NOVARTIS

Clinical Development

RTH258A/Brolucizumab

CRTH258AFR03 / NCT04264819

# A one-year, single-arm, open-label, multicenter study assessing the effect of brolucizumab on disease control in adult patients with suboptimal anatomically controlled neovascular age-related macular degeneration (SWIFT)

## Statistical Analysis Plan (SAP)

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| 27-04-2023 | Creation of amendment 1.0 | Description of PRO removed from list of abbreviation of PRO removed from list of abbreviation<br>USM description added in list of abbreviation | List of abbreviations |
| | | Updated protocol version and protocol release date | Section 1 Introduction |
| | | Updated sample size in study design | Section 1.1 Study design |
| | | Drop the PRO objective from objectives and related endpoints | Section 1.2 Study objectives and endpoints |
| | | Updated population for patient disposition and protocol deviation | Section 2.4.1 Patient disposition and<br>Section 2.4.2 Protocol deviation |
| | | Updated Baseline characteristics | Section 2.4.4 Baseline characteristics |
| | | Added section for prior and post aVEGF and concomitant procedures | Section 2.5.2 Prior and concomitant and post therapies |
| | | Updated the subgroup modalities | Section 2.6.2 Supportive analysis |
| | | Updated the population for primary and secondary endpoint<br>Added USM estimand in primary analysis | Section 2.6.1 Primary endpoint, Section 2.7.1 secondary endpoint [redacted] |
| | | Drop the percentage change from baseline for BCVA | Section 2.7.1.4 Function outcomes (BCVA) |
| | | Updated the sequence of variable for time to event analysis | Section 2.7.1.2.4 Time to dryness, Section 2.7.1.2.5 Maximum duration of dryness and Section 2.8.1.3<br>Time to no disease activity |
| | | Changed increase to gain for BCVA outcome | Section 2.8.1.4 Functional outcome (BCVA) |
| | | Added p-value in COVID-19 analysis | Section 2.8.1.5 COVID-19 pandemic |

| Date | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|
| | | Dropped MedDRA query and PT table, updated ocular categories and other updates in modalities for type of adverse event & action taken.<br>Included urgent safety measure analysis | Section 2.9.1 Adverse event |
| | | Updated the AESI section to provide more details | Section 2.9-1.1 AESI |
| | | [redacted] | [redacted] |
| | | Updated the sample size | Section 3 Sample size calculation |
| | | Added procedure and medical history (nAMD) in date imputation section | Section 5.1.3 Concomitant medication (CM)/procedure (PR) and and medical history (nAMD) date imputation |
| | | Updated MedDRA version | Section 5.2 AEs coding/grading |
| | | Dropped correlation and Bland Altman plot SAS code | Section 5.4 Statistical method |
| | | Updated severity code for protocol deviation | Section 5.5 Rule of exclusion criteria of analysis set |

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## List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| ATC | Anatomical Therapeutic Classification |
| BCVA | Best-Corrected Visual Acuity |
| CNV | Choroidal Neovascularization |
| [redacted] | [redacted] |
| CI | Confidence Interval |
| CRO | Contract Research Organization |
| CSFT | Central Sub-Field Retinal Thickness |
| CRT | Central Retinal Thickness |
| CSR | Clinical Study report |
| ENR | Enrolled set |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| FAS | Full Analysis Set |
| ECS | Edit checks specification |
| eCRF | Electronic Case Report Form |
| ICF | Informed Consent Form |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| IVT | Intravitreal |
| KM | Kaplan-Meier |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| nAMD | Neovascular Age-Related Macular Degeneration |
| OCT | Optical Coherence Tomography |
| PK | Pharmacokinetics |
| PD | Protocol deviation |
| PDS | Programming Datasets Specifications |
| PPS | Per-Protocol Set |
| PT | Preferred Term |
| q12w | Every 12 Weeks |
| SAP | Statistical Analysis Plan |
| SAF | Safety analysis set |
| SD-OCT | Spectral Domain Optical Coherence Tomography |
| SOC | System Organ Class |
| TFL | Tables, Figures, Listings |
| TtC | Treat-to-Control |
| USM | Urgent Safety Measure |
| WHO | World Health Organization |

# 1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical methods for all safety and efficacy analyses planned (Protocol-Section 12) in the clinical protocol (CRTH258AFR03, version no: 05, release date 05Apr2022). This document will be used to prepare the statistical results and the corresponding Clinical Study Report (CSR).

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

Data will be analyzed by Novartis and/or the designated Contract Research Organization (CRO). Statistical software SAS version 9.4 or higher will be used for generating TFLs.

## 1.1 Study design

This is a prospective, single-arm, open-label, multicenter study to evaluate the efficacy and safety of brolucizumab 6 mg in pretreated suboptimal anatomically controlled patients with nAMD.

Approximately 295 adult patients will be screened and included (10% dropout rate expected) in France.

Before inclusion in the study, a patient must have a washout period of 4 weeks to 8 weeks (from 26 to 62 days inclusive) *versus* his/her last administration of a licensed anti-VEGF drug (i.e. Lucentis®, Eylea®).

The maximum study duration for 1 patient is 48 to 50 weeks, according to the patient schedule.

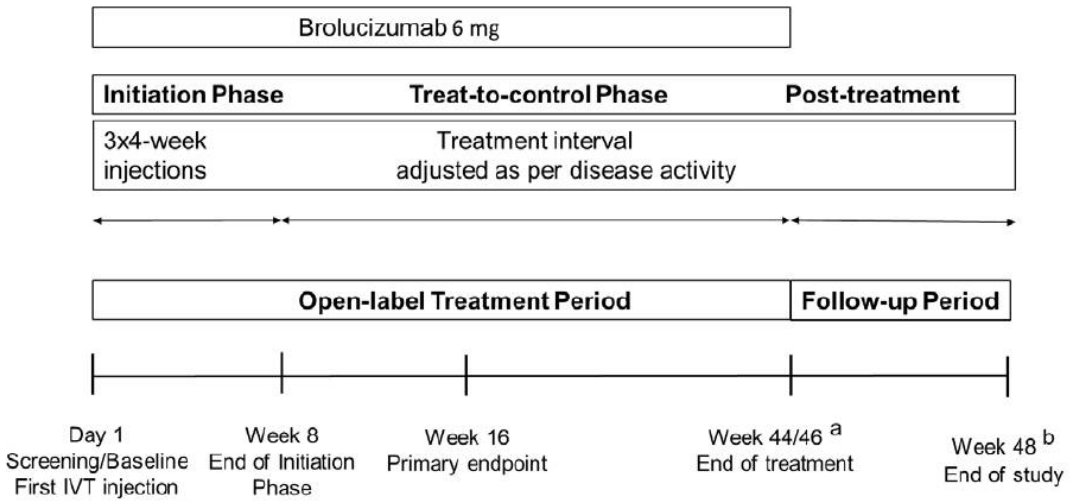
The study will consist of 2 periods (Figure 1-1):

- Open-label Treatment Period (from Screening/Baseline (Day 1) to Week 44 or Week 46 according to patient schedule)
- Follow-up Period (from Week 44 to Week 48 or from Week 46 to Week 50 according to patient schedule)

According to the patient treatment schedule, the last treatment can be at Week 44 or Week 46. If the last treatment visit is at Week 46, the End-of-study visit will be at Week 50 (at least 4 weeks after the last injection) instead of at Week 48.

Patients will require attending 5 mandatory study visits: Screening/Baseline (Day 1), Weeks 4, 8, 16, and 48/50. The other visit time points will depend on the injection regimen of the patient.

**Figure 1-1 Study design**




a End of treatment: Week 38/40/42/44/46 according to treatment schedule.
b End of study: at least 4 weeks after the end of treatment. For patients receiving the last IVT at Week 46, the EOS Visit will be at Week 50, 4 weeks following their last treatment.

The fellow eye will be treated at the discretion of the Investigator.

The Screening Visit and the Baseline Visit are the same visit in this study. Patients will receive 3 initial doses every 4 weeks (Day 1, Week 4 and Week 8). From Week 8, based on Investigator's judgment of visual and/or anatomic outcomes, the injection interval can be maintained on Q4 regimen or extended by 4 weeks at a time if there is no disease activity, as per Investigators decision, e.g. no change in visual acuity and in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.). If disease activity recurs, the injection interval should be shortened accordingly by 4 weeks at a time or to a minimal interval of 4 weeks.

Patients who show disease activity at any of visits after week 8 will be adjusted to treatment interval and will remain on this interval until the end of the study at Week 48/50.

At the Investigator's discretion, in case of interval extension, inspection visits can be performed at the midterm of the interval extension, e.g. 6 weeks after the last injection when the injection interval is extended from 4 weeks to 8 weeks. If there is no disease activity in the study eye at the inspection visit, as assessed by the Investigator, no treatment will be administered at this inspection visit; the next visit and injection will take place 2 weeks later, i.e. 8 weeks after the previous study treatment. If disease activity is observed by the Investigator in the study eye at the inspection visit, the study treatment will be administered by the Investigator; the injection interval will be reduced to 4 weeks and the next visit will be 4 weeks after the inspection visit. Similarly, inspection visits 10 weeks and 14 weeks after the last injection can be performed when the injection interval is extended from 8 weeks to 12 weeks and from 12 weeks to 16 weeks, respectively.

## 1.2 Study objectives and endpoints

**Table 2-1 Objectives and related endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary objective** | **Endpoint for primary objective** |
| • To evaluate the effect of brolucizumab 6 mg on disease control | • Proportion of patients with no disease activity at Week 16 |
| **Secondary objectives** | **Endpoints for secondary objectives** |
| • To evaluate the long term effects of brolucizumab 6 mg on disease control | • Proportion of patients with no disease activity at Week 48 |
| • To evaluate the effect of brolucizumab 6 mg on anatomical parameters | • Change from Baseline in CFST as assessed by OCT over time up to Week 48<br>• Absence of IRF, SRF, and sub-RPE fluid as assessed by OCT over time up to Week 48<br>• Proportion of patients with a dry retina (neither IRF nor SRF) up to Week 48 |
| • To evaluate the durability of brolucizumab 6 mg | • Distribution of the last interval with no disease activity up to Week 48<br>• Distribution of the maximal intervals with no disease activity up to Week 48 |
| • To evaluate functional outcomes | • Average change in BCVA from Baseline up to Week 48 |
| • To assess the safety and tolerability of brolucizumab 6 mg | • Incidence of AEs (serious and non-serious) up to Week 48 |
| [redacted] | |

AEs=adverse events, BCVA=best corrected visual acuity, [redacted] CSFT=central sub-field retinal thickness, [redacted] IRF=intraretinal fluid, OCT= optical coherence tomography, [redacted] SRF= subretinal fluid.

# 2 Statistical methods

## 2.1 Data analysis general information

Patients who consent and meet all the inclusion and none of the exclusion criteria will be screened to evaluate eligibility. After confirmation of eligibility, patients will be included and treated with brolucizumab 6 mg and data will be analyzed.

All categorical data will be presented in terms of frequencies and percentages. Summaries of continuous data will be presented in terms of n (the number of non-missing data points), mean, standard deviation (SD), median, lower and upper quartiles, minimum and maximum, the number of missing data points.

For descriptive statistics, the following rules for number of decimal places will be applied: arithmetic mean, median, lower quartile and upper quartile to 1 more decimal places than the raw data; minimum and maximum to the same number of decimal places as the raw data and SD, SE and 95% CI to 2 more decimal places than the raw data. Percentages will be presented to 1 decimal place.

### 2.1.1 General definitions

**Study treatment**: This is a single-arm study and all patients will be treated with brolucizumab 6 mg. Three loading injections (at Screening/Baseline/Day 1, Week 4 and Week 8), followed by a Treat-to-Control (TtC) regimen phase based on disease activity from Week 8 up to Week 44/46 (according to the treatment regimen). The investigator can individualize treatment intervals depending on disease activity, to adjust patient's injection regimen.

**Study treatment start and end date**: Study treatment start date is defined as the first date study treatment is administered and recorded on the Treatment Administration Record (DAR) Electronic Case Report Form (eCRF) page. Similarly, study treatment end date is defined as the last date of study treatment is administered and recorded on the Study Treatment Completion eCRF page.

Generally, study Day 1 is considered as the day of inclusion of the patient. However in this study, treatment is intended to be administered on the same day or if this is not possible, within 3 days after the day of inclusion of the patient.

Study day will be calculated as ((event date – study treatment start date) + 1 day) for events that occurred on or after study treatment start date (e.g. visit, AEs). For events prior to study treatment start date (e.g. time since diagnosis), study day will be negative and calculated as (event date – study treatment start date).

**Baseline and post-baseline**: Baseline value refers to the value of the last non-missing measurement collected prior to administration of the first dose of study treatment (Screening or Baseline visit). [redacted]

A "post-baseline" value refers to a measurement taken after the first dose of study treatment. When assessments and treatments take place on the same day, treatment must occur after completion of the efficacy assessments and pre-injection safety measures (tonometry, slit lamp

[redacted]). If study visit assessments and the corresponding treatment occur on separate days, a repeat safety check-up will be performed prior to treatment of the eye and results documented in the source documents. More post-baseline safety measurements will be recorded in source document; visit window will be applied to OCT and IVT visits.

**Change from Baseline**: The difference of measure between post-baseline and Baseline is called change from Baseline.

**Percent change from Baseline**: The percent change from baseline will be calculated as below: ((post-baseline value – Baseline value) /Baseline value)*100.

**Proportion:** A proportion refers to the fraction of the total that possesses a certain attribute. In this study attribute is disease free activity.

**Disease control:** When patients have no disease activity after taking study treatment then patient will be consider as disease control.

**On-treatment period**: The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

**Treatment duration:** The maximum planned duration of treatment for each patient is 44 to 46 weeks in accordance with the designated treatment regimen. Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the patient or the investigator.

**Treatment discontinuation**: When patients discontinue study treatment but continue in the study, the efficacy data will be used at the time the patient stopped study treatment.

**Last interval**: The last treatment interval (defined by the investigator) before Week 48.

**Maximum interval**: The longest interval of treatment reached by the patient over the study period.

**Event for no disease activity:** When patients will be with no disease status as per investigator decision after last dose in initiation phase then the patients will consider as event for no disease activity. If patients with active disease status or early discontinue then patients will be considered as censored for disease activity.

**Dry retina:** Absence of fluid (IRF/SRF/ sub-RPE) will be considered as dry retina.

**Event for dry retina**: When patients have absence of fluid then it will be considered as an event of dry retina. If patients have a presence of fluid before/at EOS or early discontinuation then will be censored.

**Study eye and fellow eye**: The investigator selects the eye with the worse BCVA at Screening as the study eye if both eyes are eligible as per the inclusion and exclusion criteria, unless the investigator deems as a study eye more appropriate to select the eye with better BCVA, based on medical reasons or local ethical requirements. If both eyes are eligible as per the inclusion and exclusion criteria, then it is recommended to select the right eye as the study eye.

The fellow eye will be examined only at Screening/Baseline and Week 48/EOS visits. Only best corrected near visual acuity (BCNVA) for the fellow eye will be analyzed. It is not requested for the purpose of this study to do any self-assessment measure of the fellow eye.

**Disease activity criteria:** Disease activity criteria will be assessed by the investigator based on whether nAMD is still active or has been re-activated. Guidance for the investigator is as follows (disease is active if at least one of the following criteria is observed by the investigator):

- BCVA decrease ≥ 5 letters from the best value since Baseline due to disease activity.
- Any significant increase in CRT (based on investigator assessment).
- Retinal hemorrhage.
- Intraretinal fluid or SRF due to disease activity (degenerative cysts allowed).
- Increase of sub-RPE fluid.

These criteria are for guidance only, the investigator may define disease activity based on his/her own assessment.

[redacted]

## 2.2 Visit windows for data analysis

Visit windows will be used for the data analysis, as per the planned visits in the protocol. During the q4w/q8w/q12w phase, i.e., from Week 16 to Week 44, the treatment visit intervals will be determined by the investigator, based on the patient's disease activity.

**Table 2-1 Assessment windows for scheduled visits**

| Analysis Visit | Week | Scheduled Day | Visit Window |
|---|---|---|---|
| Screening/Baseline | BL | 1 | -14 days to Day 1* |
| Week 4 | 4 | 28 | Day 22 – 34 |
| Week 8 | 8 | 56 | Day 50 – 62 |
| Week 12 | 12 | 84 | Day 78 – 90 |
| Week 14 | 14 | 98 | Day 92 – 104 |
| Week 16 | 16 | 112 | Day 106 – 118 |
| Week 18 | 18 | 126 | Day 120 – 132 |
| Week 20 | 20 | 140 | Day 134 – 146 |
| Week 22 | 22 | 154 | Day 148 – 160 |
| Week 24 | 24 | 168 | Day 162 – 174 |
| Week 26 | 26 | 182 | Day 176 – 188 |
| Week 28 | 28 | 196 | Day 190 – 202 |
| Week 30 | 30 | 210 | Day 204 – 216 |
| Week 32 | 32 | 224 | Day 218 – 230 |
| Week 34 | 34 | 238 | Day 232 – 244 |
| Week 36 | 36 | 252 | Day 246 – 258 |
| Week 38 | 38 | 266 | Day 260 – 272 |
| Week 40 | 40 | 280 | Day 274 – 286 |
| Week 42 | 42 | 294 | Day 288 – 300 |
| Week 44 | 44 | 308 | Day 302 – 314 |
| Week 46 | 46 | 322 | Day 316 – 328 |
| Week 48 | 48 | 336 | Day 330 – 342 |
| Week 50 | 50 | 350 | Day 344 – 356 |

* Baseline measurement before the first treatment administration.

The number of weeks between visits will vary depending on the disease activity and length of intervals between injections as determined by disease activity assessment. Study treatment at the optional inspection visits (6 weeks after the last injection when the interval is extended from 4 weeks to 8 weeks, 10 weeks after the last injection when the interval is extended from 8 weeks

to 12 weeks, and 14 weeks from the last injection when the interval is extended from 12 weeks to 16 weeks) is at the discretion of the Investigator based.

According to the patient treatment schedule, the last treatment can be at Week 44 or to Week 46. If the last treatment visit is Week 46, the end of study visit will be at Week 50 (at least 4 weeks after the last injection) instead of Week 48.

If study visit assessments and the corresponding treatment occur on separate days, a repeat safety check-up should be performed prior to treatment of the eye and results documented in the source documents. If any safety concern arises related to the study eye that, in the opinion of the investigator, may be further impacted by the study treatment or injection procedure, treatment needs to be cancelled. Injections are contraindicated in patients with active intraocular or periocular infections and in patients with active intraocular inflammation (IOI); therefore, the investigators must verify that these conditions are not present in the study eye prior to every injection. Any AEs must be recorded in the eCRF.

The injection procedure for brolucizumab will be performed according to local clinical practice. Injections will be administered by the investigator.

Data collected at unscheduled visits will not be used in 'by-visit' tabulations or graphs and will be presented in listings.

## 2.3 Analysis sets

**The Enrolled Set (ENR)** includes all patients who signed an ICF and are assigned patient numbers.

**The Safety Set (SAF)** includes all patients who received at least one IVT injection of study treatment.

**The Full Analysis Set (FAS)** will be the same as the Safety Set in this study and will be used as primary population to analyze the efficacy endpoints.

**Urgent Safety Measure Set (USM):** If any subject needs Q4 treatment interval at any time point after initial loading phase then that subject qualify for USM.

**The Per-Protocol Set (PPS)** is a subset of patients in the FAS without PDs with impact. The list of PD criteria will be provided in edit checks specification (ECS) document.

**Full Analysis Set Estimand (FAS-EST):** The FAS-EST comprises all patients who are in FAS and did not discontinue treatment in the entire study due to COVID-19.

**Per-Protocol Set Estimand (PPS-EST):** The PPS-EST is a subset of patients of the FAS-EST without PDs with impact due to COVID-19.

When assessing the robustness of the overall efficacy conclusions, considerations will be given to the analysis based on the estimand using FAS-EST and PPS-EST. The expectation for comparing of both estimands is to have similar conclusions. Inconsistencies in the results will be examined and discussed in the CSR.

## 2.4 Patient disposition, demographics and other baseline characteristics

### 2.4.1 Patient disposition

The ENR will be used to prepare a summary and listing of patient disposition.

The number and percentage of patients who completed and discontinued from the study and treatment will be summarized with reasons for premature discontinuation for the FAS. In addition, the number of screen failures with reasons will be presented for all screened patients. The patient identification number and whether patients completed or discontinued from the study will be listed, with date of last dose and primary reason for premature discontinuation.

A separate summary of disposition and listing for rescreened patients will be presented for ENR.

Study treatment will be discontinued under the following circumstances:

- Adverse event which could lead to study treatment discontinuation
- Death
- Lost to follow-up
- Physician decision
- Pregnancy
- Progressive disease
- Protocol deviation
- Study terminated by sponsor
- Technical problem
- Patient decision
- New therapy for study indication
- Lack of efficacy
- Use of prohibited treatment
- Any situation in which study participation might result in a safety risk to the patient

### 2.4.2 Protocol deviation

The number and percentage of patients with protocol deviations will be tabulated by category and deviation for the FAS. Patients with protocol deviations will be listed with date and study day of occurrence, deviation and severity codes for the ENR.

The number of patients included in each analysis set will be tabulated for all screened patients. Reasons for exclusion from analysis sets will be tabulated for the ENR. Patient exclusion from analysis sets will be listed for all patients with reasons for exclusion (i.e., both protocol and non-protocol deviations).

### 2.4.3 Demographic characteristics

Demographic and Baseline characteristics will be listed and summarized descriptively overall patients on the FAS and the SAF.

The following demographic and vital signs variables collected in the eCRF at Baseline will be summarized:

1. Sex (Male, Female)
2. Age (in years)
3. Age category (< 50, 50 - 65, 65 - 75, 75 - 85, ≥ 85)
4. Study eye (Left [OS], Right [OD])
5. Vital signs (sitting systolic/diastolic blood pressure [mmHg], sitting pulse rate [bpm])

### 2.4.4 Baseline characteristics

The following Baseline characteristics collected in the eCRF at Baseline will be summarized for study eye and fellow eye (wherever applicable):

- Study eye status at nAMD diagnosis (date of diagnosis, BCVA at diagnosis, CSFT at diagnosis)
- Time since nAMD diagnosis
- Time since nAMD diagnosis (< 2.5 - 5, 5- 8, 8-11, 11-18).
- Unilateral versus bilateral nAMD
- BCVA
- BCVA (≤55, 56 - 70, ≥71)
- BCVA categories (Count fingers, Hand motion, Light perception, No light perception) in case BCVA score is 0

- SD-OCT (analyzed by Duke [CRC])
  1. Lesion type (only at Baseline) (type 1, type 2, type 3)
  2. CSFT (µm)
  3. Baseline CSFT (< 300, ≥ 300 - 450, ≥ 450 - < 650, ≥ 650 [µm])
- Presence of fluid (Yes/No)
  1. Intraretinal fluid
  2. Subretinal fluid
  3. Sub-RPE fluid
- Volume ($mm^3$) and height (µm) of each fluid (in case of presence)
  1. Intraretinal fluid

2. Subretinal fluid
3. Sub-RPE fluid

- In case of sub-RPE/PED: nature: serious PED/fibrovascular PED / mixed PED

1. CNV lesion area (at the biggest surface) (mm²)

- Ophthalmic abnormalities (Yes, No)

- Disease activity assessment (Present)
- History of primary diagnosis:
  1. Disease (Neovascular Age-Related Macular Degeneration)
  2. Age of diagnosis
  3. Eye (OD, OS)
  4. Ongoing (Yes, No)
- History or evidence of the following in the study eye within the 90-day period prior to Screening/Baseline:
  1. Intraocular or refractive surgery
  2. Previous panretinal and peripheral laser photocoagulation
  3. Previous macular surgery or other intraocular surgical intervention
- Concomitant medication at Baseline
- Medical history
- Co morbidities
- Current medical condition

### 2.4.5 Relevant medical history/ current medical condition

Medical history/current medical conditions (general and ocular) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. History/conditions will

be summarized for the FAS by primary system organ class (SOC), preferred term (PT) by eye (study eye, fellow eye and any eye). Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study. The ongoing medical history will be considered as co morbidities. The comorbidities will be summarized and listed separately for eye (study eye, fellow eye and any eye).

## 2.5 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

### 2.5.1 Study treatment exposure

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

The following summaries will be presented:

1. Summary statistics of number of injection (n, q1, median, q3, min and max) will be provided.
2. Number of injections (n, q1, median, q3, min and max) before or at Week 8 and greater than Week 8.
3. Number of patients with injection category (1 injection, 2 injections up to the maximum number of injections) from Baseline to the end of the treatment period (Week 44/46) will be presented.
4. Treatment exposure by visit: The number and percentage of patients who received injections, missed a treatment and missed visits will be presented by visit.
5. The number of time the injection interval shorting and the number of time the injections interval increasing.
6. Summary statistics (n, mean, std, q1, median, q3, min and max) for overall duration will be provided.

The number and percentage of patients with changes in brolucizumab 6 mg treatment patterns over time (i.e. treatment interval adjustments, interruptions or permanent discontinuations) along with reasons, will be summarized. Discontinuations and primary reasons for treatment and/or study discontinuation will also be described.

Exposure data will be summarized on the SAF and the FAS. The exposure data will be listed on the FAS.

### 2.5.2 Prior, concomitant and post therapies

Each medication has the start and end dates recorded on the eCRF. Prior medications/procedures are defined as those medications which were taken and stopped prior to first dose of study treatment. Concomitant medications are defined as any medication given at least once between the day of first dose of study treatment and the last day of study visit, including those which were started pre-baseline and continued into the treatment period. The below summary tables will be reported:

- Prior medication/procedures

- Concomitant medications/procedures which started prior to first dose of study treatment
- Concomitant medications/procedures which started on/after first of study treatment

All prior and concomitant medications will be coded using the most recent version of the WHO drug dictionary. All concomitant medications (general and ocular) will be listed and summarized in alphabetic order according to Anatomical Therapeutic Chemical (ATC) classification system and PT. Tables will also show the overall number and percentage of patients receiving at least one treatment of a particular ATC.

For prior and concomitant ocular medications, as well as ocular procedures performed during the study, separate tabular summaries will be prepared for the study eye and the fellow eye. A listing of all prior and concomitant medications and concomitant procedures will be provided.

For AESIs, a separate summary of prior and post aVEGF therapies will be provided.

For handling of missing or incomplete start and end dates, see Appendix 5.1.3 of this document.

All summaries will be performed on the Safety set.

### 2.5.3 Prior and concomitant Surgery and Procedures

All prior and concomitant surgery and procedures indications will be summarized and listed by category (general, ocular) and eye (study, fellow, any).

For handling of missing or incomplete start and end dates, see Appendix 5.1.3 of this document.

All summaries will be performed on the Safety set.

### 2.5.4 History of anti – VEGF Therapy

The anti-VEGF therapy will be collected in CRF at Baseline. All recent anti-VEGF therapy will be listed and summarized. Table will present nature of the previous anti-VEGF, summary statistics for total number of previous IVTs, number of patients and percentages of previous anti-VEGF (3,4,5,6...), summary statistics for time since first anti-VGEF, time since last anti-VEGF along with below interval summary statistics.

1. Inclusion vs last anti-VEGF
2. Last anti-VEGF and second anti-VEGF
3. Second last anti-VEGF and third last anti-VEGF

The listing will include nature of the previous anti-VEGF, date of the last anti-VEGF treatment, interval of the last anti-VEGF treatment, date of the second last anti-VEGF treatment , interval of the second last anti-VEGF treatment, date of the third last anti-VEGF treatment, interval of the third last anti-VEGF treatment, date of the first anti-VEGF treatment, interval of the first anti-VEGF treatment and total number of anti-VEGF treatments (including the last one).

The below characteristics prior to first anti-VEGF will be summarized.

1. The summary statistics of BCVA and CSFT.

2. Number and percentage of IRF, SRF and Sub-RPE.

3. Summary statistics of height for IRF, SRF, Sub-RPE (if available).

The listing of above last anti-VEGF characteristics will include patients identification number, therapies name and date of therapy, BCVA, CSFT, IRF, SRF, Sub-RPE and height for IRF, SRF, Sub-RPE (if available). The above analysis will be performed on the Safety set.

## 2.6 Analysis of the primary objective

### 2.6.1 Primary endpoint

The primary objective of this study is to evaluate the effect of brolucizumab 6 mg on disease control. The primary efficacy endpoint is the proportion of patients with no disease activity at Week 16 in the study eye.

Estimation for the proportion of disease control involves only calculating the ratio of successes. In this study

Event: 1= no disease activity (disease control)

0= disease activity (failure)

Count: Frequency or number of patients with no disease activity (disease control) at Week 16.

Proportion: Number of patients with no disease activity (disease control) at Week 16/Total number of patients in the FAS.

The number of disease control patients at Week 16, total number of evaluable patients, percentage of disease control and 95% confidence interval (CI) using the Clopper-Pearson method will be provided.

Sensitivity analysis will be performed for primary endpoint using last observation carried forward (LOCF) method and considering disease activity for missing data at Week 16.

A sensitivity analysis in patients exposed and not-exposed to USM will be performed for below estimand.

a) Proportion of patients with no disease activity at Week 16.
b) Status of patients with disease activity before and after introduce of USM.

The above analysis will be done on the FAS and only on the study eye.

The analysis will be performed on the PPS, if there is more than a 10% difference in patients, between FAS and the PPS.

### 2.6.2 Supportive analyses

Subgroup analysis according to patient characteristics, like gender (male, female), age class (< 50, 50 - 65, 65 - 75, 75 - 85, ≥ 85), Baseline fluids type (IRF, SRF, both), number of previous anti-VEGF injections ( 3, 4 – 6, 7 - 9 and ≥ 10), interval (in week) since previous anti-VEGF injection (4, 5, 6, 7, 8) and time since nAMD diagnosis (2.5 – 5 month, 5 - 8 months, 8 - 11 months, 11 - 18 months and > 18 months).

## 2.7 Analysis of secondary efficacy objective(s)

### 2.7.1 Secondary endpoints

#### 2.7.1.1 Long term disease activity criteria

The first secondary objective of this study is to evaluate the effect of brolucizumab 6 mg on disease control at Week 48. The first secondary efficacy endpoint is the proportion of patients with no disease activity (disease control) at end of study (EOS) Week 48.

The number of disease control patients at Week 48, total number of evaluable patients, percentage of disease control and 95% confidence interval (CI) using the Clopper-Pearson method will be provided.

The above analysis will be done on the FAS and only on the study eye.

#### 2.7.1.2 Optical coherence Tomography (OCT)

The following secondary efficacy parameters based on OCT will be analyzed as given below.

##### 2.7.1.2.1 Central sub-field retinal thickness (CSFT)

The summary statistics of central sub-field retinal thickness (CSFT) measured by OCT for nAMD patients, change and percentage change from Baseline in CSFT will be presented by visit along with first anti-VEGF Treatment CSFT.

The number and percentage of patient with CSFT category (< 300, ≥ 300 - 450, ≥ 450 - < 650, ≥650 [µm]) will be presented by visit along with first anti-VEGF Treatment CSFT.

The above analysis will be done on the FAS and only on the study eye.

##### 2.7.1.2.2 Presence of fluid (Yes/No)

The number and percentage of patients with fluid as shown below will be presented by visit along with first anti-VEGF Treatment.

1. Intraretinal fluid
2. Subretinal fluid
3. Sub-RPE fluid
4. Without any fluid (IRF/SRF/sub-RPE)
5. In case of sub-RPE / PED : nature : (serious PED/fibrovascular PED/mixed PED)

Volume ($mm^3$) and height (µm) of intraretinal fluid, subretinal fluid and/or sub-RPE fluid will be presented the summary statistics (n, mean, std, median, min and max) by visit, if available.

The above analysis will be done on the FAS and only on the study eye.

##### 2.7.1.2.3 Dry retina

The proportion of patients without both fluids (IRF and SRF), without IRF, without SRF, without sub-RPE will be presented by visit, separately, up to Week 48/Week 50.

The proportion of patients without fluid (IRF and SRF) and having fluid (IRF and/or SRF) in entire study will be presented.

The 95% confidence interval (CI) for proportion using the Clopper-Pearson method will be provided by visit and overall.

The above analysis will be done on the FAS and only on the study eye.

#### 2.7.1.2.4 Time to dryness

The median time to dryness will be obtained from Kaplan-Meier (KM) analysis along with 2 sided 95% CI will be presented. KM plot will be provided. Details KM result will be presented including time (week), number of patients under at risk at week (without dry retina), number of patients with dry retina at week (event), probability of dry retina (survival probability) at week and 95% CI at week.

| Variable | Definition |
|---|---|
| Start date | Start date of IVT injection |
| Event | Dry retina (absence of IRF and/or SRF) |
| End date of event | Start date of first dry retina |
| Censoring (end date) | Earliest of:<br>Absence of dry retina until EOS<br>Early discontinuation without dry retina |
| Duration of time | (End date – start date) +1 |

The above analysis will be done on the FAS and only on the study eye.

#### 2.7.1.2.5 Maximum duration of dryness

The median maximum duration of dryness until Week 48/50 will be presented. The median, obtained from KM analysis will be presented along with the 2-sided 95% CI. KM plot will be provided.

The detailed Kaplan-Meier result will be presented including (week), number of patients under at risk (with fluids), number of patients without fluids (event), probability of dry retina (survival probability) and 95% CI.

| Variable | Definition |
|---|---|
| Start date | Start date of dryness |
| Event | Dryness |
| End date of event | End date of dryness |
| Censoring (end date) | Earliest of:<br>Presence of dryness until EOS<br>Early discontinuation with presence of dryness |
| Duration of time | (End date – start date) +1 (Maximum duration will be used) |

The above analysis will be done on the FAS and only on the study eye.

### 2.7.1.3 Durability

#### 2.7.1.3.1 Last interval

The last treatment interval (defined by the investigator) before or at Week 48.

The distribution of the last interval, e.g., the proportion of last interval (Q8, Q12, and Q16) will be provided.

The above analysis will be done on the FAS and only on the study eye.

#### 2.7.1.3.2 Maximal interval

The maximal interval is defined as the longest interval of treatment before 48. The duration (in days) of the maximal interval will be defined as (start date of maximal interval – start date of study drug dose). Summary statistics (n, mean, std, first quartile, median, third quartile, min and max) for the duration (in weeks) of the maximal interval will be provided.

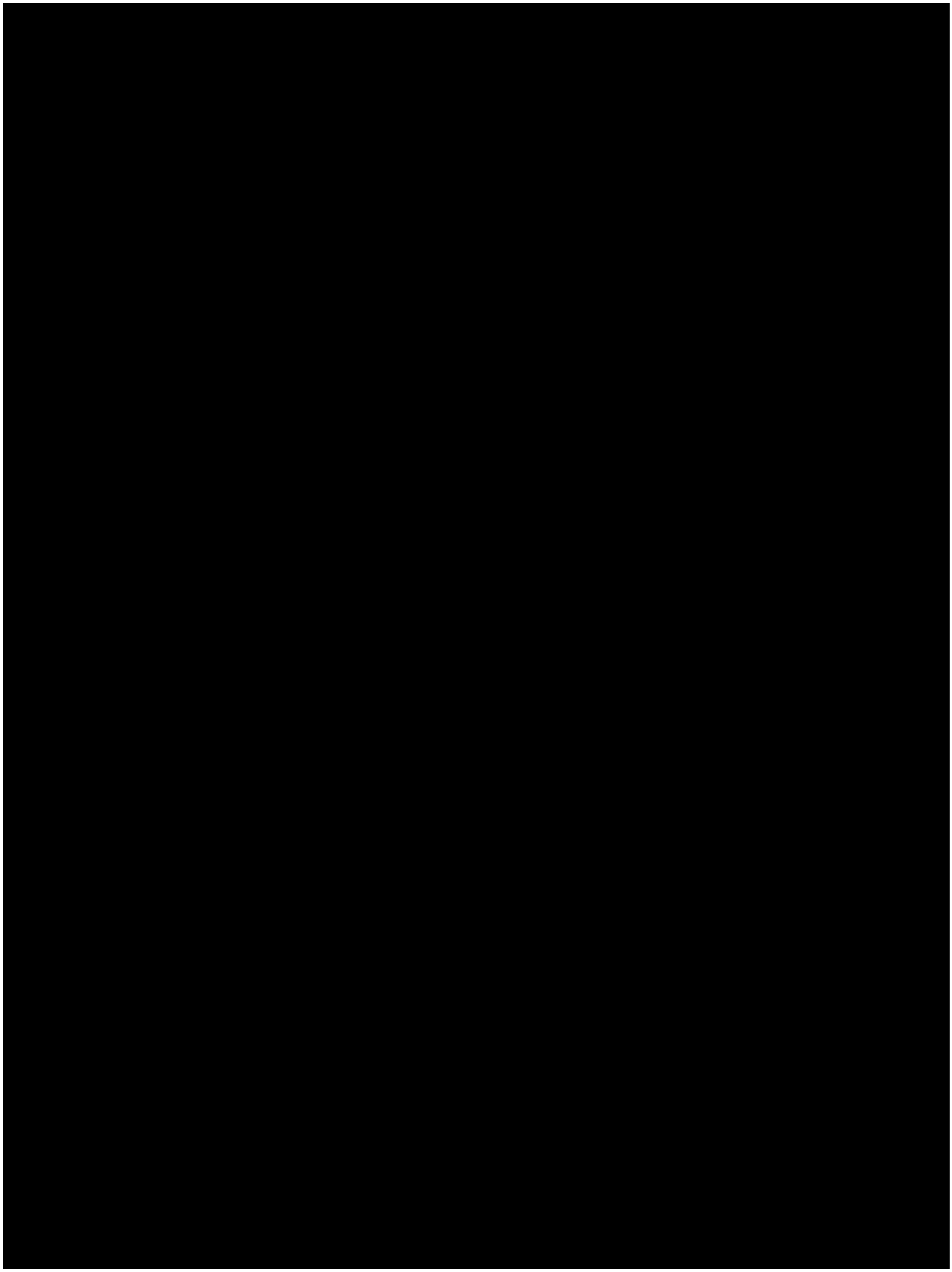
The distribution of the maximal interval is the proportion of patients with no disease activity (Q8, Q12 and Q16).

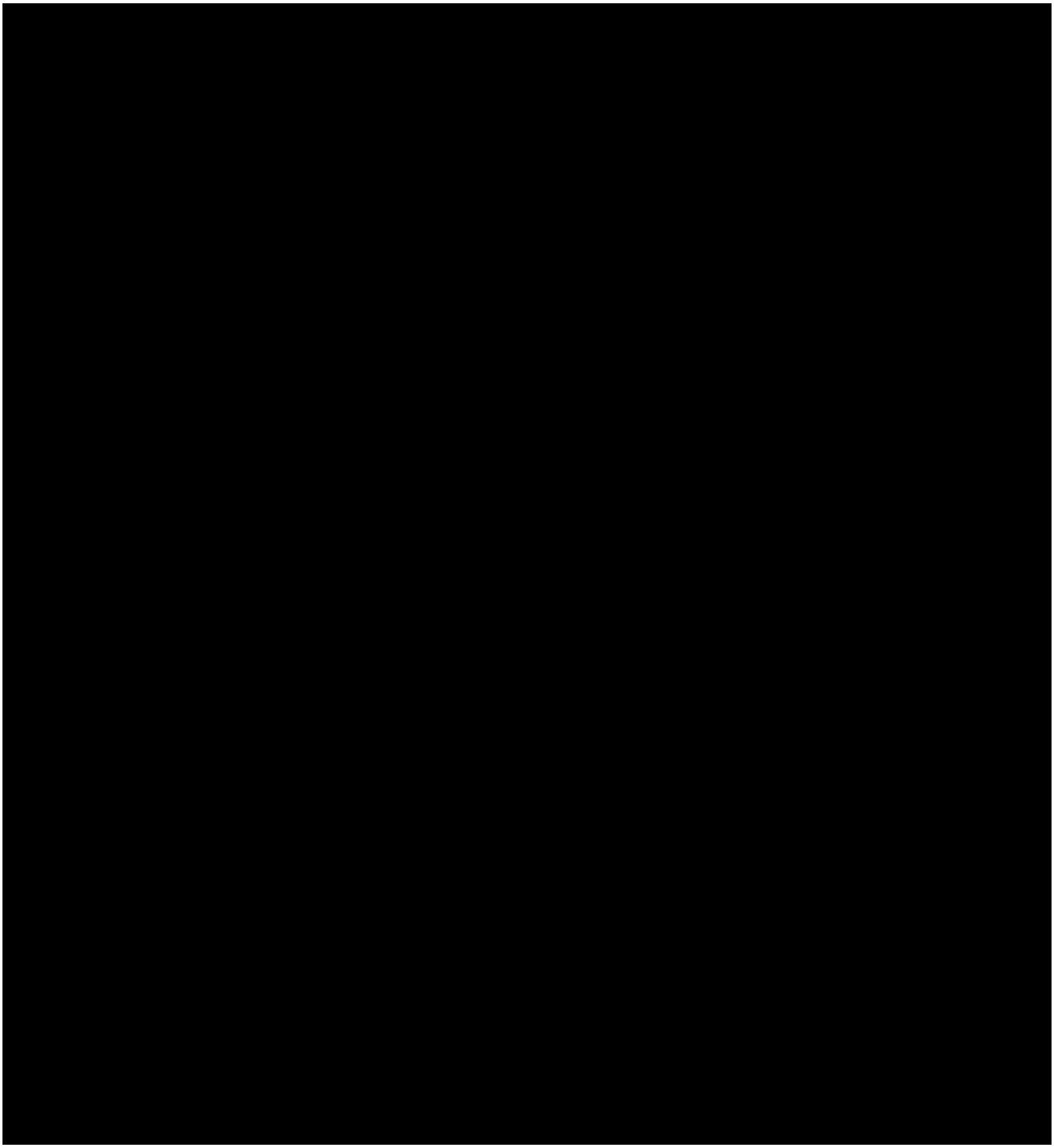
The above analysis will be done on the FAS and only on the study eye.

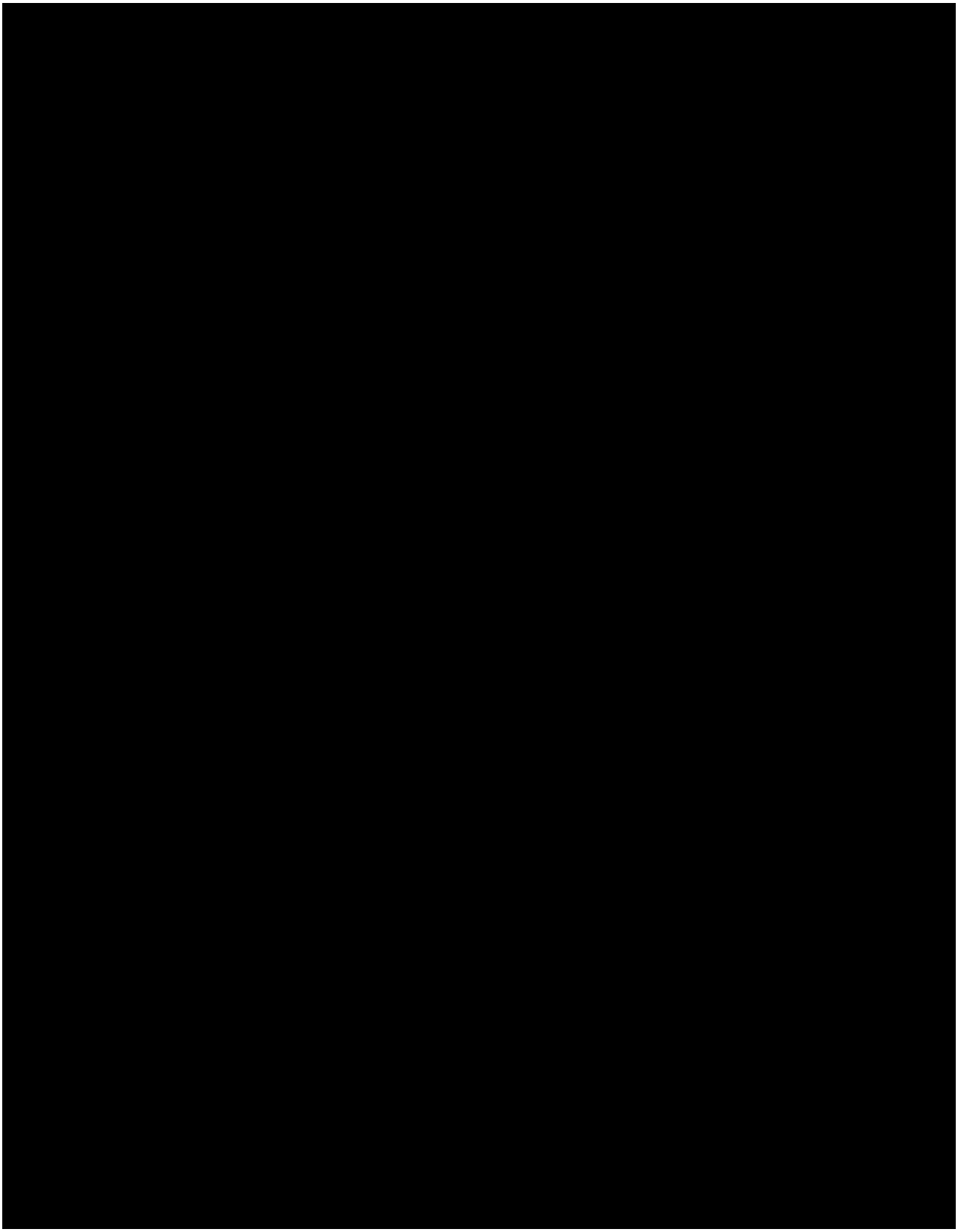
### 2.7.1.4 Function outcomes (Best Corrected Visual Acuity (BCVA))

Summary statistics (n, mean, std, median, min and max) of BCVA for nAMD patients will be presented along with change from Baseline in BCVA by visit along with first anti-VEGF Treatment BCVA.

The above analysis will be done on the FAS and only on the study eye.







## 2.9 Safety analyses

Safety measurements include duration of exposure, vital signs, and adverse events (AEs). All safety endpoints will be summarized using the Safety Set. Patients will be analyzed according to the treatment received. No imputation will be carried out for missing data.

### 2.9.1 Adverse events

All information obtained on AEs will be displayed by patient Summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (see Section 2.1.1) for definition of on-treatment period).

The count of treatment-emergent AEs, number (and percentage) of patients with treatment-emergent AEs (defined as events started after the first dose of study treatment or events present prior to start of study treatment but increased in severity based on PT) will be summarized in the following ways:

- By primary SOC and PT.
- By primary SOC, PT and maximum severity.

Separate summaries will be provided for study treatment related AEs, study procedure related AEs, need of USM, death, SAEs, other significant AEs action taken leading to study treatment withdrawn and AEs leading to dose interval adjustment (interval increase, interval reduce).

Adverse events will be summarized by presenting, the number and percentage of patients having any AE, having an AE in each primary SOC and having each individual AE (PT). Summaries will also be presented for AEs by severity. Summaries for AE will be presented for study treatment and procedure related to AEs. If a patient reported more than one AE with the same PT, the AE with the greatest severity will be presented. SOC will be presented in alphabetical order, preferred terms will be sorted within SOC in descending frequency of AEs. If a patients reported more than one AE within the same primary SOC, the patient will be counted only once with the greatest severity at the SOC level, where applicable. The AE will be presented in separate sections of ocular and non-ocular. For ocular then it will be presented by study eye, fellow eye, and any eye.

For the legal requirements of ClinicalTrials.gov and EudraCT, 2 required tables on treatment emergent AEs which are not SAEs with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by system organ class and PT on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same system organ class and PT:

- A single occurrence will be counted if there is $\leq$ 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 / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

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

In addition, all treatment emergent AEs and SAE will also be listed.

The by-patients listing will include: SOC/PT/Verbatim term, start date, end date, severity, USM, relationship to study treatment and procedures, whether or not it is a SAE, action taken with study treatment and outcome; duration will be calculated as (end date – start date + 1) and for ongoing AE (last visit date – start date + 1) by ocular and non-ocular. For ocular then it will be presented by study eye, fellow eye and any eye.

A summary of action taken with number and percentage of patients will presented with treatment interrupted, treatment withdrawn, not applicable and unknown.

#### 2.9.1.1 Adverse events of special interest / grouping of AEs

The number (%) of patients with adverse events of special interest (AESI) will be summarized by Standardized MedDRA Query and PT. A listing will also be provided.

A Case Retrieval Sheet (CRS) with the exact composition of the AE groupings is to be used to map reported AEs to the AESI 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.

The number and percentage of patients with any AESI, having an AESI in each SOC and having each individual AE (PT) will be presented by SOC and PT.

The number and percentage of patients by AESI type along with incidence rate per patient and per 1000 injections will be provided. Incidence rate per patient is defined as number of patients in AESI type/total number of patients in safety analysis set and incidence rate per 1000 injection is define as (number of occurrence of AESI type/total number of injections)*1000.

The number and type of AESI will be plotted according to the time after last brolucizumab injection and time since first brolucizumab injection.

Summary statistics for change from baseline in BCVA after end date of AESI will be provided for each AESI type and change from baseline in BCVA will be plotted overall and for each type of AESI.

Patients demographics, baseline characteristics and medical history will be provided for AESI patient with safety set.

### 2.9.2 Deaths

A separate summary of deaths including on-treatment and post-treatment deaths will be provided.

All deaths in the clinical database will be listed with the investigator-reported principal cause. Deaths occurring after the first dose of study treatment until 30 days after the date of last

treatment will be summarized. In addition, deaths occurring after the first dose of study treatment until the date of last treatment will also be summarized.

### 2.9.3 Laboratory data

Not applicable

### 2.9.4 Other safety data

Not applicable

#### 2.9.4.1 ECG and cardiac imaging data

Not applicable

#### 2.9.4.2 Vital signs

Vital signs will include blood pressure and pulse rate measurements.

All vital signs data will be listed by patient, and visit, and if ranges are available, abnormalities will be flagged. Abnormal values are marked in Section 5.3. All data, including data from unscheduled visits, will be considered when identifying abnormal values. Analysis of vital sign measurements using summary statistics for the change from Baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign. Change from Baseline will only be summarized for patients with both Baseline and post-baseline values.

## 2.10 Pharmacokinetic endpoints

Not applicable

## 2.11 PD and PK/PD analyses

Not applicable

[redacted]

## 2.13 Biomarkers

Not applicable

## 2.14 Other Exploratory analyses

Not applicable

## 2.15 Interim analysis

An interim analysis was performed when the last patient included completed the Week-16 visit.

Patients remained in the study and continued to receive treatment through the maximum planned duration of treatment of 44/46 weeks to allow for further evaluation of efficacy and safety.

# 3 Sample size calculation

The sample size calculation is based on the hypothesis of 25% to 35% of patients with no disease activity at Week 16. The sample size analyses were performed before the USM were introduced.

**Table 3-1 Confidence intervals for proportions (2 sided)**

| Confidence level | Sample size (N) | Expected proportion | Target distance from proportion to limit |
|---|---|---|---|
| 0.950 | 250 | 0.25 | 0.054 |
| 0.950 | 300 | 0.25 | 0.049 |
| 0.950 | 325 | 0.25 | 0.047 |
| 0.950 | 400 | 0.25 | 0.042 |
| 0.950 | 250 | 0.30 | 0.057 |
| 0.950 | 300 | 0.30 | 0.052 |
| 0.950 | 325 | 0.30 | 0.050 |
| 0.950 | 400 | 0.30 | 0.045 |
| 0.950 | 250 | 0.35 | 0.059 |
| 0.950 | 300 | 0.35 | 0.054 |
| 0.950 | 325 | 0.35 | 0.052 |
| 0.950 | 400 | 0.35 | 0.047 |

A sample size of 250 to 400 patients produces a 2-sided 95% confidence interval with a distance from the proportion to the limits ranges from 0.042 to 0.059 when the estimated proportion varies from 0.25 to 0.35 (nQuery Advisor version 7.0).

In the HAWK and HARRIER studies, the proportion of naïve nAMD patients treated with brolucizumab who had disease activity at Week 16 was 30% less than for patients treated by aflibercept.

To determine a similar 30% proportion of patients with no disease activity at Week 16 in this pretreated study with a precision of 5% and alpha 5% (2-sided 95% confidence interval of width 11%), a total of 265 patients have to be observed in this study.

Slow recruitment rate was observed in conduct phase of study due to COVID-19, therefore, the sample size was adjusted. The adjusted sample size was significant enough to provide 95% confidence interval.

Considering a dropout rate of 10%, a total of 295 patients will be included.

# 4 Change to protocol specified analyses

Not applicable

# 5 Appendix

## 5.1 Imputation rules

### 5.1.1 Study treatment

The following rules should be used for the imputation of the dose end date for a given study treatment component:

### Scenario 1

If the date of last IVT is completely missing and there is no end of treatment (EOT) page and no death date, the patient is considered as on-going.

The patient should be treated as on-going and the cut-off date should be used as the last dosing date.

### Scenario 2

If the dose end date is completely or partially missing and the EOT page is available:

- Case 1: The dose end date is completely missing and the EOT completion date is complete, then this latter date should be used.
- Case 2: Only year (YYYY) of the dose end date is available and YYYY < the year of EOT date, then use 31DECYYYY.
- Case 3: Only year (YYYY) of the dose end date is available and YYYY = the year of EOT date, then use EOT date.
- Case 4: Both year (YYYY) and month (MMM) are available for dose end date and YYYY = the year of EOT date and MMM < the month of EOT date, then use last day of the Month (MMM)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment.

If the imputed date is < start date of treatment, then use the treatment start date.

Otherwise, use the imputed date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

## 5.1.2 AE date imputation

AE date imputation is based only on a comparison of the partial AE start date to the treatment start date as mentioned in the below.

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 the AE year is less than the treatment year and the AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
   b. Else if the AE year is less than the treatment year and the 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 year is greater than the treatment year and the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
   b. Else if the AE year is greater than the treatment year and the AE month is not missing, the imputed AE start date is set to the month start point (01MONYYYY).
4. If the AE start date year value is equal to the treatment start date year value:
   a. And the AE month is missing or the AE month is equal to the treatment start month, the imputed AE start date is set to one day after treatment start.
   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 greater than the treatment start month, the imputed AE start date is set to the start month point (01MONYYYY).

| | **MON** | **MON < CFM** | **MON = CFM** | **MON > CFM** |
|---|---|---|---|---|
| | **MISSING** | | | |
| **YYYY MISSING** | NULL | NULL | NULL | NULL |
| | Uncertain | Uncertain | Uncertain | Uncertain |
| **YYYY < CFY** | (D) = 01JULYYYY | (C)= 15MONYYYY | (C)= 15MONYYYY | (C)= 15MONYYYY |
| | Before Treatment Start | Before Treatment Start | Before Treatment Start | Before Treatment Start |
| **YYYY = CFY** | (B)= TRTSTD+1 | (C)= 15MONYYYY | (A)= TRTSTD+1 | (A)= 01MONYYYY |
| | Uncertain | Before Treatment Start | Uncertain | After Treatment Start |
| **YYYY > CFY** | (E)= 01JANYYYY | (A)= 01MONYYYY | (A)= 01MONYYYY | (A)= 01MONYYYY |
| | After Treatment Start | After Treatment Start | After Treatment Start | After Treatment Start |
| Before Treatment Start | | Partial indicates date prior to Treatment Start Date | | |
| After Treatment Start | | Partial indicates date after Treatment Start Date | | |
| Uncertain | | Partial insufficient to determine relationship to Treatment Start Date | | |
| **LEGEND:** | | | | |
| (A) | | MAX(01MONYYYY,TRTSTD+1) | | |
| (B) | | TRTSTD+1 | | |
| (C) | | 15MONYYYY | | |
| (D) | | 01JULYYYY | | |
| (E) | | 01JANYYYY | | |

### 5.1.3 Concomitant medication (CM)/procedure (PR) and and medical history (nAMD) date imputation

This algorithm is used when event is the partial start date of the concomitant medication.

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

| | Day | Month | Year |
|---|---|---|---|
| Partial CM Start Date | Not used | MON | YYYY |
| Treatment Start Date (TRTSDT) | Not used | TRTM | TRTY |

The following matrix explains the logic behind the imputation.

| | MON MISSING | MON < TRTM | MON = TRTM | MON > TRTM |
|---|---|---|---|---|
| YYYY MISSING | (C2) Uncertain | (C1) Uncertain | (C1) Uncertain | (C1) Uncertain |
| YYYY < TRTY | (D) Before Treatment Start | (A) Before Treatment Start | (A) Before Treatment Start | (A) Before Treatment Start |
| YYYY = TRTY | (C2) Uncertain | (A) Before Treatment Start | (C1) Uncertain | (B) After Treatment Start |
| YYYY > TRTY | (E) After Treatment Start | (B) After Treatment Start | (B) After Treatment Start | (B) After Treatment Start |

The following table is the legend to the logic matrix.

| Relationship | |
|---|---|
| Before Treatment Start | Partial date indicates CMD start date prior to Treatment Start Date |
| After Treatment Start | Partial date indicates CMD start date after Treatment Start Date |
| Uncertain | Partial date insufficient to determine relationship of CMD start date relative to Treatment Start Date |
| **Imputation Calculation** | |
| (A) | 15MONYYYY |
| (B) | 01MONYYYY |
| (C1 or C2) | IF relative reference start = before treatment start THEN TRTSDT-1<br>ELSE IF relative reference start = ‘ ’ THEN TRTSDT +1 |
| (D) | 01JULYYYY |
| (E) | 01JANYYYY |

**Concomitant Medication End Date Imputation**

If not ongoing then -

Imputed date = date part of CMENDTC, if complete date

Imputed date = min (completion/discontinuation visit date, DEC 31) , if month is missing, (C2, D, E)

Imputed date = min (completion/discontinuation visit date, last day of the Month) , if day is missing. (A, B, C1)

**Concomitant Medication Date Flag**

If not a complete date then

Y - If year of the imputed date is not equal to YYYY else M – If month of the imputed date is not equal to MON else D.

## 5.2 AEs coding/grading

The verbatim term recorded on CRF will be identified as adverse event and will be coded by primary SOC and PT using the MedDRA version 25.1 and above.

## 5.3 Laboratory parameters derivations

The criteria for clinically notable abnormalities are defined as follows:

### Clinically notable elevated values

- Systolic blood pressure of ≥ 140 mmHg (hypertension)
- Diastolic blood pressure of ≥ 90 mmHg (hypertension)
- Pulse rate ≥ 100 bpm (tachycardia)

### Clinically notable below normal values

- Systolic blood pressure of < 90 mmHg (hypotension)
- Diastolic blood pressure of < 60 mmHg (hypotension)
- Pulse rate < 60 bpm (bradycardia)

## 5.4 Statistical models

The below SAS code will used for statistical value.

### Frequency and proportion:

```
proc freq data = <........>;
      tables response_variable/ chisq riskdiff;
run;
```

### Summary Statistics:

Univariate procedure will be used for continuous response.

```
proc univariate data=<........>;
      var response_variable;
      output out=<........> n=_n mean=_mean std=_sd  min=_min median=_med
      max=_max;
run;
```

### 95% CI

```
proc means data=adxe N NMISS CLM  ;
  var aval;
run;
```

### Time to event analysis

```
proc lifetest data=comb1 alpha=0.05 conftype=loglog method=KM alphaqt=0.05
outsurv=survest;
       time AVALW*cnsr(0);
run;
```

## 5.5 Rule of exclusion criteria of analysis sets

**Table 5-1 Protocol deviations that cause patients to be excluded**

| Deviation ID | Description of Deviation | Exclusion in Analyses | Severity code |
|---|---|---|---|
| INCL01 | Signed informed consent not obtained | Excluded from FAS and PPS | 1 |
| INCL02 | Age less than 50 year | Included in everything | 0 |
| INCL03 | No CNV lesions or >18M | Excluded from FAS and PPS | 1 |
| INCL04a | >1 previous anti-VEGF | Excluded from FAS and PPS | 1 |
| INCL04b | <3 previous aVEGF injections | Excluded from FAS and PPS | 1 |
| INCL04c | Prev aVEGF intvl out of range | Included in everything | 0 |
| INCL05 | No residual fluid | Excluded from FAS and PPS | 1 |
| INCL06 | Study eye BCVA out of range | Excluded from PPS | 2 |
| EXCL01 | Active inflammation/infection | Excluded from PPS | 2 |
| EXCL02 | Fellow eye ocular disease | Included in everything | 0 |
| EXCL03 | History of IOI | Included in everything | 0 |
| EXCL04 | Poor quality images | Included in everything | 0 |
| EXCL05 | Study eye atropathy or fibrosis | Included in everything | 0 |
| EXCL06 | Study eye lesion area ≥50% | Included in everything | 0 |
| EXCL07 | Study eye concomitant condition | Included in everything | 0 |
| EXCL08 | Study eye macula damage | Included in everything | 0 |
| EXCL09 | Study eye vitreous hemorrhage | Included in everything | 0 |
| EXCL10 | Study eye uncotrolled glaucoma | Included in everything | 0 |
| EXCL11 | Study eye aphakaia | Included in everything | 0 |
| EXCL12 | Other trt in study eye | Excluded from PPS | 2 |
| EXCL13 | Steroids in study eye | Included in everything | 0 |
| EXCL14 | Prior keratoplasty/vitrectomy | Included in everything | 0 |
| EXCL15a | Study eye surgery | Included in everything | 0 |
| EXCL15b | Study eye laser photocoagul | Included in everything | 0 |
| EXCL15c | Study eye macular surgery | Included in everything | 0 |
| EXCL16 | Previous laser treatment | Included in everything | 0 |

| Deviation ID | Description of Deviation | Exclusion in Analyses | Severity code |
|---|---|---|---|
| EXCL17 | previous brolucizuamb trt study eye | Excluded from FAS and PPS | 1 |
| EXCL18 | ESRD | Included in everything | 0 |
| EXCL19 | Systemic drugs toxic to eye | Included in everything | 0 |
| EXCL20 | Participation in another study | Excluded from PPS | 2 |
| EXCL21 | Systemic anti-VEGF therapy | Included in everything | 0 |
| EXCL22 | Stroke or myocardial infarction | Included in everything | 0 |
| EXCL23 | Uncontrolled blood pressure | Included in everything | 0 |
| EXCL24 | Medical condition impact | Included in everything | 0 |
| EXCL25 | Malignancy | Included in everything | 0 |
| EXCL26 | Hypersensitivity | Included in everything | 0 |
| EXCL27 | Pregnant or nursing woman | Included in everything | 0 |
| EXCL28 | WOCP | Included in everything | 0 |
| EXCL29 | Minors/protected adults | Excluded from PPS | 2 |
| COMD01 | Prohibited medication/procedures | Included in everything | 0 |
| COMD02 | Non-permitted steroid use | Included in everything | 0 |
| TRT01 | Trt > 3 days after inj visit | Included in everything | 0 |
| TRT02 | Missed injection visit | Included in everything | 0 |
| TRT03 | Wrong IP/volume administered | Included in everything | 2 |
| TRT04 | IVT interval<than 21 days | Included in everything | 0 |
| TRT05 | TRT admin prior effic/safty eval | Included in everything | 0 |
| TRT06 | COVID-19 Drug supply change | Included in everything | 0 |
| TRT07 | COVID-19 Treatment not given | Included in everything | 0 |
| TRT08 | Missed Injection loading phase | Excluded from FAS and PPS | 1 |
| TRT09 | Missed Injection | Included in everything | 0 |
| TRT10 | No Disease acty bt INJ is given | Included in everything | 0 |
| TRT11 | Treatment given at EOS | Included in everything | 0 |
| TRT12 | anti-VEGF therapy during tria | Included in everything | 0 |
| WITH01 | Withdrew consnt nt discontinued | Excluded from FAS and PPS | 1 |
| OTHER01 | Missed mandatory visit | Excluded from PPS | 2 |
| OTHER02 | Subject rescreened > once | Excluded from PPS analysis | 0 |
| OTHER03 | New ICF is missing-rescreened | Excluded from FAS and PPS | 1 |
| OTHER04 | Rescrn >14days w/o scr proc | Included in everything | 0 |
| OTHER05 | Odysight used w/o consent | Included in everything | 0 |
| OTHER06 | Temp excursion IP administered | Included in everything | 0 |
| OTHER07 | SAE not reported | Included in everything | 0 |
| OTHER08 | Crit met to failure | Included in everything | 0 |
| OTHER09 | The patient done rescreening | Included in everything | 0 |
| OTHER10 | COVID-19 Missed visit | Included in everything | 0 |
| OTHER11 | COVID-19 Visit not at site | Included in everything | 0 |
| OTHER12 | COVID-19 Assessment changed | Included in everything | 0 |

| Deviation ID | Description of Deviation | Exclusion in Analyses | Severity code |
|---|---|---|---|
| OTHER13 | COVID-19 Discontinuation | Included in everything | 0 |
| OTHER14 | Visit window > 7 days | Included in everything | 0 |
| OTHER15 | Efficacy assessment not done | Excluded from PPS | 2 |
| OTHER16 | Safety assessment not done | Included in everything | 0 |
| OTHER17 | BCVA not done correctly | Included in everything | 0 |
| OTHER18 | Trt regimen wrongly adjusted | Included in everything | 0 |
| OTHER19 | Vital signs/safety call not done | Included in everything | 0 |
| OTHER20 | Imaging analyzed after WoC | Included in everything | 0 |

**Table 5-2 Patient Classification**

| Analysis Set | Severity codes that cause a subject to be excluded |
|---|---|
| ENR | NA |
| FAS | 1 |
| PPS | 1, 2 |
| SAF | NA |

# 6 Reference

[HAWK] ClinicalTrials.gov. Identifier NCT02307682. Available at https://clinicaltrials.gov/ct2/show/NCT02307682 (link is external). Accessed November 2017.

[HARRIER] ClinicalTrials.gov. Identifier NCT02434328. Available at https://clinicaltrials.gov/ct2/show/NCT02434328 (link is external). Accessed November 2017.

NOVARTIS

Clinical Development

RTH258A/Brolucizumab

CRTH258AFR03 / NCT04264819

# A one-year, single-arm, open-label, multicenter study assessing the effect of brolucizumab on disease control in adult patients with suboptimal anatomically controlled neovascular age-related macular degeneration (SWIFT)

## Interim Analysis Statistical Analysis Plan (IA-SAP)

| | |
|---|---|
| Author: | Statistician, [redacted] |
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| Date | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|
| *18-10-2022* | *Creation of initial version* | *N/A - First version* | *NA* |
| *20-01-2023* | *Creation of addendum V.0* | | |
| | *Added imputation rule for medical history* | *Added imputation rule for medical history* | *Section 5.1.4* |
| | *Added section for confirmed SRC event* | *Added the section for safety review committee* | *Section 5.3* |
| | *Added derivation term for AESI* | *Derivation term for AESI added* | *Section 5.5* |

## Table of contents

## List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| ATC | Anatomical Therapeutic Classification |
| BCVA | Best-Corrected Visual Acuity |
| CNV | Choroidal Neovascularization |
| [redacted] | [redacted] |
| CI | Confidence Interval |
| CRO | Contract Research Organization |
| CSFT | Central Sub-Field Retinal Thickness |
| CRT | Central Retinal Thickness |
| CSR | Clinical Study report |
| ENR | Enrolled set |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| FAS | Full Analysis Set |
| ECS | Edit checks specification |
| eCRF | Electronic Case Report Form |
| IA | Interim Analysis |
| IA-SAP | Interim Analysis Statistical Analysis Plan |
| ICF | Informed Consent Form |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| IVT | Intravitreal |
| KM | Kaplan-Meier |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| nAMD | Neovascular Age-Related Macular Degeneration |
| OCT | Optical Coherence Tomography |
| PK | Pharmacokinetics |
| PD | Protocol deviation |
| PDS | Programming Datasets Specifications |
| PPS | Per-Protocol Set |
| PT | Preferred Term |
| q12w | Every 12 Weeks |
| SAP | Statistical Analysis Plan |
| SAF | Safety analysis set |
| SD-OCT | Spectral Domain Optical Coherence Tomography |
| SOC | System Organ Class |
| SRC | Safety Review committee |
| TFL | Tables, Figures, Listings |
| TtC | Treat-to-Control |
| WHO | World Health Organization |

# 1 Introduction

The purpose of this Interim Analysis Statistical Analysis Plan (IA-SAP) is to describe the implementation of the statistical methods for all safety and efficacy analyses planned (Protocol-Section 12) in the clinical protocol (CRTH258AFR03, version no: 05, release date 05Apr2022). This document will be used to prepare the statistical results and the corresponding Interim Clinical Study Report (iCSR).

The results of the interim analysis may either be submitted for publication in the form of a manuscript or poster format to a national or international conference.

This interim analysis is planned for the study. As defined in the study protocol, an interim analysis is planned to be performed when all enrolled patients have completed Week 16 evaluations to allow data collection prior to the end of the study period.

This document will be stored in the CREDI folder: RTH258AFR03/Administrative Files (study level)/RAP or RAMP Meeting.

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

Data will be analyzed by Novartis and/or the designated Contract Research Organization (CRO). Statistical software SAS version 9.4 or higher will be used for generating TFLs.

## 1.1 Study design

This is a prospective, single-arm, open-label, multicenter study to evaluate the efficacy and safety of brolucizumab 6 mg in pretreated suboptimal anatomically controlled patients with nAMD.

Approximately 295 adult patients will be screened and included (10% dropout rate expected) in France. Data up to Week 16 will be analyzed in this Interim Analysis (IA).

The cutoff date for the IA will be 20-Oct-2022.

Before inclusion in the study, a patient must have a washout period of 4 weeks to 8 weeks (from 26 to 62 days inclusive) from the last administration of a licensed anti-VEGF drug (i.e. Lucentis®, Eylea®).

The maximum study duration for 1 patient is 48 to 50 weeks, according to the patient schedule.

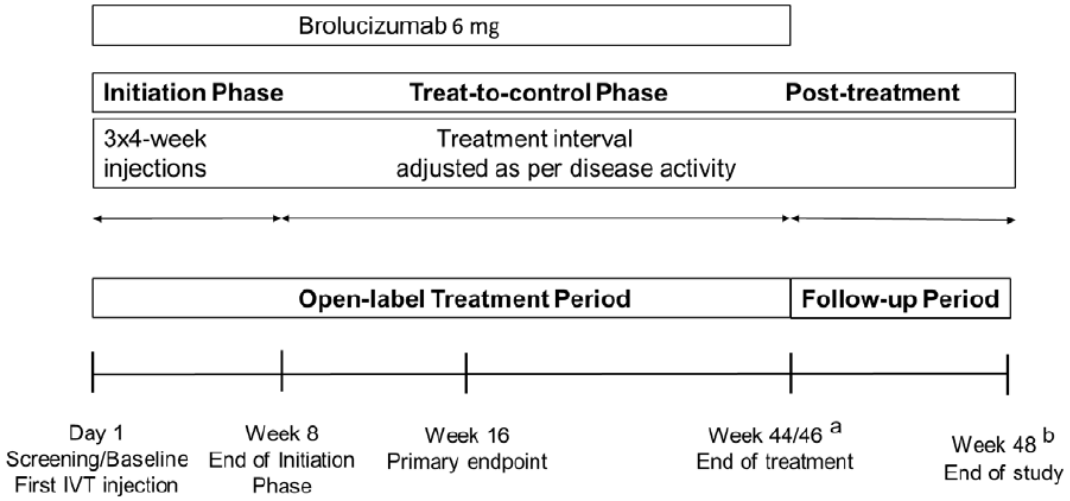
The study consists of 2 periods (Figure 1-1):

- Open-label Treatment Period (from Screening/Baseline (Day 1) to Week 44 or Week 46 according to patient schedule)
- Follow-up Period (from Week 44 to Week 48 or from Week 46 to Week 50 according to patient schedule)

According to the patient treatment schedule, the last treatment can be at Week 44 or Week 46. If the last treatment visit is at Week 46, the End-of-study visit will be at Week 50 (at least 4 weeks after the last injection) instead of at Week 48.

Patients will require attending 5 mandatory study visits: Screening/Baseline (Day 1), Weeks 4, 8, 16, and 48/50. The other visit time points will depend on the injection regimen of the patient.

**Figure 1-1 Study design**




a End of treatment: Week 38/40/42/44/46 according to treatment schedule.
b End of study: at least 4 weeks after the end of treatment. For patients receiving the last IVT at Week 46, the EOS Visit will be at Week 50, 4 weeks following their last treatment.

The fellow eye will be treated at the discretion of the Investigator.

The Screening Visit and the Baseline Visit are the same visit in this study. Patients will receive 3 initial doses every 4 weeks (Day 1, Week 4 and Week 8). From Week 8, based on Investigator's judgment of visual and/or anatomic outcomes, the injection interval can be maintained on Q4 regimen or extended by 4 weeks at a time if there is no disease activity, as per Investigators decision, e.g. no change in visual acuity and in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.). If disease activity recurs, the injection interval should be shortened accordingly by 4 weeks at a time or to a minimal interval of 4 weeks.

Patients who show disease activity at any of visits after week 8 will be adjusted to treatment interval and will remain on this interval until the end of the study at Week 48/50.

At the Investigator's discretion, in case of interval extension, inspection visits can be performed at the midterm of the interval extension, e.g. 6 weeks after the last injection when the injection interval is extended from 4 weeks to 8 weeks. If there is no disease activity in the study eye at the inspection visit, as assessed by the Investigator, no treatment will be administered at this inspection visit; the next visit and injection will take place 2 weeks later, i.e. 8 weeks after the previous study treatment. If disease activity is observed by the Investigator in the study eye at the inspection visit, the study treatment will be administered by the Investigator; the injection interval will be reduced to 4 weeks and the next visit will be 4 weeks after the inspection visit. Similarly, inspection visits 10 weeks and 14 weeks after the last injection can be performed when the injection interval is extended from 8 weeks to 12 weeks and from 12 weeks to 16 weeks, respectively.

## 1.2 Study objectives and endpoints for interim analysis

The study objectives and endpoints as per protocol are presented in Table 2-1; those that are being assessed for the IA are marked (with ‡) with relevant flag denoting assessment at Week 16 as applicable.

This IA is planned to evaluate applicable efficacy and safety endpoints for patients who have completed Week 16 evaluations.

**Table 2-1 Objectives and related endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary objective** | **Endpoint for primary objective** |
| • To evaluate the effect of brolucizumab 6 mg on disease control | • Proportion of patients with no disease activity at Week 16 ‡ |
| **Secondary objectives** | **Endpoints for secondary objectives** |
| • To evaluate the long-term effects of brolucizumab 6 mg on disease control | • Proportion of patients with no disease activity at Week 48 § |
| • To evaluate the effect of brolucizumab 6 mg on anatomical parameters | • Change from Baseline in CFST as assessed by OCT over time up to Week 48 ‡<br>• Absence of IRF, SRF, and sub-RPE fluid as assessed by OCT over time up to Week 48 ‡<br>• Proportion of patients with a dry retina (neither IRF nor SRF) up to Week 48 ‡ |
| • To evaluate the durability of brolucizumab 6 mg | • Distribution of the last interval with no disease activity up to Week 48 §<br>• Distribution of the maximal intervals with no disease activity up to Week 48 § |
| • To evaluate functional outcomes | • Average change in BCVA from Baseline up to Week 48 ‡ |
| • To assess the safety and tolerability of brolucizumab 6 mg | • Incidence of AEs (serious and non-serious) up to Week 48 ‡ |

[redacted]

§ These endpoints will not be assessed for the IA.

‡ These endpoints will be assessed for the Week 16 timepoint only for the IA.

AEs=adverse events, BCVA=best corrected visual acuity, [redacted] CSFT=central sub-field retinal thickness, [redacted] IRF=intraretinal fluid, OCT= optical coherence tomography, [redacted] SRF= subretinal fluid.

# 2 Statistical methods

## 2.1 Data analysis general information

Patients who consented and meet all the inclusion and none of the exclusion criteria was screened to evaluate eligibility. After confirmation of eligibility, patients were included and treated with brolucizumab 6 mg and data will be analyzed.

All categorical data will be presented in terms of frequencies and percentages. Summaries of continuous data will be presented in terms of n (the number of non-missing data points), mean, standard deviation (SD), median, lower and upper quartiles, minimum and maximum, the number of missing data points.

For descriptive statistics, the following rules for number of decimal places will be applied: arithmetic mean, median, lower quartile and upper quartile to 1 more decimal places than the raw data; minimum and maximum to the same number of decimal places as the raw data and SD, SE and 95% CI to 2 more decimal places than the raw data. Percentages will be presented to 1 decimal place.

### 2.1.1 General definitions

**Study treatment**: This is a single-arm study and all patients will be treated with brolucizumab 6 mg. Three loading injections (at Screening/Baseline/Day 1, Week 4 and Week 8), followed by a Treat-to-Control (TtC) regimen phase based on disease activity from Week 8 up to Week 44/46 (according to the treatment regimen). The investigator can individualize treatment intervals depending on disease activity, to adjust patient's injection regimen.

**Study treatment start and end date**: Study treatment start date is defined as the first date study treatment is administered and recorded on the Treatment Administration Record (DAR) Electronic Case Report Form (eCRF) page. Similarly, study treatment end date is defined as the last date of study treatment is administered and recorded on the Study Treatment Completion eCRF page.

Generally, study Day 1 is considered as the day of inclusion of the patient. However in this study, treatment is intended to be administered on the same day or if this is not possible, within 3 days after the day of inclusion of the patient.

Study day will be calculated as ((event date – study treatment start date) + 1 day) for events that occurred on or after study treatment start date (e.g. visit, AEs). For events prior to study treatment start date (e.g. time since diagnosis), study day will be negative and calculated as (event date – study treatment start date).

**Baseline and post-baseline**: Baseline value refers to the value of the last non-missing measurement collected prior to administration of the first dose of study treatment (Screening or Baseline visit). [redacted]

[redacted]

A "post-baseline" value refers to a measurement taken after the first dose of study treatment. When assessments and treatments take place on the same day, treatment must occur after completion of the efficacy assessments and pre-injection safety measures (tonometry, slit lamp [redacted]). If study visit assessments and the corresponding treatment occur on separate days, a repeat safety check-up will be performed prior to treatment of the eye and results documented in the source documents. More post-baseline safety measurements will be recorded in source document; visit window will be applied to OCT and IVT visits.

**Change from Baseline**: The difference of measure between post-baseline and Baseline is called change from Baseline.

**Percent change from Baseline**: The percent change from baseline will be calculated as below: ((post-baseline value – Baseline value) /Baseline value)*100.

**Proportion:** A proportion refers to the fraction of the total that possesses a certain attribute. In this study attribute is disease free activity.

**Disease control:** When patients will have no disease activity after taking study treatment then patient will be consider as disease control.

**On-treatment period**: The on-treatment period lasts from the date of first administration of study treatment to 28 days after the date of the last actual administration of any study treatment.

**Treatment duration:** The maximum planned duration of treatment for each patient is 44 to 46 weeks in accordance with the designated treatment regimen. Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the patient or the investigator.

**Treatment discontinuation**: When patients discontinue study treatment but continue in the study, the efficacy data will be used at the time the patient stopped study treatment.

**Last interval**: The last treatment interval (defined by the investigator) before Week 48.

**Maximum interval**: The longest interval of treatment reached by the patient over the study period.

**Event for no disease activity:** When patients will be with no disease status as per investigator decision after last dose in initiation phase then the patients will consider as event for no disease activity. If patients with active disease status or early discontinue then patients will be considered as censored for disease activity.

**Dry retina:** Absence of fluid (IRF/SRF/ sub-RPE) will be considered as dry retina.

**Event for dry retina**: When patients have absence of fluid then it will be considered as an event of dry retina. If patients have a presence of fluid before/at EOS or early discontinuation then will be censored.

**Study eye and fellow eye**: The Investigator selects the eye with the worse BCVA at Screening as the study eye if both eyes are eligible as per the inclusion and exclusion criteria, unless the investigator deems as a study eye more appropriate to select the eye with better BCVA, based

on medical reasons or local ethical requirements. If both eyes are eligible as per the inclusion and exclusion criteria, then it is recommended to select the right eye as the study eye.

The fellow eye will be examined only at Screening/Baseline and Week 48/EOS visits. Only best corrected near visual acuity (BCNVA) for the fellow eye will be analyzed. It is not requested for the purpose of this study to do any self-assessment measure of the fellow eye.

**Disease activity criteria:** Disease activity criteria will be assessed by the investigator based on whether nAMD is still active or has been re-activated. Guidance for the investigator is as follows (disease is active if at least one of the following criteria is observed by the investigator):

- BCVA decrease ≥ 5 letters from the best value since Baseline due to disease activity.
- Any significant increase in CRT (based on investigator assessment).
- Retinal hemorrhage.
- Intraretinal fluid or SRF due to disease activity (degenerative cysts allowed).
- Increase of sub-RPE fluid.

These criteria are for guidance only, the investigator may define disease activity based on his/her own assessment.

[redacted]

## 2.2 Visit windows for data analysis

Visit windows will be used for the data analysis, as per the planned visits in the protocol. During the q4w/q8w/q12w phase, i.e., from Week 16 to Week 44, the treatment visit intervals will be determined by the investigator, based on the patient's disease activity.

For the interim analysis data collected up to Week 16 for the efficacy analysis and all safety data collected up to the interim data-cutoff for the safety analysis.

**Table 2-1 Assessment windows for scheduled visits**

| Analysis Visit | Week | Scheduled Day | Visit Window |
|---|---|---|---|
| Screening/Baseline | BL | 1 | -14 days to Day 1* |
| Week 4 | 4 | 28 | Day 22 – 34 |
| Week 8 | 8 | 56 | Day 50 – 62 |
| Week 12 | 12 | 84 | Day 78 – 90 |
| Week 14 | 14 | 98 | Day 92 – 104 |
| Week 16 | 16 | 112 | Day 106 – 118 |
| Week 18 | 18 | 126 | Day 120 – 132 |
| Week 20 | 20 | 140 | Day 134 – 146 |
| Week 22 | 22 | 154 | Day 148 – 160 |
| Week 24 | 24 | 168 | Day 162 – 174 |
| Week 26 | 26 | 182 | Day 176 – 188 |
| Week 28 | 28 | 196 | Day 190 – 202 |
| Week 30 | 30 | 210 | Day 204 – 216 |
| Week 32 | 32 | 224 | Day 218 – 230 |
| Week 34 | 34 | 238 | Day 232 – 244 |
| Week 36 | 36 | 252 | Day 246 – 258 |
| Week 38 | 38 | 266 | Day 260 – 272 |
| Week 40 | 40 | 280 | Day 274 – 286 |
| Week 42 | 42 | 294 | Day 288 – 300 |
| Week 44 | 44 | 308 | Day 302 – 314 |
| Week 46 | 46 | 322 | Day 316 – 328 |
| Week 48 | 48 | 336 | Day 330 – 342 |
| Week 50 | 50 | 350 | Day 344 – 356 |

* Baseline measurement before the first treatment administration.

The number of weeks between visits will vary depending on the disease activity and length of intervals between injections as determined by disease activity assessment. Study treatment at the optional inspection visits (6 weeks after the last injection when the interval is extended from 4 weeks to 8 weeks, 10 weeks after the last injection when the interval is extended from 8 weeks to 12 weeks, and 14 weeks from the last injection when the interval is extended from 12 weeks to 16 weeks) is at the discretion of the Investigator based.

According to the patient treatment schedule, the last treatment can be at Week 44 or to Week 46. If the last treatment visit is Week 46, the end of study visit will be at Week 50 (at least 4 weeks after the last injection) instead of Week 48.

If study visit assessments and the corresponding treatment occur on separate days, a repeat safety check-up should be performed prior to treatment of the eye and results documented in the source documents. If any safety concern arises related to the study eye that, in the opinion of the investigator, may be further impacted by the study treatment or injection procedure,

treatment needs to be cancelled. Injections are contraindicated in patients with active intraocular or periocular infections and in patients with active intraocular inflammation (IOI); therefore, the investigators must verify that these conditions are not present in the study eye prior to every injection. Any AEs must be recorded in the eCRF.

The injection procedure for brolucizumab will be performed according to local clinical practice. Injections will be administered by the investigator.

Data collected at unscheduled visits will not be used in 'by-visit' tabulations or graphs and will be presented in listings.

## 2.3 Analysis sets

**The Enrolled Set (ENR)** includes all patients who signed an ICF and are assigned patient numbers.

**The Safety Set (SAF)** includes all patients who received at least one IVT injection of study treatment.

**The Full Analysis Set (FAS)** will be the same as the Safety Set in this study without protocol deviation with impact and will be used as primary population to analyze the efficacy endpoints.

**The Per-Protocol Set (PPS)** is a subset of patients in the FAS without PDs with impact. The list of PD criteria will be provided in edit checks specification (ECS) document.

## 2.4 Timepoints of interest

Demographics and Baseline characteristics will be summarized at Visit 1. All other parameters will be summarized based on the following timepoints: Baseline, Week 16 and other visits wherever data is available until Week 16 (e.g. Week 4, Week 8 and Week 12).

## 2.5 Patient disposition, demographics and other baseline characteristics

### 2.5.1 Patient disposition

The FAS will be used to prepare a summary and ENR will be used for listing of patient disposition.

The number and percentage of patients who completed the study and discontinued from the study till Week 8 and till Week 16 will be summarized with reasons for premature discontinuation for the FAS. In addition, the number of screen failures with reasons will be presented for all screened patients. The patient identification number and whether patients completed or discontinued from the study will be listed, with date of last dose and primary reason for premature discontinuation.
Subjects who sign an informed consent form and who are subsequently found to be ineligible to enroll will be considered a screen failure. Number and percent of subjects who are screen failures (i.e. were not enrolled) will be presented. Number (%) of patients who were enrolled (based on ICF date).

- Number (%) of patients who were enrolled.

- Number (%) of patients who enrolled and treated.
- Number (%) of patients who enrolled but not treated.

A subject is considered to have completed Week 8 if he/she did not discontinue study prior to the Week 8 visit. Discontinuation at Week 8 with exit visit assessment performed is considered as completed Week 8.

- Number (%) of patients who completed Week 8 dosing.
- Number (%) of patients who discontinued study medication before or on week 8 dosing.
- Primary reason for discontinued study medication before or on week 8 dosing.

A subject is considered to have completed the study Week 16 if he/she did not discontinue study prior to the Week 16 visit. Discontinuation at Week 16 with exit visit assessment performed is considered as completed for the Week 16 analysis.

- Number (%) of patients who are on-treatment (completed) at week 16.
- Number (%) of patients who discontinued before or on week 16.
- Primary reason for discontinued before or on week 16.
- Number (%) of patients who are on-treatment (ongoing) after week 16.

A separate summary of disposition and listing for rescreened patients will be presented for ENR.

Study treatment will be discontinued under the following circumstances:

- Adverse event which could lead to study treatment discontinuation
- Death
- Lost to follow-up
- Physician decision
- Pregnancy
- Progressive disease
- Protocol deviation
- Study terminated by sponsor
- Technical problem
- Patient decision
- New therapy for study indication
- Lack of efficacy
- Use of prohibited treatment
- Any situation in which study participation might result in a safety risk to the patient

### 2.5.2 Protocol deviation

The number and percentage of patients with protocol deviations will be tabulated by category and deviation for the FAS. Patients with protocol deviations will be listed with date and study day of occurrence, deviation and severity codes for the ENR.

The number of patients included in each analysis set will be tabulated for all screened patients. Reasons for exclusion from analysis sets will be tabulated for the ENR. Patient exclusion from analysis sets will be listed for all patients with reasons for exclusion (i.e., both protocol and non-protocol deviations).

### 2.5.3 Demographic characteristics

Demographic and Baseline characteristics will be listed and summarized descriptively overall patients on the FAS and the SAF.

The following demographic and vital signs variables collected in the eCRF at Baseline will be summarized:

1. Sex (Male, Female)
2. Age (in years)
3. Age category (< 50, 50 - 65, 65 - 75, 75 - 85, ≥ 85)
4. Study eye (Left [OS], Right [OD])
5. Vital signs (sitting systolic/diastolic blood pressure [mmHg], sitting pulse rate [bpm])

### 2.5.4 Baseline characteristics

The following Baseline characteristics collected in the eCRF at Baseline will be summarized for study eye and fellow eye (wherever applicable):

- Study eye status at nAMD diagnosis (date of diagnosis, BCVA at diagnosis, CSFT at diagnosis)
- Time since nAMD diagnosis
- Time since nAMD diagnosis (month) (< 2.5 - 5, 5- 8, 8-11, 11-18 )
- Unilateral versus bilateral nAMD
- BCVA
- BCVA (≤55, 56 - 70, ≥71)
- BCVA categories (Count fingers, Hand motion, Light perception, No light perception) in case BCVA score is 0

- SD-OCT (analyzed by Duke [CRC])
  1. Lesion type (only at Baseline) (type 1, type 2, type 3)
  2. CSFT (µm)
  3. Baseline CSFT (< 300, ≥ 300 - 450, ≥ 450 - < 650, ≥ 650 [µm])
- Presence of fluid (Yes/No)
  1. Intraretinal fluid
  2. Subretinal fluid
  3. Sub-RPE fluid
- Volume ($mm^3$) and height (µm) of each fluid (in case of presence)
  1. Intraretinal fluid
  2. Subretinal fluid
  3. Sub-RPE fluid
- In case of sub-RPE/PED: nature: serious PED/fibrovascular PED / mixed PED
  1. CNV lesion area (at the biggest surface) ($mm^2$/$µm^2$)
- Ophthalmic abnormalities (Yes, No)
- Disease activity assessment (Present)
- History of primary diagnosis:
  1. Disease (Neovascular Age-Related Macular Degeneration)
  2. Age of diagnosis
  3. Eye (OD, OS)
  4. Ongoing (Yes, No)
- History or evidence of the following in the study eye within the 90-day period prior to Screening/Baseline:
  1. Intraocular or refractive surgery
  2. Previous panretinal and peripheral laser photocoagulation

3. Previous macular surgery or other intraocular surgical intervention

- Concomitant medication at Baseline
- Medical history
- Co morbidities
- Current medical condition

### 2.5.5 Relevant medical history/current medical condition

Medical history/current medical conditions (general and ocular) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. History/conditions will be summarized for the FAS by primary system organ class (SOC), preferred term (PT) by eye (study eye and fellow eye). Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study. The ongoing medical history will be considered as co morbidities. The co-morbidities will be summarized and listed separately for eye (study eye and fellow eye).

## 2.6 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

### 2.6.1 Study treatment exposure

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

The following summaries will be presented:

1. Summary statistics of number of injection (n, q1, median, q3, min and max) will be provided.
2. Number of injections (n, q1, median, q3, min and max) before or at Week 8 and greater than Week 8.
3. Number of injections (n, q1, median, q3, min and max) before or at Week 16 and greater than Week 16.
4. Number of patients with injection category (1 injection, 2 injections up to the maximum number of injections) from Baseline to the end of the treatment period (Week 44/46) will be presented.
5. Treatment exposure by visit: The number and percentage of patients who received injections, missed a treatment and missed visits will be presented by visit.
6. The number of time the injection interval shorting and the number of time the injections interval increasing.
7. Summary statistics (n, mean, std, q1, median, q3, min and max) for overall duration will be provided.

The number and percentage of patients for changes in brolucizumab 6 mg treatment patterns over time (i.e. treatment interval adjustments, interruptions or permanent discontinuations) along with reasons, will be summarized. Discontinuations and primary reasons for treatment and/or study discontinuation will also be described.

Exposure data will be summarized on the SAF. The exposure data will be listed on the FAS.

### 2.6.2 Prior, concomitant medication and procedures

Each medication/therapies has the start and end dates recorded on the eCRF. Prior medications/ procedures are defined as those medications/procedures which were taken/done and stopped prior to the first dose of study treatment. Concomitant medications/procedures are defined as any medication/procedures given at least once between the day of first dose of study treatment and the last day of study visit, including those which were started pre-baseline and continued into the treatment period. The below summary tables will be reported:

- Prior medication/procedures
- Concomitant medications/procedures which started prior to first dose of study treatment
- Concomitant medications/procedures which started on/after first of study treatment

All prior and concomitant medications will be coded using the most recent version of the WHO drug dictionary. All concomitant medications/procedures (general and ocular) will be listed and summarized in alphabetic order according to Anatomical Therapeutic Chemical (ATC) classification system and PT. Tables will also show the overall number and percentage of patients receiving at least one treatment of a particular ATC.

For prior and concomitant ocular medications, as well as ocular procedures performed during the study, separate tabular summaries will be prepared for the study eye and the fellow eye. A listing of all prior and concomitant medications and concomitant procedures will be provided.

For AESIs, a separate summary of prior and post aVEGF procedures will be provided.

For handling of missing or incomplete start and end dates, see Appendix 5.1.3 of this document.

All summaries will be performed on the Safety set.

### 2.6.3 Prior and concomitant surgeries and procedures

All prior and concomitant surgeries and procedures indications will be summarized and listed by category (general, ocular) and eye (study and fellow).

For handling of missing or incomplete start and end dates, see Appendix 5.1.3 of this document.

All summaries will be performed on the Safety set.

### 2.6.4 History of anti–VEGF therapy

The anti – VEGF therapy will be collected in CRF at Baseline. All recent anti – VEGF therapy will be listed and summarized. Table will present nature of the previous antiVEGF, summary statistics for total number of previous IVTs, number of patients and percentages of previous antiVEGF (3,4,5,6...), summary statistics for time since first antiVGEF, time since last antiVEGF along with below interval summary statistics.

1. Inclusion vs last antiVEGF
2. Last antiVEGF and second antiVEGF
3. Second last antiVEGF and third last antiVEGF

The listing will include nature of the previous antiVEGF, date of the last anti VEGF treatment, interval of the last anti VEGF treatment, date of the second last anti VEGF treatment , interval of the second last anti VEGF treatment, date of the third last anti VEGF treatment, interval of the third last anti VEGF treatment, date of the first anti VEGF treatment, interval of the first anti VEGF treatment and total number of anti VEGF treatments (including the last one).

The below characteristics prior to first antiVEGF will be summarized.

1. The summary statistics of BCVA and CSFT.

2. Number and percentage of IRF, SRF and Sub-RPE.

3. Summary statistics of height for IRF, SRF, Sub-RPE (if available).

The listing of above last antiVEGF characteristics will include patients identification number, therapies name and date of therapy, BCVA, CSFT, IRF, SRF, Sub-RPE and height for IRF, SRF, Sub-RPE (if available). The above analysis will be performed on the Safety set.

## 2.7 Analysis of the primary objective

### 2.7.1 Primary endpoint

The primary objective of this study is to evaluate the effect of brolucizumab 6 mg on disease control. The primary efficacy endpoint is the proportion of patients with no disease activity at Week 16 in the study eye.

Estimation for the proportion of disease control involves only calculating the ratio of successes. In this study

Event: 1= no disease activity (disease control)

0= disease activity (failure)

Count: Frequency or number of patients with no disease activity (disease control) at Week 16.

Proportion: Number of patients with no disease activity (disease control) at Week 16/Total number of patients in the FAS.

The number of disease control patients at Week 16, total number of evaluable patients, percentage of disease control and 95% confidence interval (CI) using the Clopper-Pearson method will be provided.

Sensitivity analysis will be performed for the primary endpoint using last observation carried forward (LOCF) method and considering disease activity for missing data at Week 16.

The above analysis will be done on the FAS and only on the study eye.

The analysis will be performed on the PPS, if there is more than a 10% difference in patients, between FAS and the PPS.

### 2.7.2 Supportive analyses

Subgroup analysis according to patient characteristics, like gender (male, female), age class (< 50, 50 - 65, 65 - 75, 75 - 85, ≥ 85), Baseline fluids type (IRF, SRF, both), number of previous antiVEGF injections (3, 4 – 6, 7 - 9 and ≥ 10), interval (in week) since previous antiVEGF

injection (4, 5, 6, 7, 8 and >8), and time since nAMD diagnosis (2.5 – 5 month, 5 - 8 months, 8 - 11 months, 11 - 18 months and > 18 months).

## 2.8 Analysis of secondary efficacy objectives

### 2.8.1 Secondary endpoints

#### 2.8.1.1 Long-term disease activity criteria

Not applicable for IA.

#### 2.8.1.2 Optical coherence tomography (OCT)

The following secondary efficacy parameters based on OCT will be analyzed as given below.

##### 2.8.1.2.1 Central sub-field retinal thickness (CSFT)

The summary statistics of central sub-field retinal thickness (CSFT) measured by OCT for nAMD patients, change and percentage change from Baseline in CSFT will be presented by visit along with first anti VEGF Treatment CSFT.

The number and percentage of patient with CSFT category (< 300, ≥ 300 - 450, ≥ 450 - < 650, ≥650 [µm]) will be presented by visit along with first anti VEGF Treatment CSFT.

The above analysis will be done on the FAS and only on the study eye.

##### 2.8.1.2.2 Presence of fluid (Yes/No)

The number and percentage of patients with fluid as shown below will be presented by visit along with first anti VEGF Treatment.

1. Intraretinal fluid
2. Subretinal fluid
3. Sub-RPE fluid
4. Without any fluid (IRF/SRF/sub-RPE)
5. In case of sub-RPE/PED: nature: (serious PED/fibrovascular PED/mixed PED)

Volume ($mm^3$) and height (µm) of intraretinal fluid, subretinal fluid and/or sub-RPE fluid will be presented the summary statistics (n, mean, std, median, min and max) by visit, if available.

The above analysis will be done on the FAS and only on the study eye.

##### 2.8.1.2.3 Dry retina

The proportion of patients without both fluids (IRF and SRF), without IRF, without SRF, without sub-RPE will be presented by visit, separately, up to Week 16

The 95% confidence interval (CI) for proportion using the Clopper-Pearson method will be provided by visit and overall.

The above analysis will be done only on the FAS and on the study eye.

#### 2.8.1.2.4 Time to dryness

Not applicable for IA.

#### 2.8.1.2.5 Maximum duration of dryness

Not applicable for IA.

### 2.8.1.3 Durability

#### 2.8.1.3.1 Last interval

Not applicable for IA.

#### 2.8.1.3.2 Maximal interval

Not applicable for IA.

### 2.8.1.4 Function outcomes (Best Corrected Visual Acuity (BCVA))

Summary statistics (n, mean, std, median, min and max) of BCVA for nAMD patients will be presented along with change from Baseline in BCVA by visit along with first anti VEGF Treatment BCVA.

The above analysis will be done on the FAS and only on the study eye.

[redacted]

[redacted]

[redacted]

## 2.10 Safety analyses

Safety measurements include duration of exposure, vital signs, and adverse events (AEs). All safety endpoints will be summarized using the Safety Set. Patients will be analyzed according to the treatment received. No imputation will be carried out for missing data.

### 2.10.1 Adverse events

All information obtained on AEs will be displayed by patient Summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (see Section 2.1.1) for definition of on-treatment period).

The count of treatment-emergent AEs, number (and percentage) of patients with treatment-emergent AEs (defined as events started after the first dose of study treatment or events present prior to start of study treatment but increased in severity based on PT) will be summarized in the following ways:

- By primary SOC and PT.
- By primary SOC, PT and maximum severity.

Separate summaries will be provided for study treatment related AEs, study procedure related AEs, death, SAEs, other significant AEs action taken leading to study treatment withdrawn and AEs leading to dose interval adjustment (interval increase, interval reduce). Separate summaries will be provided for AESI.

Adverse events will be summarized by presenting, the number and percentage of patients having any AE, having an AE in each primary SOC and having each individual AE (PT). Summaries will also be presented for AEs by severity. Summaries for AE will be presented for study treatment and procedure related to AEs. If a patient reported more than one AE with the same PT, the AE with the greatest severity will be presented. SOC will be presented in alphabetical order, preferred terms will be sorted within SOC in descending frequency of AEs. If a patients reported more than one AE within the same primary SOC, the patient will be counted only once with the greatest severity at the SOC level, where applicable. The AE will be presented in separate sections of ocular and non-ocular. For ocular then it will be presented by study eye, fellow eye, and any eye.

Separate summaries will be presented for ≤ 16 weeks and > 16 weeks.

For the legal requirements of ClinicalTrials.gov and EudraCT, 2 required tables on treatment emergent AEs which are not SAEs with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by system organ class and PT on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same system organ class 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 / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

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

In addition, all treatment emergent AEs and SAE will also be listed.

The by-patients listing will include: SOC/PT/Verbatim term, start date, end date, severity, relationship to study treatment and procedures, whether or not it is a SAE, action taken with study treatment and outcome; duration will be calculated as (end date – start date + 1) and for ongoing AE (last visit date – start date + 1) by ocular and non-ocular. For ocular then it will be presented by study eye, fellow eye and any eye.

A summary of action taken with number and percentage of patients will presented with treatment interrupted, treatment withdrawn, not applicable and unknown.

#### 2.10.1.1 Adverse events of special interest / grouping of AEs

The number (%) of patients with adverse events of special interest (AESI) will be summarized by Standardized MedDRA Query and PT. A listing will also be provided.

A Case Retrieval Sheet (CRS) with the exact composition of the AE groupings is to be used to map reported AEs to the AESI 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.

The number and percentage of patients having any AESI, having an AESI in each SOC and having each individual AE (PT) will be presented.

The number and percentage of patients for AESI type along with incidence rate per patient and per 1000 injection will be provided. Incidence rate per patient is defined as number of patients in AESI type/total number of patients in safety analysis set and incidence rate per 1000 injection is define as (number of occurrence of AESI type/total number of injections)*1000.

The number and type of AESI will be plotted according to the time after last brolucizumab injection and time since first brolucizumab injection.

Summary statistics for change from baseline in BCVA after end date of AESI will be provided for each AESI type and change from baseline in BCVA will be plotted overall and for each type of AESI.

Patients demographics, baseline characteristics and medical history will be provided for AESI patient with safety set.

### 2.10.2 Deaths

A separate summary of deaths including on-treatment and post-treatment deaths will be provided.

All deaths in the clinical database will be listed with the investigator-reported principal cause. Deaths occurring after the first dose of study treatment until 30 days after the date of last

treatment will be summarized. In addition, deaths occurring after the first dose of study treatment until the date of last treatment will also be summarized.

### 2.10.3 Laboratory data

Not applicable.

### 2.10.4 Other safety data

Not applicable.

#### 2.10.4.1 ECG and cardiac imaging data

Not applicable.

#### 2.10.4.2 Vital signs

Vital signs will include blood pressure and pulse rate measurements.

All vital signs data will be listed by patient, and visit, and if ranges are available, abnormalities will be flagged. Abnormal values are marked in Section 5.3. All data, including data from unscheduled visits, will be considered when identifying abnormal values. Analysis of vital sign measurements using summary statistics for the change from Baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign. Change from Baseline will only be summarized for patients with both Baseline and post-baseline values.

## 2.11 Pharmacokinetic endpoints

Not applicable.

## 2.12 PD and PK/PD analyses

Not applicable.

## 2.13 Patient questionnaire

Not applicable for IA.

## 2.14 Biomarkers

Not applicable

## 2.15 Other Exploratory analyses

Not applicable

# 3 Sample size calculation

The sample size calculation is based on the hypothesis of 25% to 35% of patients with no disease activity at Week 16. The sample size analyses were performed before the urgent safety measures were introduced.

**Table 3-1 Confidence intervals for proportions (2 sided)**

| Confidence level | Sample size (N) | Expected proportion | Target distance from proportion to limit |
|---|---|---|---|
| 0.950 | 250 | 0.25 | 0.054 |
| 0.950 | 300 | 0.25 | 0.049 |
| 0.950 | 325 | 0.25 | 0.047 |
| 0.950 | 400 | 0.25 | 0.042 |
| 0.950 | 250 | 0.30 | 0.057 |
| 0.950 | 300 | 0.30 | 0.052 |
| 0.950 | 325 | 0.30 | 0.050 |
| 0.950 | 400 | 0.30 | 0.045 |
| 0.950 | 250 | 0.35 | 0.059 |
| 0.950 | 300 | 0.35 | 0.054 |
| 0.950 | 325 | 0.35 | 0.052 |
| 0.950 | 400 | 0.35 | 0.047 |

A sample size of 250 to 400 patients produces a 2-sided 95% confidence interval with a distance from the proportion to the limits ranges from 0.042 to 0.059 when the estimated proportion varies from 0.25 to 0.35 (nQuery Advisor version 7.0).

In the HAWK and HARRIER studies, the proportion of naïve nAMD patients treated with brolucizumab who had disease activity at Week 16 was 30% less than for patients treated by aflibercept.

To determine a similar 30% proportion of patients with no disease activity at Week 16 in this pretreated study with a precision of 5% and alpha 5% (2-sided 95% confidence interval of width 11%), a total of 265 patients have to be observed in this study.

Considering a dropout rate of 10%, a total of 295 patients will be included.

# 4 Change to protocol specified analyses

Not applicable

# 5 Appendix

## 5.1 Imputation rules

### 5.1.1 Study treatment

The following rules should be used for the imputation of the dose end date for a given study treatment component:

#### Scenario 1

If the date of last IVT is completely missing and there is no end of treatment (EOT) page and no death date, the patient is considered as on-going.

The patient should be treated as on-going and the cut-off date should be used as the last dosing date.

### Scenario 2

If the dose end date is completely or partially missing and the EOT page is available:

- Case 1: The dose end date is completely missing and the EOT completion date is complete, then this latter date should be used.
- Case 2: Only year (YYYY) of the dose end date is available and YYYY < the year of EOT date, then use 31DECYYYY.
- Case 3: Only year (YYYY) of the dose end date is available and YYYY = the year of EOT date, then use EOT date.
- Case 4: Both year (YYYY) and month (MMM) are available for dose end date and YYYY = the year of EOT date and MMM < the month of EOT date, then use last day of the Month (MMM)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment.

If the imputed date is < start date of treatment, then use the treatment start date.

Otherwise, use the imputed date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

### 5.1.2 AE date imputation

AE date imputation is based only on a comparison of the partial AE start date to the treatment start date as mentioned in the below.

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 the AE year is less than the treatment year and the AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
   b. Else if the AE year is less than the treatment year and the 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 year is greater than the treatment year and the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).

b. Else if the AE year is greater than the treatment year and the AE month is not missing, the imputed AE start date is set to the month start point (01MONYYYY).

4. If the AE start date year value is equal to the treatment start date year value:
   a. And the AE month is missing or the AE month is equal to the treatment start month, the imputed AE start date is set to one day after treatment start.
   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 greater than the treatment start month, the imputed AE start date is set to the start month point (01MONYYYY).

| | **MON** | **MON < CFM** | **MON = CFM** | **MON > CFM** |
|---|---|---|---|---|
| | **MISSING** | | | |
| **YYYY MISSING** | NULL | NULL | NULL | NULL |
| | Uncertain | Uncertain | Uncertain | Uncertain |
| **YYYY < CFY** | (D) = 01JULYYYY | (C)= 15MONYYYY | (C)= 15MONYYYY | (C)= 15MONYYYY |
| | Before Treatment Start | Before Treatment Start | Before Treatment Start | Before Treatment Start |
| **YYYY = CFY** | (B)= TRTSTD+1 | (C)= 15MONYYYY | (A)= TRTSTD+1 | (A)= 01MONYYYY |
| | Uncertain | Before Treatment Start | Uncertain | After Treatment Start |
| **YYYY > CFY** | (E)= 01JANYYYY | (A)= 01MONYYYY | (A)= 01MONYYYY | (A)= 01MONYYYY |
| | After Treatment Start | After Treatment Start | After Treatment Start | After Treatment Start |

| | |
|---|---|
| Before Treatment Start | Partial indicates date prior to Treatment Start Date |
| After Treatment Start | Partial indicates date after Treatment Start Date |
| Uncertain | Partial insufficient to determine relationship to Treatment Start Date |
| **LEGEND:** | |
| (A) | MAX(01MONYYYY,TRTSTD+1) |
| (B) | TRTSTD+1 |
| (C) | 15MONYYYY |
| (D) | 01JULYYYY |
| (E) | 01JANYYYY |

### 5.1.3 Concomitant medication (CM) /procedure (PR) date imputation

This algorithm is used when event is the partial start date of the concomitant medication/procedure.

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

| | Day | Month | Year |
|---|---|---|---|
| Partial CM/PR Start Date | Not used | MON | YYYY |
| Treatment Start Date (TRTSDT) | Not used | TRTM | TRTY |

The following matrix explains the logic behind the imputation.

| | MON MISSING | MON < TRTM | MON = TRTM | MON > TRTM |
|---|---|---|---|---|
| YYYY MISSING | (C2) Uncertain | (C1) Uncertain | (C1) Uncertain | (C1) Uncertain |
| YYYY < TRTY | (D) Before Treatment Start | (A) Before Treatment Start | (A) Before Treatment Start | (A) Before Treatment Start |
| YYYY = TRTY | (C2) Uncertain | (A) Before Treatment Start | (C1) Uncertain | (B) After Treatment Start |
| YYYY > TRTY | (E) After Treatment Start | (B) After Treatment Start | (B) After Treatment Start | (B) After Treatment Start |

The following table is the legend to the logic matrix.

| Relationship | |
|---|---|
| Before Treatment Start | Partial date indicates CM/PR start date prior to Treatment Start Date |
| After Treatment Start | Partial date indicates CM/PR start date after Treatment Start Date |
| Uncertain | Partial date insufficient to determine relationship of CM/PR start date relative to Treatment Start Date |
| **Imputation Calculation** | |
| (A) | 15MONYYYY |
| (B) | 01MONYYYY |
| (C1 or C2) | IF relative reference start = before treatment start THEN TRTSDT-1<br>ELSE IF relative reference start = ' ' THEN TRTSDT +1 |
| (D) | 01JULYYYY |
| (E) | 01JANYYYY |

**Concomitant Medication/Procedure End Date Imputation**

If not ongoing then -

Imputed date = date part of CMENDTC, if complete date

Imputed date = min (completion/discontinuation visit date, DEC 31) , if month is missing, (C2, D, E)

Imputed date = min (completion/discontinuation visit date, last day of the Month) , if day is missing. (A, B, C1)

**Concomitant Medication/Procedure Date Flag**

If not a complete date then

Y - If year of the imputed date is not equal to YYYY else M – If month of the imputed date is not equal to MON else D.

### 5.1.4 Medical history date of diagnosis imputation

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

- If DIAG year < study treatment start date year and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY).
- Else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY).
- If DIAG year = study treatment start date year and (DIAG month is missing OR DIAG month is equal to study treatment start month), the imputed DIAG date is set to one day before study treatment start date.

## 5.2 AEs coding/grading

The verbatim term recorded on CRF will be identified as adverse event and will be coded by primary SOC and PT using the MedDRA version 22.0 and above.

## 5.3 Confirmed SRC event

List of confirmed SRC event will be provided by study team. Trial programmer will derive below variable to performed the related analysis.

a) SRC start and SRC event date

b) Number of IVT injection prior to start of AESI event confirmed by SRC

c) Duration(day) since last IVT injection to start of AESI event confirmed by SRC

## 5.4 Laboratory parameters derivations

The criteria for clinically notable abnormalities are defined as follows:

### Clinically notable elevated values

- Systolic blood pressure of ≥ 140 mmHg (hypertension)
- Diastolic blood pressure of ≥ 90 mmHg (hypertension)
- Pulse rate ≥ 100 bpm (tachycardia)

### Clinically notable below normal values

- Systolic blood pressure of < 90 mmHg (hypotension)
- Diastolic blood pressure of < 60 mmHg (hypotension)
- Pulse rate < 60 bpm (bradycardia)

## 5.5 Statistical models

The below SAS code will used for statistical value.

### Frequency and proportion:

```
proc freq data = <........>;
       tables response_variable/ chisq;
run;
```

### Summary Statistics:

Univariate procedure will be used for continuous response.

```
proc univariate data=<........>;
       var response_variable;
       output out=<........> n=_n mean=_mean std=_sd  min=_min median=_med
       max=_max;
run;
```

### 95% CI

```
proc means data=adxe N NMISS CLM  ;
  var aval;
run;
```

### Time to event analysis

```
proc lifetest data=comb1 alpha=0.05 conftype=loglog method=KM alphaqt=0.05
outsurv=survest;
       time AVALW*cnsr(0);
run;
```

### AESI reported by investigator

```
if AEDECOD in ("Anterior chamber cell", "Anterior chamber inflammation",
"Vitritis", "Iritis", "Cyclitis", "Choroiditis", "Chorioretinitis", "Anterior
chamber fibrin", "Uveitis","Noninfective chorioretinitis", "Ophthalmia
neonatorum", "Aqueous fibrin", "Uveitis-glaucoma-hyphaema syndrome", "Retinitis",
"Tubulointerstitial nephritis and uveitis syndrome", "Toxic anterior segment
syndrome","Infective uveitis", "Vitreous haze", "Keratic precipitates", "Vitreous
abscess", "Anterior chamber flare", "Cogan''s syndrome", "Noninfective retinitis",
"Oculomucocutaneous syndrome","Eye infection intraocular", "Iridocyclitis", "Viral
uveitis", "Viral keratouveitis", "Hypopyon", "Cyclitic membrane", "Eye
inflammation", "Optic neuritis","Ocular pemphigoid", "Oculorespiratory syndrome",
"Idiopathic orbital inflammation", "Papillitis") then
       do;
            AEBODSYS1="Intraocular inflammation";
            AESI="Y";
          end;
else if  AEDECOD in ("Choroidal infarction", "Eyeinfarction", "Macular ischaemia",
"Ocular ischaemic syndrome", "Retinal artery embolism", "Retinal artery
occlusion","Retinal artery stenosis", "Retinal artery thrombosis", "Retinal
infarction", "Retinal ischaemia", "Retinal vascular occlusion", "Retinal vascular
thrombosis", "Retinal vein occlusion","Retinal vein thrombosis", "Necrotising
retinitis", "Ocular vasculitis", "Retinal vasculitis","Retinal occlusive
vasculitis") then
       do;
```

```
        AEBODSYS1="Retinal Vasculitis and / or retinal vascular occlusion";
        AESI="Y";
    end;
```

## 5.5 Rule of exclusion criteria of analysis sets

**Table 5-1 Protocol deviations that cause patients to be excluded**

| Deviation ID | Description of Deviation | Exclusion in Analyses | Severity code |
|---|---|---|---|
| INCL01 | Signed informed consent not obtained | Excluded from FAS and PPS | 1 |
| INCL02 | Age less than 50 year | Included in everything | 0 |
| INCL03 | No CNV lesions or >18M | Excluded from FAS and PPS | 1 |
| INCL04a | >1 previous antiVEGF | Excluded from FAS and PPS | 1 |
| INCL04b | <3 previous aVEGF injections | Excluded from FAS and PPS | 1 |
| INCL04c | Prev aVEGF intvl out of range | Included in everything | 0 |
| INCL05 | No residual fluid | Excluded from FAS and PPS | 1 |
| INCL06 | Study eye BCVA out of range | Excluded from PPS | 2 |
| EXCL01 | Active inflammation/infection | Excluded from PPS | 2 |
| EXCL02 | Fellow eye ocular disese | Included in everything | 0 |
| EXCL03 | History of IOI | Included in everything | 0 |
| EXCL04 | Poor quality images | Included in everything | 0 |
| EXCL05 | Study eye atropathy or fibrosis | Included in everything | 0 |
| EXCL06 | Study eye lesion area ≥50% | Included in everything | 0 |
| EXCL07 | Study eye concomitant condition | Included in everything | 0 |
| EXCL08 | Study eye macula damage | Included in everything | 0 |
| EXCL09 | Study eye vitreous hemorrhage | Included in everything | 0 |
| EXCL10 | Study eye uncotrolled glaucoma | Included in everything | 0 |
| EXCL11 | Study eye aphakaia | Included in everything | 0 |
| EXCL12 | Other trt in study eye | Excluded from PPS | 2 |
| EXCL13 | Steroids in study eye | Included in everything | 0 |
| EXCL14 | Prior keratoplasty/vitrectomy | Included in everything | 0 |
| EXCL15a | Study eye surgery | Included in everything | 0 |
| EXCL15b | Study eye laser photocoagul | Included in everything | 0 |
| EXCL15c | Study eye macular surgery | Included in everything | 0 |
| EXCL16 | Previous laser treatment | Included in everything | 0 |
| EXCL17 | previous brolucizuamb trt study eye | Excluded from FAS and PPS | 1 |
| EXCL18 | ESRD | Included in everything | 0 |
| EXCL19 | Systemic drugs toxic to eye | Included in everything | 0 |
| EXCL20 | Participation in another study | Excluded from PPS | 2 |
| EXCL21 | Systemic anti-VEGF therapy | Included in everything | 0 |
| EXCL22 | Stroke or myocardial infarction | Included in everything | 0 |
| EXCL23 | Uncontrolled blood pressure | Included in everything | 0 |

| Deviation ID | Description of Deviation | Exclusion in Analyses | Severity code |
|---|---|---|---|
| EXCL24 | Medical condition impact | Included in everything | 0 |
| EXCL25 | Malignancy | Included in everything | 0 |
| EXCL26 | Hypersensitivity | Included in everything | 0 |
| EXCL27 | Pregnant or nursing woman | Included in everything | 0 |
| EXCL28 | WOCP | Included in everything | 0 |
| EXCL29 | Minors/protected adults | Excluded from PPS | 2 |
| COMD01 | Prohibited medication/procedures | Included in everything | 0 |
| COMD02 | Non-permitted steroid use | Included in everything | 0 |
| TRT01 | Trt > 3 days after inj visit | Included in everything | 0 |
| TRT02 | Missed injection visit | Included in everything | 0 |
| TRT03 | Wrong IP/volume administered | Excluded from PPS | 2 |
| TRT04 | IVT interval<than 21 days | Included in everything | 0 |
| TRT05 | TRT admin prior effic/safty eval | Included in everything | 0 |
| TRT06 | COVID-19 Drug supply change | Included in everything | 0 |
| TRT07 | COVID-19 Treatment not given | Included in everything | 0 |
| TRT08 | Missed Injection loading phase | Excluded from FAS and PPS | 1 |
| TRT09 | Missed Injection | Included in everything | 0 |
| TRT10 | No Disease acty bt INJ is given | Included in everything | 0 |
| WITH01 | Withdrew consnt nt discontinued | Excluded from FAS and PPS | 1 |
| OTHER01 | Missed mandatory visit | Excluded from PPS | 2 |
| OTHER02 | Subject rescreened > once | Excluded from PPS analysis | 0 |
| OTHER03 | New ICF is missing-rescreened | Excluded from FAS and PPS | 1 |
| OTHER04 | Rescrn >14days w/o scr proc | Included in everything | 0 |
| OTHER05 | Odysight used w/o consent | Included in everything | 0 |
| OTHER06 | Temp excursion IP administered | Included in everything | 0 |
| OTHER07 | SAE not reported | Included in everything | 0 |
| OTHER08 | Crit met to failure | Included in everything | 0 |
| OTHER09 | The patient done rescreening | Included in everything | 0 |
| OTHER10 | COVID-19 Missed visit | Included in everything | 0 |
| OTHER11 | COVID-19 Visit not at site | Included in everything | 0 |
| OTHER12 | COVID-19 Assessment changed | Included in everything | 0 |
| OTHER13 | COVID-19 Discontinuation | Included in everything | 0 |
| OTHER14 | Visit window > 7 days | Included in everything | 0 |
| OTHER15 | Efficacy assessment not done | Excluded from PPS | 2 |
| OTHER16 | Safety assessment not done | Included in everything | 0 |
| OTHER17 | BCVA not done correctly | Included in everything | 0 |
| OTHER18 | Trt regimen wrongly adjusted | Included in everything | 0 |
| OTHER19 | Vital signs/safety call not done | Included in everything | 0 |

**Table 5-2 Patient Classification**

| Analysis Set | Severity codes that cause a subject to be excluded |
|---|---|
| ENR | NA |
| FAS | 1 |
| PPS | 1, 2 |
| SAF | NA |

# 6 Reference

[HAWK] ClinicalTrials.gov. Identifier NCT02307682. Available at https://clinicaltrials.gov/ct2/show/NCT02307682 (link is external). Accessed November 2017.

[HARRIER] ClinicalTrials.gov. Identifier NCT02434328. Available at https://clinicaltrials.gov/ct2/show/NCT02434328 (link is external). Accessed November 2017.