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Novartis Research and Development

RTH258/Brolucizumab

Clinical Trial Protocol 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)

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List of abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
AMD	Age-related Macular Degeneration
ATC	Anatomic Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
BCNVA	Best Corrected Near Visual Acuity
CI	Confidence Interval(s)
CFP	Color Fundus Photography
CFR	Code of Federal Regulation
CMO & PS	Chief Medical Office & Patient Safety
CNV	Choroidal Neovascularization
COVID-19	Coronavirus disease 2019
CRC	Central Reading Center
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRT	Central Retinal Thickness
CSFT	Central Sub-Field Thickness
CSR	Clinical Study Report
DA	Disease Activity
EDC	Electronic Data Capture
EOS	End of Study
ETD	Early Treatment Discontinuation
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAF	Fundus AutoFluorescence
FAS	Full Analysis Set
FIR	First Interpretable Results
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICG	Indocyanine Green Chorioangiography
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IOI	Intraocular Inflammation
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRF	Intraretinal Fluid
IVT	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities

MMRM	Mixed Model Repeated Measures
nAMD	Neovascular Age-Related Macular Degeneration
NIH	National Institutes of Health
OCT	Optical Coherence Tomography
PD	Protocol Deviation
PDT	Photodynamic Therapy
PED	Pigment Epithelial Detachment
PPS	Per-Protocol Set
q8w	Every 8 Weeks
q12w	Every 12 Weeks
QMS	Quality Management System
RAP	Retinal Angiomatous Proliferation
RO	Retinal Vascular Occlusion
RPE	Retinal Pigmented Epithelium
RV	Retinal Vasculitis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
scFV	Single-Chain Antibody Fragment
SD-OCT	Spectral Domain Optical Coherence Tomography
SMQ	Standardized MedDRA Query
SOC	Standard Of Care
SRF	Subretinal Fluid
Sub-RPE	Sub Retinal Pigmented Epithelium
SUN	Standardization Uveitis Nomenclature
USM	Urgent Safety Measure
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
YAG	Yttrium aluminum garnet

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Dosage	Dose of the study treatment given to the patient in a time unit.
Electronic data capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Masked/evaluating investigator	For the entire study duration and all study patients, the masked/evaluating investigator is responsible for all aspects of the study (the conduct/supervision of all assessments and treatment decisions except the injection procedures and the safety assessment following the study drug injections).
Medication number	A unique identifier on the label of each study drug package.
Medication pack number	A unique identifier on the label of each drug package.
Patient	An individual with the condition of interest
Period	A subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Screen failure	A patient who is screened but is not treated
Source data/document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study completion	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)

Study treatment discontinuation	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Patient	A trial participant (can be a healthy volunteer or a patient)
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 1 (12-Dec-2019)

Rationale

The purpose of this amendment is to incorporate change which resulted from interactions with Ethic Committee, who required to exclude patients mentioned in Articles L.1121-5 to L.1121-8 and L.1122-1-2 of the Code de Santé Publique (e.g. minors, protected adults, etc.)

Changes to the protocol

List the modifications implemented in the different sections,

- Exclusion criteria (page 24)

IECs

These changes are considered not-substantial.

The amendment is to be sent to the IECs for final approval.

These changes have no impact on the ICF.

Amendment 2 (21-Oct-2020)

Amendment Rationale

The main purpose of this amendment is to provide clarification and guidance on safety assessments in accordance to the urgent safety measure regarding the post-marketing reports with brolucizumab (Beovu®) in the treatment of nAMD, which were identified as retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation (IOI) that may result in severe vision loss. In addition, the amendment includes modifications due to the COVID-19 pandemic.

Changes to the protocol

Changes incorporated based on this emerging safety issue are as follows:

- Section 1.1 (Background): Information was added to describe a new safety signal from post-marketing case reports and its impact on the benefit-risk balance.
- Section 4.5 (Background): Information was added to describe a new safety signal from post-marketing case reports and its impact on the benefit-risk balance.
- Section 6.2.1.1 (Permitted concomitant therapy requiring caution and/or action): Restrictions in use of corticosteroids have been removed to provide flexibility using systemic steroids for the treatment of AEs at the investigator's discretion.
- Section 6.7.2 (Instructions for prescribing and taking study treatment): Additional guidance was added to this section emphasizing that if any sign of IOI is present, an IVT injection **must not** be performed and patients should be treated for IOI according to clinical practice.
- Additional examination and assessments were included to fully characterize cases of IOI in the following sections:
  - Section 8, Table 8-1 (Assessment schedule for the study eye)
  - Section 8.3.2 (Color fundus , fundus autofluorescence and fluorescein and indocyanine angiography)
  - Section 8.4.3 (Ophthalmic examination)
  - Section 8.4.4 (Appropriateness of safety measurements)

Changes incorporated to address the COVID-19 pandemic are as follows:

- Section 5.2 (Exclusion criteria): Exclusion criterion no. 16 was updated to add exception in case of temporary use for COVID-19 treatment.
- Section 6.2.2, Table 6-2 (Prohibited medication and procedures): Updated to add exception in case of temporary use of COVID-19 treatment.
- Section 8 (Visit schedule and assessments) and Section 8.4 (Safety): Added instructions to follow in case COVID-19 pandemic impacts on study visits.
- Section 12 (Data analysis)

Other changes incorporated in this amendment were as follows:

- Section 5.1 (Inclusion criteria), Protocol summary (Inclusion criteria), and Section 8.3 (Efficacy): Inclusion criterion no. 5, and other wording, was updated to clarify ETDRS testing occurs at an initial distance of 4 meters.
- Section 6.7.2 (Instructions for prescribing and taking study treatment): Language regarding the injection procedure was added replacing reference to an applicable manual**.**
- Section 8 (Visit schedule and assessments): Amended footnote no. 4 to clarify requirements for FA images. And clarification of treatment during unscheduled visit
- Section 8.4.3 (Ophthalmic examination): Added instructions for the patients in case of symptoms of inflammation.
- Section 10.1.3 (SAE reporting): Clarification of the SAE reporting period.
- Section 10.1.5, Table 10-1 (Guidance for capturing the study treatment errors including misuse/abuse): Amended to clarify that error should not be documented in the AE eCRF.
- Section 12.1 (Analysis sets): Modified to include importance of estimands per ICH E9(R1) guidance.
- Section 12.8.1 (Primary endpoint) : change of the patient recruitment period (from Jan 2020 to Sept 2020 to Jan 2021 to Sept 2021), due to study start delay ; the patient recruitment period remain of 9 months
- Section 15 (References): Added two references.

Minor editorial changes (e.g. typographical mistakes, grammatical changes, rewording) to improve flow and consistency have been made throughout the protocol.

IECs

These changes are considered substantial.

The amendment will be sent to the HA/IECs for approval.

These changes herein impact the ICF. Sites are required to update and submit for approval a revised ICF that takes into account the changes described in this protocol amendment.

Amendment 3 (14-Sept-2021)

Amendment Rationale

The main reason for the protocol amendment is to implement the Urgent Safety Measures (USM) described in the 10-Aug-21 Dear Investigator Letter (DIL) into the study protocol. The USM were implemented in response to the identification of a causal immune-mediated mechanism of the previously identified risk of – retinal vasculitis (RV), and/or retinal vascular occlusion (RO), typically in the presence of intraocular inflammation (IOI) – indicating a requirement to discontinue treatment with brolucizumab (RTH258) in patients who develop events of RV and/or RO. The protocol is hence amended to require discontinuation of study treatment in subjects who develop these events and provide clarification and guidance on the early discontinuation of study treatment.

This amendment also includes information on gender imbalance on IOI following brolucizumab treatment.

The safety sections were updated throughout the protocol including updating the Risks and Benefits section and creating a new section under Safety Monitoring to consolidate all the information regarding the risk mitigation into one section in the protocol. Additionally, as subjects treated with brolucizumab who experience intraocular inflammation may be at risk of developing retinal vasculitis and/or retinal vascular occlusion they should be closely monitored and the investigator needs to evaluate the appropriateness of continuing further with study treatment when IOI only (without RV and/or RO) is present.

Finally, clarification is provided on record of prior Intraocular or periocular use of corticosteroids in the study eye and remove of the study timelines and number of sites

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Editorial changes and spelling corrections are done throughout the protocol.

Protocol sections changed in relation to urgent safety measures (USM) are:

- Section 1.1 Background: Language was added to indicate the results of the mechanistic study BASICHR0049 of blood samples from nAMD patients exposed to brolucizumab and having subsequently developed RV and/or RO were added and that the impact on the risk/benefit balance is considered to be low when patients who develop RV and/or RO are discontinued from further treatment with brolucizumab.
- Section 3 Study design: Remove of the number of investigator sites. Clarified the difference between study completion as per protocol versus early treatment discontinuation.
- Section 4.5 Risks and Benefits: Information added to describe Urgent Safety Measures and additional information on gender imbalance on IOI following brolucizumab treatment. Added the urgent safety measures related to adverse events observed in patients treated with

brolucizumab from the MERLIN (CRTH258AUS04) study, the post marketing reports and the causal link (results of the mechanistic study BASICHR0049).

- Section 6.1.4 Treatment duration: Guidance added to clarify that subjects who prematurely discontinue from study treatment should continue in the study, and should return 4 weeks after last treatment to perform assessments for early treatment discontinuation.
- Section 6.7.2 Instruction for prescribing and taking study treatment: Text added to clarify that patients who require treatment every 4 weeks beyond the loading phase, should be discontinued from study treatment. Changes also made to update that if RV and/or RO is confirmed, subjects should be discontinued from study treatment. If only IOI (without RV and/or RO) is confirmed, the subject should be closely monitored and the investigator should evaluate the appropriateness of continuing further with study treatment. This has also been updated Table 6-3.
- Section 8: Visit schedule and assessments: Removed a sentence that two consecutive injections should be at least 21 days apart as this is not applicable in the maintenance phase, any subject who requires treatment every 4 weeks has to be discontinued from study treatment.
- Table 8-1 Assessment schedule: Columns added for early treatment discontinuation visits and for assessment visits after start of standard of care, including respective footnotes. A clarification was added in footnote #8 with respect to ophthalmic examinations and images. Updated the name of the ophthalmic examination where “and imaging” was added. Footnotes #10, #11, and #12 added with respect to ETD and EOS assessments.
- Section 8.4.5 Ophthalmic examination: Requirement of treatment discontinuation for brolucizumab was added if subject developed RV and/or RO.
- Section 9.1.1 Discontinuation of study treatment: Instructions were added for subjects who discontinue from study treatment early.
- Section 12 Data analysis and statistical methods: Language added to include analysis of impact of USM.
- Section 12.4.4 Sensitivity and supportive analyses: Sensitivity analysis added regarding impact of USM.

Other changes incorporated in this amendment:

- List of abbreviations: New abbreviations added in line with amendment 3.
- Protocol summary: Aligned with amendment 3.
- Section 6.2.1 Concomitant therapy: added instruction to record intraocular or periocular use of corticosteroids in the study eye taken up 6 months prior to Screening/Baseline
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action: Added guidance regarding SARS-CoV-2 vaccinations which should occur at least 7 days before or after the administration of study treatment.
- Section 8: Visit schedule and assessments: Clarification that 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.
- Section 8.4 Safety: Added a reference for monitoring, assessment and management of adverse events of inflammation, retinal vasculitis and/or retinal vascular occlusion.

- Section 8.4.4 Ophthalmic examination: Added “and imaging” to the header and to the related paragraph.
- Section 10 Safety monitoring and reporting: Consolidated the requirements for monitoring of adverse events of special interest that were already included in the previous version. Added the new requirement that if RV and/or RO is confirmed, subjects should be discontinued from study treatment. If only IOI (without RV and/or RO) is confirmed, the subject should be closely monitored and the investigator should evaluate the appropriateness of continuing further with study treatment.
- Section 10.1.3 SAE reporting: Clarified the timing for SAE reporting to Novartis as per latest protocol template.
- Section 12.8.1 Primary endpoints: Clarification regarding sample size analyses. Remove of the patient recruitment period duration and of the number of investigator sites

IECs

These changes are considered substantial.

The amendment will be sent to the IECs and HA for approval.

These changes have impact on the ICF.

Amendment 4 (16-Nov-2021)

Amendment Rationale

The main reason for the protocol amendment is to revise the sample size calculation. The initial sample size calculation for this study was done prior to COVID-19 pandemic and prior to the implementation of Urgent Safety Measures (USM). Due to COVID-19 and USMs, the originally planned number of patients can not be achieved. Thus, the sample size was re-assessed. This estimation can be achieved with acceptable precision with a sample size of 210. The study objectives will still be assessed with the revised sample size

[redacted]

This amendment also includes the Beovu brolucizumab EU SmPC update on 'Warnings and precautions for use' section, Patients treated with Beovu with a medical history of intraocular inflammation and/or retinal vascular occlusion (within 12 months prior to the first brolucizumab injection) should be closely monitored, since they are at increased risk of developing retinal vasculitis and/or retinal vascular occlusion. Besides, for patients developing intraocular inflammation events, even if not associated with retinal vasculitis and/or retinal vascular occlusion, treatment with Beovu should be discontinued and the events should be promptly managed.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Editorial changes and spelling corrections are done throughout the protocol.

Protocol sections changed in relation to the sample size revision are:

- Protocol summary: Aligned with amendment 4.
- Section 3 "study design" and Section 5 "Population" : change of number of patients to include
- Section 12.8.1 "Sample size calculation – Primary endpoint" : consideration of new estimation with acceptable precision

[redacted]

- [redacted]

Protocol sections changed in relation to the Beovu EU SmPC update on 'Warnings and precautions for use' section are:

- Protocol summary: Aligned with amendment 4.
- Section 1.1 'Background' and Section 4.5 'Risk and benefits': add of the new EU SmPC wording on intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion
- Section 5.2 'Exclusion criteria": add of the exclusion criteria "Medical history of intraocular inflammation and/or retinal vascular occlusion within 12 months prior to Screening/Baseline"
- Section 6.1.4 'Treatment duration': precision that treatment must be discontinued in case of any intraocular inflammation event
- Section 6.7.2 'Instruction for prescribing and taking study treatment' and Section 'Ophthalmic examination and imaging' and Section 9.1.1 'Discontinuation of study treatment" and Section 10 "Safety monitoring and reporting": clarification that treatment must be discontinued in case of any intraocular inflammation event, even if IOI only.

IECs

These changes are considered substantial.

The amendment will be sent to the IECs and HA for approval.

These changes have impact on the ICF.

Protocol summary

Protocol number	CRTH258AFR01
Full Title	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
Brief title	Study of brolucizumab in adult patients with neovascular age-related macular degeneration
Sponsor and Clinical Phase	Novartis/ Phase 3b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This multicenter study of patients with treatment-naïve neovascular age-related macular degeneration (nAMD) is being performed to assess both short and long-term effects of brolucizumab, a new generation of anti-vascular endothelial growth factor (anti-VEGF), on choroidal neovascularization (CNV) structure and activity. The safety and efficacy of brolucizumab has been demonstrated in 2 randomized, multicenter, double-masked, active controlled Phase 3 studies in nAMD patients (RTH258-C001 and RTH258-C002). Anatomical changes were evaluated in these studies using spectral domain optical coherence tomography (SD-OCT), which relied on indirect parameters for the diagnosis of active CNV. Since then, a new angiography tool, OCT-angiography (OCT-A) has been developed that allows direct visualization of retinal circulation. OCT-A has become an essential, widely used tool for imaging CNV and vascular diseases of the retina. The literature suggests OCT-A is a good marker for assessing anti-VEGF therapeutic response, especially 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), as well as changes in other OCT-A features up to Week 48.
Primary objective	• To evaluate the short-term effect of brolucizumab on CNV lesion area as measured by OCT-A in nAMD patients.
Secondary objectives	• To evaluate the long-term effects of brolucizumab on CNV morphology as measured by OCT-A in nAMD patients. • To evaluate the effect of brolucizumab on anatomical parameters as assessed by SD-OCT and fluorescein angiography (FA) up to Week 48. • To evaluate the efficacy of brolucizumab up to Week 48 by assessing changes in best-corrected visual acuity (BCVA). • To estimate the proportion of patients treated at every 12 weeks (q12w) frequency with brolucizumab. • To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab. • To evaluate the time from last intravitreal (IVT) injection in the initiation phase to first visit with no disease activity. • To evaluate the safety of brolucizumab.

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 every 8 weeks (q8w). Patients will receive 3 initial doses every 4 weeks (Day 1, Week 4 and Week 8), followed by treatment q12w with the possibility of adjusting to treatment q8w based on disease activity. Disease activity will be assessed by visual acuity and anatomical parameters at 2 visits (Week 16 and Week 20) during the first q12w interval and at each subsequent scheduled q12w visit (at Week 32 and Week 44). Patients who show disease activity at any of these visits will be adjusted to an q8w treatment regimen and will remain on this regimen until the end of the study at Week 48.
Population	The study population will be male and female patients ≥ 50 years old diagnosed with treatment-naïve active CNV secondary to nAMD and able to comply with study or follow-up procedures.
Key inclusion criteria	• Patients must give written informed consent before any study related procedures are performed. • Patients must be 50 years of age or older at Screening/Baseline. **Study eye:** • Active CNV lesions secondary to AMD that affect the central subfield, including retinal angiomatous proliferation (RAP) with a CNV component, confirmed by presence of active leakage from CNV seen by fluorescein angiography and sequellae of CNV, e.g. pigment epithelial detachment (PED), subretinal hemorrhage or sub-retinal pigment epithelium (sub-RPE) hemorrhage, blocked fluorescence, macular edema. • Intra and/or subretinal fluid affecting the central subfield of the study eye at Screening/Baseline. • BCVA between 83 and 23 letters, inclusive, in the study eye at Screening/Baseline using early treatment diabetic retinopathy study (ETDRS) at an initial testing distance of 4 meters.
Key exclusion criteria	• Any active intraocular or periocular infection or active intraocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis) in **either eye** at Screening/Baseline. • Medical history of intraocular inflammation and/or retinal vascular occlusion within 12 months prior to Screening/Baseline **Study eye:** • Poor quality of OCT-A and SD-OCT images at Screening/Baseline. • Patient has received any approved or investigational treatment for nAMD (other than vitamin supplements) in the study eye at any time. • Concomitant conditions or ocular disorders in the study eye, including retinal diseases other than nAMD, that, in the judgment of the investigator, could require medical or surgical intervention during the course of the study to prevent or treat visual loss that might result from that condition, or that limits the potential to gain visual acuity upon treatment with the investigational product.

	• Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication or according to investigator's judgment at Screening/Baseline. • Stroke or myocardial infarction in the 6-month period prior to Screening/Baseline. • Systemic anti-VEGF therapy at any time. • Women of childbearing potential, defined as all women less than 1 year postmenopausal or less than 6 weeks since sterilization at Screening/Baseline
Study treatment	Brolucizumab 6 mg 120 mg/mL (RTH258 6 mg/ 0.05 mL) solution for injection in pre-filled syringe
Efficacy assessments	• OCT-A • SD-OCT • Color Fundus Photography (CFP) • Fundus AutoFluorescence (FAF) • Fluorescein Angiography (FA) and Indocyanine Green Chorioangiography (ICG) (optional) • BCVA (EDTRS)
Key safety assessments	• Ophthalmology examination and imaging • Adverse events (AEs) • Vital signs
Data analysis	**Primary analysis data set** The primary data set for efficacy evaluation is the full analysis set (FAS). The FAS includes all patients to whom study treatment has been assigned and who received at least one IVT injection of study treatment. Supportive and sensitivity analyses will be performed which may include using the Per Protocol Set (PPS) and alternative methods of handling missing values including a mixed model repeated measures (MMRM). **Primary endpoint** The primary endpoint is the percentage change from baseline in CNV lesion area measured by OCT-A at Week 12. **Primary statistical method** Descriptive statistics 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% confidence interval (CI) using Student's t-distribution will also be provided. The interim database lock for the primary analyses will be conducted when the last patient included completed Week 12 visit. Subjects will remain in the study and will continue to receive treatment through the planned study duration of 48 weeks, to allow for further evaluation of efficacy and safety. [redacted] **Sample size justification** A sample size of 180 to 400 patients produces a 2-sided 95% CI with a distance from the mean difference in percentage change in CNV lesion area

	measured by OCT-A from baseline to Week 12 to the limits ranging from 5.1 to 3.4 when the estimated standard deviation is 35. Therefore, to have a precision of 5.0%, a sample size of 189 patients will be needed. To take into account a dropout rate and uninterpretable images of 10%, a total of 210 patients will be included.
Ethical and regulatory obligations	The study will be performed in accordance with • The European Directive 2001/20/EC. • The European General Data Protection Regulation. • The ICH Harmonized Tripartite Guidelines for GCP. • The ethical principles laid down in the Declaration of Helsinki.
Key words	Neovascular age-related macular degeneration, anti-VEGF, choroidal neovascularization, OCT-A

1 Introduction

1.1 Background

Neovascular age-related macular degeneration (nAMD) is characterized by the presence of choroidal neovascularization (CNV). Choroidal neovascularization consists of abnormal blood vessels originating from the choroid and can lead to hemorrhage, fluid exudation, and fibrosis, resulting in photoreceptor damage and vision loss.

Vascular endothelial growth factor (VEGF) has been shown to be elevated in patients with nAMD and is thought to play a key role in the neovascularization process (Spilsbury et al 2000). Anti-vascular endothelial growth factor (anti-VEGF) treatments, such as ranibizumab (Lucentis®) and aflibercept (Eylea®) have been demonstrated to improve visual acuity in patients with nAMD in multiple clinical trials.

Brolucizumab is a new generation of anti-VEGF. Brolucizumab is the first humanized single-chain antibody fragment (scFv), which inhibits vascular endothelial growth factor A (VEGF-A). The safety and efficacy of brolucizumab were assessed in 2 randomized, multicenter, double-masked, active treatment-controlled Phase 3 studies in nAMD patients (the HAWK study (RTH258-C001 [NCT02307682]) and the HARRIER study (RTH258-C002 [NCT02434328]) comparing brolucizumab every 12 weeks (q12w) or every 8 weeks (q8w) to aflibercept q8w according to its approved label.

In these studies, patients in both treatment arms received 3 loading doses every 4 weeks (Day 0, Week 4 and Week 8), followed by an q12w/q8w maintenance regimen for brolucizumab 6 mg arm and an q8w maintenance regimen for the aflibercept 2 mg arm. For the q12w/q8w treatment regimen, q12w/q8w treatment frequencies were allocated according to patient's individual treatment need based on disease activity assessments performed by the investigator at pre-specified visits. Within the q12w/q8w regimen, the initial treatment schedule after the loading phase was q12w. If disease activity was identified by the investigator in brolucizumab-treated patients at any of the disease activity assessments, dosing was adjusted to q8w (i.e. "q12w/q8w regimen"). Once patients were adjusted to a q8w interval, they stayed on that interval until the end of the study (Week 96/Exit).

Brolucizumab met the primary endpoint of non-inferiority in change in best-corrected visual acuity (BCVA) from Baseline to Week 48 vs. aflibercept and achieved pre-specified superior anatomic outcomes vs. aflibercept for the following: mean change from Baseline in central sub-field retinal thickness (CSFT); percentage of patients with intraretinal fluid and/or subretinal fluid; percentage of patients with subretinal pigment epithelium (sub-RPE) fluid; and percentage of patients with no disease activity. The anatomical changes were evaluated with spectral domain-optical coherence tomography (SD-OCT) systems. As SD-OCT is not able to define the vascular network of CNV, the diagnosis of active CNV via SD-OCT relies on indirect parameters including assessment of the presence of subretinal or intraretinal fluid that is not specific to CNV.

Since the first global marketing authorization approval in the US, in Oct-2019, for the treatment of nAMD, adverse events (AEs) of intraocular inflammation (IOI), including retinal vasculitis and/or retinal vascular occlusion, that may result in severe vision loss, have been reported from post-marketing experience with brolucizumab (Beovu®). Results of the mechanistic study

BASICHR0049 of blood samples from nAMD patients exposed to brolucizumab and having subsequently developed Retinal Vasculitis (RV) and/or Retinal Vascular Occlusion (RO), taken together with accumulated data of the association of treatment-emergent immunogenicity and intraocular inflammation (IOI) indicate a causal link between the treatment-emergent immune reaction against brolucizumab and the brolucizumab-related "Intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion". This finding supports the requirement to discontinue treatment with brolucizumab in patients who develop events of intraocular inflammation, including RV and/or RO.

These impacts on the risk/benefit balance of the product are considered to be low and the overall risk/benefit assessment remains positive, when patients who develop RV and/or RO are discontinued from further treatment with brolucizumab.

A new angiography tool, namely optical coherence tomography-angiography (OCT-A), was developed around 2010 to directly visualize retinal circulation (Jia et al 2012). OCT-A is a dye-less angiographic procedure based on split-spectrum-decorrelation-amplitude angiography. It enables the capture of scattered intra-vessel particles (mainly erythrocyte cells) at all levels of the retinal and inner-choroidal vasculature, thus providing 3-D imaging of the retinal circulation. OCT-A was not used for the HAWK and HARRIER studies.

OCT-A has since become an essential and widely used tool, particularly for imaging CNV and vascular diseases of the retina (Mastropasqua et al 2015). Follow-up of nAMD by means of OCT-A has been widely studied in recent years in the literature, describing OCT-A characteristics using both qualitative and quantitative criteria. A recent study (Malamos et al 2017) showed concordance between the changes demonstrated by B-scan OCT and the alterations of CNV flow morphology depicted by OCT-A in nAMD patients treated by anti-VEGF. Furthermore, several manuscripts have described OCT-A changes after anti-VEGF treatment.

The literature suggests that OCT-A is a good marker for assessing anti-VEGF therapeutic response, especially lesion size, which has been demonstrated to decrease under anti-VEGF therapy (de Carlo et al 2015, Miere et al 2017). A 75% decrease in mean lesion area (SD: 21%) 1 month (29.6 days) after anti-VEGF injection in 17 naïve eyes with type 3 nAMD was reported in one study (Phasukkijwatana et al 2017). This remarkable response was associated with resolution of intraretinal and subretinal fluid on structural OCT in all cases. Similarly, another study (Muakkassa et al 2015) in CNV treatment-naïve patients (including patients with nAMD) reported a 23.6% mean decrease in greatest linear CNV dimension and 29.8% mean decrease in CNV area 4.8 weeks after initiation of a single anti-VEGF treatment.

Another study (Coscas et al 2015) reported on the response of patients with a mixed type I–II CNV to aflibercept therapy, with a reduction of the lesion area by 24% in the type II CNV component and by 11.3% in the type I CNV component at Week 12, 4 weeks after the last injection of a series of 3-monthly aflibercept injections. The anti-VEGF loading treatment effect in nAMD type I, type II and mixed CNV has been demonstrated in another study (Miere et al 2018) with a significant 65% decrease in CNV lesion area at Month 3, 4 weeks after the last loading phase injection in 13 naïve patients treated with anti-VEGF (from $0.66 \pm 0.84\ mm^2$ at

Baseline to $0.23 \pm 0.3\ mm^2$ at Month 3, Wilcoxon signed-rank test). This suggests that CNV lesion size might be a marker for assessing therapeutic response.

The long-term evolution of OCT-A features have been described in another study (Miere et al 2017) that reported a 21.6% decrease in CNV lesion area after a mean treatment duration of 11.7 months and 7.1 anti-VEGF treatments.

1.2 Purpose

Considering the efficacy and safety findings demonstrated in the pivotal trials of brolucizumab, and the literature findings summarized above, this multicenter study of treatment-naïve nAMD patients is being performed to assess both early (at Week 12 just after loading phase) and long term (48 weeks [12 months]) effects of brolucizumab on CNV structure and activity.

2 Objectives and endpoints

Table 2-1 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

3 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.

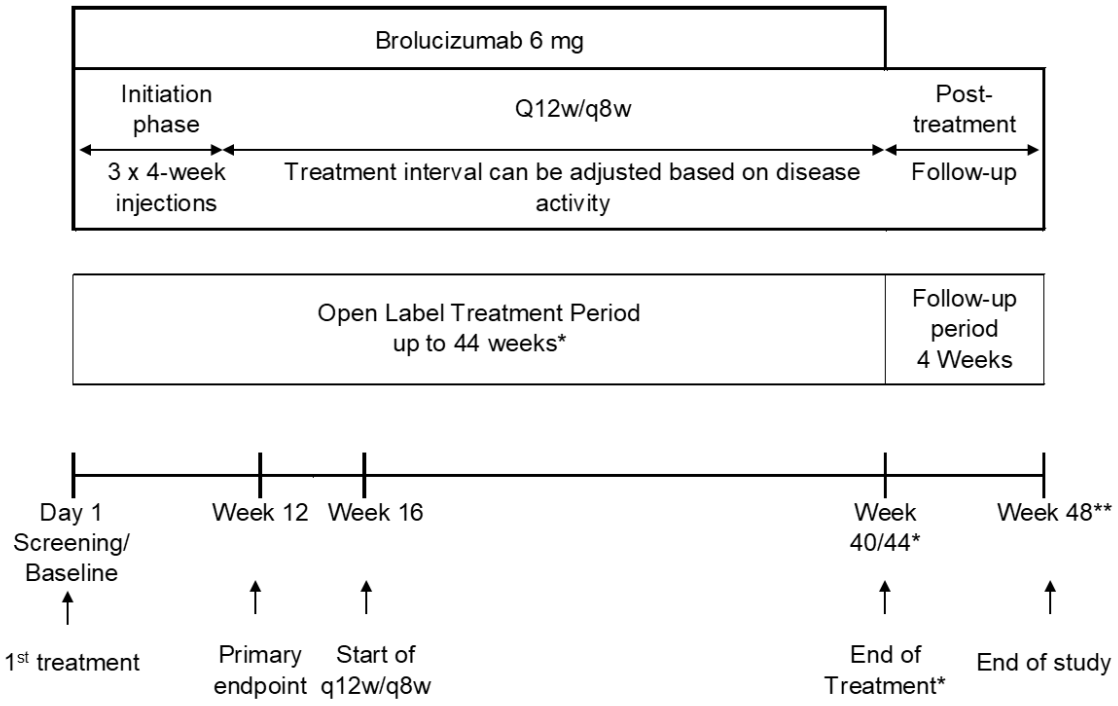
Patients who consent and meet all the inclusion and none of the exclusion criteria will be screened to evaluate eligibility. After confirmation of eligibility, patients will be included and treated with brolucizumab 6 mg.

Approximately 210 adult patients will be screened and included (10% drop-out 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 3-1):

- 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 3-1 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

Treatment period: Day 1 to Week 40/Week 44

The Screening Visit and Baseline Visit (see Table 8-1) are the same visit.

One time re-assessment of patients is allowed, except for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the patient (except if image quality is poor and needs to be redone). As long as testing can be repeated within 14 days of the first screening, the other screening assessments do not need to be repeated. If rescreening is to occur beyond 14 days from the original Screening Visit date, then all screening procedures must be repeated. Medical judgment should be exercised to ensure that treatment of nAMD is not withheld in order for a patient to participate in the study.

After confirmation of eligibility, patients will be included in the study. A study visit schedule will be established at the time of Screening/Baseline Visit for all patients. All efforts should be made to adhere to the study visit schedule within a ± 7-day window. For a given protocol visit, assessments can be performed on 2 consecutive days, provided both days are within the ± 7-day window. Treatment (including at Screening/Baseline) is intended to be administered on the day of the study visit, or if this is not possible, within 3 days after the study visit when the per-protocol assessments will have taken place. 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.

The Screening/Baseline Visit is defined as Screening/Baseline/Day 1. For all patients, the last potential study treatment will be at the Week 40 visit or at the Week 44 visit depending on whether patients receive the study treatment under the q8w or under the q12w schedule. The initiation phase starts on Day 1 and ends on Week 8. The q12w/q8w treatment regimen starts on Week 16 and ends on either Week 40 or Week 44 (see Section 6.7.2).

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 (see Section 6.7.2). Patients who require study treatment every 4 weeks after the initiation phase will be discontinued from further study treatment at the next visit.

The mandatory study visits during the treatment phase are Day 1, Week 4 and Week 8 (assessment of CNV lesion evolution during initiation phase), Week 12 (primary endpoint), Week 16 (first time to reach disease activity criteria and first possible treatment) and Week 48 (last efficacy assessment) 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. No visits are planned between the injection visits (see Section 6.7.2).

Post-treatment follow-up period: from Week 40/44 to Week 48

For all patients completing the study as per protocol, the End of Study (EOS) assessment will be performed at Week 48, 4 weeks (for patients treated at Week 44) or 8 weeks (for patients treated at Week 40) (± 7 days) following their last possible study treatment administration.

Patients withdrawn from the study prior to study completion will be asked to return for an EOS/Early Discontinuation Visit, 4 weeks (± 7 days) following their last study treatment administration. For early treatment discontinuations (ETD) refer to Section 9.1.1.

4 Rationale

4.1 Rationale for study design

This multicenter study of treatment-naïve nAMD patients is being performed to assess both early (at Week 12 just after loading phase) and long term (48 weeks) effects of brolucizumab, a new generation anti-VEGF treatment, on CNV structure and activity.

The safety and efficacy of brolucizumab has been demonstrated in 2 randomized, multicenter, double-masked, active controlled Phase 3 studies in nAMD patients (RTH258-C001 and RTH258-C002) up to 96 weeks as described in Section 1.1. Anatomical changes were evaluated in these studies using SD-OCT, which relied on indirect parameters for the diagnosis of active CNV. Since then, a new angiography tool, OCT-A has been developed that allows direct visualization of retinal circulation.

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.

The CNV lesion area percentage reduction measured by OCT-A from Baseline to Week 48, and change in OCT-A features from Baseline by visit at Week 12 up to Week 48, will be assessed as secondary endpoints. This will allow the long-term effects of brolucizumab on CNV morphology to be assessed.

4.1.1 Rationale for choice of background therapy

Not applicable.

4.2 Rationale for dose/regimen and duration of treatment

The dose and regimen for brolucizumab is based on the following considerations:

- Brolucizumab is well tolerated at a dose of 6 mg administered 3 times every 4 weeks during the loading phase, based on the previous pivotal registration clinical phase 3 program in which 1088 patients with nAMD received brolucizumab ([redacted]). The q12w/q8w treatment regimen used in the present study is the same as the [redacted] and [redacted] studies (see Section 1.1).
- In line with current clinical practice, ophthalmology association recommendations, and labels of approved anti-VEGF drugs in most countries worldwide, the treatment frequency can be adjusted based on the investigator assessment of disease activity.
- The route of administration is an intravitreal (IVT) injection as for all anti-VEGF treatments currently approved for the treatment of nAMD.
- Prefilled syringes (PFS) have been selected for administration of study treatment in this study, as this form will be the one commercialized in France.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable.

4.4 Purpose and timing of interim analyses

The primary analysis will be conducted when all ongoing patients have completed their Week 12 visit. An interim analysis will be performed when the last included patient completed Week 12 visit.

Patients will remain in the study and will continue to receive treatment for the maximum planned duration of treatment of 40 to 44 weeks in accordance with the designated treatment regimen to allow for further evaluation of efficacy and safety.

4.5 Risks and benefits

In a comprehensive Phase 3 program (see Section 1.1), consisting of 2 large, randomized, double-masked, multicenter, studies (RTH258-C001 and RTH258-C002) treatment with brolucizumab resulted in robust visual gains and superior anatomical outcomes compared to aflibercept, with the majority of patients maintained on an q12w dosing interval at 48 weeks, and the remainder maintained on an q8w dosing interval. Anatomical benefits and vision gains were maintained for 2 years.

The RTH258-C001 and RTH258-C002 studies successfully evaluated a novel treatment regimen, combining the prolonged duration of effect of brolucizumab with treatment frequency guided by disease activity. Reflecting clinical practice, investigators assessed disease activity using both visual function and anatomical disease parameters (e.g. retinal thickness and retinal fluid). Robust clinically meaningful results were observed for both functional and anatomical outcomes in a representative nAMD population over 48 weeks and sustained up to 96 weeks.

These benefits were consistent across subgroups (e.g. age, gender, race, Baseline visual acuity, Baseline retinal thickness, lesion type, lesion size, fluid status), replicated in 2 independent Phase 3 studies. Less than half of patients were identified with disease activity after the loading phase and most disease activity with adjustment of dosing interval was identified during the initial q12w interval; the vast majority of patients without disease activity during the initial q12w interval continued to be maintained on an q12w treatment interval for the remainder of the treatment period indicating the benefit of early treatment monitoring in maintaining long-term efficacy. These results thus addressed the unmet medical need of delivering efficacy comparable to standard of care, while reducing the treatment and monitoring burden.

Sustained visual acuity is a key validation for the q12w/q8w regimen, as it relates to the unmet medical need of maintaining patients' long-term vision.

The overall safety and tolerability profile of brolucizumab was consistent with aflibercept, an established therapy in patients with nAMD. While there was a higher incidence of intraocular inflammation (IOI) AEs for brolucizumab compared to aflibercept, no preferred term (PT) was reported for more than 1.5% of patients. Over 90% of IOI AEs were mild to moderate in severity and 79% resolved with no sequelae. The impact of IOI on the benefit-risk balance of brolucizumab is considered to be low.

Adverse events (AEs) of Intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion have occurred since the Oct-2019 marketing authorization approval for brolucizumab (Beovu®) in the treatment of nAMD. These AEs may result in severe vision loss. Results of the mechanistic study BASICHR0049 of blood samples from nAMD patients exposed to brolucizumab and having subsequently developed Retinal Vasculitis (RV) and/or Retinal Vascular Occlusion (RO) taken together with accumulated data of the association of treatment-emergent immunogenicity and intraocular inflammation (IOI) indicate a causal link between the treatment-emergent immune reaction against brolucizumab and the brolucizumab-related "Intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion". This finding supports the requirement to discontinue treatment with brolucizumab in patients who develop events of Intraocular inflammation, including RV and/or RO.

Based on clinical studies, IOI related adverse events, including retinal vasculitis and retinal vascular occlusion, were reported more frequently in female patients treated with brolucizumab than male patients (e.g. 5.3% females vs. 3.2% males in HAWK and HARRIER, Novartis data on file).

In addition, based on USM (CRTH258AUS04 FIR), the brolucizumab dosing interval should not be less than 8 weeks beyond the loading period, that is not allowed in the present study protocol.

Intravitreal injections, including those with brolucizumab, have been associated with endophthalmitis and retinal detachment. The injection procedure must be carried out under aseptic conditions. Patients should be instructed to report any symptoms suggestive of the above-mentioned events without delay.

Transient and sustained increases in intraocular pressure (IOP) have been seen with brolucizumab, similar to those observed with IVT administration of other VEGF inhibitors. Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately.

Brolucizumab must not be administered in case of hypersensitivity to the active substance or to any of the excipients, active or suspected ocular or periocular infection, or active intraocular inflammation (IOI).

Appropriate eligibility criteria are included in this protocol. The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring described in Section 6.7.2, Section 8.4.4 and Section 10.

Women of child bearing potential will be excluded.

Sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

In conclusion, the benefit-risk balance of brolucizumab 6 mg, when treatment interval is not less than every 8 weeks after the first 3 monthly initial doses (loading phase) is positive, and comparable to aflibercept (an established therapy in nAMD) in the treatment of patients with nAMD.

5 Population

The study population will be male and female patients ≥ 50 years old diagnosed with treatment-naïve active CNV secondary to nAMD and able to comply with study or follow-up procedures.

Approximately 210 adult patients will be screened and included (10% dropout rate and uninterpretable images at Baseline and Week 12 expected) in France.

If both eyes are eligible as per the inclusion and exclusion criteria described below, the eye with the worse BCVA at Screening should be selected as the study eye, unless the investigator deems it more appropriate to select the eye with better BCVA, based on medical reasons or local ethical requirements. If both eyes have the same BCVA, then it is recommended to select the right eye as the study eye.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Patients must provide written informed consent before any study related procedures are performed.
2. Patients must be 50 years of age or older at Screening/Baseline.

Study eye:

3. Active CNV lesions secondary to AMD that affect the central subfield, including retinal angiomatous proliferation (RAP) with a CNV component, confirmed by presence of active leakage from CNV seen by fluorescein angiography and sequellae of CNV, e.g. pigment epithelial detachment (PED), subretinal hemorrhage or sub-retinal pigment epithelium (sub-RPE) hemorrhage, blocked fluorescence, macular edema.

4. Intra- and/or subretinal fluid affecting the central subfield of the study eye at Screening/Baseline.
5. BCVA between 83 and 23 letters, inclusive, in the study eye at Screening/Baseline using early treatment diabetic retinopathy study (ETDRS) at an initial testing distance of 4 meters.

5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study.

Ocular conditions

1. Any active intraocular or periocular infection or active intraocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis) in **either eye** at Screening/Baseline.
2. Presence of amblyopia, amaurosis or ocular disorders in the **fellow eye** with BCVA < 35 ETDRS letters at Screening (except when due to conditions whose surgery may improve visual acuity, e.g. cataract).
3. Medical history of intraocular inflammation and/or retinal vascular occlusion within 12 months prior to Screening/Baseline

Study eye

4. Poor quality of OCT-A and SD-OCT images at Screening/Baseline.
5. Atrophy or fibrosis involving the center of the fovea in the study eye, as assessed by color fundus photography and fundus autofluorescence (FAF) at Screening/Baseline.
6. The total area of fibrosis or subretinal blood affecting the foveal center point comprising ≥ 50% of the lesion area in the study eye at Screening/Baseline.
7. Concomitant conditions or ocular disorders in the study eye, including retinal diseases other than nAMD, that, in the judgment of the investigator, could require medical or surgical intervention during the course of the study to prevent or treat visual loss that might result from that condition, or that limits the potential to gain visual acuity upon treatment with the investigational product.
8. Structural damage within 0.5 disc diameter of the center of the macula in the study eye, e.g. vitreomacular traction, epiretinal membrane, retinal pigment epithelium (RPE) rip/tear scar, laser burn, at the time of Screening that in the investigator's opinion could preclude visual function improvement with treatment.
9. Current vitreous hemorrhage or history of vitreous hemorrhage in the study eye within 4 weeks prior to Screening/Baseline.
10. Uncontrolled glaucoma in the study eye defined as IOP > 25 mmHg on medication or according to the investigator's judgment at Screening/Baseline.
11. Aphakia and/or absence of the posterior capsule in the study eye at Screening/Baseline.

Ocular treatments (study eye)

12. Patient has received any approved or investigational treatment for nAMD (other than vitamin supplements) in the study eye at any time.
13. Intraocular or periocular use of corticosteroids in the study eye during the 6-month period prior to Screening/Baseline.

14. Previous penetrating keratoplasty or vitrectomy at any time prior to Screening/Baseline.
15. History or evidence of the following in the study eye within the 90-day period prior to Screening/Baseline:
    - Intraocular or refractive surgery.
    - Previous panretinal photocoagulation.
    - Previous submacular surgery, other surgical intervention or laser treatment for nAMD including photodynamic therapy (PDT).

Systemic conditions or treatments

16. End stage renal disease requiring dialysis or renal transplant.
17. Systemic medications known to be toxic to the lens, retina or optic nerve (e.g. deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol) used during the 6-month period prior to Screening/Baseline except temporary use for COVID-19 treatment.
18. Participation in an investigational drug, biologic, or device study within 30 days or the duration of 5 half-lives of the investigational product (whichever is longer) prior to Screening/Baseline. Note: observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary.
19. Systemic anti-VEGF therapy at any time.
20. Stroke or myocardial infarction in the 6-month period prior to Screening/Baseline.
21. Uncontrolled blood pressure defined as a systolic value $\geq$ 160 mmHg or diastolic value $\geq$ 100 mmHg at Screening/Baseline. (In case there is an elevated blood pressure measurement, it should be repeated after 20 minutes. If the repeat measurement is elevated, then the patient is not eligible to be enrolled into the study).
22. History of a medical condition (disease, metabolic dysfunction with exception of type 1 or 2 diabetes mellitus, physical examination finding, or clinical laboratory finding) that, in the judgment of the investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product.
23. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
24. History of hypersensitivity to any component of the test article, control article, or clinically relevant sensitivity to fluorescein dye, as assessed by the investigator.

Other

25. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) pregnancy test.
26. Women of childbearing potential, defined as all women less than 1 year postmenopausal or less than 6 weeks since sterilization at Screening/Baseline

    Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least 6 weeks before

taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

27. Patients mentioned in Articles L.1121-5 to L.1121-8 and L.1122-1-2 of the Code de Santé Publique (e.g. minors, protected adults, etc.)

6 Treatment

6.1 Study treatment

6.1.1 Investigational treatment

Study treatment characteristics are presented in Table 6-1.

Table 6-1 Investigational drug

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Supplier
Brolucizumab 6 mg (RTH258 6 mg/ 0.05 mL)	Solution for injection	Intravitreal use	Pre-filled syringe	Novartis

Brolucizumab will be provided in a single use, sterile PFS containing sufficient brolucizumab to deliver a 6 mg dose when administering a volume of 0.05 mL

The content of the study drug PFS must **not** be split.

Novartis will ensure sufficient supplies of brolucizumab for treatment use to allow for completion of the study.

6.1.2 Additional study treatments

No other treatment beyond the investigational drug is included in this trial.

6.1.3 Treatment arms

This is a single-arm study in which all patients will be treated with:

- Brolucizumab 6 mg: 3 loading injections (at Screening/Baseline, Week 4 and Week 8), followed by maintenance treatment from Week 16/Week 20 up to Week 40/Week 44.

6.1.4 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.

After the initiation phase (Week 8), study treatment will be discontinued for patients who require injections every 4 weeks.

If intraocular inflammation, including retinal vasculitis, and/or retinal vascular occlusion, is confirmed, patients must be discontinued from study treatment.

Patients who prematurely discontinue study treatment for any reason, except for withdrawal of consent, should continue in the study. Patients should return 4 weeks after last study treatment to perform the assessments for early treatment discontinuation (ETD). Please refer to Table 8-1.

6.2 Other treatments

6.2.1 Concomitant therapy

Prior medication, i.e. any medication taken up to 90 days prior to Screening/Baseline, must be recorded on the appropriate electronic case report forms (eCRFs). Intraocular or periocular use of corticosteroids in the study eye taken up 6 months prior to Screening/Baseline must be recorded.

The investigator must instruct the patient to notify the study site about any new medications the patient takes after enrollment in the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded on the appropriate eCRFs.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medications. If in doubt the investigator should contact the Novartis medical monitor before enrolling a patient or allowing a new medication to be started. If the patient is already enrolled, Novartis should be contacted to determine if the patient should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

During the study, standard of care or other treatments (according to the investigator's practice) for nAMD and other diseases in the fellow eye are permitted at any time and must be recorded in the appropriate eCRF page. Treatment of the fellow eye must be scheduled in a way so as not to disturb the schedule for visits and treatments in the study eye. The fellow eye must be monitored according to routine practice and adverse events (AEs) captured in the eCRF.

Administration of topical ocular corticosteroids in the study eye is allowed during the study. Corticosteroids administered via intra-nasal, inhaled, intra-articular or non-extensive dermal route (< 20% total body surface area) are also permitted during the study. For other routes of corticosteroid administration, refer to Section 6.2.2.

If cataract surgery is necessary, it should be scheduled ≥ 7 days after the most recent study treatment, if possible. Study treatment may be resumed ≥ 14 days after cataract surgery, assuming an absence of surgically-related complications.

If yttrium aluminum garnet (YAG) laser is necessary, it should be performed ≥ 7 days prior to the scheduled study visit.

Ideally, while adhering to the visit schedule specified in the protocol, study drug should be administered at least 7 days before or after SARS-CoV-2 vaccinations. This will allow to separate potential drug-drug interactions and side effects caused by vaccination. This 7-day time window would also be recommended for the first study treatment at the Baseline visit.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed after Screening/Baseline.

Table 6-2 Prohibited medication and procedures

Medication/Procedure	Prohibition period	Action taken
Study eye		
Any periocular injection or intraocular administration of corticosteroids (except if needed as short term treatment of AE)	Anytime	Discontinue study treatment (except if for treatment of AE)
Anti-VEGF therapy other than assigned study medication	Anytime	Discontinue study treatment
Panretinal laser, PDT laser, or focal laser photocoagulation with involvement of the macular area	Anytime	Discontinue study treatment
Any investigational drug, biologic or device	Anytime	Discontinue study treatment
Systemic		
Anti-VEGF treatment	Anytime	Discontinue study treatment
Any investigational drug, biologic or device	Anytime	Discontinue study treatment
Medications known to be toxic to the lens, retina or optic nerve, including ethambutol, chloroquine, hydroxychloroquine, deferoxamine, phenothiazines and tamoxifen (except temporary use for COVID-19 treatment)	Anytime	Discontinue study treatment

PDT: photodynamic therapy

In the fellow eye, treatment with investigational product (drug, biologic or device) is prohibited. Any marketed medication used to treat the fellow eye should be recorded in the appropriate eCRF page.

6.2.3 Rescue medication

There will be no rescue medication for nAMD in the study eye.

In case of lack of efficacy with the investigational drug for nAMD and if the investigator deems it is in the best interest of the patient to receive prohibited treatment (Section 6.2.2) in the study eye, the investigator should follow the instructions for study treatment discontinuation or study discontinuation provided in Section 9.

6.3 Patient numbering, treatment assignment, randomization

6.3.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.) that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (4 digit number for Center No. as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it (3 digit number for Patient No.), so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form (ICF),

the patient is assigned to the next sequential Patient No. available in the electronic data capture (EDC) system.

Patients who have been screen failures but are rescreened (see Section 8.1) will be assigned a new Patient No.

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study. The assignment of patients to treatment will be coordinated by Novartis.

6.4 Treatment masking

Treatment will be open to patients, investigator staff, persons performing the assessments, the Clinical Trial Team, and the Central Reading Center (CRC).

6.5 Dose escalation and dose modification

In this study, brolucizumab 6 mg (0.05 mL) will be administered by IVT injection every 4 weeks (monthly) for the first 3 doses. Thereafter, brolucizumab is administered every 12 weeks (3 months). The investigator can individualize treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters so that the treatment interval can be as frequent as every 8 weeks (2 months). Patients needing the q8w treatment regimen will remain on this regimen until the end of the treatment at Week 40/Week 44.

No study treatment dose modification is allowed and no deviation to the allowed dose intervals (in accordance with disease activity assessments) is allowed.

Interruption of study treatment is allowed if warranted by an AE or cataract surgery (Section 6.2.1.1).

6.5.1 Follow-up for toxicities

Not applicable.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The date and time of all study treatment injections administered during the study and any deviations from the protocol treatment schedule will be captured by the study personnel or by the field monitor on the appropriate study treatment dispensing form.

Exposure to the study treatment will be based on the number of injections administered. Compliance with the study treatment will be assessed by the field monitor at each visit using PFS counts and information provided by the pharmacist or study personnel.

6.6.2 Emergency breaking of assigned treatment code

Not applicable as this is a single-arm, open-label study.

6.7 Preparation and dispensing of study treatment

Each study site will be supplied with study drug in packaging as described under the investigational drugs section (Section 6.1.1).

A unique medication number is printed on the study medication label. The study medication has a 2-part label (base plus tear-off label); immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document. The number must be written into the eCRF.

6.7.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secure location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure (IB). Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

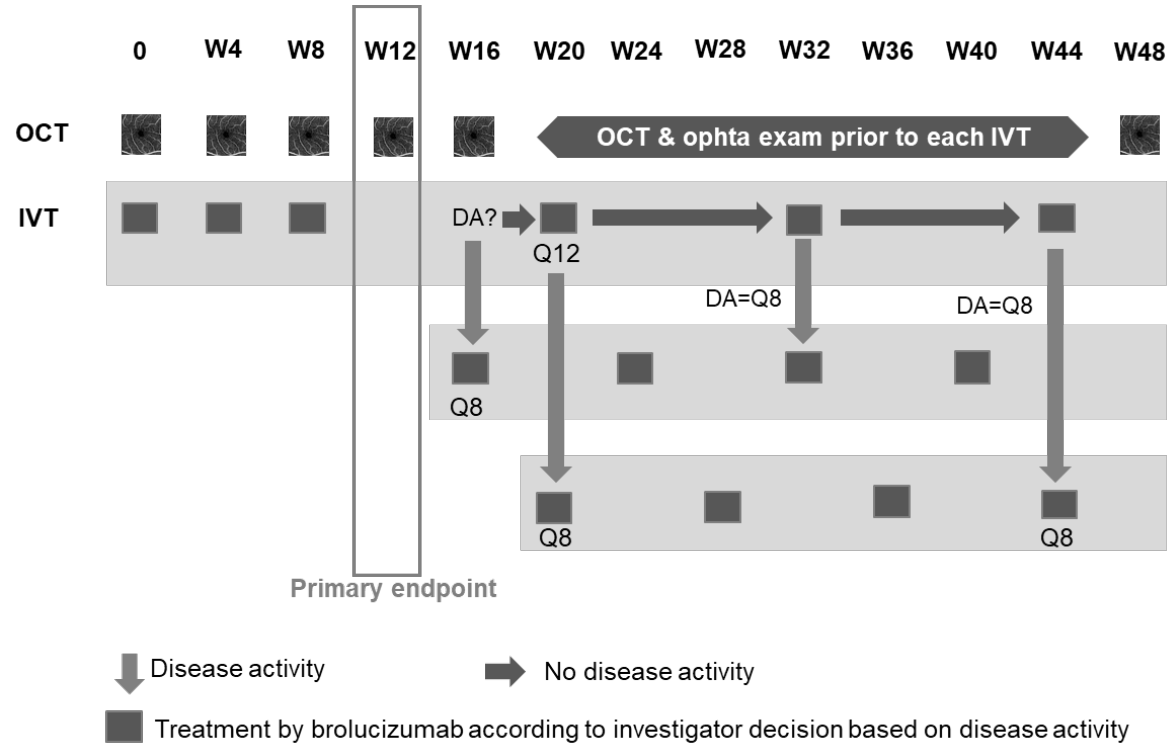
The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.2 Instruction for prescribing and taking study treatment

There will be 2 treatment phases (see Figure 6-1).

Figure 6-1 Treatment regimen



* The end of treatment will occur at either Week 40 or Week 44 according to the treatment schedule.
DA=disease activity, IVT=intravitreal, Q8=every 8 weeks, Q12=every 12 weeks, W=week, OCT= optical coherence tomography

Initiation phase

In the initiation phase, treatment with brolucizumab 6 mg will initially be injected 3 times at 4-week intervals, at Screening/Baseline/Day 1, Week 4 and Week 8. Following the loading doses, each patient will be injected q12w or q8w up to Week 40 or Week 44 (according the treatment regimen).

During the initiation phase, disease activity will be assessed at Day 1, Week 4 and Week 8.

q12w/q8w treatment phase

The mandatory visit at Week 12 will be performed to evaluate the primary endpoint of the study. No treatment will be administered at Week 12; the next visit will take place at Week 16. Disease activity will be assessed at Week 12 for endpoint assessment purposes.

The q12w/q8w treatment phase starts at Week 16 and is defined as follows:

- Following Week 8, treatment intervals will be either 8 weeks or 12 weeks. A patient must be discontinued from further study treatment if treatment is required more frequently, i.e., every 4 weeks.
- The first assessment of disease activity during this phase will be performed at the Week 16 visit by the investigator.
- Based on investigator's judgment of visual and/or anatomic outcomes, the treatment can be adjusted by the investigator to a q8w treatment regimen if there is disease activity as

provided in the guidance to the investigators, e.g. decrease of visual acuity and/or other signs of the disease (e.g. IRF, SRF, sub-RPE fluid, retinal hemorrhage, CRT increase, etc.).

- The disease activity assessment is performed at each subsequent visit by the investigator.
- If disease activity is identified, the patient will be reassigned to receive injections q8w thereafter up to Week 40/Week 44.
- Regardless of treatment administration, Week 16 and Week 48 visits are mandatory.
- 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.
- No visits are planned between the injection visits.
- The last potential study treatment may be administered at the Week 40 visit or at the Week 44 visit according to the patient's treatment regimen.
- A disease activity assessment will also be performed at the Week 48/EOS visit; however, no study treatment will be administered.

The different types of visits occurring through the study are summarized in Table 6-3 with a description of when disease activity assessment and treatment take place.

Table 6-3 Disease activity assessment and treatment occurrence according to visit type

Type	Study Period or Phase	Disease Activity Assessment	Treatment
Screening / Baseline (Day 1) visit	Initiation phase	Yes	Yes
Week 4 visit	Initiation phase	Yes	Yes
Week 8 visit	Initiation phase	Yes	Yes
Week 12 visit	Primary endpoint	Yes	No
Week 16 visit	Q12w / q8w phase	Yes	Yes, according to disease activity assessment
Treatment visits (interim visits between Week 20 and Week 48 where treatment is administered)	Q12w / q8w phase	Yes	Yes
ETD visit and EOS visit (Week 48)	Follow-up	Yes	No

Brolucizumab should be administered in the study eye on the day of the study visit or, if this is not possible, within 3 days after the occurrence of the study visit or no later than within the visit window (± 7 days) as described in Section 3 and Section 8. When assessments and treatments take place on the same day, treatment must occur after completion of the efficacy assessments described in Section 8.3 and pre-injection safety measures (tonometry, slit lamp and fundus examinations) described in Section 8.4.3. 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 IOI; therefore, the investigators must verify that these conditions are not present in the study eye prior to every injection. Any AEs must be recorded in the eCRF.

If any signs of IOI are present, then an IVT injection **must not** be performed. Additional ophthalmic examination and imaging should be performed to evaluate IOI (see Section 8.4.3).

If intraocular inflammation, including retinal vasculitis, and/or retinal vascular occlusion, is confirmed, subjects should be discontinued from study treatment.

The injection procedure for brolucizumab including aseptic and antimicrobial requirements, will be performed according to local clinical practice. Injections will be administered by the investigator.

Every effort should be made to ensure that the patient adheres to the visit/treatment schedule.

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 are 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.

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 CRC will have no involvement in assessment of disease activity, which is solely the investigator's responsibility.

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 an 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.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given

his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed ICF that complies with the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. As new information becomes available, informed consent to be updated and then must be discussed with the subject.

Male patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule for the study eye (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. All data requested by eCRF must be entered in a timely manner (see Section 11.1).

A planned study visit schedule will be established at Screening/Baseline/Day 1 for all patients. All post-Baseline and/or subsequent scheduled visits will be calculated based on the Screening/Baseline/Day 1 visit date. During the q12w/q8w phase, from Week 16 to Week 44, the treatment visit intervals will be determined by the investigator, based on the patient's disease activity (see Section 6.7.2). All efforts should be made to adhere to all scheduled visits and assessments as outlined in the assessment schedule (Table 8-1).

A ± 7-day visit window is allowed should the patient be unable to return per the scheduled visit. All efforts should be made to revert back to the planned visit schedule taking into consideration the restrictions on the minimum treatment interval for the study medication (brolucizumab).

Assessments can be performed on 2 consecutive days in which both days must occur within the ± 7 days visit window.

Treatment is intended to be administered on the day of the study visit, or if this is not possible, within 3 days after the study visit at which the per-protocol assessments took place. 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. For all visits, efficacy assessments (Section 8.3) and safety assessments (Section 8.4) should be performed prior to any administration of study treatment.

Missed or rescheduled visits should not lead to automatic discontinuation.

If the COVID-19 pandemic limits or prevents on-site study visits, study treatment should not be administered and other study assessments may not be performed. Alternative methods of safety monitoring may be implemented. Depending on local regulations, site capabilities and patients' visit status in the study, phone calls or virtual contacts (e.g. teleconsult) can be performed for safety follow-up for the duration of the pandemic, until it is safe for the participant to visit the site again.

Patients who prematurely discontinue study treatment for any reason should return for the EOS visit assessments as scheduled in Table 8-1, except for patients who withdraw their consent from the study and do not wish to do so (refer to Section 9.1.2).

Table 8-1 Assessment schedule for the study eye

Period	Treatment Period							Follow-up	
	Initiation Phase			q12w/q8w Phase					
Visit	Screening/Baseline[1]					Interim Visits[2]	EOT‡	EOS [10] ETD [11]	M [12]
	Day 1	Week 4	Week 8	Week 12	Week 16	Every 8 or 12 weeks according to treatment regimen	Week 40/ Week 44	Week 48	
Informed consent	X								
Inclusion/exclusion criteria	X								
Demography	X								
Medical history/current medical conditions	X								
Vital signs	X	X	X	X	X	X	X	X	
Prior/concomitant medications (including surgery and procedures)	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
BCVA score (ETDRS)	X	X	X	X	X	X	X	X	X
IOP	X							X	
Ophthalmic examination and imaging [3,8]	X	X	X	X	X	X	X	X	
SD-OCT[8]	X	X	X	X	X	X	X	X	
OCT-A[8]	X	X	X	X	X	X	X	X	
CFP[8]	X			X				X	
FAF	X			X				X	
FA[8]	X [4]			X					
ICG [5,8]	X			X					
Disease activity assessment	X	X	X	X	X	X	X	X	
Study drug IVT injection [7]	X	X	X		X[6]	X[6]	X[6]		
Telephone follow-up post injection [9]	X after 1st injection								

Note: Mandatory study visits are highlighted in grey.

Abbreviations: BCVA=best-corrected visual acuity, CFP=color fundus photography, EOS=end of study, ETDRS=early treatment diabetic retinopathy study, FA=fluorescein angiography, FAF=fundus autofluorescence, ICG=indocyanine green chorioangiography, IVT=intravitreal, OCT=optical coherence tomography

‡ The end of treatment will occur at either Week 40 or Week 44 according to the treatment schedule.

[1] The Screening/Baseline visit are performed on the same Visit.

[2] The number of weeks between visits will vary depending on the disease stability and length of intervals between injections as determined by disease activity assessment.

[3] Include slit lamp examination and fundus examination

[4] If FA has been made as required by the protocol during the 15 days prior to screening, FA does not need to be repeated on Screening/Baseline visit. In this case, FA image needs to be collected and reviewed by the CRC.

[5] ICG is optional at the discretion of the investigator. ICG should be performed at week 12 if it has been performed at Screening/Baseline.

[6] Treatment according to investigator decision based on disease activity assessment.

[7] Intraocular pressure (IOP) will be assessed in the study eye, pre-dose and post-dose at every injection. The same method of tonometry has to be used through the whole study. Close monitoring of IOP should be performed by the investigator for any non-transient elevation in IOP (≥ 25 mmHg). Intravitreal injection is not recommended unless normalization of the IOP has been achieved. Post-dose IOP should be assessed within 60 minutes after injection and if ≥ 25 mmHg, assessment should be repeated until back to normal. Monitoring of the optic nerve head perfusion after injection may be appropriate, at the discretion of the investigator. Results of these procedures will be recorded as appropriate in the source documents and if the findings constitute an AE, it should be recorded in the eCRF.

[8] Additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation (IOI), retinal vasculitis, and/or retinal vascular occlusion.

[9] A telephone follow-up on safety should be performed one week after the first injection (a window for the phone call is +7 days). From the second injection onwards, similar phone calls should be made at investigator's discretion per local practice.

[10] The week 48 EOS assessments only apply to patients who completed the study per protocol. The assessments are not required for patients who have undergone ETD assessments and continued in the study without study treatment.

[11] ETD: Early treatment discontinuation applies to patients who discontinue early from study treatment and continue in the study. The assessments should be performed 4 weeks after the last injection of study drug. This can occur at any time point.

[12] For patients who continue in the study after ETD and up to Week 48 (end of study) while patient is on standard of care. Additional safety assessments and imaging can also be performed if required, as per investigators discretion. In addition, after ETD, subjects are not required to attend the mandatory visits at Week 12 and Week 48 The last visit should be at week 48. This can occur at any time point.

Assessments in the fellow eye

The following assessments will be performed for the fellow eye:

- At Screening : BCVA, ophthalmic examination, IOP, SD-OCT, CFP, FAF and FA (and optional ICG).
- At Week 48: BCVA, ophthalmic examination, IOP, SD-OCT, CFP and FAF.

The fellow eye will be examined only at Screening/Baseline and Week 48/EOS visits. Other assessments of the fellow eye may be performed at the investigator's discretion in accordance with routine practice at other time points; however, these will not be collected or analyzed in this study.

All data obtained from these assessments must be supported in the patient's source documentation.

Only best corrected near visual acuity (BCNVA) for the study eye will be analyzed. It is not requested for the purpose of this study to do any self-assessment measure of the fellow eye.

Unscheduled visits

If a patient returns to the site prior to his/her next scheduled study visit, the investigator will capture the unscheduled visit in the eCRF only in the case of a clinically significant abnormal finding.

If this finding leads to an AE and/or the decision to treat the patient prior to his/her next scheduled treatment, all the procedures listed for the Interim Visit need to be conducted and captured in the eCRF.

In the case of a treatment decision for nAMD treatment is made during the unscheduled visit (at the exception of AE treatment), the assigned study medication can not be administrated. In case of administration of an anti-VEGF medication during an unscheduled visit, it will be considered as the use of a prohibited treatment and should be managed as described in Section 9.1.1.

8.1 Screening

The Screening Visit and Baseline Visit (see Table 8-1) are the same Visit.

For the purpose of Screening/Baseline, FA images from a previous **routine** evaluation may be used as long as the FA was performed within 15 days of the Screening/Baseline Visit.

One time re-assessment of patients is allowed, **except** for the purpose of capturing new BCVA assessments that previously failed to qualify the patient (except if the image quality is poor and needs to be redone). As long as testing can be repeated within 14 days of the first screening, the other screening assessments do not need to be repeated (see Table 8-1). If rescreening is to occur beyond 14 days from the original screening visit date, then the patient must be re-consented and all Screening/Baseline procedures must be repeated. Medical judgment should be exercised to ensure that treatment of nAMD is not withheld in order for a patient to participate in the study.

Patients must have confirmed nAMD at Screening/Baseline.

8.1.1 Information to be collected on screening failures

Patients who sign an ICF and who are subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF page. The demographic information, informed consent, inclusion/exclusion and disposition eCRF pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a SAE during the Screening Phase (see Section 10.1.2 for reporting details). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

Patients who sign an ICF and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition eCRF.

8.2 Patient demographics/other baseline characteristics

The following information will be collected/documented at the Screening/Baseline Visit for each enrolled patient:

- Age
- Sex
- Vital signs
- Study eye
- BCVA
- CNV characteristics (assessed via SD-OCT, OCT-A, CFP and FA, and optional ICG)
- Intraocular pressure
- Ophthalmic examinations (fundus examination and slit lamp examination)
- Retinal imaging (assessed via SD-OCT, OCT-A, CFP, FAF, and FA)
- Concomitant medications (including surgery and procedures)
- Medical history and current medical conditions

Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever, in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

The following assessments will be performed to evaluate the effect of brolucizumab on retinal structure, vascular leakage, and visual function:

- Anatomical retinal evaluation of OCT-A and SD-OCT images
- CFP
- FAF
- Vascular evaluation by FA (and optionally by ICG)
- BCVA with ETDRS-like charts at an initial testing distance of 4 meters

All efficacy assessments should be performed **prior** to any administration of study treatment and/or rescue medication.

8.3.1 Optical coherence tomography

Optical coherence tomography angiography (OCT-A) images will be obtained and assessed in the study eye at the visits indicated in the visit assessment schedule (Table 8-1). OCT-A will be used to identify or confirm the presence of CNV and its evolution.

OCT-A will be performed using a 3 x 3 and a 6 x 6 scanning area.

Spectral domain optical coherence tomography (SD-OCT) images will be obtained and assessed in the study eye at the visits indicated in the visit assessment schedule (Table 8-1). Only SD-OCT machines can be used (i.e. no time-domain nor swept-source OCT).

Central sub-field thickness (CSFT) will be measured by SD-OCT. The CSFT evaluated in this study represents the average retinal thickness of the circular area within 1 mm diameter around the foveal center.

For disease activity assessment, both OCT-A and SD-OCT assessments will be performed **after** BCVA assessment and **prior** to any study drug administration. The investigator will

evaluate the OCT-A and SD-OCT images to assess the status of disease stability. The OCT-A and SD-OCT machines used for an individual patient should not change for the duration of the study.

The investigator will evaluate the images according to their standard of clinical practice and may use any of the OCT-A and SD-OCT imaging findings to inform his/her decision for treatment.

A CRC will be used in this study only for the study endpoint assessment. The CRC will not be in charge of eligibility assessments or disease activity assessments, which will be evaluated only by the investigator.

The CRC will read OCT-A and SD-OCT at all Visits: Screening / Baseline, Week 4, Week 8, Week 12, Week 16, at all Interim Visits and Week 48.

The CRC will provide sites with a Study Manual and training materials for the specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software will be validated by the CRC as specified in the Study Manual. All OCT-A and SD-OCT images will be obtained by trained site personnel at the study sites. All OCT-A and SD-OCT images will be forwarded to the CRC for independent standardized analysis. All OCT-A and SD-OCT images will also be forwarded to Novartis or designated Contract Research Organization (CRO) for storage.

For eligibility assessments, the Screening/Baseline Visit will be used at the investigator's discretion. For the primary and secondary endpoints of anatomical change analysis, images read by the CRC for Screening/Baseline and the identified follow-up time points will be referenced.

The CRC will create a database with the agreed variables as indicated in the CRC grading charter (a separate document) and will transfer the data from this database to Novartis for analysis. The CRC data will be used for the evaluation of the objectives having OCT-A and SD-OCT parameters to ensure a standardized evaluation. For further procedural details, the investigator should refer to the applicable manual provided by the CRC.

8.3.2 Color fundus, fundus autofluorescence and fluorescein and indocyanine angiography

Color fundus photography (CFP), **fundus autofluorescence** (FAF) and **fluorescein angiography** (FA) will be performed in the study eye at the visits indicated in the visit assessment schedule (Table 8-1). CFP, FAF and FA may be performed at other visits at the investigator's discretion but they are not mandatory for the study.

For the purpose of Screening/Baseline, FA images from a previous routine evaluation may be used as long as FA was performed within 15 days of the Screening/Baseline Visit.

An ICG could be performed at Screening/Baseline at the investigator discretion. ICG should be performed at week 12 if it has been performed at Screening/Baseline.

In case of premature discontinuation from the study, there is no need to repeat the CFP and FAF if there was a CFP and FAF performed within the previous 12 weeks, **except if there is significant disease worsening, in the opinion of the investigator**.

CFP and FAF assessments will not be reviewed by the CRC, the investigator will evaluate the images according to their standard of clinical practice.

FA and ICG assessments at Screening / Baseline and Week 12 will be reviewed by the CRC. The CRC will provide sites with a Study Manual and training materials for the specified study ocular images. All FA and ICG images will be forwarded to the CRC for independent standardized analysis and will also be forwarded to Novartis or designated CRO for storage.

Additional images will be taken in case of any signs of IOI. OCT, color fundus photography, FA and indocyanine green chorioangiography (preferably wide-field or with peripheral sweeps) should be performed for safety evaluation as described in Section 8.4.3.

8.3.3 Visual acuity

Visual acuity will be assessed in the study eye at the visits indicated in the visit assessment schedule as described in Table 8-1 using best correction determined from protocol refraction (via BCVA). BCVA of the fellow eye will be assessed at Screening/Baseline and at Week 48/EOS Visit. BCVA measurements will be taken in a sitting position using ETDRS-like visual acuity testing charts at an initial testing distance of 4 meters.

8.3.4 Appropriateness of efficacy assessments

The use of SD-OCT images to analyze anatomical changes are standard assessments in this indication, and were used in the pivotal trials of brolucizumab in patients with nAMD.

Since the pivotal trials were performed, a new angiography tool, OCT-A, has become an essential and widely used tool for imaging CNV and vascular diseases of the retina. It will therefore be used in this study to analyze anatomical changes in patients with nAMD as described in Section 4.1. The literature suggests that OCT-A is a good marker for assessing anti-VEGF therapeutic response, especially lesion size that has been shown to decrease under anti-VEGF therapy.

CFP and FAF are used to inspect retinal pathology.

FA is also an established procedure that helps to classify the type of lesion and is used to assess vascular leakage. ICG will be an optional procedure at the discretion of the investigator.

BCVA is used as a standard measure of retinal function in this indication.

8.4 Safety

Safety assessments will include vital signs, and ophthalmic examinations as well as monitoring and recording type, frequency, and severity for all AEs.

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on monitoring, assessment and management of adverse events of inflammation, retinal vasculitis and/or retinal vascular occlusion, refer to Section 10. For details on AE collection and reporting, refer to Section 10.1.

If the COVID-19 pandemic limits or prevents on-site study visits, study treatment should not be administered and other study assessments may not be performed. Alternative methods of

safety monitoring may be implemented. Depending on local regulations, site capabilities and patient's visit status in the study, phone calls or virtual contacts (e.g. teleconsult) can be performed for safety follow-up for the duration of the pandemic, until it is safe for the participant to visit the site again.

8.4.1 Vital sign assessments

Vital signs include assessment of sitting blood pressure (systolic and diastolic pressure in mmHg) and pulse rate (beats per minute) and will be collected at the visits indicated in the visit assessment schedule (Table 8-1). In case there is an elevated blood pressure measurement as specified in the exclusion criteria, at the Screening/Baseline visits, the blood pressure measurement should be repeated after 20 minutes. If the repeat measurement is elevated as specified in the exclusion criteria, then the patient is not eligible to be enrolled into the study.

On days when study treatment is administered, vital signs will be measured **before** administration of study medication. The results will be recorded in the eCRF.

8.4.2 Pregnancy and assessments of fertility

All women of childbearing potential, defined as all women less than 1 year postmenopausal or less than 6 weeks since sterilization at Screening/Baseline, are excluded from this study. No pregnancy test is needed. Subsequent medical documentation must be retained as source documents to confirm that the woman is not of childbearing potential.

Male patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

8.4.3 Ophthalmic examination and imaging

The ophthalmic exam will consist of the following:

- **Intraocular pressure** (IOP) will be assessed in the study eye, pre-dose and post-dose at listed scheduled visit. The same method of tonometry has to be used through the whole study. IOP will be captured on eCRF only at Screening/Baseline and Week48/EOS, or in case of AE. In the fellow eye, IOP will be assessed at Screening/Baseline and Week 48 / EOS. The pre-dose values recorded in mmHg for either eye will be entered into the eCRF. Treatment and close monitoring of IOP should be performed by the investigator for any non-transient elevation in IOP ($\geq$ 25 mmHg). Intravitreal injection is not recommended unless normalization of the IOP has been achieved. Post-dose IOP should be assessed within 60 minutes after injection and if $\geq$ 25 mmHg, assessment should be repeated until back to normal. Monitoring of the optic nerve head perfusion after injection may be done. Results of these procedures will be recorded as appropriate in the source documents and if the findings constitute an AE, it should be recorded in the eCRF.
- **Anterior biomicroscopy (slit lamp examination)** will be completed at every (scheduled and unscheduled) visit to examine the anterior segment structures (e.g. eyelids/lashes, conjunctiva, cornea, anterior chamber, iris, lens and anterior part of the vitreous) of the study eye. The fellow eye will be examined at screening/baseline and at the discretion of the investigator. The results of the examination of either eye must be recorded in the source documents. Slit lamp examination must be carefully performed before each study treatment.

If there are any signs of IOI, severity of anterior chamber cells and flare should be assessed according to the standardization uveitis nomenclature (SUN) working group grading system (Jabs et al 2005). The test results will be recorded in the source documents (e.g. ophthalmic examination tool) and captured in the appropriate eCRF as applicable.

- **Posterior segment (indirect fundus) examination** will be conducted by the investigator at the Screening/Baseline Visit for both eyes. An examination of the peripheral retina must also be conducted to ensure that the IVT injection can safely be performed. Posterior segment examination must be performed carefully before each study treatment. The results of the examination including any abnormalities (e.g. vitreous cells/haze, retinal tear/detachment, hemorrhage and vascular occlusion, vasculitis, etc.) should be recorded in the source documents. If there are any signs of IOI, vitreous cells and haze should be assessed using National Institutes of Health (NIH) grading system (Nussenblatt et al 1985). The outcome of the examination will be documented in the source document (e.g. ophthalmic examination tool) and appropriate eCRF page as applicable.
- The fundus examination and FAF will be performed at the ophthalmic exam visits indicated in the visit assessment schedule (Table 8-1) for the study eye only. Except for Screening/Baseline visit and Week 48/EOS Visit, the fellow eye will be examined at the discretion of the investigator. The results of the examination of either eye must be recorded in the source documents.

Pupil dilation for slit lamp examination and indirect ophthalmoscopy is optional according to investigator practice.

Clinically significant abnormal findings (as judged by the investigator) from the slit lamp or ophthalmoscopy observations should be recorded as an AE in the eCRF.

A phone call one week after the first injection (a window for the phone call is +7 days) must be made to check whether there are any changes in vision or any symptoms of intraocular inflammation. It should be documented in the source document. From the second injection onwards, similar phone calls should be made at investigator's discretion per local practice.

Instruct the patient to contact the site for any changes in vision or any symptoms of inflammation between scheduled visits. Every effort should be made to bring the subject for immediate examination.
Imaging : When IOI, retinal vasculitis, and/or retinal Vascular occlusion (RO) is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and will conduct OCT, fluorescein angiography, indocyanine green chorioangiography and color fundus photography (preferably wide-field or with peripheral sweeps). These additional assessments will be documented in the source and appropriate eCRF pages as applicable. The images are requested to be uploaded onto the CRC portal.
If subject develops intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion, based on the investigator's evaluation, the study treatment of brolucizumab must be discontinued.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population. If there are any signs of IOI, additional assessments will be performed as described in Section 8.4.3.

8.5 Additional assessments

Not applicable

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

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.

The investigator must discontinue study treatment for a given patient if he/she believes that continuation would negatively impact the patient's well-being.

The investigator and/or referring physician will recommend the appropriate follow-up medical care, if needed, for all patients who are prematurely withdrawn from the study.

Study treatment must be discontinued under the following circumstances:

- Patient requires treatment on a q4w interval after the initiation phase, i.e., after the three monthly injections at Baseline, Week 4, and Week 8, followed by the first interval extension
- Patient develops intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion
- Patient/guardian decision
- Pregnancy
- Use of prohibited treatment
- Any situation in which study participation might result in a safety risk to the patient

If premature discontinuation of study treatment occurs, the following should be done as appropriate:

- The investigator should make a reasonable effort to understand and document the primary reason for the patient's premature discontinuation of study treatment using the appropriate eCRF page.
- Patients who prematurely discontinue study treatment for any reason should return 4 weeks after last study treatment to perform the assessments for early treatment discontinuation (ETD). Please refer to Table 8-1, except for patients who withdraw their consent from the study and do not wish to do so (refer to Section 9.1.2).
- After these assessments are performed, patient can be switched to standard of care (SOC) anti-VEGF IVT as per investigators discretion. IVT injection is contraindicated in patients with active intraocular or periocular infections and in patients with active intraocular inflammation; therefore, the investigators must verify that these conditions are not present in the study eye prior to every injection.
- After premature study treatment discontinuation, at a minimum till week 48, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:
  - New/concomitant treatments

- Adverse events/Serious Adverse Events
- BCVA

Additional safety assessments and imaging can be performed if required, as per investigator's discretion.

Dosing of SOC and follow-up visits as per investigators discretion. Patients are not required to attend the mandatory visits at Week 16 and Week 48.

- Patients who decide not to participate in the study further should NOT be considered withdrawn from the study, UNLESS they withdraw their consent (see Section 9.1.2). **Where possible, patients should return for the EOS visit assessments to be performed as scheduled** in Table 8-1. EOS visit assessments on Table 8-1 do not need to be repeated at week 48 for patients on standard of care as they would have been performed as ETD assessment prior to standard of care switch.
- If a patient fails to return for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed (see Section 9.1.3). If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

9.1.1.1 Replacement policy

Patients who started treatment but prematurely discontinued treatment and/or study will not be replaced.

9.1.2 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table (Table 8-1).

Novartis will continue to keep and use collected study information. according to applicable law.

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

A patient should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time. Reasons for early termination may include:

- Unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- Discontinuation of study drug development
- Practical reasons, including slow enrollment
- Regulatory or medical reasons

In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last patient finishes their EOS/Early Withdrawal Visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator, or in the event of an early study termination decision, the date of that decision.

After study completion, the patient may receive standard of care or other treatments, at the discretion of the investigator and/or referring physician, if needed.

10 Safety monitoring and reporting

Patients should be closely monitored for adverse events.

For adverse events of special interest, intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion please ensure compliance with the following:

- Instruct the patient to contact the site for any changes in vision or any symptoms of Intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion, between scheduled visits (refer to the optional patient brochure). Every effort should be made to bring the subject for immediate examination.
- Close patient monitoring and thorough examination of the eye should be done to detect potential signs of inflammation (Section 8.4.4).
- When IOI, retinal vasculitis, and/or retinal vascular occlusion is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and will conduct OCT,

fluorescein angiography and color fundus photography (preferably wide-field or with peripheral sweeps). The images are requested to be uploaded onto the CRC portal.

- If any signs of intraocular inflammation is present, an IVT injection must not be performed. Therefore investigators must verify that these conditions are not present in the study eye prior to every injection.
- If Intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion, is confirmed, patients should be discontinued from study treatment.
- Patients should be treated for these events promptly according to clinical practice.

For additional information related to safety assessments refer to Section 6.7.2 and Section 8.4.4

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g. any unfavorable and unintended sign, symptom or disease) in a patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual patient and identifying AEs.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. AEs may also be detected when they are volunteered by the patient during or between visits or through physical examination findings, or other assessments.

AEs must be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade (mild, moderate or severe as defined below)
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment and the ocular injection procedure. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality to study treatment will usually be ‘Not suspected’. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of treatment arms, not on a single patient.
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.

4. Whether it constitutes a SAE (see for definition of SAE) and which seriousness criteria have been met.
5. Action taken with the study treatment. All AEs must be treated appropriately. Treatment may include one or more of the following:
   - No action taken (e.g. Further observation only)
   - Investigational treatment interrupted/withdrawn
   - Concomitant medication or non-drug therapy given
   - Patient hospitalized/patient's hospitalization prolonged (see Section 10.1.2 for definition of SAE)
6. Its outcome:
   - Not recovered/not resolved
   - Recovered/resolved
   - Recovered/resolved with sequelae
   - Fatal or unknown.
7. Its location (ocular event / non ocular event)

Conditions that were already present at the time of informed consent should be recorded in the medical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued until 30 days (safety follow-up) after the last administration of study treatment (see “Post-treatment follow-up period” in Section 3).

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from Baseline or the previous visit, or values which are considered to be non-typical in patients with the underlying disease. Investigators have the responsibility for managing the safety of individual patients and identifying AEs.

10.1.2 Serious adverse events

An SAE is defined as any AE (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- Fatal

- Life-threatening
  - Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the study indication, not associated with any deterioration in condition.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

In this study, nAMD recurrences and their clinical manifestations are exempt from reporting. Patient treatment is based on disease activity, which is assessed and recorded throughout the study in the eCRF. Moreover, nAMD is a progressive disease while its treatment is a non-continuous drug administration so disease activity might mean that a patient needs more frequent dosing rather than lack of efficacy.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event (SAE) irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until the last study visit or 30 days after the last administration of study treatment whichever is later must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office & Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an investigator notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected unexpected serious adverse reactions (SUSARs) will be collected and submitted to the Competent Authorities and relevant Ethics Committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements.

Any SAE occurring after the patient has provided informed consent and until the last study visit or 30 days after the last administration of study treatment whichever is later will be reported.

Any SAEs experienced after the above mentioned period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Women of childbearing potential are excluded from this study.

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence (female participants only).

The pregnancy (for female participants) should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis CMO & PS Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to brolucizumab (investigational) with any pregnancy outcome.

Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (European Medicines Agency definition).

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record in the eCRF and in the Dispensing Log at the study site, irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes (only date and time of injection)	No	Only if associated with an SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections (Section 10.1.1, Section 10.1.2 and Section 10.1.3).

10.1.6 Adjudication committee

Not applicable.

11 Data collection and database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRFs. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulations (CFR) Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the patient data for archiving at the investigative site.

All data must be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis (or designated CRO) personnel will review the data entered by investigative staff for completeness and accuracy. Electronic data queries stating the nature of the problem and

requesting clarification will be created for discrepancies and missing values and sent to the investigative site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Ocular images will be handled as described in Section 8.3.1 and Section 8.3.2. The Data management staff will review data received from the CRC. Data Review will be done for data structure and data completeness / accuracy as defined in Vendor Data Transfer Specifications.

The occurrence of relevant PDs will be determined at Week 12 before the interim database lock for the primary analysis and at the conclusion of the study. Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/ designated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/ designated CRO. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, retinal images (CFP, FAF, FA, ICG, OCT-A, SD-OCT), and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original ICF signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

12 Data analysis and statistical methods

The primary efficacy and safety analysis will be based on the Week 12 data, i.e. data up to and including Week 12. This analysis will be performed once all patients have completed their Week 12 visit or prematurely discontinued the study before/on their Week 12 visit, while patients will continue to receive study treatment until their Week 40/Week 44 visit, dependent on their treatment regimen. The analysis of the data after the EOS/Week 48 visit will be performed once all patients have completed or prematurely discontinued the study.

The data will be analyzed by Novartis and/or a designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

It is planned that the data from all centers that participate in this protocol will be pooled, so that an adequate number of patients will be available for analysis.

In addition to the statistical methods outlined below, further details will be described in the Statistical Analysis Plan (SAP).

[redacted]

12.1 Analysis sets

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

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

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

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

However, when assessing the robustness of the overall efficacy conclusions, considerations will be given to the analysis based on the estimand using FAS and PPS. Expectation of comparing of both estimands is to have similar conclusions. Inconsistencies in the results will be examined and discussed in the Clinical Study Report (CSR).

12.2 Patient demographics and other baseline characteristics

Demographic and other Baseline data including disease characteristics will be listed and summarized descriptively for the FAS.

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

The last available assessment taken prior to the first IVT injection of study treatment is taken as the “Baseline” assessment.

Relevant medical histories and current medical conditions at Baseline will be listed.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The extent of exposure to study treatment as the number of IVT injections received from Baseline to the end of the treatment period will be descriptively summarized. In addition, the number of patients at each injection category (1 injection, 2 injections up to the maximum number of injections) from Baseline to the end of the treatment period will be presented.

Prior medications are defined as treatments taken and stopped prior to first IVT injection. Any medication given at least once between the day of first IVT injection and the date of the last study visit will be a concomitant medication, including those which were started pre-Baseline and continued into the period where study treatment is administered.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed according to the Anatomical Therapeutic Chemical (ATC) classification system.

Anti-VEGF medications (other than the study treatment) will be summarized separately.

12.4 Analysis of the primary endpoint

12.4.1 Definition of primary endpoint

The primary endpoint is the percentage change in CNV lesion area measured by OCT-A from Baseline to Week 12. This analysis will focus on the study eye only.

The analysis of the primary variable will be based on the following estimand:

- Analysis set: FAS
- Variable of interest: Percentage change from Baseline in CNV lesion area measured by OCT-A to Week 12
- Intervention effects: Effect at Week 12, while on study treatment
- Intercurrent events: Discontinuing study treatment; treatment interruption
- Measure of intervention effect: Difference from Baseline in variable means

12.4.2 Statistical model, hypothesis, and method of analysis

Descriptive statistics 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 two-sided 95% CI using Student's t-distribution will also be provided.

12.4.3 Handling of missing values/censoring/discontinuations

For patients who:

- Discontinue study treatment but continue in the study, the efficacy data will be censored at the time the patient stopped study treatment in the study eye.
- Interrupt treatment, the efficacy data will be censored at the time the study treatment was first interrupted.

12.4.4 Estimand and Sensitivity analyses

In case of significant outliers or deviations from normality assumptions, a non-parametric analysis may be performed.

In order to assess the robustness of the primary endpoint, estimand and sensitivity analyses are planned. These may include, but are not limited to:

- Consistent results from analyses based on the FAS and the PPS increases confidence in the trial results. Difference between FAS and PPS in incidence of intercurrent of event like COVID-19 regardless of whether patients discontinue assigned treatment. Performing comparison on the observed data between FAS vs PPS with the same handling rules for censoring as outlined in Section 12.4.3. for the efficacy endpoints.
- Repeating the primary analysis using the PPS.

Sensitivity estimand in exposed and non-exposed to the urgent safety measures: As a sensitivity analysis for the change in CNV lesion area measured by OCT-A at Week 12, the change in CNV lesion area measured by OCT-A at Week 12 will be compared before and after the urgent safety measures were introduced. The analyses will be performed in FAS and PPS.

Further details about the analyses will be given in the SAP. Any major discrepancies in the results across analyses will be investigated as needed.

Age, Baseline lesion type, and time since nAMD diagnosis subgroup analyses will also be performed on the primary endpoint.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoints

All secondary efficacy analyses will be based on the FAS. The analyses performed at eye level will focus on the study eye only.

The secondary efficacy endpoints are as follows:

- Functional outcomes of brolucizumab
  - Change in BCVA from Baseline up to Week 48.
- Anatomical outcomes of brolucizumab
  - 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.
  - Change in SD-OCT features assessed by qualitative and quantitative criteria (e.g. CSFT, sub- and/or intraretinal fluid, sub-RPE fluid) from Baseline by visit at Week 12 up to Week 48.

The continuous functional and anatomical outcomes will be analyzed using the same primary method of analysis as the primary efficacy analysis. The factors in the respective model will be defined by the study Steering Committee. These details will be provided in the SAP. The qualitative dichotomous anatomical outcomes with 2 categories will be assessed using Cochran's Q Test and those with more than 2 categories by the Generalized McNemar's Test. In addition, the functional and anatomical outcomes will be described descriptively.

- Dosing regimen of brolucizumab
  - Proportion of patients who are maintained on an exclusive q12w interval following the loading phase through Week 48.
  - The probability of the first q12w interval for determining successful q12w maintenance at Week 48.
  - Time from last IVT injection in the initiation phase to first visit with no disease activity

The binomial proportion and 95% confidence interval (CI) using the Clopper-Pearson method will be provided for disease status (i.e. q12w treatment status) at each disease activity assessment visit. The estimate of the probability for a patient to be maintained on the q12w regimen up to end of treatment will be summarized based on a Kaplan-Meier analysis of time to first q8w need. The time from last IVT injection in the initiation phase to first visit with no disease activity will also be summarized using a Kaplan-Meier analysis. In addition, descriptive statistics will also be provided.

12.5.2 Safety endpoints

For all safety analyses, the Safety Set will be used.

The secondary safety endpoint of this study is as follows:

- Incidence of AEs (serious and non serious) reported in patients treated with brolucizumab.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of Baseline data, which will also be summarized where appropriate (e.g. change from Baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events of special interest (AESIs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of IVT injection of study treatment to 30 days after the date of the last actual administration of IVT injection of study treatment.

Adverse events

All information obtained on AEs will be displayed by patient.

The number (and percentage) of patients with treatment emergent AEs (events started after the first IVT injection of study medication or events present prior to start of IVT injection but increased in severity based on preferred term) will be summarized in the following ways:

- Primary system organ class and preferred term.
- Primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related AEs, death, serious AESIs, other AEs leading to discontinuation.

The number (and proportion) of patients with AEs of special interest will be summarized by Standardized MedDRA Query (SMQ) and preferred term.

A patient with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by patient and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by visit.

Other safety evaluations

All ophthalmic examinations data will be listed by patient and visit and if normal ranges are available, abnormalities will be flagged. In addition, summary statistics for clinically relevant abnormalities will be provided by visit/time.

12.5.3 Patient reported outcomes

Not applicable

12.6 Analysis of exploratory endpoints

Not applicable.

12.7 Interim analyses

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 completed or prematurely discontinued the study.

12.8 Sample size calculation

12.8.1 Primary endpoint

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 8.0). Therefore, to have a precision of 5.0%, a sample size of 189 patients will be needed (Table 12-1).

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

Table 12-1 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

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written ICF, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required.

If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality control and quality assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request.

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16 Appendices

None.