NOVARTIS

Clinical Development

RTH258/Brolucizumab

CRTH258AFR01 / NCT04239027

A one-year, single-arm, open-label, multicenter study assessing the anatomic outcomes of brolucizumab assessed by OCT-A in adult patients with neovascular age-related macular degeneration (OCTOPUS)

Statistical Analysis Plan (SAP)

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Date	Reason for update	Outcome for update	Section and title impacted (Current)
02-03-2020	Creation of initial version	N/A - First version	NA
20-11-2020	Amendment v1.0		
	Visit window modified	Visit window updated as per protocol	Section 2.1.2
	Baseline characteristics include more variables	Additional Baseline characteristics from central reading center in Vienna are included	Section 2.3.4
	Prior and concomitant Surgery and Procedures was not included	Added Prior and concomitant Surgery and Procedures as a new section	Section 2.4.3
	Study treatment exposure removed, the not required compliance section	Updated study treatment exposure	Section 2.4.1
	Dry retina details	Section added for dry retina	Section 2.5.1
	Presence of fluid add more details	Updated presence of fluid	Section 2.6.1
	Fluorescein Angiography (FA) add more details	Updated Fluorescein Angiography (FA)	Section 2.6.1
	Estimand not included	Added section for estimand as new section	Section 2.7
	Dry retina	Section added for dry retina	Section 2.6.1
	[redacted]	[redacted]	[redacted]
25-01-2023	Update in protocol	Updated protocol version number and release date	Section 1
	Update number of patients and drop the number of site	Sample size re – estimated and number of planned site dropped, change disease activity assesment	Section 1.1
	[redacted]	[redacted]	[redacted]
	Update in on-treatment period defination	On treatment period updated to 28 days from last treatment day	Section 2.1.1
	Update in visit window interval	Lower and upper value for visit window updated	Section 2.1.2

Date	Reason for update	Outcome for update	Section and title impacted (Current)
	Update in population for disposition and protocol deviation	Population set for disposition table and listing updated	Section 2.3.1 and 2.3.2
	Update in baseline characteristics	nAMD category added [redacted]	Section 2.3.4
	Update in ocular category	Ocular category was updated	Section 2.3.5, 2.4.2, 2.4.3 and 2.9.1
	Update in treatment exposure	New category added	Section 2.4.1
	Update in unit	CNV lesion area unit updated	Section 2.5.1
	Update in BCVA group	Loss of BCVA category updated	Section 2.6.1.4
	Update in date	Start date and end date consideration updated	Section 2.6.1.5.1
		Start date consideration updated	Section 2.6.1.6.1
	Update in CPF and fundus examination question	Vasculitis added in CFP and fundus examination	Section 2.8.1 and 2.8.5
	Update in FAF question	Foveal atrophy added in FAF question	Section 2.8.2
	Update in AEs section	Added procedure related, remove EudraCT requirement	Section 2.9.1
	Update in AESI analysis	Details for AESI analysis is added	Section 2.9.1.1
	[redacted]	[redacted]	[redacted]
	Update in sample size calculation	Sample size re-estimation	Section 3
	Added protocol change analysis	Added protocol change analysis for estimand	Section 4
	Update in statistical methodology	SAS code for correlation and Bland-Altman plot is deleted. Added code AESI derivation	Section 5.4
	Update in protocol deviation list and severity code	New protocol deviation category added, severity updated and patient classification updated	Section 5.5

Hyperlinks were not updated for the aendment v1.0 for the versions dated 20-11-2020 due change in section numbers.

Table of contents

List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
BCVA	Best-Corrected Visual Acuity
BCNVA	Best Corrected Near Visual Acuity
CNV	Choroidal Neovascularization
CFP	Color Fundus Photography
COVID-19	Coronavirus disease 2019
CI	Confidence Interval
CRC	Central Reading Center
CRO	Contract Research Organization
CSFT	Central Sub-Field Retinal Thickness
CRT	Central Retinal Thickness
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ENR	Enrolled set
FA	Fluorescein Angiography
FAF	Fundus AutoFluorescence
FAS	Full Analysis Set
ICF	Informed Consent Form
IGC	Indocyanine Green Chorioangiography
IOP	Intraocular Pressure
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
q8w	Every 8 Weeks
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 commitee
TFL	Tables, Figures, Listings
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 (Section 12) in the clinical protocol (CRTH258AFR01, version no: 04, release date 16Nov2021). This document will be used to prepared 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 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 patients with nAMD.

Patients will be required to attend 6 mandatory study visits: Screening/Baseline Visit (Day 1), Week 4, Week 8, Week 12, Week 16 and Week 48 visits. The timing of the interim visits between Week 16 and Week 48 will depend on the patient's injection regimen, i.e. q12w or q8w.

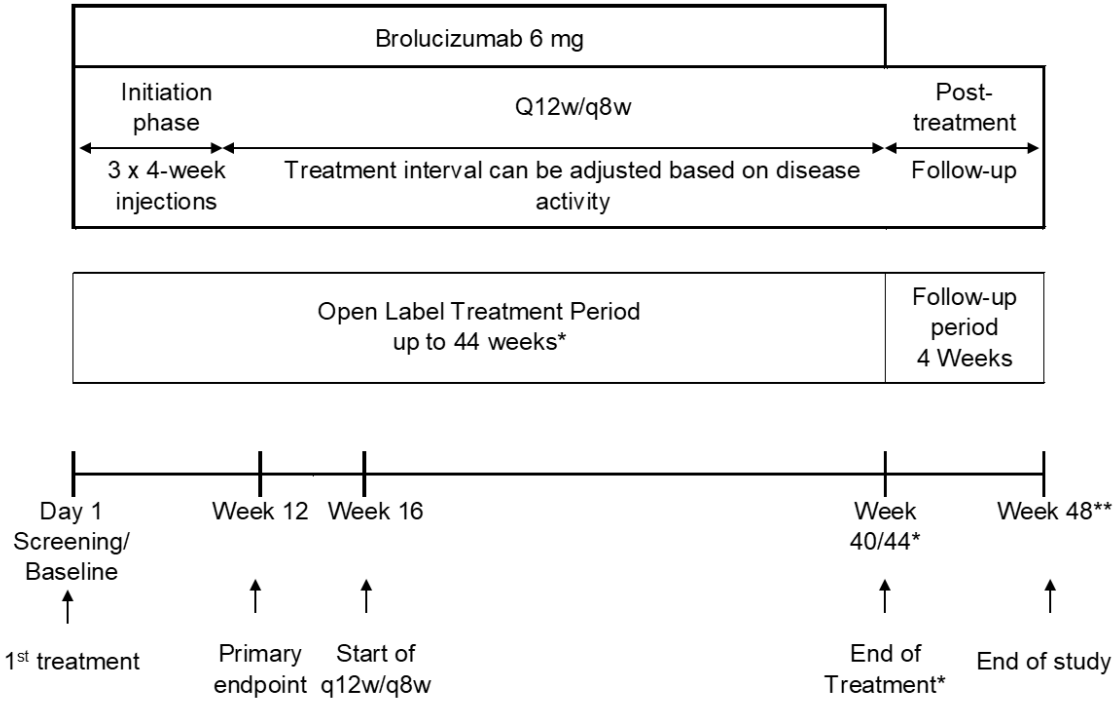
Planned number of patients

Approximately 210 adult patients will be screened and included (10% dropout rate and uninterpretable images at Baseline and Week 12 are expected) in France. The maximum study duration for 1 patient is 48 weeks, including Screening.

There will be 2 periods in this study (see Figure 1-1):

- Open-label treatment period: from Screening/Baseline (Day 1) to Week 40/Week 44 (depending on assigned regimen)
- Follow-up period: Week 40/Week 44 to Week 48

Figure 1-1 Study design



* Week 40 or Week 44 according to treatment schedule

** End of study visit: 4 or 8 weeks after the last IVT, depending on the last IVT date

Patients will receive 3 initial doses every 4 weeks (Day 1, Week 4 and Week 8) loading phase), which should be at least 21 days apart, followed by treatment q12w with the possibility of adjusting to treatment q8w based on disease activity.

Disease activity will be assessed based on investigator's judgment of visual acuity and anatomical parameters as provided in the guidance to the investigators, e.g. decrease of visual acuity and/or other signs of the disease (e.g. intraretinal fluid (IRF), subretinal fluid (SRF), sub-retinal pigmented epithelium (sub-RPE) fluid, retinal hemorrhage, central retinal thickness (CRT) increase, etc.). Disease activity will be assessed during the first q12w interval at Week 16. If no disease activity is observed by the investigator in the study eye, disease activity will be assessed every 12 weeks (at Week 20, Week 32 and Week 44). If disease activity is observed by the investigator in the study eye at any of these visits, the study treatment will be adjusted by the investigator to a q8w treatment regimen and will remain on this regimen until Week 40/Week 44. Patients who require study treatment every 4 weeks after the initiation phase will be discontinued from further study treatment at the next visit.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objectives	**Endpoints for primary objectives**
• To evaluate the short-term effect of brolucizumab on CNV lesion area as measured by OCT-A in nAMD patients.	• Percentage change in CNV lesion area measured by OCT-A from Baseline to Week 12.
Secondary objectives	**Endpoints for secondary objectives**
• To evaluate the long-term effects of brolucizumab on CNV morphology as measured by OCT-A in nAMD patients.	• Percentage change in CNV lesion area measured by OCT-A from Baseline to Week 48. • Change in OCT-A features assessed by qualitative and quantitative criteria from Baseline by visit at Week 12 up to Week 48.
• To evaluate the effect of brolucizumab on anatomical parameters as assessed by SD-OCT and FA from Week 12 up to Week 48.	• Change in SD-OCT and FA features assessed by qualitative and quantitative criteria (e.g. CSFT, sub- and/or intraretinal fluid, sub-RPE fluid) from Baseline by visit up to Week 48.
• To evaluate the efficacy of brolucizumab up to Week 48 by assessing changes in BCVA.	• Change in BCVA from Baseline up to Week 48.
• To estimate the proportion of patients treated at q12w frequency with brolucizumab.	• Proportion of patients who are maintained on an exclusive q12w interval following the loading phase through to Week 48.
• To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab.	• The probability of the first q12w interval for determining successful q12w maintenance at Week 48.
• To evaluate the time from last IVT injection in the initiation phase to first visit with no disease activity.	• Time from last IVT injection in the initiation phase to first visit with no disease activity.
• To evaluate the safety of brolucizumab.	• Incidence of AEs (serious and non-serious) reported in patients treated with brolucizumab.

AEs= adverse events, BCVA= best corrected visual acuity, CNV= choroidal neovascularization, CSFT= central sub-field retinal thickness, FA= fluorescein angiography, IVT= intravitreal nAMD= neovascular age-related macular degeneration, OCT-A= optical coherence tomography-angiography, SD-OCT= spectral domain optical coherence tomography, sub-RPE= subretinal pigmented epithelium

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, maximum and 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 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 maintenance treatment from Week 16/Week 20 up to Week 40/Week 44. 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 CRF 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). Intraocular pressure (IOP) will be assessed in the study eye, pre-dose and post-dose at every injection. The last available assessment taken prior to the first IVT injection of study treatment is taken as the "Baseline" assessment.

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 and fundus examinations). 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.

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 40 to 44 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.

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

Event for maintenance q12w interval: In case the investigator selects q12w interval for a patient and the patient maintains the q12w interval until the first q8w interval has started then this will be considered as an event. In case the investigator maintains q12w interval (does not select q8w interval at any time in study) until EOS or patients got early discontinuation from study then patients will be considered as censored.

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 disease activity. If patients with active disease status or early discontinue then patients will be considered as censored for disease activity.

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. Otherwise, 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.

CNV lesion area

A new angiography tool, namely optical coherence tomography-angiography (OCT-A) is a dye-less angiographic procedure based on split-spectrum-decorrelation-amplitude angiography that has become an essential and widely used tool, particularly for imaging CNV and vascular

diseases of the retina. The literature suggests that OCT-A is a good marker for assessing anti-VEGF therapeutic response, especially the lesion size that has been demonstrated to decrease under anti-VEGF therapy.

OCT-A will be used in this study to assess the morphological response of patients to brolucizumab in terms of percentage change in CNV lesion area in the short term (i.e. at Week 12 just after loading doses) and in the long term (i.e. at Week 48 [12 months]), as well as changes in other OCT-A features up to Week 48.

The primary endpoint is the percentage change in CNV lesion area measured by OCT-A from Baseline to Week 12. The Week 12 time point has been selected as peak efficacy has been demonstrated in the pivotal trials of brolucizumab for this time point.

Anatomic parameters measured by OCT-A and SD-OCT

Anatomic parameters measured by OCT-A and by SD-OCT will be analyzed by a CRC. The main aim of the CRC analysis is to confirm anatomic features from OCT-A and SD-OCT images for the primary endpoint. The investigator will evaluate the OCT-A and SD-OCT images to assess the status of disease stability.

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.

A patient who misses Week 16 will undergo the disease activity assessment at Week 20 as he/she would have done if the visit had not been missed. If, however, a patient misses any of the following disease activity assessment visits (Week 20, Week 32) then the patient will be assumed to have met the disease activity criterion at the missed visit and will be reassigned to a q8w regimen up to study exit.

If a patient misses Week 12, then the Week 8 values will be applied as the reference for disease activity assessments up to and including Week 44.

Fluorescein angiography: Fluorescein angiography (FA) is a diagnostic procedure that uses a special camera to record the blood flow in the RETINA – the light sensitive tissue at the back of the eye.

Color fundus photography (CFP): CFP is a diagnostic procedure that involves the use of a device known as a fundus camera to record colored images of the interior surface of the eye. The goal of this procedure is to monitor the presence of disorders and their change with time.

Fundus autofluorescence (FAF): Fundus autofluorescence imaging is an *in vivo* imaging method for metabolic mapping of naturally or pathologically occurring fluorophores of the ocular fundus.

Indocyanine green angiography (ICG): ICG is a diagnostic procedure that uses ICG dye to examine the blood flow in the choroid – the layer of blood vessels that lies underneath the retina. ICG is injected into a vein in the arm/hand. As the dye passes through the blood vessels of the eye, photographs are taken to record the blood flow.

Intraocular pressure (IOP): IOP is the fluid pressure of the eye. IOP is measured in millimeters of mercury (mmHg). Normal eye pressure is usually considered to be between 10 and 25 millimeters of mercury (mmHg).

Fundus examination: Fundus examination used to assess diagnose vitro-retinal diseases (such as retinal haemorrhage, vitreal haemorrhage, retinal tear and detachment), optic nerve defects and hereditary diseases.

[redacted]

2.1.2 Visit windows for data analysis

Visit windows will be used for the data analysis, as per the planned visits in the protocol. During the q12w/q8w 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 71 – 97
Week 16	16	112	Day 99 – 119
Week 20	20	140	Day 127 – 153
Week 24	24	168	Day 155 – 182
Week 28	28	196	Day 183 – 209
Week 32	32	224	Day 211 – 237
Week 36	36	252	Day 239 – 265
Week 40	40	280	Day 267 – 293
Week 44	44	308	Day 395 – 321
Week 48	48	336	Day 323 – 349

* Baseline measurement before the first treatment administration.

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; therefore, the investigators should 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.

2.2 Analysis sets

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

Full Analysis Set (FAS): The FAS comprises all patients to whom study treatment has been assigned and who received at least one IVT injection of study treatment.

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

Per-Protocol Set (PPS): The 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 the 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.

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 both estimands is to have similar conclusions. Inconsistencies in the results will be examined and discussed in the CSR.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The FAS will be used to prepare the 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 will be summarized with reasons for premature discontinuation for the ENR. 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 the ENR.

Study treatment will be discontinued under the following circumstances:

- Adverse event
- 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

2.3.2 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 enrolled 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).

2.3.3 Demographic characteristics

Demographic and Baseline characteristics will be listed and summarized descriptively for overall patients on FAS and Safety Set.

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

- Sex (male, female)
- Age (in years)
- Age category (< 50, 50 - 65, 65 - 75, 75 - 85, ≥ 85)
- Study eye (left [OS], right [OD])
- Vital signs (sitting systolic/diastolic blood pressure [mmHg], sitting pulse rate [bpm]) only on the days study treatment is administered, it is measured prior study treatment

2.3.4 Baseline characteristics

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

- Time since nAMD diagnosis

- Time since nAMD diagnosis (< 1 month, 1-3 months and > 3 months)
- 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
- FA (analyzed by Vienna [CRC])
  1. Lesion type (only at Baseline) (predominantly classic, minimally classic, occult)
  2. Lesion type (only at Baseline) (type 1 / type 2 / type 3 / type 1 with aneuvrism / polyps)
  3. CNV location (subfoceal, juxtafoveal, extrafoveal)
  4. Area of lesion associated with CNV (mm^2)
- ICG (analyzed by Vienna [CRC])
  1. Lesion type (only at Baseline) (type 1 / type 2 / type 3 / type 1 with aneuvrism / polyps)
  2. Area of lesion associated with CNV (mm^2)
- SD-OCT (analyzed by Vienna [CRC])
  - Lesion type (only at Baseline) (type 1, type 2, type 3)
  - CSFT (µm)
  - 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
- OCT-A (analyzed by Vienna)
  1. CNV location (only at Baseline)
  2. CNV lesion area (at the biggest surface) (mm^2/$µm^2$)
- Fundus observation
  1. Retinal hemorrhage (none, retinal macular and retinal non-macular)
  2. Presence of vitreal hemorrhage (Yes, No)
  3. Retinal tear/ detachment (none, tear, detachment, both)
- Color fundus photography (CFP)
  1. Presence of retinal or subretinal hemorrhage (Yes, No)
  2. Presence of fibrosis (Yes, No)
  3. Presence of atrophy (Yes, No)
  4. Subretinal blood affecting foveal center point and/ or > 50% of total lesion (Yes, No)
- Fundus autofluorescence (FAF)
  1. Presence of macular atrophy (Yes, No)
  2. Area of macular atrophy

- Intraocular pressure
- Intraocular pressure (≤ 10, 10-25, 25-30 and ≥ 30 [mmHg])
- Disease activity assessment (Present)
- History of primary diagnosis:
  1. Disease (neovascular age-related, macular degeneration [nAMD])
  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 photocoagulation
  3. Previous submacular surgery, other surgical intervention or laser treatment for nAMD including photodynamic therapy (PDT)
- Concomitant medication at Baseline
- Medical history
- Co morbidities

2.3.5 Relavent 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 (any 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 (any eye, study eye and fellow eye and both eye).

2.4 Treatments (study treatment, rescue medication, concomitant therapies

2.4.1 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. Overall number of injections (n, q1, median, q3, min and max) will presented.
2. Number of injection (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 12 and greater than Week 12.
4. Number of patients with injection (1 injection, 2 injections up to the maximum number of injections) from Baseline to the end of the treatment period 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. Summary statistics (n, mean, std, median, 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. 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 for the Safety Set and FAS. The exposure data will be listed for the FAS.

2.4.2 Prior, concomitant and post therapies

Each medication has the start and end dates recorded on the eCRF. Prior medications 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
- Concomitant medications which started prior to first dose of study treatment
- Concomitant medications 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 any eye, study eye and the fellow eye. A listing of all prior and concomitant medications and concomitant 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.

2.4.3 Prior and concomitant surgery and procedures

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

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 Analysis of the primary objective

2.5.1 Primary endpoint

OCT-A will be used in this study to assess the morphological response of patients to brolucizumab. In terms of percentage change in CNV lesion area (at the biggest surface) (mm^2).

The primary endpoint is the percentage change in CNV lesion area measured by OCT-A from Baseline to Week 12 in the study eye. The percentage change from Baseline at Week 12 in the lesion area will be derived as follows:

([Lesion area at Week 12 – Lesion area at Baseline]*100)/ Lesion area at Baseline

Descriptive statistics (n, mean, std, median, min and max) for the primary endpoint (actual value, change from Baseline, percentage change from Baseline) will be presented based on observed data using the FAS. Furthermore, a 2-sided 95% CI using Student's t-distribution will also be provided. In case of significant outliers or deviations from normality assumptions then IQR will be presented.

The last observation carried forward (LOCF) method will be used as sensitivity analysis to impute missing record for CNV lesion area at post baseline. If there is significant amount of missing record then another table with LOCF records should be created.

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

2.5.2 Supportive analyses

Subgroups analyses according to patient characteristics, like sex (male, female), age class (≤ 64, > 65 - 75, 75 - 85, ≥ 85), Baseline lesion type (type 1, type 2, type 3) and time since nAMD diagnosis (< 1 month, 1-3 months, and > 3 months).

2.6 Analysis of secondary efficacy objectives

2.6.1 Secondary endpoints

2.6.1.1 Oct-A long-term effects

The first secondary endpoint is the percentage change in CNV lesion area (mm^2) measured by OCT-A for nAMD patients from Baseline to Week 48. Descriptive statistics (n, mean, std, median, min and max) for the change in CNV lesion (actual value, change from Baseline, percentage change from Baseline) will be presented based on observed data by visit. Furthermore, a 2-sided 95% CI using Student's t-distribution will be provided.

The number and percentage of lesion type (predominantly classic, minimally classic and occult) will be presented by visit.

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

2.6.1.2 Spectral domain optical coherence tomography (SD-OCT)

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

2.6.1.2.1 Central sub-field retinal thickness (CSFT)

Summary statistics of central sub-field retinal thickness (CSFT) measured by SD-OCT for nAMD patients will be presented by visit along with change and percentage change from Baseline in CSFT.

The number and percentage of patient with CSFT category (< 300, ≥ 300 - 450, ≥ 450 - < 650, ≥ 650 (μm)) will be presented by visit.

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

2.6.1.2.2 Presence of fluid (YES/NO)

The number and percentage of patients with below fluid will presented by visit.

1. Intraretinal fluid
2. Subretinal fluid
3. Sub-RPE fluid
4. Without IRF or SRF
5. Without any fluid (IRF/SRF/sub-RPE)
6. 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 only on the study eye. The analysis will be performed on the FAS.

2.6.1.2.3 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 only on the study eye. The analysis will be performed on the FAS.

2.6.1.2.4 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. Detailed KM results will be presented including time (week), number of patients with dry retina at visit, number of patients under risk at visit (without dry retina), probability of dry retina (survival probability) at visit and 95% CI at visit.

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: • Absence of dry retina until EOS • Early discontinuation without dry retina
Duration of time	(End date – start date) +1

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

2.6.1.2.5 Maximum duration of dryness

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

Detailed KM results will be presented including time (week), total number of patients having fluids, number of patients under risk, probability of with 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: • Presence of dryness until EOS • 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 only on the study eye. The analysis will be performed on FAS.

2.6.1.3 Fluorescein angiography (FA)

The number and percentage of CNV location (subfocal, juxtafoveal, extrafoveal) at Week 12 will be presented for both study eye and fellow eye.

The summary statistics (n, mean, std, median, min and max) of area of lesion associated with CNV (mm**2) will be presented at Week 12 for study eye and fellow eye, along with change from Baseline and percentage change from Baseline.

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

2.6.1.4 Best corrected visual acuity (BCVA)

The summary statistics (n, mean, std, median, min and max) of BCVA for nAMD patients will be presented along with change and percentage change from Baseline in BCVA by visit. Along with below BCVA category.

1. BCVA (≤ 55, 56 - 70 and ≥ 71).
2. Increase of ≥ 5, ≥ 10 and ≥ 15 letters in BCVA from Baseline up to Week 48.
3. Loss of ≥ 5, ≥ 10, ≥ 15 and ≥ 30 letters in BCVA from Baseline up to Week 48.
4. BCVA ≥ 84.

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

2.6.1.5 Dosing regimen of brolucizumab

The binomial proportion and 95% CI using the Clopper-Pearson method will be provided for patients who are maintained on an exclusive q12w interval following the loading phase through Week 48.

The number and percentage of q8w dose frequency patients will be presented along with 95% CI using the Clopper-Pearson method.

Duration of dose is defined as (date of last dose – start date of dose).

The summary statistics (n, mean, std, first quartile, median, third quartile, min and max) for duration of dose will be provided for patients who are maintained on an exclusive q12w interval following the loading phase through Week 48. In the study design the 3 × 4-week dosing frequency, in initiation phase.

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

2.6.1.5.1 Predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab

The probability of the first q12w interval will be derived from KM time to event analyses. KM plot will be provided. Detailed KM results will be presented including time (week), number of patients with first q8w or discontinue at visit, number of patients under risk at visit, probability of maintaining on q12w (survival probability) and 95% CI for maintaining on q12w.

Variable	Definition
Start date	First date when patients on q12w interval
Event	Maintain q12w interval
End date	Last date of initital q12w interval (before or on first start of q8w interval) End of study (week 48)
Censoring (end date)	Earliest of: • In case investigator does not select first q8w interval until EOS. • Early discontinue from study.
Duration of time	(End date – start date) +1

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

2.6.1.6 Disease activity assessments

The number and percentage will be presented by visit for disease activity assessment.

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

2.6.1.6.1 Duration of time from start of dose to till no disease activity

The median of duration of time is obtained from KM analysis along with 2-sided 95% CI will be presented. KM plots will be provided.

Detailed KM results will be presented including time (week), number of patients with no disease activity at visit, number of patients under risk at visit (with disease activity), probability of disease activity (survival probability) at visit and 95% CI at visit.

Variable	**Definition**
Start date	Start date of start of IVT injection/ last IVT injection in the initiation phase
Event	No disease activity
End date of event	Date of first visit with no disease activity
Censoring (end date)	Earliest of: • With disease activity until EOS • Early discontinuation
Duration of time	(End date – start date) +1

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

[redacted]

2.8 Analysis of other efficacy variables

2.8.1 Color fundus photography

The number and percentage will be provided at Screening/Baseline, week 12 and end of study (Week 48) for below questions:

- Was color fundus photography performed? If not, then reason for not performed CFP.
- Presence of retinal hemorrhage in central subfield.
- Presence of subretinal hemorrhage in central subfield.
- Presence of fibrosis in the central subfield the diameter of 3000 µm.
- Presence of atrophy in the central subfield the diameter of 3000 µm.
- Is there subretinal blood affecting the foveal center point and/or >50% of total lesion.
- Presence of Vasculitis.

The above analysis will be done on both eyes. The analysis will be performed on the FAS.

2.8.2 Fundus autofluorescence (FAF)

The number and percentage will be provided at Baseline, week 4 and end of study (week 48) for below question.

- Fundus auto-fluorescennce performed at visit. If not then reason for not performed FAF.
- Presence of macular atrophy in the central subfield (center 1 mm circle).
- Presence of foveal atrophy.

The summary statistics (n, mean, std, median, min and max) of area of macular atrophy (mm^2) will be presented at Baseline, Week 4 and Week 48 along with change from Baseline and percentage change from Baseline in FAF.

The above analysis will be done on the both eye. The analysis will be performed on FAS.

2.8.3 Indocyanine green angiography (ICG)

The number and percentage of lesion type (only at Baseline) (type 1 / type 2 / type 3 / type 1 with aneuvrism / polyps) at Baseline will be provided.

The summary statistics (n, mean, std, median, min and max) for area of lesion associated with CNV (mm^2) at Baseline and Week 12 will be provided along with summary statistics for change from Baseline and percentage change from Baseline at week 12 for area of lesion.

The above analysis will be done on both eyes. The analysis will be performed on the FAS.

2.8.4 Intraocular pressure

Intraocular pressure will be collected in the CRF at Baseline and Week 48. The summary statistics of IOP for nAMD patients will be presented at Week 48 along with change from Baseline and percentage change from Baseline in IOP. In addition, the number and percentage of patients with IOP ($\leq$ 10, 10-25, 25-30 and $\geq$ 30 [mmHg]) will be presented at Week 48.

The above analysis will be done on both eyes. The analysis will be performed on the FAS.

2.8.5 Fundus examination

The below variables of number and percentage will presented for study eye and fellow eye by visit.

- Retinal hemorrhage (none, retinal macular and retinal non-macular)
- Presence of vitreal hemorrhage (no, yes)
- Retinal tear/detachment (0- none, 1- retinal tear, 2- retinal detachment, 3- retinal tear and detachment)
- Presence of intraocular inflammation (no, yes)
- Presence of vasculitis.

Listing of fundus examination parameter will be provided by patient and visit.

The above analysis will be done on the both eye. The analysis will be performed on the FAS.

2.9 Safety analyses

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

2.9.1 Adverse events (AEs)

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, procedure related, death, SAEs andother significant AEs action taken leading to study study treatment interruption & treatment withdrawn .

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. System organ classes will be presented in alphabetical order, PTs 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 any eye, study eye and fellow eye.

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 AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

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

In addition, all treatment emergent AEs 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 any eye, study eye and fellow eye.

A summary of action taken with number and percentage of patients will presented with dose increased, no dose change, dose reduced, treatment interrupted, drug withdrawn, not applicable and unknown.

2.9.1.1 Adverse events of special interest / grouping of AEs

The number (%) of patients with AESIs will be summarized by standardized MedDRA query and PT. Listing will also be provided.

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.live 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, AESI by SOC(confirmed by SRC) and 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.

2.9.2 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 for each 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

2.12 Biomarkers

Not applicable.

2.13 Other exploratory analyses

Not applicable.

2.14 Interim analysis

The analysis based on the Week 12 data, i.e. data up to and including Week 12 will be the primary (first) analysis for this study.

A second planned analysis of the data after the EOS/Week 48 visit will be performed once all patients have completed or prematurely discontinued the study.

3 Sample size calculation

The primary objective of the study is to evaluate the effect of brolucizumab on CNV lesion area as measured by OCT-A in nAMD patients starting treatment with brolucizumab. This will be evaluated by the percentage change in CNV lesion area measured by OCT-A from Baseline to Week 12. The sample size calculation is based on the hypothesis of a standard deviation of 35% for this reduction proportion (Miere et al 2018).

A sample size of 180 to 400 patients produces a 2-sided 95% CI with a distance from the mean to the limits ranges from 5.1 to 3.4 when the estimated standard deviation is 35.0 (nQuery Advisor version 7.0). Therefore, to have a precision of 5%, a sample size of 189 patients will be needed (Table 3-1).

To take into account a dropout rate and uninterpretable images of 10%, a total of 210 patients will be included.

Table 3-1 Confidence intervals for one mean numeric results for 2-sided confidence intervals with unknown standard deviation

Confidence Level	Sample Size (N)	Distance from Mean to Limits	Standard Deviation (S)
0.950	180	5.1	35.0
0.950	189	5.0	35.0
0.950	233	4.5	35.0
0.950	250	4.4	35.0
0.950	300	4.0	35.0
0.950	350	3.7	35.0
0.950	385	3.5	35.0
0.950	400	3.4	35.0

4 Change to protocol specified analyses

[redacted]

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.

- 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.
- If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
  1. 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).
  2. 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).
- If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
  1. 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).

2. 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).

- If the AE start date year value is equal to the treatment start date year value:
  1. 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.
  2. 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).
  3. 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 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 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 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 Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 and above.

5.3 Vital signs 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 methodology

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;
```

Paired t-test

```
proc ttest data = cnv_w12;
       paired FAS_EST*PPS_EST;
run;
```

Wilcoxon rank-sum test

```
proc npar1way wilcoxon data = rnksm (label='CNV lesion area at week 12');
       class estimand;
       var area;
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 analysis	1
INCL02	Age less than 50 year	Included in everything	0
INCL03	No active CNV lesions	Excluded from FAS and PPS	1
INCL04	No Intra- and/or subretinal fluid	Excluded from FAS and PPS	1
INCL05	Study eye BCVA out of range	Excluded from PPS	2
EXCL01	Active infection in either eye	Excluded from PPS	2
EXCL02	Fellow eye ocular disease	Included in everything	0
EXCL03	Poor quality images	Included in everything	0
EXCL03a	History of IOI	Included in everything	0
EXCL05	Study eye lesion area ⩾50%	Included in everything	0
EXCL05a	Study eye atropathy or fibrosis	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 uncontrolled glaucoma	Included in everything	0
EXCL11	Study eye aphakaia	Included in everything	0
EXCL12	Other treatment in study eye	Excluded from PPS	2
EXCL13	Steroids in study eye	Included in everything	0
EXCL14	Prior keratoplasty/vitrectomy	Included in everything	0
EXCL15	Study eye previous ocular treatment	Included in everything	0
EXCL16	End stage renal disease requiring dialysis or renal transplant	Included in everything	0
EXCL17	Systematic drug toxic to eye	Included in everything	0
EXCL18	Participation in another study	Excluded from PPS	2
EXCL19	Systematic anti-VEGF therapy	Included in everything	0
EXCL20a	Stroke or myocardial infraction	Included in everything	0
EXCL21	Uncontrolled blood pressure	Included in everything	0
EXCL22	Malignancy	Included in everything	0
EXCL22a	Medical condition impact	Included in everything	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
EXCL24	Hypersensitivity	Included in everything	0
EXCL25	Pregnant or nursing woman	Included in everything	0
EXCL26	Women of childbearing potential	Included in everything	0
EXCL27	Minor or protected adult	Excluded from PPS	2
COMD01	Prohibited medication/procedures	Included in everything	0
COMD02	Steroids use 5 days prior to IP	Included in everything	0
TRT01	Wrong IP administered	Excluded from PPS	2
TRT02	Incorrect dose administered	Excluded from PPS	2
TRT03	Pregnancy but not discontinued	Included in everything	0
TRT04	Short treatment window between treatment	Included in everything	0
TRT05	Treatment > 3 days after injection visit	Included in everything	0
TRT06	Injection given at Week 12	Excluded from PPS	2
TRT07	Q8W IVT out of window	Included in everything	0
TRT08	Q12W IVT out of window	Included in everything	0
TRT09	COVID-19 Drug supply change	Included in everything	0
TRT10	COVID-19 Treatment not given	Included in everything	0
TRT11	Missed Injection loading phase	Excluded from PPS	1
TRT12	Missed Injection	Included in everything	0
TRT13	No Disease activity but injection is given	Included in everything	0
TRT14	Treatment admin prior effic/safty evaluation	Included in everything	0
TRT15	Treatment given at EOS	Included in everything	0
WITH01	Withdrew consent not discontinued	Excluded from FAS and PPS	1
OTHER01	Patient rescreened > once	Included in everything	0
OTHER02	Severe ICH-GCP non-compliance	Excluded from FAS and PPS	1
OTHER03	New ICF is missing-rescreened	Excluded from FAS and PPS	1
OTHER04	Mishandling IP	Included in everything	0
OTHER05	Temperature excursion IP administered	Included in everything	0
OTHER06	Treatment regimen wrongly adjusted	Included in everything	0
OTHER07	Missed mandatory visit	Excluded from PPS	2
OTHER08	Missed injection visit	Included in everything	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
OTHER09	FA out of window	Included in everything	0
OTHER10	Rescreen due to BCVA results	Included in everything	0
OTHER11	Rescreen >14days w/o screening procedure	Included in everything	0
[redacted]			
OTHER13	COVID-19 Missed visit	Included in everything	0
OTHER14	COVID-19 Visit not at site	Included in everything	0
OTHER15	COVID-19 Assessment changed	Included in everything	0
OTHER16	COVID-19 Discontinuation	Included in everything	0
OTHER17	Efficacy assessment not done	Excluded from PPS	2
OTHER18	Safety assessment not done	Included in everything	0
OTHER19	BCVA not done correctly	Included in everything	0
OTHER20	Visit window > 7 days	Included in everything	0
OTHER21	Vital signs/safety call not done	Included in everything	0
OTHER22	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
FAS-EST	1
PPS	1,2 (All specified PD in Table 5.1 due to COVID)
PPS-EST	1, 2 (All specified PD in Table 5.1 due to COVID-19)
SAF	NA

6 Reference

Miere A, Oubraham H, Amoroso F, et al (2018) Optical Coherence Tomography Angiography to Distinguish Changes of Choroidal Neovascularization after Anti-VEGF Therapy: Monthly Loading Dose versus Pro Re Nata Regimen. J Ophthalmol. Epublished at [doi: 10.1155/2018/3751702].

NOVARTIS

Clinical Development

RTH258/Brolucizumab

CRTH258AFR01 / NCT04239027

A one-year, single-arm, open-label, multicenter study assessing the anatomic outcomes of brolucizumab assessed by OCT-A in adult patients with neovascular age-related macular degeneration (OCTOPUS)

Statistical Analysis Plan (SAP)

Author:	Statistician, [redacted]
Document type:	SAP Documentation
Document status:	Addendum version 1.0
Release date:	21-Jun-2023
Number of pages:	39

Document History – Changes compared to previous final version of SAP

Date	Reason for update	Outcome for update	Section and title impacted (Current)
02-03-2020	Creation of initial version	N/A - First version	NA
20-11-2020	Amendment v1.0		
	Visit window modified	Visit window updated as per protocol	Section 2.1.2
	Baseline characteristics include more variables	Additional Baseline characteristics from central reading center in Vienna are included	Section 2.3.4
	Prior and concomitant Surgery and Procedures was not included	Added Prior and concomitant Surgery and Procedures as a new section	Section 2.4.3
	Study treatment exposure removed, the not required compliance section	Updated study treatment exposure	Section 2.4.1
	Dry retina details	Section added for dry retina	Section 2.5.1
	Presence of fluid add more details	Updated presence of fluid	Section 2.6.1
	Fluorescein Angiography (FA) add more details	Updated Fluorescein Angiography (FA)	Section 2.6.1
	Estimand not included	Added section for estimand as new section	Section 2.7
	Dry retina	Section added for dry retina	Section 2.6.1
	[redacted]	[redacted]	[redacted]
25-01-2023	Amendment v2.0		
	Update in protocol	Updated protocol version number and release date	Section 1
	Update number of patients and drop the number of site	Sample size re – estimated and number of planned site dropped, change disease activity assessment	Section 1.1
	[redacted]	[redacted]	[redacted]
	Update in on-treatment period definition	On treatment period updated to 28 days from last treatment day	Section 2.1.1
	Update in visit window interval	Lower and upper value for visit window updated	Section 2.1.2

Date	Reason for update	Outcome for update	Section and title impacted (Current)
	Update in population for disposition and protocol deviation	Population set for disposition table and listing updated	Section 2.3.1 and 2.3.2
	Update in baseline characteristics	nAMD category added [redacted]	Section 2.3.4
	Update in ocular category	Ocular category was updated	Section 2.3.5, 2.4.2, 2.4.3 and 2.9.1
	Update in treatment exposure	New category added	Section 2.4.1
	Update in unit	CNV lesion area unit updated	Section 2.5.1
	Update in BCVA group	Loss of BCVA category updated	Section 2.6.1.4
	Update in date	Start date and end date consideration updated	Section 2.6.1.5.1
		Start date consideration updated	Section 2.6.1.6.1
	Update in CPF and fundus examination question	Vasculitis added in CFP and fundus examination	Section 2.8.1 and 2.8.5
	Update in FAF question	Foveal atrophy added in FAF question	Section 2.8.2
	Update in AEs section	Added procedure related, remove EudraCT requirement	Section 2.9.1
	Update in AESI analysis	Details for AESI analysis is added	Section 2.9.1.1
	[redacted]	[redacted]	[redacted]
	Update in sample size calculation	Sample size re-estimation	Section 3
	Added protocol change analysis	Added protocol change analysis for estimand	Section 4
	Update in statistical methodology	SAS code for correlation and Bland-Altman plot is deleted. Added code AESI derivation	Section 5.4
	Update in protocol deviation list and severity code	New protocol deviation category added, severity updated and patient classification updated	Section 5.5
05-04-2023	Amendment V3.0		

Date	Reason for update	Outcome for update	Section and title impacted (Current)
	Update in visit window	Lower limit for Week 44 updated	Section 2.1.2
	Dropped category for ≤ Week 12 and > Week 12	Under drug exposure ≤ Week 12 and > Week 12 dropped	Section 2.4.1
	Update in sequence of variable	Sequence of expected variable changed	Section 2.6.1.2.4, 2.6.1.2.5, 2.6.1.5.1
	[redacted]	[redacted]	[redacted]
	Update in Date imputation rule	The same method for date imputation used for medical history (nAMD)	Section 5.1.3
	Updated in SAS code for t-test	SAS code for t-test updated	Section 5.4
15-06-2023	Addendum V1.0		
	Added definition for maximum duration of dry retina	Added definition for maximum duration of dry retina	Section 2.1.1 General definitions
	Updated date and censor	Logic for start date, end date and censor was updated	Section 2.6.1.2.5 Maximum duration of dryness
	Event and censor logic updated	Updated event and censor description for need of first q12w	Section 2.6.1.5.1 Predictive value of first q12w cycle maintenance
	nAMD date impution rule	Rule for partial nAMD history dates should similar to prior concomitant medication	Section 5.1.3 Concomitant medication and medical history (nAMD) date imputation

Hyperlinks were not updated for the amendment v1.0 for the versions dated 20-11-2020 due change in section numbers.

Table of contents

List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
BCVA	Best Corrected Visual Acuity
BCNVA	Best Corrected Near Visual Acuity
CNV	Choroidal Neovascularization
CFP	Color Fundus Photography
COVID-19	Coronavirus disease 2019
CI	Confidence Interval
CRC	Central Reading Center
CRO	Contract Research Organization
CSFT	Central Sub-Field Retinal Thickness
CRT	Central Retinal Thickness
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ENR	Enrolled set
FA	Fluorescein Angiography
FAF	Fundus AutoFluorescence
FAS	Full Analysis Set
ICF	Informed Consent Form
IGC	Indocyanine Green Chorioangiography
IOP	Intraocular Pressure
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
q8w	Every 8 Weeks
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 commitee
TFL	Tables, Figures, Listings
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 (Section 12) in the clinical protocol (CRTH258AFR01, version no: 04, release date 16Nov2021). This document will be used to prepared 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 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 patients with nAMD.

Patients will be required to attend 6 mandatory study visits: Screening/Baseline Visit (Day 1), Week 4, Week 8, Week 12, Week 16 and Week 48 visits. The timing of the interim visits between Week 16 and Week 48 will depend on the patient's injection regimen, i.e. q12w or q8w.

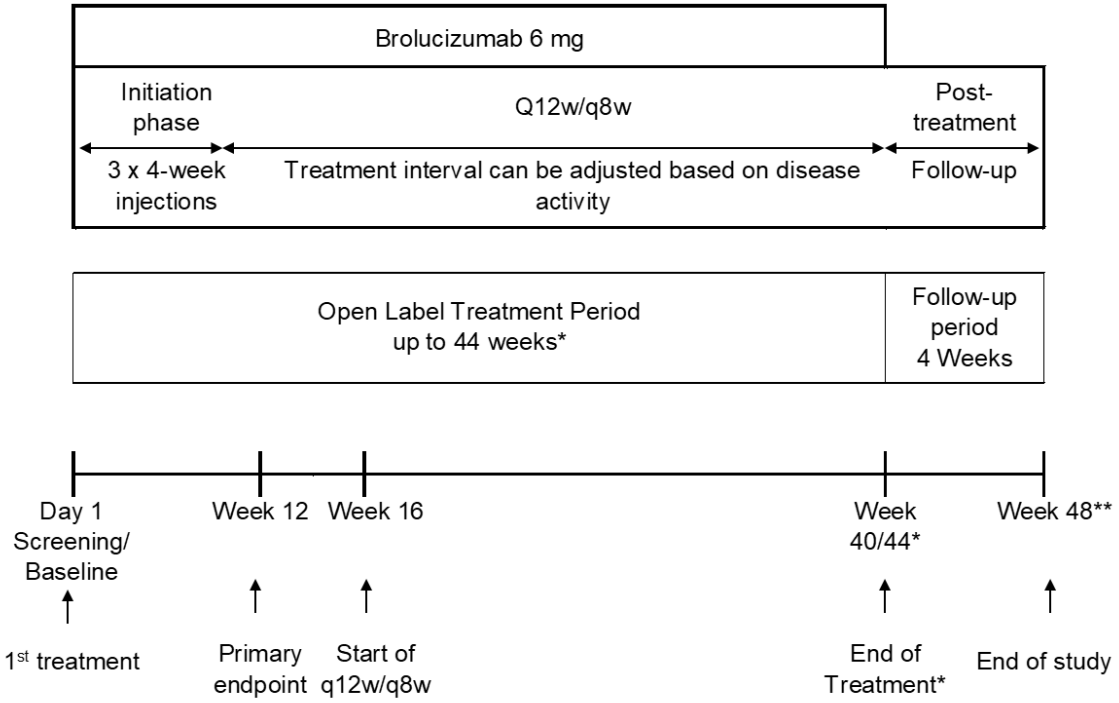
Planned number of patients

Approximately 210 adult patients will be screened and included (10% dropout rate and uninterpretable images at Baseline and Week 12 are expected) in France. The maximum study duration for 1 patient is 48 weeks, including Screening.

There will be 2 periods in this study (see Figure 1-1):

- Open-label treatment period: from Screening/Baseline (Day 1) to Week 40/Week 44 (depending on assigned regimen)
- Follow-up period: Week 40/Week 44 to Week 48

Figure 1-1 Study design



* Week 40 or Week 44 according to treatment schedule

** End of study visit: 4 or 8 weeks after the last IVT, depending on the last IVT date

Patients will receive 3 initial doses every 4 weeks ((Day 1, Week 4 and Week 8) loading phase), which should be at least 21 days apart, followed by treatment q12w with the possibility of adjusting to treatment q8w based on disease activity.

Disease activity will be assessed based on investigator's judgment of visual acuity and anatomical parameters as provided in the guidance to the investigators, e.g. decrease of visual acuity and/or other signs of the disease (e.g. intraretinal fluid (IRF), subretinal fluid (SRF), sub-retinal pigmented epithelium (sub-RPE) fluid, retinal hemorrhage, central retinal thickness (CRT) increase, etc.). Disease activity will be assessed during the first q12w interval at Week 16. If no disease activity is observed by the investigator in the study eye, disease activity will be assessed every 12 weeks (at Week 20, Week 32 and Week 44). If disease activity is observed by the investigator in the study eye at any of these visits, the study treatment will be adjusted by the investigator to a q8w treatment regimen and will remain on this regimen until Week 40/Week 44. Patients who require study treatment every 4 weeks after the initiation phase will be discontinued from further study treatment at the next visit.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objectives	**Endpoints for primary objectives**
• To evaluate the short-term effect of brolucizumab on CNV lesion area as measured by OCT-A in nAMD patients.	• Percentage change in CNV lesion area measured by OCT-A from Baseline to Week 12.
Secondary objectives	**Endpoints for secondary objectives**
• To evaluate the long-term effects of brolucizumab on CNV morphology as measured by OCT-A in nAMD patients.	• Percentage change in CNV lesion area measured by OCT-A from Baseline to Week 48. • Change in OCT-A features assessed by qualitative and quantitative criteria from Baseline by visit at Week 12 up to Week 48.
• To evaluate the effect of brolucizumab on anatomical parameters as assessed by SD-OCT and FA from Week 12 up to Week 48.	• Change in SD-OCT and FA features assessed by qualitative and quantitative criteria (e.g. CSFT, sub- and/or intraretinal fluid, sub-RPE fluid) from Baseline by visit up to Week 48.
• To evaluate the efficacy of brolucizumab up to Week 48 by assessing changes in BCVA.	• Change in BCVA from Baseline up to Week 48.
• To estimate the proportion of patients treated at q12w frequency with brolucizumab.	• Proportion of patients who are maintained on an exclusive q12w interval following the loading phase through to Week 48.
• To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab.	• The probability of the first q12w interval for determining successful q12w maintenance at Week 48.
• To evaluate the time from last IVT injection in the initiation phase to first visit with no disease activity.	• Time from last IVT injection in the initiation phase to first visit with no disease activity.
• To evaluate the safety of brolucizumab.	• Incidence of AEs (serious and non-serious) reported in patients treated with brolucizumab.

AEs= adverse events, BCVA= best corrected visual acuity, CNV= choroidal neovascularization, CSFT= central sub-field retinal thickness, FA= fluorescein angiography, IVT= intravitreal nAMD= neovascular age-related macular degeneration, OCT-A= optical coherence tomography-angiography, SD-OCT= spectral domain optical coherence tomography, sub-RPE= subretinal pigmented epithelium

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, maximum and 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 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 maintenance treatment from Week 16/Week 20 up to Week 40/Week 44. 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 CRF 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). Intraocular pressure (IOP) will be assessed in the study eye, pre-dose and post-dose at every injection. The last available assessment taken prior to the first IVT injection of study treatment is taken as the "Baseline" assessment.

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 and fundus examinations). 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.

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 40 to 44 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.

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

Event for maintenance q12w interval: In case the investigator selects q12w interval for a patient and the patient maintains the q12w interval until the first q8w interval has started then this will be considered as an event. In case the investigator maintains q12w interval (does not select q8w interval at any time in study) until EOS or patients got early discontinuation from study then patients will be considered as censored.

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 disease activity. If patients with active disease status or early discontinue then patients will be considered as censored for disease activity.

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.

Maximum duration of dry retina: The longest consecutive interval of dryness will be considered as maximum duration of dryness. This duration will be obtained from end date of dryness and start date of dryness for longest interval. If subjects obtain dryness at end of study then duration will be obtained from end of treatment.

Study eye and fellow eye: The investigator selects the eye with the worse BCVA at Screening as the study eye. Otherwise, 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.

CNV lesion area

A new angiography tool, namely optical coherence tomography-angiography (OCT-A) is a dye-less angiographic procedure based on split-spectrum-decorrelation-amplitude angiography that has become an essential and widely used tool, particularly for imaging CNV and vascular diseases of the retina. The literature suggests that OCT-A is a good marker for assessing anti-VEGF therapeutic response, especially the lesion size that has been demonstrated to decrease under anti-VEGF therapy.

OCT-A will be used in this study to assess the morphological response of patients to brolucizumab in terms of percentage change in CNV lesion area in the short term (i.e. at Week 12 just after loading doses) and in the long term (i.e. at Week 48 [12 months]), as well as changes in other OCT-A features up to Week 48.

The primary endpoint is the percentage change in CNV lesion area measured by OCT-A from Baseline to Week 12. The Week 12 time point has been selected as peak efficacy has been demonstrated in the pivotal trials of brolucizumab for this time point.

Anatomic parameters measured by OCT-A and SD-OCT

Anatomic parameters measured by OCT-A and by SD-OCT will be analyzed by a CRC. The main aim of the CRC analysis is to confirm anatomic features from OCT-A and SD-OCT images for the primary endpoint. The investigator will evaluate the OCT-A and SD-OCT images to assess the status of disease stability.

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.

A patient who misses Week 16 will undergo the disease activity assessment at Week 20 as he/she would have done if the visit had not been missed. If, however, a patient misses any of the following disease activity assessment visits (Week 20, Week 32) then the patient will be assumed to have met the disease activity criterion at the missed visit and will be reassigned to a q8w regimen up to study exit.

If a patient misses Week 12, then the Week 8 values will be applied as the reference for disease activity assessments up to and including Week 44.

Fluorescein angiography: Fluorescein angiography (FA) is a diagnostic procedure that uses a special camera to record the blood flow in the RETINA – the light sensitive tissue at the back of the eye.

Color fundus photography (CFP): CFP is a diagnostic procedure that involves the use of a device known as a fundus camera to record colored images of the interior surface of the eye. The goal of this procedure is to monitor the presence of disorders and their change with time.

Fundus autofluorescence (FAF): Fundus autofluorescence imaging is an *in vivo* imaging method for metabolic mapping of naturally or pathologically occurring fluorophores of the ocular fundus.

Indocyanine green angiography (ICG): ICG is a diagnostic procedure that uses ICG dye to examine the blood flow in the choroid – the layer of blood vessels that lies underneath the retina. ICG is injected into a vein in the arm/hand. As the dye passes through the blood vessels of the eye, photographs are taken to record the blood flow.

Intraocular pressure (IOP): IOP is the fluid pressure of the eye. IOP is measured in millimeters of mercury (mmHg). Normal eye pressure is usually considered to be between 10 and 25 millimeters of mercury (mmHg).

Fundus examination: Fundus examination used to assess diagnose vitro-retinal diseases (such as retinal haemorrhage, vitreal haemorrhage, retinal tear and detachment), optic nerve defects and hereditary diseases.

[redacted]

2.1.2 Visit windows for data analysis

Visit windows will be used for the data analysis, as per the planned visits in the protocol. During the q12w/q8w 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 71 – 97
Week 16	16	112	Day 99 – 119
Week 20	20	140	Day 127 – 153
Week 24	24	168	Day 155 – 182
Week 28	28	196	Day 183 – 209
Week 32	32	224	Day 211 – 237
Week 36	36	252	Day 239 – 265
Week 40	40	280	Day 267 – 293
Week 44	44	308	Day 295 – 321
Week 48	48	336	Day 323 – 349

* Baseline measurement before the first treatment administration.

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; therefore, the investigators should 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.

2.2 Analysis sets

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

Full Analysis Set (FAS): The FAS comprises all patients to whom study treatment has been assigned and who received at least one IVT injection of study treatment.

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

Per-Protocol Set (PPS): The 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 the 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.

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 both estimands is to have similar conclusions. Inconsistencies in the results will be examined and discussed in the CSR.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The FAS will be used to prepare the 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 will be summarized with reasons for premature discontinuation for the ENR. 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 the ENR.

Study treatment will be discontinued under the following circumstances:

- Adverse event
- 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

2.3.2 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 enrolled 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).

2.3.3 Demographic characteristics

Demographic and Baseline characteristics will be listed and summarized descriptively for overall patients on FAS and Safety Set.

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

- Sex (male, female)
- Age (in years)
- Age category (< 50, 50 - 65, 65 - 75, 75 - 85, ≥ 85)
- Study eye (left [OS], right [OD])
- Vital signs (sitting systolic/diastolic blood pressure [mmHg], sitting pulse rate [bpm]) only on the days study treatment is administered, it is measured prior study treatment

2.3.4 Baseline characteristics

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

- Time since nAMD diagnosis
- Time since nAMD diagnosis (< 1 month, 1-3 months and > 3 months)
- 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
- FA (analyzed by Vienna [CRC])
  1. Lesion type (only at Baseline) (predominantly classic, minimally classic, occult)
  2. Lesion type (only at Baseline) (type 1 / type 2 / type 3 / type 1 with aneuvrism / polyps)
  3. CNV location (subfoceal, juxtafoveal, extrafoveal)
  4. Area of lesion associated with CNV (mm^2)
- ICG (analyzed by Vienna [CRC])
  1. Lesion type (only at Baseline) (type 1 / type 2 / type 3 / type 1 with aneuvrism / polyps)
  2. Area of lesion associated with CNV (mm^2)
- SD-OCT (analyzed by Vienna [CRC])
  - Lesion type (only at Baseline) (type 1, type 2, type 3)
  - CSFT (µm)
  - 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
- OCT-A (analyzed by Vienna)
  1. CNV location (only at Baseline)
  2. CNV lesion area (at the biggest surface) (mm^2/μm^2)
- Fundus observation
  1. Retinal hemorrhage (none, retinal macular and retinal non-macular)
  2. Presence of vitreal hemorrhage (Yes, No)
  3. Retinal tear/ detachment (none, tear, detachment, both)
- Color fundus photography (CFP)
  1. Presence of retinal or subretinal hemorrhage (Yes, No)
  2. Presence of fibrosis (Yes, No)
  3. Presence of atrophy (Yes, No)
  4. Subretinal blood affecting foveal center point and/ or > 50% of total lesion (Yes, No)
- Fundus autofluorescence (FAF)
  1. Presence of macular atrophy (Yes, No)
  2. Area of macular atrophy
- Intraocular pressure
- Intraocular pressure (≤ 10, 10-25, 25-30 and ≥ 30 [mmHg])
- Disease activity assessment (Present)
- History of primary diagnosis:
  1. Disease (neovascular age-related, macular degeneration [nAMD])
  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 photocoagulation
  3. Previous submacular surgery, other surgical intervention or laser treatment for nAMD including photodynamic therapy (PDT)
- Concomitant medication at Baseline
- Medical history
- Co morbidities

2.3.5 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 (any 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 (any eye, study eye and fellow eye and both eye).

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

2.4.1 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. Overall number of injections (n, q1, median, q3, min and max) will presented.
2. Number of injection (n, q1, median, q3, min and max) before or at Week 8 and greater than Week 8.
3. Number of patients with injection (1 injection, 2 injections up to the maximum number of injections) from Baseline to the end of the treatment period 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. Summary statistics (n, mean, std, median, 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. 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 for the Safety Set and FAS. The exposure data will be listed for the FAS.

2.4.2 Prior, concomitant and post therapies

Each medication has the start and end dates recorded on the eCRF. Prior medications 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
- Concomitant medications which started prior to first dose of study treatment
- Concomitant medications 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 any eye, study eye and the fellow eye. A listing of all prior and concomitant medications and concomitant 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.

2.4.3 Prior and concomitant surgery and procedures

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

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 Analysis of the primary objective

2.5.1 Primary endpoint

OCT-A will be used in this study to assess the morphological response of patients to brolucizumab. In terms of percentage change in CNV lesion area (at the biggest surface) (mm^2).

The primary endpoint is the percentage change in CNV lesion area measured by OCT-A from Baseline to Week 12 in the study eye. The percentage change from Baseline at Week 12 in the lesion area will be derived as follows:

([Lesion area at Week 12 – Lesion area at Baseline]*100)/ Lesion area at Baseline

Descriptive statistics (n, mean, std, median, min and max) for the primary endpoint (actual value, change from Baseline, percentage change from Baseline) will be presented based on observed data using the FAS. Furthermore, a 2-sided 95% CI using Student's t-distribution will also be provided. In case of significant outliers or deviations from normality assumptions then IQR will be presented.

The last observation carried forward (LOCF) method will be used as sensitivity analysis to impute missing record for CNV lesion area at post baseline. If there is significant amount of missing record then another table with LOCF records should be created.

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

2.5.2 Supportive analyses

Subgroups analyses according to patient characteristics, like sex (male, female), age class (≤ 64, > 65 - 75, 75 - 85, ≥ 85), Baseline lesion type (type 1, type 2, type 3) and time since nAMD diagnosis (< 1 month, 1-3 months, and > 3 months).

2.6 Analysis of secondary efficacy objectives

2.6.1 Secondary endpoints

2.6.1.1 Oct-A long-term effects

The first secondary endpoint is the percentage change in CNV lesion area (mm^2) measured by OCT-A for nAMD patients from Baseline to Week 48. Descriptive statistics (n, mean, std, median, min and max) for the change in CNV lesion (actual value, change from Baseline, percentage change from Baseline) will be presented based on observed data by visit. Furthermore, a 2-sided 95% CI using Student's t-distribution will be provided.

The number and percentage of lesion type (predominantly classic, minimally classic and occult) will be presented by visit.

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

2.6.1.2 Spectral domain optical coherence tomography (SD-OCT)

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

2.6.1.2.1 Central sub-field retinal thickness (CSFT)

Summary statistics of central sub-field retinal thickness (CSFT) measured by SD-OCT for nAMD patients will be presented by visit along with change and percentage change from Baseline in CSFT.

The number and percentage of patient with CSFT category (< 300, ≥ 300 - 450, ≥ 450 - < 650, ≥ 650 (μm)) will be presented by visit.

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

2.6.1.2.2 Presence of fluid (YES/NO)

The number and percentage of patients with below fluid will presented by visit.

1. Intraretinal fluid
2. Subretinal fluid
3. Sub-RPE fluid
4. Without IRF or SRF
5. Without any fluid (IRF/SRF/sub-RPE)
6. 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 only on the study eye. The analysis will be performed on the FAS.

2.6.1.2.3 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 only on the study eye. The analysis will be performed on the FAS.

2.6.1.2.4 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. Detailed KM results will be presented including time (week), number of patients under risk at visit (without dry retina), number of patients with dry retina at visit (event), probability of dry retina (survival probability) at visit and 95% CI at visit.

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: • Absence of dry retina until EOS • Early discontinuation without dry retina
Duration of time	(End date – start date) +1

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

2.6.1.2.5 Maximum duration of dryness

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

Detailed KM results will be presented including time (week), total number of patients having fluids (risk), number of patients under achieved maximum duration (event), probability of maximum duration of dryness (survival probability) and 95% CI.

Variable	Definition
Start date	Start date of treatment
Event	Dryness
End date of event	Start date of dryness
Censoring (end date)	Earliest of: • Absence of dryness until EOS

Duration of time	• Early discontinuation with absence of dryness (End date – start date) +1 (Maximum duration will be used)

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

2.6.1.3 Fluorescein angiography (FA)

The number and percentage of CNV location (subfocal, juxtafoveal, extrafoveal) at Week 12 will be presented for both study eye and fellow eye.

The summary statistics (n, mean, std, median, min and max) of area of lesion associated with CNV (mm**2) will be presented at Week 12 for study eye and fellow eye, along with change from Baseline and percentage change from Baseline.

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

2.6.1.4 Best corrected visual acuity (BCVA)

The summary statistics (n, mean, std, median, min and max) of BCVA for nAMD patients will be presented along with change and percentage change from Baseline in BCVA by visit. Along with below BCVA category.

1. BCVA (≤ 55, 56 - 70 and ≥ 71).
2. Increase of ≥ 5, ≥ 10 and ≥ 15 letters in BCVA from Baseline up to Week 48.
3. Loss of ≥ 5, ≥ 10, ≥ 15 and ≥ 30 letters in BCVA from Baseline up to Week 48.
4. BCVA ≥ 84.

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

2.6.1.5 Dosing regimen of brolucizumab

The binomial proportion and 95% CI using the Clopper-Pearson method will be provided for patients who are maintained on an exclusive q12w interval following the loading phase through Week 48.

The number and percentage of q8w dose frequency patients will be presented along with 95% CI using the Clopper-Pearson method.

Duration of dose is defined as (date of last dose – start date of dose).

The summary statistics (n, mean, std, first quartile, median, third quartile, min and max) for duration of dose will be provided for patients who are maintained on an exclusive q12w interval following the loading phase through Week 48. In the study design the 3 × 4-week dosing frequency, in initiation phase.

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

2.6.1.5.1 Predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab

The probability of the first q12w interval will be derived from KM time to event analyses. KM plot will be provided. Detailed KM results will be presented including time (week), number of patients under risk at visit, number of patients with first q12w or discontinue at visit, probability of maintaining on q12w (survival probability) and 95% CI for maintaining on q12w.

Variable	Definition
Start date	First date when patients on q12w interval
Event	Fail maintain to q12w interval
End date	Last date of initial q12w interval (before or on first start of q8w interval)
Censoring (end date)	Completed/Discontinue with q12w
Duration of time	(End date – start date) +1

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

2.6.1.6 Disease activity assessments

The number and percentage will be presented by visit for disease activity assessment.

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

2.6.1.6.1 Duration of time from start of dose to till no disease activity

The median of duration of time is obtained from KM analysis along with 2-sided 95% CI will be presented. KM plots will be provided.

Detailed KM results will be presented including time (week), number of patients with no disease activity at visit, number of patients under risk at visit (with disease activity), probability of disease activity (survival probability) at visit and 95% CI at visit.

Variable	Definition
Start date	Start date of start of IVT injection/ last IVT injection in the initiation phase
Event	No disease activity
End date of event	Date of first visit with no disease activity
Censoring (end date)	Earliest of: • With disease activity until EOS • Early discontinuation
Duration of time	(End date – start date) +1

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

2.8 Analysis of other efficacy variables

2.8.1 Color fundus photography

The number and percentage will be provided at Screening/Baseline, week 12 and end of study (Week 48) for below questions:

- Was color fundus photography performed? If not, then reason for not performed CFP.
- Presence of retinal hemorrhage in central subfield.
- Presence of subretinal hemorrhage in central subfield.
- Presence of fibrosis in the central subfield the diameter of 3000 µm.
- Presence of atrophy in the central subfield the diameter of 3000 µm.
- Is there subretinal blood affecting the foveal center point and/or >50% of total lesion.
- Presence of Vasculitis.

The above analysis will be done on both eyes. The analysis will be performed on the FAS.

2.8.2 Fundus autofluorescence (FAF)

The number and percentage will be provided at Baseline, week 4 and end of study (week 48) for below question.

- Fundus auto-fluorescennce performed at visit. If not then reason for not performed FAF.
- Presence of macular atrophy in the central subfield (center 1 mm circle).
- Presence of foveal atrophy.

The summary statistics (n, mean, std, median, min and max) of area of macular atrophy (mm^2) will be presented at Baseline, Week 4 and Week 48 along with change from Baseline and percentage change from Baseline in FAF.

The above analysis will be done on the both eye. The analysis will be performed on FAS.

2.8.3 Indocyanine green angiography (ICG)

The number and percentage of lesion type (only at Baseline) (type 1 / type 2 / type 3 / type 1 with aneuvrism / polyps) at Baseline will be provided.

The summary statistics (n, mean, std, median, min and max) for area of lesion associated with CNV (mm^2) at Baseline and Week 12 will be provided along with summary statistics for change from Baseline and percentage change from Baseline at week 12 for area of lesion.

The above analysis will be done on both eyes. The analysis will be performed on the FAS.

2.8.4 Intraocular pressure

Intraocular pressure will be collected in the CRF at Baseline and Week 48. The summary statistics of IOP for nAMD patients will be presented at Week 48 along with change from Baseline and percentage change from Baseline in IOP. In addition, the number and percentage of patients with IOP ($\leq$ 10, 10-25, 25-30 and $\geq$ 30 [mmHg]) will be presented at Week 48.

The above analysis will be done on both eyes. The analysis will be performed on the FAS.

2.8.5 Fundus examination

The below variables of number and percentage will presented for study eye and fellow eye by visit.

- Retinal hemorrhage (none, retinal macular and retinal non-macular)
- Presence of vitreal hemorrhage (no, yes)
- Retinal tear/detachment (0- none, 1- retinal tear, 2- retinal detachment, 3- retinal tear and detachment)
- Presence of intraocular inflammation (no, yes)
- Presence of vasculitis.

Listing of fundus examination parameter will be provided by patient and visit.

The above analysis will be done on the both eye. The analysis will be performed on the FAS.

2.9 Safety analyses

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

2.9.1 Adverse events (AEs)

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, procedure related, death, SAEs and other significant AEs action taken leading to study treatment interruption & treatment withdrawn.

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. System organ classes will be presented in alphabetical order, PTs 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 any eye, study eye and fellow eye.

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 AEs in a $\leq$ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

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

In addition, all treatment emergent AEs 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 any eye, study eye and fellow eye.

A summary of action taken with number and percentage of patients will presented with dose increased, no dose change, dose reduced, treatment interrupted, drug withdrawn, not applicable and unknown.

2.9.1.1 Adverse events of special interest / grouping of AEs

The number (%) of patients with AESIs will be summarized by standardized MedDRA query and PT. Listing will also be provided.

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.live 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, AESI by SOC (confirmed by SRC) and 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.

2.9.2 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 for each 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

2.12 Biomarkers

Not applicable.

2.13 Other exploratory analyses

Not applicable.

2.14 Interim analysis

The analysis based on the Week 12 data, i.e. data up to and including Week 12 will be the primary (first) analysis for this study.

A second planned analysis of the data after the EOS/Week 48 visit will be performed once all patients have completed or prematurely discontinued the study.

3 Sample size calculation

The primary objective of the study is to evaluate the effect of brolucizumab on CNV lesion area as measured by OCT-A in nAMD patients starting treatment with brolucizumab. This will be evaluated by the percentage change in CNV lesion area measured by OCT-A from Baseline to Week 12. The sample size calculation is based on the hypothesis of a standard deviation of 35% for this reduction proportion (Miere et al 2018).

A sample size of 180 to 400 patients produces a 2-sided 95% CI with a distance from the mean to the limits ranges from 5.1 to 3.4 when the estimated standard deviation is 35.0 (nQuery Advisor version 7.0). Therefore, to have a precision of 5%, a sample size of 189 patients will be needed (Table 3-1).

To take into account a dropout rate and uninterpretable images of 10%, a total of 210 patients will be included.

Table 3-1 Confidence intervals for one mean numeric results for 2-sided confidence intervals with unknown standard deviation

Confidence Level	Sample Size (N)	Distance from Mean to Limits	Standard Deviation (S)
0.950	180	5.1	35.0
0.950	189	5.0	35.0

0.950	233	4.5	35.0
0.950	250	4.4	35.0
0.950	300	4.0	35.0
0.950	350	3.7	35.0
0.950	385	3.5	35.0
0.950	400	3.4	35.0

4 Change to protocol specified analyses

[redacted]

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.

- 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.
- If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
  1. 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).
  2. 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).
- If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
  1. 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).
  2. 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).
- If the AE start date year value is equal to the treatment start date year value:
  1. 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.
  2. 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).
  3. 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 and medical history (nAMD) date imputation

This algorithm is used when event is the partial start date of the concomitant medication and medical history (nAMD).

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 StartTRTSDT)	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 ELSE IF relative reference start = TRTSDT+1 ' ' THEN
(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 Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 and above.

5.3 Vital signs 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 methodology

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;
```

t-test

```
proc ttest data = pccnv_w12;
      class population_group;
      var pchg
run;
```

Wilcoxon rank-sum test

```
proc npar1way wilcoxon data= rnksm (label='CNV lesion area at week 12');
      class estimand;
      var area;
```

```
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 analysis	1
INCL02	Age less than 50 year	Included in everything	0
INCL03	No active CNV lesions	Excluded from FAS and PPS	1
INCL04	No Intra- and/or subretinal fluid	Excluded from FAS and PPS	1
INCL05	Study eye BCVA out of range	Excluded from PPS	2
EXCL01	Active infection in either eye	Excluded from PPS	2
EXCL02	Fellow eye ocular disease	Included in everything	0
EXCL03	Poor quality images	Included in everything	0
EXCL03a	History of IOI	Included in everything	0
EXCL05	Study eye lesion area ⩾50%	Included in everything	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
EXCL05a	Study eye atropathy or fibrosis	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 uncontrolled glaucoma	Included in everything	0
EXCL11	Study eye aphakaia	Included in everything	0
EXCL12	Other treatment in study eye	Excluded from PPS	2
EXCL13	Steroids in study eye	Included in everything	0
EXCL14	Prior keratoplasty/vitrectomy	Included in everything	0
EXCL15	Study eye previous ocular treatment	Included in everything	0
EXCL16	End stage renal disease requiring dialysis or renal transplant	Included in everything	0
EXCL17	Systematic drug toxic to eye	Included in everything	0
EXCL18	Participation in another study	Excluded from PPS	2
EXCL19	Systematic anti-VEGF therapy	Included in everything	0
EXCL20a	Stroke or myocardial infraction	Included in everything	0
EXCL21	Uncontrolled blood pressure	Included in everything	0
EXCL22	Malignancy	Included in everything	0
EXCL22a	Medical condition impact	Included in everything	0
EXCL24	Hypersensitivity	Included in everything	0
EXCL25	Pregnant or nursing woman	Included in everything	0
EXCL26	Women of childbearing potential	Included in everything	0
EXCL27	Minor or protected adult	Excluded from PPS	2
COMD01	Prohibited medication/procedures	Included in everything	0
COMD02	Steroids use 5 days prior to IP	Included in everything	0
TRT01	Wrong IP administered	Excluded from PPS	2
TRT02	Incorrect dose administered	Excluded from PPS	2
TRT03	Pregnancy but not discontinued	Included in everything	0
TRT04	Short treatment window between treatment	Included in everything	0
TRT05	Treatment > 3 days after injection visit	Included in everything	0
TRT06	Injection given at Week 12	Excluded from PPS	2
TRT07	Q8W IVT out of window	Included in everything	0
TRT08	Q12W IVT out of window	Included in everything	0
TRT09	COVID-19 Drug supply change	Included in everything	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
TRT10	COVID-19 Treatment not given	Included in everything	0
TRT11	Missed Injection loading phase	Excluded from PPS	1
TRT12	Missed Injection	Included in everything	0
TRT13	No Disease activity but injection is given	Included in everything	0
TRT14	Treatment admin prior effic/safty evaluation	Included in everything	0
TRT15	Treatment given at EOS	Included in everything	0
WITH01	Withdrew consent not discontinued	Excluded from FAS and PPS	1
OTHER01	Patient rescreened > once	Included in everything	0
OTHER02	Severe ICH-GCP non-compliance	Excluded from FAS and PPS	1
OTHER03	New ICF is missing-rescreened	Excluded from FAS and PPS	1
OTHER04	Mishandling IP	Included in everything	0
OTHER05	Temperature excursion IP administered	Included in everything	0
OTHER06	Treatment regimen wrongly adjusted	Included in everything	0
OTHER07	Missed mandatory visit	Excluded from PPS	2
OTHER08	Missed injection visit	Included in everything	0
OTHER09	FA out of window	Included in everything	0
OTHER10	Rescreen due to BCVA results	Included in everything	0
OTHER11	Rescreen >14days w/o screening procedure	Included in everything	0
OTHER13	COVID-19 Missed visit	Included in everything	0
OTHER14	COVID-19 Visit not at site	Included in everything	0
OTHER15	COVID-19 Assessment changed	Included in everything	0
OTHER16	COVID-19 Discontinuation	Included in everything	0
OTHER17	Efficacy assessment not done	Excluded from PPS	2
OTHER18	Safety assessment not done	Included in everything	0
OTHER19	BCVA not done correctly	Included in everything	0
OTHER20	Visit window > 7 days	Included in everything	0
OTHER21	Vital signs/safety call not done	Included in everything	0
OTHER22	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
FAS-EST	1
PPS	1,2 (All specified PD in Table 5.1 due to COVID)
PPS-EST	1, 2 (All specified PD in Table 5.1 due to COVID-19)
SAF	NA

6 Reference

Miere A, Oubraham H, Amoroso F, et al (2018) Optical Coherence Tomography Angiography to Distinguish Changes of Choroidal Neovascularization after Anti-VEGF Therapy: Monthly Loading Dose versus Pro Re Nata Regimen. J Ophthalmol. Epublished at [doi: 10.1155/2018/3751702].