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Novartis Research and Development

RTH258/Brolucizumab

Clinical Trial Protocol CRTH258AFR03 / NCT04264819

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

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Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
BCVA	Best-Corrected Visual Acuity
BCNVA	Best-Corrected Near Visual Acuity
[redacted]	[redacted]
CFR	Code of Federal Regulation
CMO & PS	Chief Medical Office & Patient Safety
CNV	Choroidal Neovascularization
CRC	Central Reading Center
CRF	Case Report/Record Form (paper or electronic)
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organization
CSFT	Central Sub-Field Retinal 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
[redacted]	[redacted]
[redacted]	[redacted]
FAS	Full Analysis Set
FIR	First Interpretable Results
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
[redacted]	[redacted]
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IOI	Intraocular Inflammation
[redacted]	[redacted]
IRB	Institutional Review Board
IRF	Intraretinal Fluid
IVT	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	Neovascular Age-Related Macular Degeneration
NIH	National Institutes of Health
OCT	Optical Coherence Tomography
PDT	Photodynamic Therapy
PED	Pigment Epithelial Detachment

PFS	Pre-Filled Syringe
[redacted]	[redacted]
Q4	Every 4 Weeks
Q8	Every 8 Weeks
Q12	Every 12 Weeks
RO	Retinal Vascular Occlusion
RPE	Retinal Pigmented Epithelium
RV	Retinal Vasculitis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
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	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 Code of Federal Regulation (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 will be 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
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.
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
Unmasked/treating Investigator	For the entire study duration and all study patients, the treating Investigator only performs the treatment (injection active/sham) and assesses patient safety following the active/sham injections.
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 is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Amendment 1 (27-Jan-2020)

Rationale

The purpose of this amendment is to incorporate changes which resulted from interactions with Regulatory Authorities, who required to clarify the washout period between the last dose of the anti-VEGF treatment received by the subject prior to be included in the study and the first dose of brolucizumab administrated in the study.

In addition, changes have been made to clarify number of mandatory visits in the study and data to collect for the fellow eye.

Changes to the protocol

List the modifications implemented in the different sections,

- Clarification of the washout period: Protocol summary, Study design, Inclusion criteria, Treatment duration, Concomitant therapy, Visit schedule and assessments (pages 32 and 35)
- Clarification on the number of mandatory visits: Study design
- Clarification on the data to collect for the fellow eye: 8 Visit schedule and assessments

IECs

These changes are considered not-substantial.

The amendment is to be sent to the IECs for information.

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 the modifications due to COVID-19 pandemic.

Changes to the protocol

Protocol sections changed in relation to this emerging safety issue are:

- Section 1.1 Background: Information was added to describe 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 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 intraocular inflammation (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 included to fully characterize cases of intraocular inflammation (IOI) were added in the following sections:
  - Table 8-1 Assessment schedule [redacted]
  - Section 8.4.3 Ophthalmic Examination
  - Section 8.4.4 Appropriateness of safety measurements

Changes were incorporated to address the COVID-19 pandemic in the following sections:

- Section 5.2 Exclusion Criteria
- Section 6.2.2 Prohibited Medication
- Section 8 Visit Schedule and Assessments
- Section 8.4 Safety
- Section 12 Data Analysis

Other changes incorporated in this amendment:

- Increase of the number of study sites from 50 to 75, to insure the feasibility of patient recruitment in a 9-month period (Sections 3, 5 and 12.8)
- Section 5.2 Exclusion Criteria: clarification on previous treatments (to avoid discrepancy between criteria #16 and criteria #12-15)

- Section 6.7.2 Instruction for Prescribing and Taking Study Treatment: Language regarding the injection procedure was added replacing reference to an applicable manual.
- Section 6.7.2.2 Treat-to-Control Phase: instruction in case of a patient misses a disease activity assessment visits.
- Section 8.4.3 Ophthalmic examination: Added instructions for the patients in case of symptoms of inflammation.
- Section 8 Visit Schedule and Assessments: clarification of treatment during unscheduled visit.
- Section 10.1.4 SAE Reporting: Clarification of the SAE reporting period.
- Section 12.1 Analysis Sets: Modified to include importance of Estimands per ICH E9(R1) guidance.
- Section 12.8 (Primary endpoint): change of the patient recruitment period (from April 2020 to December 2020 to January 2021 to September 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 IECs and HA for approval.

These changes have impact on the ICF.

Amendment 3 (01-Sept-2021)

Amendment Rationale

The main reasons for the protocol amendment are:

(1) To provide clarification and guidance on the early discontinuation of study treatment that is required for those subjects who are currently on q4w dosing beyond the first 3 monthly loading doses ("loading phase") or would need q4w dosing beyond the "loading phase" based on the investigator's assessment. This is as per the urgent safety measure dated 27-May-2021 based on CTH258AUS04 (MERLIN) Year 1 first interpretable results (FIR) indicating a higher frequency of IOI including Retinal Vasculitis (RV), and Retinal Vascular Occlusion (RO) in brolucizumab 6 mg q4w when compared to aflibercept 2 mg q4w (IOI: 9.3% vs 4.5% of which RV: 0.8% vs 0.0%; RO: 2.0% vs 0.0%, respectively).

(2) Additionally, as per the Urgent Safety Measure dated 10-August-2021, the results of the mechanistic study BASICHR0049 identified a causal link with an immune-mediated mechanism of the previously identified risk of Retinal vasculitis (RV), and/or Retinal vascular occlusion (RO), typically in the presence of IOI. The protocol is hence amended to require discontinuation of study treatment in subjects who develop these events.

(3) 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.

(4) 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 that the interval between two brolucizumab doses should not be shorter than 8 weeks beyond loading, and that the impact on the risk/benefit balance is considered to be low when patients are dosed ≥q8w after the loading phase. Clarified that treatment intervals after the initiation phase will range from 8 weeks to 16 weeks. In addition, 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.
- Section 3 Study design: Remove of the number of investigator sites. Clarified that if disease activity is observed at Week 14/Week 16, then the study treatment will be administered at

this visit and the further injections will be discontinued. Clarified the difference between study completion as per protocol versus early treatment discontinuation. Clarified that only during the loading phase injections should be at least 21 days apart.

- Section 3 Study design; Section 4.2 Rationale for dose/regimen and duration of treatment; Section 6.7.2 Instruction for prescribing and taking study treatment: Modified to clarify the shortest treatment interval in the TtC phase.
- Section 4.2 Rationale for dose/regimen and duration of treatment: Language added to provide background of the USM and impact on design.
- Section 4.5 Risks and Benefits: Added the three 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 for subjects requiring injections every 4 weeks. Added a paragraph 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 show the treatment intervals allowed in the maintenance phase, following Week 8. In addition, changes made to clarify that subjects who require treatment every 4 weeks beyond the loading phase, should be discontinued from study treatment. Paragraph describing inspection visits at Week 14 for an interval extension from 4 weeks to 8 weeks was clarified. 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.
- Figure 6-1 Treatment regimen: Updated the range for treatment intervals.
- Table 6-3 Disease activity assessment and treatment occurrence according to visit type: Remove of Week 12 visit. Added newly implemented visit type “ETD”.
- Section 8 Visit schedule and assessments: Removed a sentence that two consecutive injections should be at least 21 days apart as this is no longer applicable since in the maintenance phase, any subject who requires treatment every 4 weeks has to be discontinued from study treatment.
- Table 8-1 Assessment schedule: Remove of column for Week 12, no more possible. Columns added for early treatment discontinuation visits and for assessment visits after start of standard of care, including respective footnotes. In addition, footnotes #2 was updated to reflect the requirement to discontinue subjects from further treatment in case of disease activity at the inspection visit at Week 14; and a clarification was added in footnote #12 with respect to ophthalmic examinations and images. Updated the name of the ophthalmic examination where “and imaging” was added. Footnotes #14, #15, and #16 added with respect to ETD and EOS assessments.
- Section 8.3.1 Optical coherence tomography: clarification of CRC OCT review for all study visits.
- 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 (25-Nov-2021)

Amendment Rationale

[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.

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

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 summary has been aligned with amendment 4.

Protocol sections changed in relation to the [redacted] remove are:

- Section 2 "Objectives and endpoints" and Table 2-1 "Objectives and related endpoints": [redacted]
- Section 3 "Study Design": [redacted]
- Section 7 "Informed consent procedures": [redacted]
- Table 8-1 "Assessment schedule for the study eye": [redacted]
- Section 8.1 "Screening": [redacted]
- Section 8.2 "Patient demographics/other baseline characteristics": [redacted]

- Section 11.2 “Database management and quality control”: [redacted]
- Section 13.2 “Responsibilities of the investigator and IRB/IEC”: [redacted]
- Section 15 “References”: [redacted]

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

- 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 8.4.3 ‘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.

Protocol sections changed in relation to information on gender imbalance on IOI following brolucizumab treatment are:

- Section 4.5 Risks and Benefits: Information added to describe information on gender imbalance on IOI following brolucizumab treatment.

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 5 (5-Apr-2022)

Amendment Rationale

The 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 295. The study objectives will still be assessed with the revised sample size

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 5.
- 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

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	CRTH258AFR03
Full title	A one-year, single-arm, open-label, multicenter study assessing the effect of brolucizumab on disease control in adult patients with suboptimal anatomically controlled neovascular age-related macular degeneration (SWIFT)
Brief title	Study of brolucizumab in adult patients with suboptimal anatomically controlled neovascular age-related macular degeneration
Sponsor and Clinical Phase	Novartis/Phase 3b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Based on clinical data, it is expected that switching suboptimal anatomically controlled patients treated with current licensed anti-VEGF to a presumably more effective and longer lasting anti-VEGF agent like brolucizumab may lead to optimized disease control. The purpose of this study is to assess both early (at Week 16 just after the loading phase) and long-term (48 weeks) effects of brolucizumab on disease control in suboptimal anatomically controlled neovascular age-related macular degeneration (nAMD) patients.
Primary objective	To evaluate the effect of brolucizumab 6 mg on disease control
Secondary objectives	• To evaluate the long term effects of brolucizumab 6 mg on disease control • To evaluate the effect of brolucizumab 6 mg on anatomical parameters • To evaluate the durability of brolucizumab 6 mg • To evaluate functional outcomes • To assess the safety and tolerability of brolucizumab 6 mg
Study design	This is a prospective, single-arm, open-label, multicenter study to evaluate the efficacy and safety of brolucizumab 6 mg in pretreated suboptimal anatomically controlled patients with nAMD. Approximately 295 adult patients will be screened and included (10% dropout rate expected) in France. The maximum study duration for 1 patient is 48 to 50 weeks, according to the patient schedule. Treatment intervals after the initiation phase will be either 8 weeks, 12 weeks, or 16 weeks. More frequent injections, i.e., treatment intervals of <8 weeks are not allowed.
Population	The study population will be male and female patients ≥ 50 years old diagnosed with active CNV secondary to nAMD and able to comply with study or follow-up procedures.
Key inclusion criteria	• Patients must provide 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 nAMD diagnosed < 18 months prior to Screening/Baseline 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 (FA) and sequelae of CNV, e.g. pigment epithelial detachment (PED), subretinal hemorrhage or sub-retinal pigmented epithelium (sub-RPE) hemorrhage, blocked fluorescence, or macular edema. • Previous treatment with only one licensed anti-VEGF drug (i.e. Lucentis®, Eylea®) with a ≥ Q4 and ≤ Q8 treatment (treatment interval of 26 to 62 days inclusive) with licensed anti-VEGF (a minimal washout period of 4 weeks / 26 days is required). Patients must have received at least 3

	injections of this anti-VEGF drug in the 6 months prior to Screening/Baseline • Presence of residual fluid (intraretinal fluid (IRF) or subretinal fluid (SRF) that affects the central subfield under, as seen by OCT). • Best-corrected visual acuity (BCVA) score must be ≤ 83 and ≥ 38 letters at an initial testing distance of 4 meters starting distance using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity charts at Screening/Baseline.
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**. • Presence of amblyopia, amaurosis, or ocular disorders in the **fellow eye** with BCVA < 35 ETDRS letters at Screening/Baseline (except when due to conditions whose surgery may improve visual acuity, e.g. cataract). • Medical history of intraocular inflammation and/or retinal vascular occlusion within 12 months prior to Screening/Baseline **Study eye** • Poor quality of OCT images at Screening/Baseline. • Atrophy or fibrosis involving the center of the fovea in the study eye, as assessed by CFP and fundus autofluorescence (FAF). • The total area of fibrosis or subretinal blood affecting the foveal center point comprising ≥ 50% of the lesion area in the study eye. • 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. • Previous laser treatment for nAMD including photodynamic therapy (PDT) laser at any time prior to Screening/Baseline. **Systemic conditions or treatments** • Stroke or myocardial infarction in the 6-month period prior to Screening/Baseline. • Systemic anti-VEGF therapy at any time. **Other** • Women of childbearing potential, defined as all women less than 1 year postmenopausal or less than 6 weeks since sterilization.
Study treatment	Brolucizumab 6 mg (RTH258 6 mg/ 0.05 mL) solution for injection in pre-filled syringe
Efficacy assessments	• OCT [redacted] • Visual acuity using BCVA (EDTRS) [redacted]
Key safety assessments	• Vital signs • Ophthalmic examination ([redacted] biomicroscopy, indirect ophthalmoscopy) and imaging

	• Adverse events (AEs)
Other assessments	[redacted]
Data analysis	**Primary endpoint** The primary objective of this study is to evaluate the effect of brolucizumab 6 mg on disease control. The primary efficacy endpoint is the proportion of patients with no disease activity at Week 16. This analysis will be performed in the FAS and will focus on the study eye only. The number (%) and proportion of patients with no disease activity at Week 16 will be provided with the associated 95% confidence interval. The interim database lock for the primary analyses will be conducted when the last patient included has completed the Week 16 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]
Keywords	Neovascular age-related macular degeneration, anti-VEGF, choroidal neovascularization, disease control

1 Introduction

1.1 Background

Neovascular age-related macular degeneration is characterized by the presence of choroidal neovascularization (CNV), which consists of abnormal blood vessels originating from the choroid that 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 studies.

Brolucizumab is a new generation of anti-VEGF. Brolucizumab is the first humanized single-chain antibody fragment (scFv), which inhibits 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]) (Dugel et al 2019) comparing brolucizumab every 12 weeks (Q12) or every 8 weeks (Q8) to aflibercept Q8 according to its approved label. In these studies, patients in both treatment arms received 3 loading doses every 4 weeks, followed by a Q12/Q8 maintenance regimen according to patient's disease activity for the brolucizumab 6-mg arm and a Q8 maintenance regimen for the aflibercept 2-mg arm. For the Q12/Q8 treatment regimen, Q12/Q8 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 Q12/Q8 regimen, the initial treatment schedule after the loading phase was Q12. If disease activity was identified by the Investigator in brolucizumab-treated patients at any of the disease activity assessments, dosing was adjusted to Q8 (i.e. "Q12/Q8 regimen"). Once patients were adjusted to a Q8 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 at Week 48 for the following mean change from Baseline in central subfield retinal thickness (CSFT); percentage of patients with intraretinal fluid and/or subretinal fluid (IRF and/or SRF); percentage of patients with subretinal pigment epithelium (sub-RPE) fluid; and at Week 16 for the percentage of patients with no disease activity (Dugel et al 2019). Safety was comparable between the treatment arms over 2 years.

Since the first global marketing authorization approval in the US, in Oct-2019, for the treatment of nAMD, adverse events 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.

In addition, based on the USM (CRTH258AUS04 first interpretable results [FIR]), the interval between two brolucizumab doses should not be shorter than 8 weeks beyond the loading phase.

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 are dosed at q8w or longer after the loading phase and when patients who develop RV and/or RO are discontinued from further treatment with brolucizumab.

Despite the interesting results of brolucizumab treatment with a Q12/Q8 regimen in naïve nAMD patients, the most popular and used anti-VEGF treatment, both internationally (Wykoff et al 2018) and in France (Bourrhis 2019), is the Treat-and-Extend regimen (T&E). Accordingly, a new Phase 3b study (TALON, CRTH258A2303) is being conducted to evaluate the efficacy and safety of brolucizumab in a Treat-to-Control (TtC) regimen for the treatment of naïve patients with nAMD. In this TtC regimen, patients receive 3 consecutive injections every 4 weeks and then the injection interval is extended by 4 weeks up to a maximum of a 16-week interval. The decision to extend or reduce the injection interval is taken by the Investigator at each visit based on his/her judgment of disease activity, according to the patient visual and/or anatomic outcomes. If there is no disease activity, the injection interval can be extended by 4 weeks; if disease activity occurs or recurs, the injection interval should be shortened accordingly by 4 weeks at a time or to a minimal interval of 8 weeks. The injection interval can also be maintained if the Investigator deems that the patient do not benefit from injection interval extension.

Since all these studies were conducted in a naïve nAMD patient population, no data are available on the efficacy and safety of brolucizumab in pretreated nAMD patients who still present active exudation.

Indeed, in interventional studies (EXCITE, Schmidt-Erfurth et al 2011; TREND, Silva et al 2018; ALTAIR, Masahito 2017; FLUID, Guymer et al 2019; RIVAL, Gillies et al 2019) and real-life studies (LUEUR, Souied et al 2015; RAINBOW, Weber et al 2019), a number of patients treated with ranibizumab or aflibercept still presented persistent fluid when extended to Q6 or longer treatment intervals.

Switching to another anti-VEGF treatment has become the second-line strategy for suboptimal anatomically controlled patients (Empeslidis et al 2019). Several studies have assessed the efficacy of switching nAMD patients to another anti-VEGF following unsatisfactory response to prior therapy. Despite very limited benefit from switching to another anti-VEGF in terms of visual outcome, the majority of the studies have shown substantial gains in terms of interval between injections and anatomical outcomes, with a total fluid resolution on OCT in 60% to 72% of patients 1 year after the switch (Pinheiro-Costa et al 2015, Arcinue et al 2015, Sarao et al 2016).

In conclusion, based on all these data, we could expect that switching suboptimal anatomically controlled patients treated with current licensed anti-VEGF to a presumably more effective and

longer lasting anti-VEGF agent like brolucizumab may lead to optimized fluid and disease control.

The SWIFT study intends to complement the current clinical dataset on brolucizumab by generating new evidence in suboptimal anatomically controlled nAMD patients despite the anti-VEGF treatment. The study will evaluate the efficacy and safety of brolucizumab administered in a 4-week-adjustment TtC regimen with treatment intervals from 8 to 16 weeks after the initial three consecutive monthly injections and one treatment interval extension by 4 weeks from Week 8 to Week 16 ("initiation phase"). Subjects requiring injections every 4 weeks after the initiation phase will be discontinued from further study treatment. The study will assess if treatment with brolucizumab results in better disease control at Week 16 and over the 48 weeks in these suboptimal anatomically controlled patients.

1.2 Purpose

The purpose of this study is to assess both early (at Week 16 just after the loading phase) and long-term (48 weeks) effects of brolucizumab on disease control in suboptimal anatomically controlled nAMD patients.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

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

Objectives	Endpoints
• To evaluate functional outcomes	• Average change in BCVA from Baseline up to Week 48
• To assess the safety and tolerability of brolucizumab 6 mg	• Incidence of AEs (serious and non-serious) up to Week 48
[redacted]	

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

3 Study design

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

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

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

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

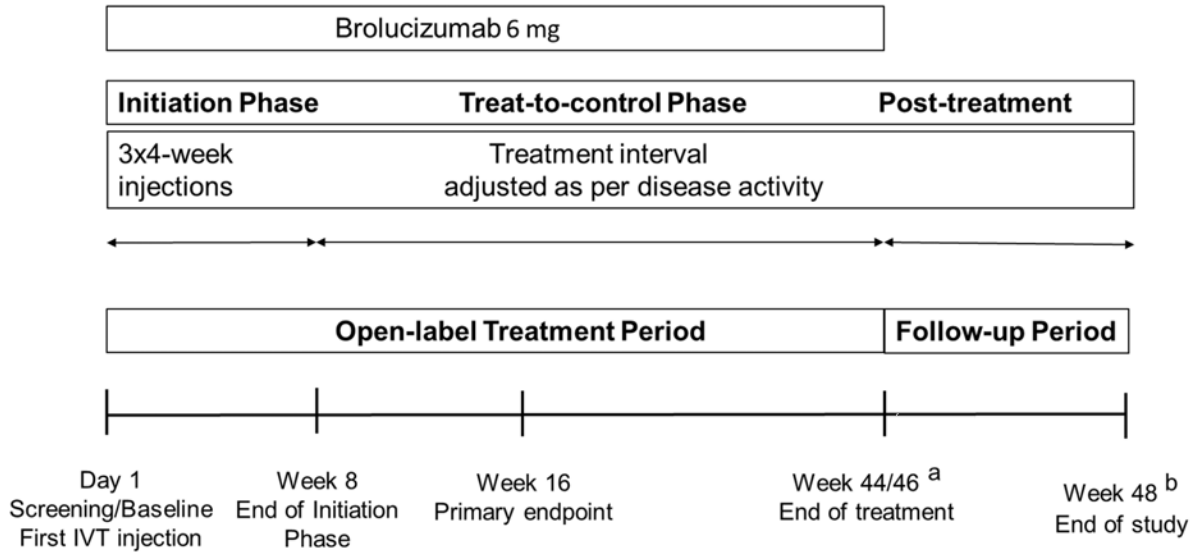
The study will consist of 2 periods (Figure 3-1):

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

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

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

Figure 3-1 Study design



[a] End of treatment: Week 38/40/42/44/46 according to treatment schedule.

[b] End of study: at least 4 weeks after the end of treatment. For patients receiving the last IVT at Week 46, the EOS Visit will be at Week 50, 4 weeks following their last treatment

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

Open-label Treatment Period: from Day 1 to Week 44/46

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

One time re-assessment of patients will be 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.

Patients must have confirmed nAMD at Screening/Baseline and have received his/her last licensed anti-VEGF injection from 4 weeks to 8 weeks (from 26 to 62 days inclusive).

After confirmation of eligibility, patients will be included and treated with brolucizumab 6 mg in a TtC regimen. A study visit schedule will be established at the time of inclusion for all patients. All efforts should be made to adhere to this 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 visit window. Treatment (including at Screening/Baseline) is intended to be administered on the day of study visit, or if this is not possible, within 3 days

after the study visit when the per-protocol assessments would have taken place, in which case study treatment administration should occur within the next 24 hours. 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-44 visit or at the Week-46 visit if the patients had received the study treatment at an odd number of inspection visits (see below). The Initiation Phase starts on Day 1 and ends on Week 8. The TtC regimen spans from Week 8 until end of treatment (Week 44/46).

Patients will receive 3 consecutive injections every 4 weeks at Screening/Baseline, Week 4, and Week 8 (loading phase), which should be at least 21 days apart.

At Week 8, based on Investigator's judgment of visual and/or anatomic outcomes, the injection interval will be extended by 4 weeks at a time if there is no disease activity, as provided in the guidance to the Investigators, e.g. no change in visual acuity and in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.). From Week 16, the injection interval can be maintained on Q8 (or Q12 from Week 28) if the Investigator deems that the patient will not benefit from treatment interval extension, with a minimal interval of 8 weeks. If disease activity recurs, the injection interval should be shortened accordingly by 4 weeks at a time or to a minimal interval of 8 weeks. The injection interval can also be maintained if the Investigator deems that the patient will not benefit from injection interval extension (see Section 6.7.2 for further details). Patients who require study treatment every 4 weeks after the initiation phase will be discontinued from further study treatment at the next visit.

At the Investigator's discretion, in case of interval extension, inspection visits can be performed at the midterm of the interval extension, e.g. 6 weeks after the last injection when the injection interval is extended from 4 weeks to 8 weeks. If there is no disease activity in the study eye at the inspection visit, as assessed by the Investigator, no treatment will be administered at this inspection visit; the next visit and injection will take place 2 weeks later, i.e. 8 weeks after the previous study treatment. If disease activity is observed by the Investigator in the study eye at the inspection visit at Week 14, the study treatment will be administered by the Investigator and the patient will be discontinued from further study treatment at the next visit. Inspection visits 10 weeks and 14 weeks after the last injection can be performed when the injection interval is extended from 8 weeks to 12 weeks and from 12 weeks to 16 weeks, respectively (see Section 6.7.2).

Follow-up Period: from Week 44/46 to Week 48/50

For all patients completing the study as per protocol, the End-of-Study (EOS) assessment will be performed at Week 48 (or Week 50 for patients receiving their last treatment at Week 46), at least 4 weeks (± 7 days) following the last possible study treatment administration. For patients who receive their last IVT at Week 46, the EOS assessment will be performed at Week 50 (± 7 days), at least four weeks (± 7 days) following their last possible study treatment administration. For clarity reason, the EOS visit will be named Week 48 in the rest of this protocol.

Patients withdrawn from the study prior to study completion will be asked to return for an early discontinuation (EOS) 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 pretreated suboptimal anatomically controlled nAMD patients will be performed to assess both early (at Week 16) and long-term (48 weeks) effects of brolucizumab, a new-generation anti-VEGF treatment, on disease activity in a TtC regimen.

The TtC regimen emphasizes sustained disease control to determine the optimal treatment interval for each patient rather than solely adjusting treatment intervals. For instance, it allows patients that may not benefit from treatment interval adjustment to be temporarily or lastingly maintained on a treatment interval. This treatment adjustment is particularly needed in these difficult-to-treat patients that are not controlled with a previous anti-VEGF treatment.

The safety and efficacy of brolucizumab has been demonstrated in naive nAMD patients in 2 randomized, multicenter, double-masked, active-controlled Phase 3 studies (HAWK RTH258-C001 and HARRIER RTH258-C002) up to 96 weeks (see Section 1.1), an additional Phase 3b study (TALON CRTH2582303) will evaluate the efficacy and safety of brolucizumab in a TtC regimen. Disease control was evaluated in these studies using visual and/or anatomic outcomes, and HAWK and HARRIER studies have demonstrated that brolucizumab increase disease control in more patients compared to aflibercept, with relative additional 30% more patients without disease activity at Week 16 with brolucizumab compared to aflibercept (respectively $p = 0.0013$ and $p = 0.0021$).

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 (RTH258-C001, RTH258-C002). The nAMD study results regarding Q12/Q8 maintenance dosing interval support stretching the interval between injections during the Treat-to-Control Phase to reduce the treatment burden (see Section 1.1).
- CRTH258AUS04 (MERLIN) is a two-year, multicenter, randomized, double masked, Phase IIIa study evaluating brolucizumab 6 mg q4w versus aflibercept 2 mg q4w in patients with nAMD with persistent fluid. Review of the 52-week FIR led to an urgent safety communication based on an increased incidence of intraocular inflammation (IOI) and related adverse events including retinal vasculitis (RV), and retinal vascular occlusion (RO) in patients with q4w dosing with brolucizumab beyond the “loading phase”. IOI including RV, and RO were reported at a higher frequency in brolucizumab 6 mg q4w when compared to aflibercept 2 mg q4w (IOI: 9.3% vs 4.5% of which RV: 0.8% vs 0.0%; RO: 2.0% vs 0.0%,

respectively). Accordingly, the CRTH258AFR03 protocol is being amended to discontinue subjects from study treatment who require treatment every 4 weeks.

- 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's assessment of disease activity.
- Current evidence from large ranibizumab studies in nAMD (CRF002A2411 - TREND, CRF002ACA06 - CAN-TREAT, CRF002AAU15 - FLUID, CRF002AAU17 - RIVAL) indicates that the Treat-and-Extend regimen is efficient and clinically comparable to monthly injections in improving visual acuity while reducing the number of visits and treatments (see Section 1.1).
- In this SWIFT study, patients will be suboptimal anatomically controlled (active CNV with residual IRF and/or SRF) despite a Q4 to Q8 anti-VEGF treatment. For these non/partially responder patients, the treatment should be as frequent as needed. That is why a Q8 treatment will be allowed since Week 8 and the interval extension will be optional after the loading phase.
- The route of administration is intravitreal (IVT) as for all anti-VEGF treatments currently approved for nAMD.
- Prefilled syringes (PFS) have been selected for administration of study treatment because 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-16 visit. An interim analysis will be performed when the last patient included completed Week-16 visit.

Patients will remain in the study and continue to receive treatment for the maximum planned duration of treatment of 44/46 weeks. The final analysis will be performed at the end of study when all patients have completed their last study visit.

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 Q12 dosing interval at 48 weeks, and the remainder maintained on an Q8 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, and 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 Q12 interval; the vast majority of patients without disease activity during the initial Q12 interval continued to be maintained on an Q12 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.

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.

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 immediately.

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 study 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 childbearing 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 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 active CNV secondary to nAMD and able to comply with study or follow-up procedures.

Approximately 295 adult patients will be screened and included in France.

If both eyes are eligible as per the inclusion and exclusion criteria described below, the eye with the worse BCVA at Screening/Baseline 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

Eligible patients 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 nAMD diagnosed < 18 months prior to Screening/Baseline that affect the central subfield, including retinal angiomatous proliferation (RAP) with a CNV component, confirmed by presence of active leakage from CNV seen by FA and sequelae of CNV, e.g. pigment epithelial detachment (PED), subretinal hemorrhage or sub-RPE hemorrhage, blocked fluorescence, or macular edema.
4. Previous treatment with only one licensed anti-VEGF drug (i.e. Lucentis®, Eylea®) with a ≥ Q4 and ≤ Q8 treatment (treatment interval of 26 to 62 days inclusive) with licensed anti-VEGF (a minimal washout period of at least 4 weeks / 26 days is required). Patients must

have received at least 3 injections of this anti-VEGF in the 6 months prior to Screening/Baseline.

5. Presence of residual fluid (IRF or SRF that affects the central subfield under, as seen by OCT)
6. BCVA score must be ≤ 83 and ≥ 38 letters at an initial distance of 4 meters starting distance using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity charts at Screening/Baseline.

5.2 Exclusion criteria

Patients meeting any of the following criteria will not be eligible for inclusion in the 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/Baseline (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 image at Screening/Baseline.
5. Atrophy or fibrosis involving the center of the fovea in the study eye, as assessed by CFP and fundus autofluorescence (FAF).
6. The total area of fibrosis or subretinal blood affecting the foveal center point comprising ≥ 50% of the lesion area in the study eye.
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, RPE rip/tear scar, laser burn, at the time of Screening/Baseline 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.

Ocular treatments (study eye)

12. Patient has received any investigational treatment for nAMD (other than vitamin supplements) in the study eye at any time.
13. Previous use of intraocular or periocular of corticosteroids in the study eye within 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 and peripheral laser photocoagulation.
    - Previous macular surgery or other intraocular surgical intervention

16. Previous laser treatment for nAMD including photodynamic therapy (PDT) laser at any time prior to Screening/Baseline.
17. Previous treatment with investigational drugs.

Systemic conditions or treatments

18. End-stage renal disease requiring dialysis or renal transplant.
19. 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 Baseline except temporary use for COVID-19 treatment.
20. 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 Baseline. Note: observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary.
21. Systemic anti-VEGF therapy at any time.
22. Stroke or myocardial infarction in the 6-month period prior to Screening/Baseline.
23. Uncontrolled blood pressure defined as a systolic value $\geq$ 160 mmHg or diastolic value $\geq$ 100 mmHg. (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).
24. 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.
25. 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.
26. History of hypersensitivity to the study drug or its excipients or to drugs of similar classes, or clinically relevant sensitivity to fluorescein dye, as assessed by the Investigator.

Other

27. 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.
28. Women of childbearing potential, defined as all women less than 1 year postmenopausal or less than 6 weeks since sterilization.

    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.
29. 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 Pre-Filled Syringe (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 study.

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 Baseline, Week 4, and Week 8), followed by a TtC regimen phase based on disease activity from Week 8 up to Week 44/46 (according to the treatment regimen).

6.1.4 Treatment duration

The study treatment will be start after a minimum washout period of at least 4 weeks / 26 days and maximum 8 weeks/62 days after the last licensed antiVEGF injection.

The maximum planned duration of treatment for each patient is 44 or 46 weeks in accordance with the 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 14/Week 16), study treatment will also 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). The last licensed antiVEGF injection must be received at least 4 weeks / 26 days and at maximum 8 weeks / 62 days before patient inclusion in the study. 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 is 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 AEs captured in the eCRF.

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

If cataract surgery were 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 surgery-related complications.

If yttrium aluminum garnet laser (YAG) were 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 Table 6-2 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 AEs)	Anytime	Discontinue study treatment (except if for treatment of AEs)
Anti-VEGF therapy other than assigned study medication	Anytime	Discontinue study treatment
Panretinal laser, photodynamic therapy 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

In the fellow eye, treatment with investigational products (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 study. The Patient No. consists of the study site number (4-digit number assigned by Novartis) with a sequential patient number suffixed to it (3-digit number), 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 failed screening, 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 (at Screening/Baseline, Week 4, and Week 8). After the Week 8 treatment visit, the Investigator can decide, based on disease activity, to extend the injection interval by 4 weeks to an 8-week interval to Week 16.

From Week 8, based on Investigator's judgment of visual and/or anatomic outcomes, the injection interval can be extended by 4 weeks at a time, if there is no disease activity, as provided in the guidance to the Investigators, e.g. no change in visual acuity and in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.). From Week 16, the injection interval can be maintained on Q8 (or Q12 from Week 28) if there is no disease activity. If disease activity recurs, the injection interval should be shortened accordingly by 4 weeks at a time or to a

minimal interval of 8 weeks. The injection interval can also be maintained if the Investigator deems that the patient will not benefit from injection interval adjustment (see Figure 6-1).

Neither study treatment dose modification nor deviations from the allowed dose intervals (in accordance with disease activity assessments) will be permitted.

Interruption of study treatment will be 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, study 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 study 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 legal requirements. They will include storage conditions for the study treatment, but not information about the patient except for the medication number.

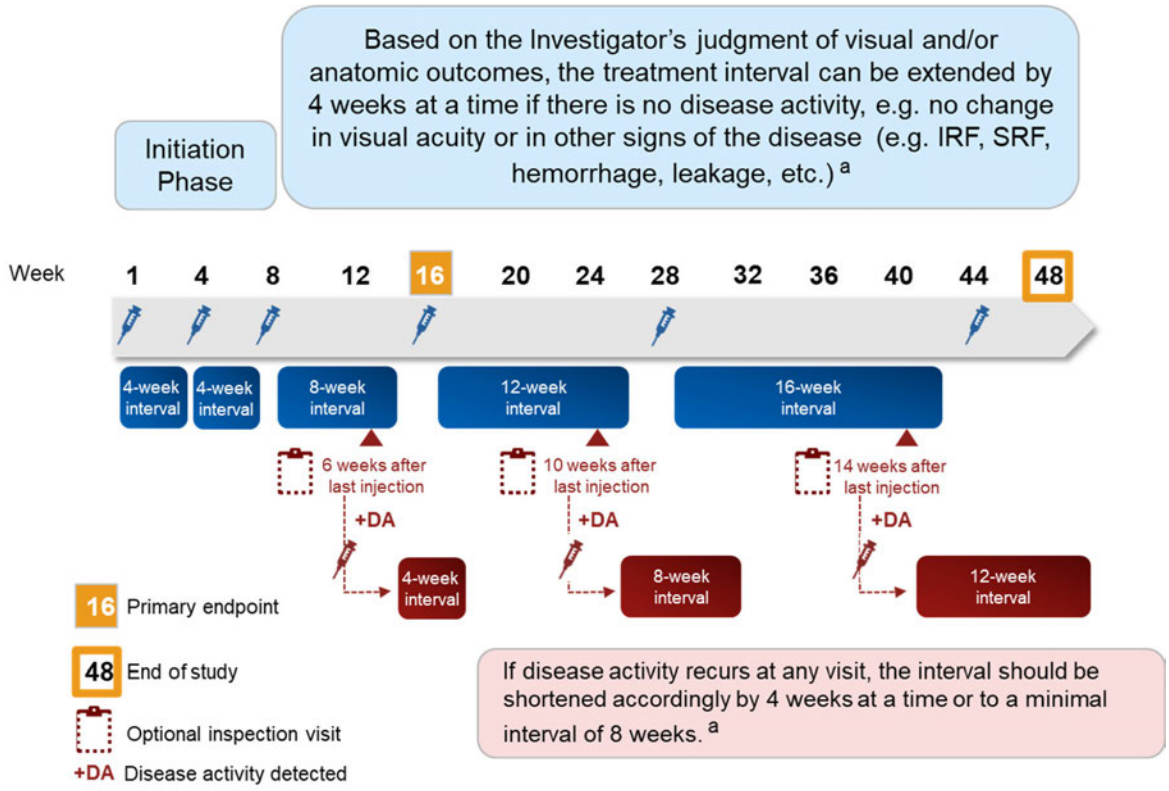
The Investigator must maintain an accurate record of the shipment and dispensing of study treatment in a Drug Accountability Log. Drug accountability will be performed by monitors during study site visits or remotely, and at the completion of the study.

At the conclusion of the study, and as appropriate during its course, 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 study 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



[a] From Week 16, the treatment interval can also be maintained if the Investigator deems that the patient will not benefit from treatment interval extension, with a minimal interval of 8 weeks.

6.7.2.1 Initiation Phase

In the Initiation Phase, brolucizumab 6 mg will be injected 3 times at 4-week intervals, at Screening/Baseline (Day 1), Week 4, and Week 8.

6.7.2.2 Treat-to-Control Phase

After the Initiation Phase, the Treat-to-Control Phase will start from Week 8, where the injection interval will be extended by 4 weeks to Week 16 (according to disease activity).

The Treat-to-Control Phase rules are defined as follows:

- Following Week 8, treatment intervals will be either 8 weeks, 12 weeks, or 16 weeks. A patient must be discontinued from further study treatment if treatment is required more frequently, i.e., every 4 weeks.
- The assessment of disease activity will be performed at each visit by the Investigator.
- At Week 8, based on Investigator's judgment of visual and/or anatomic outcomes, treatment intervals will be extended by 4 weeks at a time, if there is no disease activity, i.e. no change in visual acuity and in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.). From Week 16, the injection interval can be maintained on Q8 (or Q12 from Week 28) if the Investigator deems that the patient will not benefit from treatment interval extension, with a minimal interval of 8 weeks.
- If disease activity recurs, treatment intervals should be shortened accordingly by 4 weeks at a time or to a minimal interval of 8 weeks.
- At the Investigator's discretion, an inspection visits at Week 14, i.e. 6 weeks after the 3rd injection, can be performed. If there is no disease activity in the study eye at Week 14, as assessed by the Investigator, the study treatment will not be administered; the next visit and injection will take place at Week 16. If disease activity is observed by the Investigator in the study eye at Week 14, the study treatment will be administered by the Investigator, and the subject will be discontinued from further study treatment.
- Inspection visits 10 weeks after the last injection can be performed at the Investigator's discretion when the injection interval is extended from 8 weeks to 12 weeks. If there is no disease activity in the study eye at the inspection visit as assessed by the Investigator, the study treatment will not be administered; the next visit and injection will take place 2 weeks later, i.e. 12 weeks after the previous study treatment. If disease activity is observed by the Investigator in the study eye at the inspection visit, the study treatment will be administered by the Investigator; the injection interval will be reduced to 8 weeks and the next injection visit will be 8 weeks after the inspection visit.
- Similarly, inspection visits 14 weeks after the last injection can be performed at the Investigator's discretion when the injection interval is extended from 12 weeks to 16 weeks, respectively. If there is no disease activity in the study eye at the inspection visit as assessed by the Investigator, the study treatment will not be administered; the next visit and injection will take place 2 weeks later, i.e. 16 weeks after the previous study treatment. If disease activity is observed by the Investigator in the study eye at the inspection visit, the study treatment will be administered by the Investigator; the injection interval will be reduced to 12 weeks and the next injection visit will be 12 weeks after the inspection visit.
- The last potential study treatment may be administered at Week 44/46 according to the treatment schedule.
- A disease activity assessment will also be performed at the Week 48/EOS visit; however, no study treatment will be administered.

If a patient misses a disease activity assessment visits (Week 8 and the following), the patient should come to the visit as soon as possible. The investigator is recommended to consider the

patient to have met the disease activity criterion at the missed visit and the patient next treatment interval should be modified accordingly (e.g. shortened by 4 weeks).

If a patient misses Week 16, then the last visit values (Week 8 or Week 14) will be applied as the reference for disease activity assessments for the primary endpoint.

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 will take place.

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

Type	Study phase	Disease activity assessment	Treatment
Screening/Baseline (Day 1) Visit	Initiation Phase	Yes	Yes
Weeks 4 and 8 visits	Initiation Phase	Yes	Yes
Week 16 visit	Treat-to-Control Phase	Yes	Yes [a]
Treatment visits	Treat-to-Control Phase	Yes	Yes [a]
Inspection visits (optional)	Treat-to-Control Phase	Yes	Based on DA, as per Investigator's judgment
ETD visit and EOS visit (Week 48/50[b])	Follow up	Yes	No

[a] Treatment according to Investigator's decision based on assessment of disease activity.

[b] The EOS Visit will take place at least 4 weeks after the last injection, e.g. at Week 48 or at Week 50 for patients receiving his/her last injection at Week 46.

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 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 the results documented in the source documents. If any safety concern related to the study eye arises that, in the opinion of the Investigator, may be further impacted by the study treatment or injection procedure, the treatment needs to be cancelled.

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

If any signs of intraocular inflammation (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.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation) 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 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 after 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).

The study treatment will be administrated after a minimum washout period of at least 4 weeks / 26 days and maximum 8 weeks / 62 days after the last licensed antiVEGF injection (see Inclusion Criteria section).

A planned study visit schedule will be established at Screening/Baseline/Day 1 for all patients. All post-Screening/Baseline and/or subsequent scheduled visits will be calculated based on the Day 1 visit date. During the Treat-to-Control Phase, from Week 8 to Week 44/46, 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 will be 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 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 could 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.

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			Treat-to-Control Phase			
Visit name	Screening/ Baseline[1]	W4	W8	W16	n[2]	EOS [14] ETD [15]	m [16]
Week	Day 1	4	8	16	14 to 44/46	48/50[3]	
Informed consent	X						
Inclusion/exclusion criteria	X						
Demographics	X						
Vital signs[4]	X	X	X	X	X	X	
Prior/concomitant medications (including surgery and procedures)	X	X	X	X	X	X	X
Study eye status at nAMD diagnosis	X						
History of treatment with the previous antiVEGF in the study eye	X						
Adverse events	X	X	X	X	X	X	X
BCVA score (ETDRS)	X	X	X	X	X	X	X
[redacted]							
Ophthalmic examination and imaging[5,12]	X	X	X	X	X	X	
[redacted]							
OCT[12]	X	X	X	X	X	X	
[redacted]							
Disease activity assessment	X	X	X	X	X	X	
[redacted]							
Telephone follow-up post injection [13]	X after 1st injection						
[redacted]							

Note: Mandatory study visits are highlighted in grey.

1) The Screening/Baseline assessments are performed on the same visit.

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

from the last injection when the interval is extended from 12 weeks to 16 weeks) is at the discretion of the Investigator based on disease activity assessment.

At the investigator's discretion, an inspection visit may be performed at Week 14. If there is no disease activity in the study eye at Week 14, the next visit and treatment will take place at Week 16. If disease activity is observed in the study eye, the study treatment will be administered and the patient will be discontinued from further study treatment.

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

4) Vital signs include sitting blood pressure and pulse rate.

5) Include slit lamp examination [redacted].

[redacted]

13) 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.

14) The week 48/50 EOS assessments only apply to patients who completed the study per protocol. The assessments are not required for subjects who have undergone ETD assessments and continued in the study without study treatment.

15) ETD: Early treatment discontinuation applies to subjects 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.

16) For patients who continue in the study after ETD and up to Week 48/50 (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 16 and Week 48/50 The last visit should be at week 48. This can occur at any time point.

Assessments in the fellow eye

The fellow eye will be examined (data collected and analyzed) only at the Screening/Baseline and the Week 48/EOS visits as follows:

- At Screening/Baseline: BCVA, ophthalmic examination, [redacted] OCT, [redacted].
- At Week 48/EOS: BCVA, ophthalmic examination, [redacted] OCT [redacted].

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.

Concerning Odysight® optimal self-assessment, 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

For patients who return to the study site before the next scheduled study visit, the Investigator will capture the unscheduled visit in the eCRF only in the case of a clinically significant abnormality finding.

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

If 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, this will be considered as the use of a prohibited treatment and should be managed as described in Table 6-2 and Section 9.1.1.

8.1 Screening

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

[redacted]

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 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 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.

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent form (ICF) and who are subsequently found to be ineligible will be considered screen failures. The reason for screen failure should be recorded on the appropriate eCRF page.

The demographic information, informed consent, inclusion/exclusion criteria, and disposition eCRF pages must also be completed for screen failures. No other data will be entered into the clinical database for screen failures, unless the patient experienced an SAE during the Screening

Period (see Section 10.1.2 for reporting details). Non-serious AEs 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 early terminators. 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
- Study eye status at nAMD diagnosis (date of diagnosis, BCVA at diagnosis, CSFT at diagnosis...)
- History of treatment with the previous antiVEGF of the study eye (nature of the previous antiVEGF, date of the first IVT, date of the last IVT, total number of previous IVTs, total number of monitoring consultations...)
- BCVA
- CNV characteristics (assessed via OCT, [redacted])
[redacted]
- Ophthalmic examinations ([redacted] slit-lamp examination)
- Retinal imaging (assessed via OCT, [redacted])
- 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 images [redacted]
[redacted]
- 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 images will be obtained and assessed in the study eye as indicated in Table 8-1 and in the fellow eye at Screening/Baseline and Week48/EOS. No time-domain can be used.

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

[redacted]

OCT [redacted] assessments will be performed by a trained technician or Investigator at the study sites and should be performed **after** BCVA assessment and **prior** to any study drug administration. The Investigator will evaluate the OCT image to assess the status of disease activity. The OCT [redacted] machines used for an individual patient should not change for the duration of the study.

The Investigators will evaluate the images according to their standard of clinical practice and may use any of the OCT imaging findings to inform their decision for treatment.

A Central Reading Center (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 [redacted] images at all visits: Screening/Baseline, Week 4, Week 8, Week 16, at all interim visits, and Week 48/EOS.

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

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 [redacted] OCT parameters to ensure a standardized evaluation. For further procedural details, the Investigator should refer to the applicable manual provided by the CRC.

[redacted]

8.3.3 Visual acuity

Visual acuity will be assessed in the study eye as indicated in Table 8-1 using BCVA. BCVA of the fellow eye will be assessed at Screening/Baseline and at Week 48/EOS Visit. 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 OCT images to analyze anatomical changes are standard assessments in this indication and were used in the pivotal studies of brolucizumab in patients with nAMD.

[redacted]

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

8.4 Safety

Safety assessments will include vital signs and ophthalmic examination and imaging 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 could 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 in mmHg) and pulse rate (beats per minute) and will be collected as indicated in Table 8-1. If 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 will not be 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 assessment 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:

[redacted]

[redacted]

- **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 on 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.

[redacted] Except for the Screening Visit and the 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 will be optional according to Investigator's 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 RO (Retinal Vascular Occlusion) is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and will conduct OCT, [redacted]

[redacted]

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).

[redacted]

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 affect 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 (Week 14/Week16), 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 study 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 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 study.

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, [redacted]. 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 study-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 study 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 Screening/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).

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 Protocol exemption from reporting

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.

10.1.4 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 study 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.

10.1.5 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.

10.1.6 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 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).

11 Data collection and database management

11.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the eCRFs, which have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Study 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 study 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 study site via the EDC system. Designated Study 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 protocol deviations will be determined at Week 16 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 study 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 study sites' data. The field monitor will visit the study 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 study site's data may be performed by a centralized Novartis/ designated CRO. Additionally, a central analytics organization may analyze data & identify risks & trends for study site operational parameters, and provide reports to Novartis clinical teams to assist with study 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 ([redacted] 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 analysis will be based on the Week 16 data, i.e. data up to and including Week 16. This analysis will be performed once all patients have completed their Week 16 visit or prematurely discontinued the study before/on their Week 16 visit, while patients will continue to receive study treatment until their Week 44/Week 46 visit, dependent on their treatment schedule. The analysis of the data after the EOS (Week 48/50) visit will be performed once all patients have completed or prematurely discontinued the study.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

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

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

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 Screening/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, n, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

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

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

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 number of IVT injections received from Screening/Baseline to the end of the treatment period will be descriptively summarized. Furthermore, the number of patients in each injection category (1 injection, 2 injections up to the maximum number of injections) from Screening/Baseline to the end of the treatment period will be presented.

The dosing regimen received at W48 will be presented descriptively.

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-Screening/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 the primary endpoint

The primary objective of this study is to evaluate the effect of brolucizumab 6 mg on disease control. The primary efficacy endpoint is the proportion of patients with no disease activity at Week 16. This analysis will be performed in the FAS and will focus on the study eye only.

12.4.2 Statistical model, hypothesis, and method of analysis

The number (%) and proportion of patients with no disease activity at Week 16 will be provided with the associated 95% confidence interval using Clopper-Pearson method.

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 Sensitivity and supportive analyses

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

- Imputation of missing data :
  - Considering missing data as disease activity
  - LOCF imputation
- Repetition of the primary analysis using the PPS.

Sensitivity estimand in exposed and non-exposed to the urgent safety measures: As a sensitivity analysis for the disease activity at Week 16, the proportion of subjects with no disease activity at Week 16 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 fluids type (IRF, SRF), number of previous antiVEGF injections, and time since nAMD diagnosis subgroup analyses will also be performed on the primary endpoint.

12.5 Analysis of secondary endpoints

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

12.5.1 Effects of brolucizumab 6 mg on disease activity

The number (%) and proportion of subjects with no disease activity up to Week 48 will be provided.

12.5.2 Effect of brolucizumab 6 mg on anatomical parameters

Summary statistics of the change from Baseline in CSFT up to Week 48 will be provided.

The number (%) and proportion of subjects with absence of IRF, SRF, and sub-RPE fluid as assessed by OCT over time up to Week 48 will be presented.

The number (%) and proportion of subjects with dry retina (no IRF nor SRF) up to Week 48 will be presented.

12.5.3 Durability of brolucizumab 6 mg

Summary statistics of the time (in days) of the last interval with no disease activity before or at Week 48 will be provided. If there is disease activity, the last interval will be shortened by 4 weeks down to a minimum of 4 weeks. The distribution of the last interval is the proportion of subjects with no disease activity (Q4, Q8, and Q12) up to Week 48.

Summary statistics of time (in days) of the longest interval of treatment with no disease activity before or at Week 48 will be provided. The distribution of the maximal interval is the proportion of patients with no disease activity (Q8, Q12 and Q16) up to Week 48.

12.5.4 Functional outcomes

Summary statistics of the average change from Baseline in BCVA at Week 48 will be provided.

12.5.5 Safety endpoints

The Safety Set will be used for all safety analyses.

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.

12.5.5.1 Adverse events

Summary tables for AEs will summarize only on-treatment events with start date during the on-treatment period. Separate summary tables will be provided for AEs of the study eye, the fellow eye, and for non-ocular AEs.

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the last administration of study treatment or EOS whichever is the latest.

All information obtained on AEs will be displayed by patient. All collected AEs will be listed.

The number (%) of patients with treatment-emergent AEs will be summarized in the following ways:

- by visit, primary system organ class and preferred term.
- by visit, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for AEs related to study medication, deaths, SAEs, AESIs and other AEs leading to discontinuation.

The number (%) of patients with AEs of special interest will be summarized by visit, primary system organ class and preferred term.

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

[redacted]

[redacted]

12.7 Interim analyses

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

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

12.8 Sample size calculation

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

Table 12-1 Confidence intervals for proportions (2 sided)

Confidence level	Sample size (N)	Expected proportion	Target distance from proportion to limit
0.950	250	0.25	0.054
0.950	300	0.25	0.049
0.950	325	0.25	0.047
0.950	400	0.25	0.042
0.950	250	0.30	0.057
0.950	265	0.30	0.055
0.950	300	0.30	0.052
0.950	325	0.30	0.050
0.950	400	0.30	0.045
0.950	250	0.35	0.059
0.950	300	0.35	0.054
0.950	325	0.35	0.052
0.950	400	0.35	0.047

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

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

To determine a similar 30% proportion of patients with no disease activity at Week 16 in this pretreated study with a precision of 5.5% and alpha 5% (2-sided 95% confidence interval of width 11%), a total of 265 patients have to be observed in this study.

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

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 IEC

Before initiating a study, the Investigator/institution must obtain approval/favorable opinion from the IEC for the study 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, IECs, and regulatory authorities as required.

If an inspection of the study 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 study will be submitted for publication and posted in a publicly accessible database of clinical study results, such as the Novartis clinical study 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 study 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 study sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical study. 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 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 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 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 IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

Not applicable.