62
- Post-treatment follow-up period: from Week 60/62 to Week 64.

Figure 1-1 Study design



Week 14 if inspection visit
** Week 62 (depending on visit schedules)

The primary analyses will be conducted when all ongoing subjects have completed their Week 32 visit. Subjects will remain in the study and will continue to receive the masked treatment through the planned study duration of 64 weeks, to allow for further evaluation of efficacy and safety. Treatment masking of individual subjects will remain in effect for all subjects, masked investigators and selected staff from the Sponsor who have access to the patient data and have contact with investigators until the final database lock has occurred.

The final analysis for the CSR will be conducted after final database lock. No primary analysis CSR will be written at the interim database lock.

1.2 Study objectives and endpoints

The study objectives and corresponding endpoints as specified in the protocol are provided in Table 1-1.

Table 1-1 Study objectives

Primary objectives	Co-primary endpoints	Analysis
1. To demonstrate that brolucizumab is superior to aflibercept with respect to the duration of treatment intervals at Week 32	• Distribution of the last interval with no disease activity up to Week 32 (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks*) • Average change in BCVA from	Section 2.5.2

2. To demonstrate that brolucizumab is non-inferior to aflibercept with respect to average change in BCVA from baseline at Weeks 28 and 32	baseline at Weeks 28 and 32	
Secondary objectives	**Secondary endpoints**	**Analysis**
1. To evaluate the durability of brolucizumab relative to aflibercept	• Distribution of the last interval with no disease activity up to Week 64 (if there was disease activity, the last interval will be shortened by 4 weeks down to a minimum of 4 weeks) • Distribution of the maximal intervals with no disease activity up to Week 64 • Proportion of patients with no disease activity at Weeks 14 and 16 • Time from the last loading injection to the first visit with no disease activity up to Week 64 • Time to first dry retina (no IRF and no SRF) up to Week 64 • Time to first sustained dry retina (no IRF and no SRF at >=2 consecutive visits) up to Week 64	Section 2.7.1
2. To evaluate the functional outcomes with brolucizumab relative to aflibercept	• Average change in BCVA from baseline at Weeks 60 and 64 • Change in BCVA from baseline by visit to Week 32 (Week 64) • Occurrence of BCVA improvements of ≥ 10 and ≥ 15 letters from baseline at Week 32, Week 64, and at the last injection visit • Occurrence of BCVA ≥ 69 letters at Week 32, at Week 64, and at the last injection visit	Section 2.7.1
3. To evaluate the anatomical outcomes with brolucizumab relative to aflibercept	• Average change from baseline in CSFT as assessed by SD-OCT at Weeks 28 and 32 • Average change from baseline in CSFT as assessed by SD-OCT at Weeks 60 and 64 • Change in CSFT from baseline by visit to Week 32 (Week 64) • Number of visits with presence of	Section 2.7.1

	IRF and/or SRF, and sub-RPE fluid in the central subfield, as assessed by SD-OCT at Weeks 28 and 32 • Number of visits with presence of IRF and/or SRF, and sub-RPE fluid in the central subfield as assessed by SD-OCT at Weeks 60 and 64	
4. To evaluate the effect of brolucizumab relative to aflibercept on Patient-Reported Outcomes (PRO)	• Change in Visual Function Questionnnaire-25 (VFQ-25) total and subscale scores from baseline at Weeks 32 and 64	Section 2.11
5. To assess the safety and tolerability of brolucizumab relative to aflibercept	• Incidence of Ocular and Non-ocular AEs up to Week 64	Section 2.8
[redacted]		

*Subjects who will be assigned to a 4-week interval will be analyzed in the q4w category but discontinued from further study treatment.

2 Statistical methods

2.1 Data analysis general information

All analyses described in the SAP will be performed by Novartis GMA programming team ([redacted] programming team using SAS v 9.4 or above).

Categorical data will be presented as frequencies and percentages. For continuous data, n, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented (when applicable).

The primary analysis including the analysis on primary and key secondary endpoints will be performed after all patients have completed their Week 32 visit or have discontinued the study. Final analysis will occur once all patients have completed the study or discontinued the study.

2.1.1 General definitions

Study treatment is defined as brolucizumab 6 mg/0.05 mL, or aflibercept 2 mg/0.05 mL.
Date of first administration of study treatment is defined as the first date when a non-zero dose of study treatment is administered and recorded on the CRF dose administration page. The date of first administration of study treatment will also be referred to as start of study treatment.
Date of last administration of study treatment is defined as the last date when a non-zero dose of study treatment is administered and recorded on the CRF dose administration page. The last administration of study treatment will also be referred as end of treatment (EOT).

Study day will be calculated as:

- The date of the event (visit date, onset date of an event, assessment date etc.) – treatment start date + 1, if event is on or after the treatment start date.
- The date of the event (visit date, onset date of an event, assessment date etc.) – treatment start date, if event precedes the treatment start date.

Day 1 is the date of first injection.
The study day will be displayed in data listings. All data from scheduled and unscheduled visits will be analyzed based on "Week XX" recorded in the CRF (except for baseline), unless otherwise stated. Data recorded on 'Unscheduled Visit' form will not be summarized in by visit tables but will be used for imputation and other analysis purposes.

Baseline is defined as the last available assessment on or prior to randomization (assignment of study treatments). As per the protocol, first injection must occur on day of randomization (within 24 hours).

On-treatment period is defined from the date of first administration of study treatment to 30 days after the last administration of study treatment (EOT) or end of study (EOS) whichever is the latest. Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate. For the Week 32 analysis, the on-treatment period included Week 32 visit date + 30 days, if the Week 32 visit occurred, or the week 32 visit is estimated from the baseline visit as Baseline date + 32*7 + 30 days.

Treatment interval is defined as the time period from one injection until the next injection. In this study, treatment interval of q4w, q8w, q12w and q16w -meaning that there are 4, 8, 12 and 16 weeks between 2 injections- are of special interest. The last (treatment) interval at week X is referred to the last complete interval where injections at both ends of the inteval have occurred on or before Week X. The last interval with/without disease activity is referred to the last interval with/without disease activity as observed at the end of the interval.

2.2 Analysis sets

The **Randomized Analysis Set (RAS)** consists of all randomized subjects. Patients who have signed informed consent form (ICF) will be considered as the **Enrollment Set**. All data listings will be based on the Randomized Analysis Set, unless otherwise specified.

The **Full Analysis Set (FAS)** comprises all randomized subjects who received at least one dose of the study treatment. Subjects will be analyzed according to the treatment they have been assigned during the randomization procedure.

The **Safety Set (SS)** includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the other study treatment received if the randomized treatment was never received.

The **Per-Protocol Set (PPS)** is a subset of subjects of the Full Analysis Set with no important protocol deviation (with impact). Patients with important PDs but without impact will be reported as PD and will be included in PPS. The list of protocol deviations criteria will be provided in the edit check specification document. Please refer to Table 5-1 for more details.

2.2.1 Subgroup of interest

All analysis will be done by treatment arms (brolucizumab 6 mg vs. aflibercept 2 mg).

In addition, primary endpoint analysis for BCVA will be conducted using the baseline BCVA and age categories as follows:

Baseline BCVA categories: (<55, 55-<73, ≥73 letters read),

Age categories: <75, ≥75 years old.

Subgroup analyses to evaluate impact of COVID-19 pandemic: As per internal guidance, a sensitivity analysis to assess the impact of the COVID-19 pandemic on study subjects will be conducted. The definition of start and end dates by geographical areas to be used for the sensitivity analysis are as in Table 2.2.1.

Table 2.2.1: Start and end dates of COVID-19 pandemic.

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

Impacted subjects to COVID-19 pandemic were defined as subjects who:

- Missed at least one planned visit or discontinued treatment and/or study due to COVID-19.

Non-impacted subjects to COVID-19 are therefore defined as subjects who:

- Did not miss any planned visits or discontinued treatment and/or study due to COVID-19.

Subgroup analyses will be conducted using the same model and analyses strategies described for the primary and the following selected secondary endpoints in the impacted and non-impacted subgroups: Last interval with no disease activity (week 32 and week 64), maximal intervals with no disease activity for week 64; Best Corrected Visual Acuity (BCVA) (letters read) for week 32 and 64; Central Subfield Thickness (CSFT) (week 32 and 64), presence of SRF and/or IRF. In addition, demographics, baseline characteristics, protocol deviations, serious ocular AEs for the study eye, AESIs and deaths, SAE or AEs leading to study discontinuation will be summarized for impacted and non-impacted subjects.

Subgroup analyses in exposed and non-exposed to the urgent safety measures: The urgent safety measures were introduced on May 27, 2021. Per internal guidance, a sensitivity analysis related to the introduction of the urgent safety measures will be conducted.

For the interim analysis at Week 32, the exposed to the urgent safety measures subgroup is

- the subgroup who has not reached Week 28 visit on study treatment by May 27, 2021, and did not discontinue the study treatment by May 27, 2021.

The non-exposed subgroup is therefore defined as

- the subgroup who has reached Week 32 visit on study treatment or discontinued study treatment by May 27, 2021.

For the analyses at Week 64, the exposed to the urgent safety measures subgroup is

- the subgroup who has not reached Week 60 visit on study treatment by May 27, 2021, and did not discontinue the study treatment by May 27, 2021.

The non-exposed subgroup is therefore defined as

- The subgroup of subjects who have reached Week 64 visit on study treatment or discontinued study treatment by May 27, 2021

Subgroup analyses will be conducted for the primary and selected secondary endpoints listed for the COVID impacted subgroup analysis in the exposed and non-exposed subgroups. In addition, demographics, baseline characteristics, protocol deviations, serious ocular AEs for the study eye, AESIs and deaths, SAE or AEs leading to study discontinuation will be summarized for exposed and non-exposed subgroups.

2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized by appropriate descriptive statistics by treatment arm for the FAS. A listing will also be provided.

Baseline disease characteristic table will also include:

- primary diagnosis of nAMD, time since diagnosis of nAMD (days), whether nAMD is unilateral or bilateral
- BCVA (as a continuous variable and using categories (<55, 55-<73, ≥73 letters read)),
- [redacted],
- SD-OCT parameters (IRF, SRF, sub-PRE, CSFT (as a continuous variable and using categories (<400, ≥400 μm)) and lesion type),
- CFP parameters (intra-retinal hemorrhage – central subfield, sub-retinal hemorrhage – central subfield, RPE atrophy – outer subfield, RPE atrophy – central subfield, fibrosis – inner subfield, fibrosis – central subfield),
- FA parameters (type of CNV, area of CNV within the lesion, CNV location, leakage from CNV).

Relevant ocular and non-ocular medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment arm for the FAS.

Medical history/current medical conditions are coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of the analyses. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

2.3.1 Patient disposition

Patient disposition will be summarized by treatment arm based on the Enrolment Set. A listing will also be provided. Number (%) of participants in FAS, SS and PPS will be presented based on the RAS. A listing of participants excluded from FAS, SS and PPS including the corresponding reasons.

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

2.4 Treatments (study treatment, concomitant therapies)

2.4.1 Study treatment

The Safety Set will be used for the analyses below.

The extent of exposure to study treatments as number of injections from baseline to Week 64 will be descriptively summarized by treatment arm. Furthermore, number of subjects at each injection category (e.g., 1 injection, 2 injections, etc.) from baseline to Week 64 by treatment arm will be provided. All collected study treatment/injection data will be listed.

2.4.2 Prior and concomitant and therapies

Prior medications are defined as medications 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 (PT) by treatment arm. Ocular medications will be listed for the study eye and the fellow eye separately.

Ocular and non-ocular surgical and medical procedures will be summarized.

2.5 Analysis of the primary objective

The primary objectives of this study are:

- To demonstrate that brolucizumab is superior to aflibercept with respect to the duration of treatment intervals at Week 32; AND
- To demonstrate that brolucizumab is non-inferior to aflibercept with respect to average change in BCVA from baseline at Weeks 28 and 32.

2.5.1 Primary endpoint

The co-primary endpoints of this study are:

- Distribution of last interval (number (%) of patients in q4w, q8w and q12w) with no disease activity up to Week 32 (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks); AND
- Average change in BCVA from baseline at Week 28 and Week 32.

The FAS will be used as primary population to analyze the co-primary endpoints.
Both criteria in the co-primary endpoint must be met to satisfy the primary objective of this study.

2.5.2 Statistical hypothesis, model, and method of analysis

The first step in assessing the primary endpoint is to identify the last (treatment) interval with respect to Week 32 for each patient, i.e., the last interval for which injections have occurred at both ends of this interval before/at Week 32. If there is a disease activity at the end of the last

interval, then the last interval will be shortened by 4 weeks, down to a minimum of q4w. In case of any treatment interruption or permanent study treatment discontinuation, the imputation techniques as per the estimand framework in Section 2.5.3 will be considered. Then, proportion of patients with last interval of q4w, q8w and q12w in both treatment arms can be specified. These proportions will be referred as the distribution of the last interval.

To test the superiority of brolucizumab vs aflibercept in terms of the distribution of the last interval with no disease activity (q4w, q8w, and q12w) up to Week 32, a one-sided Wilcoxon test for 2 ordered multinomial distribution with type I error of $\alpha = 0.025$ will be considered.

Specifically, the Wilcoxon test will assess the following hypothesis:
H0: brolucizumab and aflibercept interval distributions are equal, vs.
H1: brolucizumab interval distribution is stochastically larger than aflibercept interval distribution.
g
The number (%) of patients in q4w, q8w, and q12w at Week 32 together with the respective P-value of the Wilcoxon test will be provided.

The Wilcoxon test statistic is equivalent to the score statistic for testing global treatment difference in interval distributions from the proportional odds cumulative logistic model (Natarajan et al 2012). Therefore, the one-sided P-value from testing global treatment difference (score test) in a cumulative logistic regression model is equivalent to P-value of Wilcoxon test. (Refer to Section 5.4.1)

To test the non-inferiority of brolucizumab compared to aflibercept in terms of average change in BCVA from baseline at Week 28 and Week 32, a two-sided 95% confidence interval for the treatment difference will be derived from an analysis of variance (ANOVA) model with treatment arm, baseline BCVA categories and age categories as fixed effects. The baseline BCVA categories (<55, 55-<73, ≥73 letters read) and age categories (<75, ≥75 years old) will be considered. If BCVA Week 28 data is not available, BCVA Week 30 will be used instead of Week 28.

In order to demonstrate non-inferiority of average change in BCVA from baseline at Week 28 and Week 32, the lower limit of the two-sided 95% confidence interval for the treatment difference (brolucizumab – aflibercept) must be greater than -4 letters representing the non-inferiority margin. Furthermore, the respective one-sided P-value for non-inferiority in terms of change in BCVA assessed at significance level of 0.025 will be provided.

Upon significance of both non-inferiority of average change in BCVA from baseline at Week 28 and Week 32 and superiority of distribution of the last interval without disease activity up to Week 32, the primary objective of this study will be satisfied.

2.5.3 Handling of missing values/censoring/discontinuations

The imputation of missing data will be handled by defining the estimand framework. The primary estimands are described by the following four attributes:

1. The **target population** is defined by the study inclusion and exclusion criteria. The protocol defines the use of allowed concomitant medications for this target population, as well as medications which are prohibited.

2. The **co-primary variable 1** is proportion of patients in q4w, q8w, and q12w intervals (interval distribution) at last interval with no disease activity up to Week 32 (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks). The **co-primary variable 2** is average of change in BCVA from baseline at Week 28 and Week 32.

3. The **intervention effect** describes how events that occur after randomization are captured when assessing the co-primary variables. Post-randomization events of interest in this study are assessed as:
    - Discontinuation of study treatments
    - Treatment interruption

4. The **summary measure**s are the P-values of the hypothesis testings to demonstrate superiority of brolucizumab compared to aflibercept in terms of interval distribution at Week 32 as per the co-primary variable 1 AND to demonstrate non-inferiority of brolucizumab compared to aflibercept with respect to average of change in BCVA from baseline at Week 28 and Week 32, as per the co-primary variable 2.

The primary estimands and other supportive estimands of interest are described in Table 2-1 below, together with their key attributes.

Table 2-1 Primary and supportive estimands

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Primary estimand 1 (interval distribution)	Proportion of patients in q4w, q8w, q12w intervals at the last treatment interval with no disease activity assessed at Week 32	FAS	Before Week 16 (initiation phase): q4w. From Week 16 included (TtC phase): last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	*Last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	Superiority testing using a one-sided Wilcoxon test
Primary estimand 2 (change in BCVA)	Average BCVA change from baseline at Week 28 and Week 32	FAS, data collected until the participant discontinued the study treatment and started alternative treatment(s) will be included.	Last Observation Carried Forward (LOCF)	LOCF	Analysis of variance (ANOVA) model including terms for treatment arm (factor), baseline BCVA categories and age categories

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Supportive estimand 1 (interval distribution)	Proportion of patients in q4w, q8w, q12w intervals at the last treatment interval with no disease activity assessed at Week 32; excluding patients with important protocol deviations as per definition of PPS	PPS**	Before Week 16 (initiation phase): q4w; From Week 16 included (TtC phase): last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	*Last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	Superiority testing using a one-sided Wilcoxon test
Supportive estimand 2 (change in BCVA)	Average BCVA change from baseline at Week 28 and Week 32; excluding patients with important protocol deviations as per definition of PPS	PPS** data collected until the participant discontinued study treatment and started alternative treatment(s) will be included.	LOCF	LOCF	Analysis of variance (ANOVA) model including terms for treatment arm (factor), baseline BCVA categories and age categories

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Sensitivity to primary estimand 1 (interval distribution)	Proportion of patients in (q4w, q8w, q12w) at the last treatment interval with no disease activity assessed at Week 32	FAS	Before Week 16 (initiation phase): q4w; From Week 16 included (TtC phase): last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	*Last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	Cumulative logistic model with the proportional odds assumption
Sensitivity to primary estimand 2 (change in BCVA)	Average BCVA change from baseline at Week 28 and Week 32	FAS, data collected until the participant discontinued study treatment and started alternative treatment(s) will be included.	LOCF	LOCF	Analysis of covariance (ANCOVA) model including terms for treatment arm (factor), baseline BCVA (as continous variable) and age (as continous variable)

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Sensitivity to primary estimand 2.1 (change in BCVA)	Average BCVA change from baseline at Week 28 and Week 32	FAS, data collected until the participant discontinued study treatment and started alternative treatment(s) will be included.	Observed data	Observed data	MMRM including terms for treatment arm (factor), baseline BCVA (continuous variable) and age (continuous variable)
Sensitivity to primary estimand 2 (proportion in at least q12w)	Proportion of subjects with at least 12-weeks duration of the last treatment interval with no disease activity assessed at Week 32	FAS	Before Week 16 (initiation phase): q4w; From Week 16 included (TtC phase): last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	*Last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	Logistic regression model

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Sensitivity to primary estimand 3 (proportion in at least q12w)	Proportion of subjects with at least 12-weeks duration of the last treatment interval with no disease activity assessed at Week 32	PPS**	Before Week 16 (initiation phase): q4w; From Week 16 included (TtC phase): last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	*Last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	Logistic regression model

LOCF: Last Observation Carried Forward
*: If the duration of the last interval falls within the following ranges of [q4w, q8w) or [q8w, q12w) or $\geqslant$ q12w then the floor value of these ranges i.e. q4w, q8w, or q12w, respectively, will be used for imputation.
**: Patients who take prohibited concomitant medication are already excluded from PPS as taking prohibited medication is considered an important protocol deviation.

Note that throughout this document, analyses of Week 28 and other efficacy data are performed if Week 28 data are available. If Week 28 BCVA and other efficacy data are not available, Week 30 BCVA and other efficacy data will be used instead of Week 28 data, respectively. Otherwise, LOCF will be used to impute missing BCVA as per the estimand framework.

For the primary and supportive estimands related to BCVA, data collected up to and including the start date of alternative treatment will be included.

2.5.4 Supportive analyses

Sensitivity analyses
As a sensitivity analysis for the superiority of brolucizumab compared to aflibercept with respect to the last interval distribution with no disease activity (q4w, q8w, and q12w) at Week 32 using a parametric method, a cumulative logistic model with consideration of the

proportional odds assumption will be performed based on FAS (Table 2-1). The point estimate of the odds ratio of making response at or below any category of interval distribution between aflibercept and brolucizumab obtained from the model, the respective 95% confidence interval of the odds ratio and the P-value of the treatment effect in this model using the likelihood ratio test assessed at one-sided significance level of 0.025 will also be provided. (Refer to Section 5.4.1)

In case the proportional odds assumption test is violated i.e., P-value for proportional odds assumption < 0.05, the non-proportional odds assumption might be considered.

As a sensitivity analysis for the non-inferiority of brolucizumab compared to aflibercept with respect to average change in BCVA from baseline at Week 28 and Week 32, analysis of covariance (ANCOVA) including independent variables of treatment arm (factor), age (continuous variable) and baseline BCVA (continuous variable) will be provided (Table 2-1). Sensitivity analyses will also be performed based on mixed effects model for repeated measures (MMRM) with age at the baseline and BCVA at the baseline as continuous variables.

Supportive analyses
As a supportive analysis, the analysis of the co-primary endpoints will be repeated based on PPS (Table 12-1). All aforementioned missing data handling approaches will also be applied for this supportive analysis.

Subgroup analyses will be conducted for primary and selected secondary endpoints in the COVID-19 pandemic impacted/non-impacted subgroups and in those subgroups exposed/non-exposed to urgent safety measures. The subgroup definitions and the selected secondary endpoints are in Section 2.2.1.

Supplementary estimand to assess the impact of COVID-19 pandemic:
Another supplementary estimand might be defined to assess the impact of intercurrent events associated with study treatment discontinuation due to COVID-19 on the study conclusions. For subjects who discontinue study treatment due to COVID-19 pandemic but continue the study, data collected after the treatment discontinuation will be censored for the analysis. Censored data will be replaced using LOCF with the last observation collected prior to the study treatment discontinuation. This analysis will be conducted on the FAS if at least 5% of subjects discontinue treatment due to COVID-19.

Sensitivity estimand in exposed and non-exposed to the safety measures:
As a sensitivity analysis for the superiority of brolucizumab compared to aflibercept with respect to the last interval distribution with no disease activity at Week 32, the proportion of subjects with 12-week interval as the last interval with no disease activity at the Week 32 is compared between the treatment arms in exposed and non-exposed subsets. The analyses are performed in FAS and PPS based on the Binomial test of proportions and the logistic regression model with adjustments for the baseline age and BCVA.

2.6 Analysis of the key secondary objective

There is no key secondary objective in this study.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

The secondary efficacy objectives and endpoints of this study are as follows:

To evaluate the durability of brolucizumab relative to aflibercept

- Distribution of the last interval (number (%) of patients in q4w, q8w, q12w and q16w) with no disease activity up to Week 64 (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks) for both arms will be provided. Analysis will be performed as per the primary endpoint.
- Distribution of the maximal interval (number (%) of patients in q4w, q8w, q12w and q16w) with no disease activity up to Week 64 for both arms will be provided. Analysis will be performed as per the primary endpoint.
- Number (%) of patients with no disease activity at Weeks 14 and 16 for both arms will be provided. Odds ratio and 95% CI will be provided.
- Time to first dry retina, defined as no IRF and no SRF, will be analyzed using Kaplan-Meier method. Proportions of subjects with event will be presented by treatment group and time point, together with 95% CI (using Greenwood's formula). KM curves presenting the cumulative probability of first event will be provided by treatment group, log-rank test will be used for between treatment group comparison. Subjects in the FAS with at least one fluid present at baseline will be used for this analysis.
-

The FAS will be used to analyze durability outcomes.

To evaluate the functional outcomes of brolucizumab relative to aflibercept

- The primary analysis of average change in BCVA from baseline at Week 28 and Week 32 will be repeated for the secondary endpoint of "average change from baseline at Week 60 and 64". A Line plot of LSM (+/- SE) by visit will also be provided for the treatment arms. Note that Week 62 BCVA data will be used in lieu of Week 60 BCVA data if the latter are not available. Otherwise, LOCF will be used to impute missing BCVA as per the estimand framework. In addition, a separate summary statistics of change in BCVA from Baseline at Weeks 4, 8, 28, 32, 60 and 64, together with box plots and a trend line will be provided.
- Summary statistics of average change in BCVA from baseline by visit per treatment arm will be provided.
- Number (%) of patients with occurrence of BCVA improvements of ≥ 5, ≥ 10, and ≥ 15 letters from baseline or BCVA ≥ 84 Letters at Week 32, Week 64 and the last injection visit per treatment arm will be provided.
- Number (%) of patients with occurrence of BCVA ≥ 69 letters at Week 32, Week 64 and the last injection visit per treatment arm will be provided.

The FAS will be used to analyze functional outcomes.

To evaluate the anatomical outcomes with brolucizumab relative to aflibercept

- Average change in CSFT from baseline as assessed by SD-OCT at Weeks 28 and 32 per treatment arm will be provided. In addition, equivalent summaries will be provided at the date of the last treatment and 4 weeks after for patients who discontinued the study treatment early. Note that Week 30 CSFT data will be used in lieu of Week 28 CSFT data if it is not available. The same analysis model as used for change from baseline in BCVA will be used with the baseline BCVA categories replaced by baseline CSFT categories (<400, >=400 μm).
- Average change in CSFT from baseline as assessed by SD-OCT at Weeks 60 and 64 per treatment arm will be provided. In addition, equivalent summaries will be provided at the date of the last treatment and 4 weeks after for patients who discontinued the study treatment early. Note that Week 62 CSFT data will be used in lieu of Week 60 CSFT data if it is not available. This will be analyzed as for CSFT at Weeks 28 and 32. A line plot by treatment of LSM (+/-SE) will be produced.
- Summary statistics of change in CSFT from baseline by visit, together with box plots and a trend line will also be provided for the treatment arms.
- Number (%) of patients with presence of IRF and/or SRF and sub-RPE fluid in the central subfield, as assessed by SD-OCT at Weeks 4, 8, 12, 16, 28 and 32, by visit and by number of visits (0, 1, 2 visits) per treatment arm will be provided. In addition, equivalent summaries will be provided at the date of the last treatment and 4 weeks after for patients who discontinued the study treatment early. Note that Week 30 IRF/SRF/sub-RPE data will be used in lieu of Week 28 IRF/SRF/sub-RPE data if it is not available.
- Number (%) of patients with presence of IRF and/or, SRF, and sub-RPE fluid in the central subfield, as assessed by SD-OCT at Weeks 60 and 64 and by number of visits (0, 1, 2 visits) per treatment arm will be provided. In addition, equivalent summaries will be provided at the date of the last treatment and 4 weeks after for patients who discontinued the study treatment early. Note that, Week 62 IRF/SRF/sub-RPE data will be used in lieu of Week 60 IRF/SRF/sub-RPE data if it is not available. Only observed data will summarized.

The FAS will be used to analyze anatomical outcomes.

Note:

For secondary endpoints regarding distribution of last and maximal interval, if the duration of the interval falls within the following ranges of [q4w, q8w) or [q8w, q12w) or[q12w, q16w) or $\geqslant$ q16w then the floor value of these ranges i.e. q4w, q8w, q12w, or q16w respectively, will be used for imputation.

Throughout this document, analyses of Week 60 BCVA and other efficacy data are performed if Week 60 data are available. If Week 60 BCVA and other efficacy data are not available, Week 62 BCVA and other efficacy data will be used instead of Week 60 data, respectively.

Otherwise, LOCF will be used to impute missing BCVA/CSFT as per the estimand framework.

To assess the potential confounding effects related to the impact of COVID-19 on the interval distribution assessment at Week 64, the analysis for secondary endpoints of last and maximal interval will be repeated using FAS by excluding subjects whose DAA has been impacted by COVID-19 (e.g. DAA not performed due to COVID-19 site impact).

2.7.2 Statistical hypothesis, model, and method of analysis described above.

2.7.3 Handling of missing values/censoring/discontinuations

Similar missing data imputation strategy as described in the estimand framework in Table 2-1 will be used for analyses up to Week 64. In case of treatment interruption, if the duration of the last/maximal interval falls within the following ranges of [q4w, q8w) or [q8w, q12w) or [q12w, q16w) or ≥ q16w then the floor value of these ranges i.e. q4w, q8w, q12w or q16w, respectively, will be used for imputation.

2.8 Safety analyses

The safety set will be used for all safety analyses.
The secondary safety objective and endpoint of this study is as follows:

To assess the safety and tolerability of brolucizumab relative to aflibercept

- Incidence of ocular and non-ocular AEs up to Week 32 and up to Week 64 per treatment arm will be provided.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., change from baseline summaries).

2.8.1 Adverse events (AEs)

All information obtained on adverse events will be displayed by treatment arm. All collected AEs will be listed based on Safety Set.

A separate summary table will be provided for ocular AEs of study eye and fellow eye; and non-ocular AEs by treatment, primary system organ class (for non-ocular AEs only) and preferred term.

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

Adverse events will be coded using the MedDRA dictionary and presented by system organ class (SOC), preferred term (PT) and treatment arm. Treatment-emergent AEs 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 at each analysis timepoint (Week 32, Week 64) in the following ways:

Table 2-7 TEAE summary

TEAE summary	AE categories		
	Ocular AE in the study eye	**Ocular AE in the fellow eye**	**Non-ocular AE**
Frequent AEs by PT†	Y		Y
AEs by primary SOC and PT	Y	Y	Y
AEs by primary SOC and PT (excluding events with onset date after start of alternative treatment)	Y		Y
AEs by maximum severity, SOC and PT	Y		Y
AEs related to study treatment by SOC and PT	Y		Y
AEs related to injection procedure by SOC and PT	Y		
AEs leading to permanent discontinuation of study treatment by SOC and PT	Y		Y
AEs leading to temporary interruption of study treatment by SOC and PT	Y		Y
SAEs by SOC and PT	Y	Y	Y
SAEs by SOC and PT (excluding events with onset date after start of alternative treatment)	Y		Y
SAEs related to study treatment by SOC and PT	Y		Y
SAEs related to injection procedure by PT	Y		

Note: Ocular AEs will be summarized by PT only. Non-ocular AEs will be summarized by SOC and PT.

Ocular AE reported in >=1% and non-ocular AEs reported in >=2% will be summarized.

Subject listings of all adverse events will be provided. Deaths and SAEs (i.e., 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.

Subgroup analysis for impacted/non-impacted subjects to COVID-19 and exposed/non-exposed to the urgent safety measures as defined in Section 2.2.1 will be produced for Ocular SAEs in the study eye, AESIs, and for the summary table for death, SAEs, or AEs leading to study discontinuation.

2.8.1.1 Adverse events of special interest / grouping of AEs

The number (%) of subjects with ocular events of special interest (AESIs) in the study eye and other safety topics of interest will be summarized by treatment primary system organ class (for non-ocular AEs only) and preferred term.

AESIs related to the study treatment and/or study treatment procedure will be summarized by treatment and PT term.

Additional image grading outputs from the reading center will be listed for subjects with an adverse event of special interest.

A Case Retrieval Sheet (CRS) with the exact composition of the AE groupings is to be used to map reported AEs to the AESI and other safety topics of interest groupings. This file may be updated (i.e., it is a living document) based on review of accumulating trial data, and therefore the groupings are also subject to potential change. The most up-to-date version of the CRS will be used at the time of the analysis.

2.8.2 Deaths

On-treatment deaths and all deaths including those occurred outside the on-treatment period will be summarized by primary system organ class and preferred term. A listing will also be provided.

2.8.3 Loss in Best Corrected Visual Acuity

Number and % of subjects who lost ≥ 15/ >=30 letters in BCVA from baseline up to Week 32 and up to Week 64 will be presented for the study eye. Missing data will not be imputed. Number of subjects with >=15/>=30 letter loss at the last visit will also be summarized. In addition, a listing for subjects who lost >=15/ >=30 letters in the study eye from the baseline at Week 32 and Week 64 will be provided.

2.8.4 Laboratory data

Abnormal laboratory values of potential clinical importance including hematology, clinical chemistry and urinalysis parameters will be listed by treatment arm, subject, and visit/study day and if normal ranges are available, abnormalities (H: above ULN, L: below LLN) will be flagged.

Hematology

Observed values and change from baseline values for each hematology parameter will be presented descriptively by visit and treatment group. In addition, descriptive summaries will be presented graphically using boxplots. For the parameters presented in Table 2.2, each value will be categorized as low, not meeting alert criteria, or high using the clinically notable ranges as given in the table. A shift table showing category of each parameter at baseline relative to each post-baseline visit, to the last assessment, to the most extreme increase and most extreme decrease will be presented by treatment group.

Listings for subjects with at least one value satisfying the clinically notable criteria given on Table 2-2 will be presented.

Clinical Blood Chemistry

The blood chemistry parameters will be analyzed and presented in the same manner as the hematology variables.

Urinalysis

Two of the urinalysis variables (specific gravity and reaction pH) are continuous variables and will be presented in the same manner as the hematology and chemistry variables. Specific gravity will be represented with 3 decimal places. The remaining variables are categorical and will be presented in shift tables as described above.

Table 2-2 Clinically notable laboratory values

Panel/Test	Type	Gender/ Age	Conventional Units	Conventional Low	Conventional High	SI Units	SI Low	SI High	Non-numeric
Chemistry/ Calcium	alert	all	mg/dL	6.1	12.9	mmol/L	1.52	3.32	
Chemistry/ Creatinine	alert	all	mg/dL	0.7	1.4	Micromol/L	62	124	
Chemistry/ Glucose (non-fasting)	alert	all	mg/dL	40	450	mmol/L	2.22	24.98	
Chemistry/ Potassium	alert	all	mEq/L	2.8	6.3	mmol/L	2.8	6.3	
Chemistry/	alert	all	mEq/L	117	160	mmol/L	117	160	

Sodium									
HCG	alert	all							Negative, inconclusive
Hematology/ Hematocrit	alert	all	%	18	60	%	18	60	
Hematology/ Hemaglobin	alert	all	g/dL	8	22	g/L	80	220	
Hematology/ Platelet	alert	all	K/cu mm	30	900	X10E9/L	30	900	
Hematology/ WBC	alert	all	K/cu mm	2	25	X10E9/L	2	25	

2.8.5 Other safety data

2.8.5.1 ECG and cardiac imaging data

Not applicable.

2.8.5.2 Vital signs

Clinically relevant abnormalities in vital signs data i.e., sitting blood pressure (systolic and diastolic pressure in mmHg) and pulse rate (beats per minute) will be listed by treatment arm, subject, and visit/study day and abnormalities as per normal range and critical values as per Table 2.3 will be flagged.

Number (%) of patients with critical abnormalities will also be provided.

Table 2-3 Critical changes in 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

Summary statistics will also be provided by treatment and visits (Baseline, Week 4, Week 8, Week 28, Week 32, Week 60, Week 64, EOT and EOS).

2.8.5.3 Intraocular pressure (IOP)

Intraocular pressure (IOP) measurements will be recorded in mmHg.

Summary statistics of pre-dose observed IOP values and change from baseline for both study and fellow eyes will be presented by treatment and visit.

Furthermore, summary statistics of pre-dose and post-dose observed IOP values and respective change from pre-dose for the study eye will be presented by treatment and visit. In addition, number of subjects with sustained IOP elevation, defined as three consecutive IOP >=21 mmHg in the study eye.

Listing of clinically significant elevations in pre- and post-dose IOP measurements for both study and fellow eyes will be provided by treatment and visit/study day and elevated IOPs (≥25 mmHg) and subjects with sustained IOP elevation will be flagged.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

The secondary objective and endpoint for PRO in this study is as follows:

To evaluate the effect of brolucizumab relative to aflibercept on PRO

- VFQ-25 change from baseline at Week 32 and 64 in total and subscale scores.

The FAS will be used to analyze PRO outcomes.

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 2-4. A missing response will not be re-scaled (except for the response to question 15c, see below, which will be re-set to 0 if the response to question 15b is 1).

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

Table 2-4 Rescalling 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	NA	0	NA	NA

- Note that the answer to question 15c will subsequently be adjusted based on the answer to question 15b.
    - If the answer to 15b is 1 then the answer to 15c will be re-set to 0.
    - If the answer to 15b is 2 or 3 then the answer to 15c will be re-set to missing

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

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

Subscales will be calculated where at least one of the (re-scaled) questions contributing to that subscale is non-missing, and otherwise set to missing. The scales and corresponding questions are shown in Table 2.5.

Table 2-5 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

The composite score is the average of the 11 subscales shown in Table 2.5. It will be set to missing if at least six of the subscales are missing.

The composite score and the subscales will be summarized by treatment and visit (Week 32 and Week 64). In addition, these endpoints will be analyzed using and analysis of covariance model (ANCOVA) that includes treatment and the baseline composite or subscale score as appropriate.

2.12 Biomarkers

Not applicable.

[redacted]

2.14 Interim analysis

The primary analyses will be conducted when all ongoing subjects have completed their Week 32 visit. Subjects will remain in the study and will continue to receive masked treatment through the planned study duration of 64 weeks, to allow for further evaluation of efficacy and safety.

Treatment masking of individual subjects will remain intact for all subjects, masked investigators and selected staff from the Sponsor who have contact with subjects or investigators until the final database lock has occurred.

3 Sample size calculation

The sample size calculation is based on the co-primary endpoint of the distribution of the last interval with no disease activity up to Week 32 and average change in BCVA from baseline at Weeks 28 and 32 using the following assumptions derived from the HAWK and HARRIER studies.

- expected interval distribution for aflibercept 2 mg and brolucizumab 6 mg (Table 3-1)

Table 3-1 Expected interval distribution for aflibercept 2 mg and brolucizumab 6 mg

Treatment	4w	8w	12w
Aflibercept	20%	35%	45%
Brolucizumab	13%	32%	55%

- common standard deviation of change in BCVA from baseline of 13 letters for both brolucizumab and aflibercept.

In order to calculate the sample size for the co-primary endpoint of:

1. Superiority of brolucizumab over aflibercept in terms of interval distribution; AND
2. Non-inferiority of brolucizumab compared to aflibercept in terms of average change in BCVA from baseline at Week 28 and Week 32.

Two one-sided tests each with $\alpha = 0.025$ and power of 80% are conducted.
For superiority of the interval distribution, a one-sided Wilcoxon test for comparing two ordered multinomial populations (H0: brolucizumab and aflibercept interval distribution are equal, vs. H1: brolucizumab interval distribution is larger than aflibercept interval distribution) is performed which results in a sample size of 622 patients.

Secondly, for non-inferiority of average change in BCVA from baseline, a one-sided T-test assuming equal means with non-inferiority margin of 4 letters and a common standard deviation of 13 letters is performed which provides a sample size of 334 patients.

As in this co-primary endpoint, both superiority in terms of interval distribution and noninferiority in terms of change in BCVA from baseline must be met, the maximum sample size of two hypothesis testings, i.e., 622, is considered. With the sample size of 622 patients, an overall power of 77.5% for the co-primary endpoint is obtained (97% re-calculated power for non-inferiority in terms of BCVA).

Finally, to take into account loss to follow-up of 10%, the required sample size of the study will be 692 patients, who will be randomized to each treatment arm in a 1:1 ratio (346 patients in each treatment arm).

The sample size analyses were conducted before the urgent safety measures were introduced.

The sample size calculations were performed using StatXact 9.0 and PASS 11.

4 Change to protocol specified analyses

Added in the SAP are the secondary endpoints to evaluate

- Durability
    - Time to first dry retina (no IRF and no SRF) at Week 64

- Functional outcomes
    - Change in BCVA from baseline by visit to Week 32 (Week 64)
- Anatomical outcomes
    - Change in CSFT from baseline by visit to Week 32 (Week 64)
- Safety outcomes
    - Number of subjects who lost >=30 letters from baseline up to Week 32 and up to Week 64.
    - Number of subjects with sustained IOP elevation.
    - Sensitivity analysis for selected AEs by excluding events with onset date after start of alternative treatment)

The endpoints and statistical analyses are described in Sections 1.2, 2.7.1, 2.8.1.

The definition of exposed to USM is clarified in SAP that the non-exposed group consists of the set of subjects who completed Week 32 visit and a set of subjects who discontinued the study treatment and/or study at/before Week 32.

Full Analysis Set is amended to consist of subjects who were randomized and received at least one dose of the study treatment.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Adverse event 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.

If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

Adverse event start date imputation

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

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

	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 Treatme	**(2.b)** Before Treatme	**(2.b)** Before Treatme	**(2.b)** Before Treatme
YYYY = TRTY	**(4.a)** Uncertain	**(4.b)** Before Treatment Start	**(4.c)** Uncertain	**(4.c)** After Treatment Start
YYYY > TRTY	**(3.a)** After Treatment Start	**(3.b)** After Treatment Start	**(3.b)** After Treatment Start	**(3.b)** After Treatment Start

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

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

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

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

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

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

5.1.3 Concomitant medication date imputation

Concomitant medication (CM) 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 follow up period date, 31DECYYYY, and 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 follow up period date, last day of the month, date of death).

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.

Concomitant medication start date imputation

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 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.

5.1.3.1 Prior therapies date imputation

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Other imputations

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 mid- month point (15MON YYYY)
   c. else if DIAG month > treatment start month => data error

If DIAG year > treatment start date year => data error

5.2 AEs coding/grading

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

The below severity grade will be used in this study:

- 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 derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

Cumulative logistic regression model:
Let Y be an ordinal outcome with J categories. Then $P(Y \leq j)$ is the cumulative probability of Y less than or equal to a specific category $j = 1, \dots, J-1$. Note that $P(Y \leq J) = 1$.

The odds of being less than or equal a particular category can be defined as

$$\frac{P(Y \leq j)}{P(Y > j)}$$

for $j = 1, \dots, J-1$ since $P(Y > J) = 0$ and dividing by zero is undefined.
Alternatively, you can write $P(Y > j) = 1 - P(Y \leq j)$. The **log odds** is also known as the **logit**, so that

$$\log\left(\frac{P(Y \leq j)}{P(Y > j)}\right) = logit(P(Y \leq j))$$

The ordinal logistic regression model can be defined as

$$logit\big(P(Y \leq j)\big) = \beta_{j0} + \beta_{j1}x_1 + \cdots + \beta_{jp}x_p$$

for $j = 1, \dots, J-1$ and p predictors. Due to the **parallel lines assumption** (know as proportional odds assumption), the intercepts are different for each category but the slopes are constant across categories, which simplifies the equation above to

$$logit\big(P(Y \leq j)\big) = \beta_{j0} + \beta_1 x_1 + \cdots + \beta_p x_p$$

In this study, we will have j= "1=q4w" and "2=q8w"; p=1 and the predictor x=treatment(Bro, Afl); therefore,

$$logit\big(P(Y \leq q4w)\big) = \beta_{10} + \beta * treatment$$

$$logit\big(P(Y \leq q8w)\big) = \beta_{20} + \beta * treatment$$

The point estimate of the odds ratio of making response at or below any category of interval distribution between aflibercept and brolucizumab is exp (β).

One-sided Wilcoxon test:

Step 1: The data will be defined as "treatment (1=BRO, 2=AFL)", "rsp (1=q4w, 2=q8w, 3=q12w)" and "count (number of patients falls into q4w, q8w and q12w as per the primary endpoint)".

Step 2: The proc logistic in SAS with order option of "*order=internal descending"* will be used to indicate the ordinal scale of q4w, q8w and q12w.

The class statement of "*class treatment/param=ref"* will be considered.
The model statement of "*model rsp = treatment/link=clogit expb*" with the link function of "*link=clogit*" will be used for the cumulative logit model.
The freq statement of "*freq count*" and format statement of "*format treatment xx. rsp yy.*" Will be used.

Step 3: If the P-value of the score test for proportional odds assumption < 0.05 then non-proportional odds assumption can be considered by adding "*unequalslopes*" option to the model statement.

Step 4: The P-value for testing global null hypothesis BETA=0 from Score test is equal to the Wilcoxon test. The one-sided Wilcoxon P-value is equal to "Pr>ChiSq" devided by 2, from score test.

Analysis of variance (ANOVA):

Proc mixed in SAS will be used for the BCVA non-inferiority analysis of co-primary endpoint. The following statements will be considered:

- class (<treatment>, <BL BCVA category>, <age category>)",
- model <mean BCVA change from BL> = <treatment> < BL BCVA category > < age category >/ solution
- lsmeans <treatment> / diff cl alpha= 0.05 OM;

The terms in the brackets are to be adjusted according to the real data set and variable names.

Analysis of covariance (ANCOVA):

Proc mixed in SAS will be used for the sensitivity analysis of BCVA (non-inferiority analysis of co-primary endpoint) with *continuous* BL BCVA and *continuous* age variables together with treatment (as a factor).

5.4.2 Key secondary analysis

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Important protocol deviations are defined in the Protocol Deviations requirement. Table 5-1 includes the important protocol deviations which lead to exclusion of a subject from one or more analysis sets.

Table 5-1 Important protocol deviations leading to exclusion from analyses

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 50yrs	Patient less than 50 years of age at baseline	Exclude from PPS analysis
M_INCL03_No Active CNV secondary to AMD	No Active CNV secondary to nAMD in the study eye	Exclude from PPS analysis
M_EXCL01_Confounding condition in the study eye	Study eye: Confounding ocular concomitant conditions or ocular disorders	Exclude from PPS analysis
M_EXCL03_Confounding concomitant medications or procedures in the study eye	Study eye: Confounding concomitant medications or procedures	Exclude from PPS analysis
M_EXCL04_Confouding systemic condition or systemic treatment	Confounding systemic condition, including blood pressure or systemic treatments	Include in all analyses if due to systemic conditions (Protocol Section 5.2: 14, 15, 16), but exclude in PP analyses if due to systemic treatments (Protocol Section 5.2: 17, 18)
M_EXCL07_Systemic investigational drugs	Use of systemic investigational drugs within 5 half-lives of baseline or within 30 days/until the expected pharmacodynamic effect has returned to baseline	Exclude from PPS analysis

Deviation ID	Description of Deviation	Exclusion in Analyses
M_TRT01_Wrong IP administered	Wrong IP administered during the study	Exclude from PPS analysis
M_TRT03_Under-treatment during loading phase	Under-treatment during loading phase: missed a planned injection (not due to any safety event)	Exclude from PPS analysis
M_TRT04_Under-treatment after loading phase	Under-treatment after loading phase; missed a planned injection (not due to any safety event)	Exclude from PPS analysis
M_TRT05_Over-treatment	Over-treatment, when treatment was given prior to scheduled injection/inspection visit and not due to DA reactivation	Exclude from PPS analysis
M_OTH01_Masking process not followed	Masking process not followed as per protocol with impact on data integrity	Exclude from PPS analysis
M_OTH02_Trt interval wrongly adjusted	A patient with DA whose interval is not reduced/maintained by mistake or a patient with no DA whose interval is reduced by mistake	Exclude from PPS analysis
M_OTH08_Any other PD with impact	Any other protocol deviation with impact on the efficacy assessment or safety of the patient	Exclude from PPS analysis
M_OTH09_Sample analyzed after WoC	Sample analyzed after withdrawal of consent	Exclude from all analysis
M_COMD01_Prohibited meds or procedure	Prohibited medication and/or procedure and history of systemic treatments and not discontinued	Exclude from PPS analysis
M_WITH02_Prohibit med and not withdrawn	Subject received prohibited medication but not withdrawn	Exclude from PPS analysis

Table 5-2 lists the non-protocol deviations (analysis restrictions, AR) that may lead to exclusion from per-protocol analysis. AR address limitations in the evaluability which result from missing or confounding data with underlying background not qualifying as a PD (e.g. early study terminations, early treatment discontinuations, missing DAA or BCVA assessments).

Subject evaluability is based on two components:

- Exclusion from analysis set
- Censoring of specific data points from an analysis.

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 systemic bias.

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

Table 5-2 Non-protocol deviations (analysis restrictions)

AR ID	Description of AR	Category of reason	Inclusion/Exclusion in Analysis
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 PPS
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 study treatment termination due to reasons other than lack of efficacy/safety	0	Exclude from PPS analyses
AR_MD_01	No valid BCVA assessment between Week 28 and Week 32	0	Exclude from PPS 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

Table 5-3 describes classification with regards to analysis sets. Patients with PDs as per the PD specification document will be excluded from the PPS.

Table 5-3 Patient Classification

Analysis Set	PD ID that cause patients to be excluded	Non-PD criteria that cause patients to be excluded
Randomized Analysis Set	P_INCL01_ICF not obtained M_OTH09_Sample analyzed after WoC	Not randomized
FAS	P_INCL01_ICF not obtained M_OTH09_Sample analyzed after WoC	Not in Randomized Analysis Set Mistakenly randomized and no double-masked study treatment taken Did not receive at least one study injection
PPS	P_INCL01_ICF not obtained before start P_INCL02_Age less than 50 yrs M_INCL03_No Active CNV secondary to AMD P_INCL05_Out of Range BCVA study eye M_INCL04_Ansence of IRF/SRF study eye at screening M_EXCL01_Confounding condition in the study eye M_EXCL03_Confounding concomitant medications or procedures in the study eye M_EXCL04_Confouding systemic condition ot treatment if due to systemic treatments M_EXCL07_Systemic investigational drugs M_TRT01_Wrong IP administered	Not in FAS AR_EST_03 AR_ETD_03 AR_MD_01

Analysis Set	PD ID that cause patients to be excluded	Non-PD criteria that cause patients to be excluded
	M_TRT03_Under-treatment during loading phase M_TRT04_Under-treatment after loading phase M_TRT05_Over-treatment M_OTH01_Masking process not followed M_OTH02_Treatment interval wrongly adjusted M_OTH08_Any other PD P_OTH09_Sample analyzed after WoC M_WITH02_Prohibited med and not withdrawn M_COMD01_Prohibited meds or procedures	
Safety Set	P_INCL01_ICF not obtained M_EXCL04_Confouding systemic condition or treatment if due to systemic treatments M_OTH09_Sample analyzed after WoC	Did not receive at least one study injection

-*: Note that patients with important PDs but without impact as specified in the edit check specification document will be reported as PD and will also be included in PPS for analysis. Some examples of PDs without impact are: “Ocular conditions fellow eye w/o impact: presence of amblyopia, amaurosis or ocular disorders in the fellow eye with BCVA < 20/200 at screening” or “confounding study eye concomitant medications or procedures w/o impact”. Please refer to the latest edit check specification document for the list of PDs with/without impact.

6 Reference

Natarajan S, Lipsitz SR, Fitzmaurice GM, et al (2012) An extension of the Wilcoxon Rank-Sum test for complex sample survey data. J R Stat Soc Ser C Appl Stat p. 653-664.