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RTH258/Brolucizumab

Clinical Trial Protocol CRTH258AIT04 / NCT04774926

One year, single arm, open label, multicenter, phase IV study using multimodal imaging to guide disease activity assessment through innovative early predictive anatomical biomarkers of fluid resolution in wAMD patients treated with brolucizumab– *IMAGINE* study

Document type:	Amended Protocol Version
EUDRACT number:	2020-002452-20
Version number:	02 (Track changes)
Clinical Trial Phase:	Phase IV
Release date:	11-Nov-2021

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List of abbreviations

AE	Adverse Event
AIC	Akaike Information Criterion
AMD	Age-related Macular Degeneration
BCVA	Best-corrected visual acuity
CDS	Core Data Sheet
CFP	Color Fundus Photography
CFR	Code of Federal Regulation
CMO&PS	Chief Medical Office and Patient Safety
CNV	Choroidal Neovascularization
COVID-19	Coronavirus Disease 2019
CRC	Central Reading Center
CRO	Contract Research Organization
CRT	Central Retinal Thickness
CSR	Clinical study report
CSFT	Central Subfield Thickness
DA	Disease Activity
DAA	Disease Activity Assessment
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELM	External Limiting Membrane
EOS	End-of-Study
EOT	End-of-Treatment
EQ-5D-5L	EuroQoL five dimensions and five levels
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
IB	Investigator's Brochure
ICF	Informed Consent Form
ICGA	Indocyanine Green Angiography
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IOI	Intraocular Inflammation
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRF	Intraretinal Fluid
IVT	Intravitreal injection
LOCF	Last Observation Carried Forward

MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
NIH	National Institutes of Health
OCT	Optical Coherence Tomography
OCTA	Optical Coherence Tomography
PCV	Polypoidal Choroidal Vasculopathy
PED	Pigment Epithelium Detachment
PFS	Prefilled Syringe
PRN	*Pro re nata*
PRO	Patient Reported Outcomes
q8w	every 8 weeks
q12w	every 12 weeks
QMS	Quality Management System
RPE	Retinal Pigment Epithelium
RAO	Retinal Artery Occlusion
RAP	Retinal Angiomatous Proliferation
RECPAM	Recursive Partitioning and Amalgamation
RV	Retinal Vasculitis
RVO	Retinal Vascular occlusion
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
ScFv	single-chain antibody fragment
SD-OCT	Spectral Domain Optical Coherence Tomography
SHRM	Subretinal Hyperreflective Material
SLn	Simultaneous Significance Levels
SmPC	Summary of Product Characteristics
SRF	Subretinal Fluid
SUN	Standardization uveitis nomenclature
sub-RPE	sub-Retinal Pigment Epithelium
SUSAR	Suspected Unexpected Serious Adverse Reaction
T&E	Treat-and-Extend
VAS	Visual Analogue Scale
VEGF	Vascular endothelial growth factor
wAMD	wet Age-related Macular Degeneration
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 participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned

Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
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
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 1 11-Nov-2021

Amendment rationale

The main purpose of this amendment is to implement the Urgent Safety Measures (USM) described the 10-Aug-2021 Dear Investigator Letter (DIL) into the study protocol. The USM were implemented for ongoing studies not achieving Last Patient Last Visit (LPLV) by 11-Aug-2021 and in response to the identification of a causal immune-mediated mechanism of the previously identified risk of retinal vasculitis (RV), and/or retinal vascular occlusion (RO), typically in the presence of intraocular inflammation (IOI) indicating a requirement to discontinue treatment with brolucizumab (RTH258) in patients who develop events of RV and/or RO.

This amendment also includes information on gender imbalance on IOI following brolucizumab treatment and recommendations on the time window for a study subject to receive the COVID-19 vaccine or vitrectomy. Some other administrative changes have also been incorporated.

Changes to the protocol

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

- Section 1.1 Background: Information added to describe Urgent Safety Measures.
- Section 4.5 Risk and benefits: Information added to describe Urgent Safety Measures and additional information on gender imbalance on IOI following brolucizumab treatment.
- Section 6.7.2 Instruction for prescribing and taking study treatment: Requirement of treatment discontinuation for brolucizumab was added if subject developed RV and/or RO.
- Section 8.4.2 Ophthalmic examination: Requirement of treatment discontinuation for brolucizumab was added if subject developed RV and/or RO.
- Section 9.1.2 Clarified the definition of Withdrawal of Consent (WoC).

Other changes incorporated in this amendment

- The list of abbreviations and the glossary of terms has been updated to the latest template wording.
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action: added recommendations on the time window for a study subject to receive the COVID-19 vaccine or vitrectomy.
- Section 8.4.1 Pregnancy: Clarified when serum pregnancy test is positive brolucizumab treatment must be discontinued.
- Section 9.1.1 Discontinuation of study treatment: Changes were made as follows:
  - Subject developing retinal a vasculitis and/or a retinal vascular occlusion event with brolucizumab.
  - Unsatisfactory therapeutic effect.
- Other minor clarifications and corrections were made where applicable.

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

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Change1 to the original protocol (v00 11-May-2020)

Change rational

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, that may result in severe vision loss. In addition, the amendment includes the modifications due to COVID-19 pandemic.

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

- Section 1.1 Background. Information was added to describe new safety signal from post-marketing case reports.
- Section 6.2.2 Prohibited medications. 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 Instruction for prescribing and taking study treatment. Additional guidance was added to this section emphasizing that if any sign of intraocular inflammation 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 were made in the following sections:
    - Section 8-1 Assessment schedule.
    - Section 8.3.1 Fluorescein angiography and indocyanine green angiography
    - Section 8.3.2 Optical coherence tomography
    - Section 8.3.3 Optical coherence tomography angiography
    - Section 8.3.4 Color fundus photography
    - Section 8.4.2 Ophthalmic Examination
    - Section 8.4.5 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 and statistical methods

Other changes incorporated in this version:

- Section 2 Objective and endpoint and related: added CFP for basal lesion type definition
- Section 4.5 Risks and benefits and related: added IB for further information
- Section 5.1 Added specification of other imaging modalities
- Section 8.4.2 Ophthalmic Examination: clarification on timing for post-injection IOP measurement
- Section 9 Added clarification about discontinuation

- Section 12 Database management and quality control: specification on the anonymization of the images sent to the CRC
- Section 15 References
- List of abbreviations

Minor editorial changes (e.g. typographical mistakes, grammatical changes, rewording) to improve flow and consistency have been made throughout the protocol. Changes to specific sections of the protocol are shown in the track changes version of the protocol.

Protocol summary

Protocol number	CRTH258AIT04
Full Title	One year, single arm, open label, multicenter, phase IV study using multimodal **Ima**ging to **G**uide disease activity assessment through **In**novative **E**arly predictive anatomical biomarkers of fluid resolution in wAMD patients treated with brolucizumab– ***IMAGINE*** study
Brief title	Study of innovative multimodal imaging biomarkers to predict anatomical outcome in naive patients with wAMD treated with brolucizumab
Sponsor and Clinical Phase	Novartis Farma S.p.A Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To identify innovative early imaging parameters that could predict the long-term clinical response to brolucizumab in terms of fluid resolution, in patients with neovascular age-related macular degeneration also called wet AMD (wAMD), with the purpose to evaluate their potential in supporting the treatment regimen choice (q12w i.e. every 12 weeks or q8w i.e. every 8 weeks).
Primary Objective(s)	The primary objective of this study is to assess the predictive value of early anatomical parameters measured by multimodal imaging from Baseline to Week 16, in brolucizumab-treated participants with wAMD who present fluid resolution at Week 48 and have maintained the q12w treatment regimen up to Week 48 after the loading phase (defined also as fluid-free response). The primary clinical question of interest is: what are the early anatomical parameters detectable by multimodal imaging techniques used for the diagnosis and monitoring of patients with wAMD that could predict the long-term clinical response to brolucizumab in terms of fluid resolution with a stable q12w treatment regimen?
Secondary Objectives	The secondary objectives of this study are: • To evaluate the effect of brolucizumab on the evolution of qualitative and quantitative anatomical and functional parameters in wAMD patients from Baseline to Week 48 • To evaluate the reasons underlying the Investigators' choice of brolucizumab treatment regimen (q8w or q12w) at Week 16 • To evaluate the effect of brolucizumab treatment on Patient-Reported Outcomes (quality of life and anxiety/depression) • To assess the safety and tolerability of brolucizumab
Study design	The study is a one-year, open-label, single arm, multicenter, phase IV study in patients with wAMD.
Study population	The study will enroll approximately 263 (male and female) participants aged 50 years or older with untreated active subfoveal choroidal neovascularization (CNV) secondary to wAMD in the study eye at approximately 30 centers located in Italy.
Key Inclusion criteria	• Signed written informed consent must be obtained prior to participation in the study

	• Male or female patients ≥ 50 years of age at Screening • Active CNV secondary to AMD that affects the central subfield, including retinal angiomatous proliferation (RAP) with a CNV component, confirmed by presence of active leakage from CNV seen by fluorescein angiography (or other imaging modalities) and sequelae of CNV, e.g. pigment epithelial detachment (PED), subretinal or sub-retinal pigment epithelium (sub-RPE) hemorrhage, blocked fluorescence, macular edema **in the study eye** at Screening. • Presence of intraretinal fluid (IRF) or subretinal fluid (SRF) affecting the central subfield (study eye), as seen by SD-OCT **in the study eye** at Screening. • Best-corrected visual acuity (BCVA) score greater than or equal to 23 letters measured at 4-meters starting distance using Early Treatment Diabetic Retinopathy Study (EDTRS) visual acuity charts at both Screening and Baseline visits **in the study eye**.
Key Exclusion criteria	• Any active intraocular or periocular infection or active intraocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis) in **study eye** at Screening or Baseline • Not interpretable OCTA and SD-OCT images according to Investigator's clinical judgment at Screening **in the study eye** • Concomitant conditions or ocular disorders **in the study eye**, at Screening or Baseline which, in the opinion of the Investigator, could prevent response to study treatment or may confound interpretation of study results, compromise visual acuity or require planned medical or surgical intervention during the course of the study. • Uncontrolled glaucoma **in the study eye** defined as intraocular pressure (IOP) > 25 mmHg on medication or according to Investigator's judgment at Screening or Baseline. • Previous treatment with any anti-vascular endothelial growth factor (anti-VEGF) drugs or investigational drugs (other than vitamin supplements) **in the study eye** at any time prior to Screening • Systemic anti-VEGF therapy at any time • Stroke or myocardial infarction in the 6-month period prior to Baseline.
Study treatment	Brolucizumab 6 mg, 120 mg/mL (RTH258 6mg/ 0.05 mL) solution for injection in pre-filled syringe
Efficacy assessments	• Spectral-domain OCT (SD-OCT) • OCT Angiography (OCTA) • Color Fundus Photography (CFP) • Fluorescein Angiography (FA) • Indocyanine Green Angiography (ICGA) • BCVA using ETDRS-like charts • Hospital Anxiety and Depression Scale (HADS)

	• EuroQol-5D-5L (EQ-5D-5L)
Key safety assessments	• Monitoring of Adverse Events (AE) • Ophthalmology examination • IOP • Vital signs • Pregnancy testing
Data analysis	The primary analysis will be conducted when all enrolled participants have completed their Week 48 visit or discontinued prior to Week 48. In order to test whether any early anatomical parameter is a predictor of response in terms of fluid resolution, i.e. q12w fluid-free participants (participants without IRF and SRF at Week 48 who have maintained a stable q12w treatment regimen up to Week 48), the following imaging variables will be taken into account: • Basal CNV lesion type, as assessed by SD-OCT, FA, ICGA and CFP at Screening • OCTA parameters, of which the main quantitative parameters are CNV flow size and vessel density and the main qualitative ones are branching vessels, peripheral anastomotic arcades, vascular loops and dark halo. • SD-OCT parameters, of which the main are sub-RPE fluid, central retinal thickness (CRT), status of the External Limiting Membrane (ELM), subretinal hyperreflective material (SHRM), outer retinal tubulation and PED volume. A Recursive Partitioning and Amalgamation (RECPAM) classification-tree analysis will be used to evaluate interactions between imaging parameters assessed by OCT, OCTA, FA, ICGA and CFP to identify distinct and homogeneous subgroups of patients in terms of q12w fluid-free patients at Week 48. A multivariable logistic regression will be applied to investigate the association between q12w fluid-free patients at Week 48 with different imaging parameters using the variables and cut-off selected by the RECPAM analysis. FA, ICGA and CFP variables included in the model are measured at Screening, while OCTA and SD-OCT variables included in the model are assessed at Screening, Baseline, 4, 8, 12 and 16 Week. The variable selection will be based on an automated stepwise selection. An interim analysis is planned to obtain a preliminary evaluation of the reasons among BCVA and/or 3-field CFP and/or IRF, SRF, sub-RPE fluid, hemorrhage and/or CRT and/or other OCTA parameters which underlie the Investigators' choice of brolucizumab treatment regimen at Week 16 (secondary objective). The interim database lock for the interim analysis will be conducted when 50% of participants who are planned to be enrolled have completed their Week 16 visit. Participants will remain in the study and will continue to receive treatment throughout the planned study duration of 48 weeks, to allow for further evaluation of efficacy and safety. For continuous variables, summary statistics will generally include: n, mean, standard deviation, median, minimum and maximum. For categorical variables, these will include: absolute and relative frequencies.

Key words	Neovascular age-related macular degeneration, anti-VEGF, brolucizumab, choroidal neovascularization, multimodal imaging biomarkers, fluid resolution

1 Introduction

1.1 Background

Age-related macular degeneration (AMD) is a chronic, progressive disease that affects the macular region of the retina. AMD is a leading cause of visual impairment and severe vision loss in people, affecting 11.6% to 18.5% of individuals between 60 and 69 years old and 31.6% to 45.3% of individuals between 80 and 84 years old in North America, Europe, and Oceania (Wong et al., 2014). Globally, people who had moderate or severe vision impairment from AMD in 2015 were estimated to be 8.41 million, with AMD being the cause of 5.64% of cases of legal blindness (1.96 million people) (Flaxman et al., 2017).

AMD is a multifactorial disorder influenced by several genetic and environmental factors. Age is the strongest risk factor, with the majority of AMD cases occurring in people older than 60 years, while smoking is the strongest modifiable risk factor for AMD (Mitchell et al., 2018).

Early-stage AMD is often asymptomatic and is characterized by the accumulation of extracellular deposits such as drusen, as well as abnormalities of the retinal pigment epithelium (RPE). Late-stage AMD affects central vision and can progress into two different clinical subtypes: the neovascular (exudative or wet) form (in weeks or months), and the non-neovascular (atrophic) or dry form (in years or decades) (Mitchell et al., 2018). Although only 20% of patients with AMD are diagnosed with wet AMD (wAMD) – also called as neovascular AMD - it causes 90% of vision loss cases (Nguyen et al., 2020).

The loss of central vision that accompanies late-stage AMD pathology has a high personal cost, including a loss of independence and social interaction, decreased quality of life, increased levels of depression and greater risk for anxiety disorders (Cimarolli et al., 2016; Taylor et al., 2016).

AMD is generally diagnosed by stereoscopic biomicroscopy and additional examination of the macula by multimodal imaging, including fluorescein angiography (FA), indocyanine green angiography (ICGA) and optical coherence tomography (OCT). The patient's visual status can be monitored with best-corrected visual acuity (BCVA) testing using Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts (Schmidt-Erfurth et al., 2014).

Neovascular AMD is characterized by the presence of choroidal neovascularization (CNV), a pathologic form of angiogenesis whereby new abnormal blood vessels originating from the choriocapillaris spread beneath the retina into the subretinal or below the sub-RPE space. The CNV complex in wAMD incorporates several typical lesions: presence of fluid or retinal hemorrhage (which can be intraretinal, subretinal, or below the RPE), retinal pigment epithelial detachments (PEDs), hard exudate, or subretinal fibrous scar (Mitchell et al., 2018). These clinical abnormalities lead to gradual loss of retinal photoreceptors, resulting in decreased vision and even blindness if disease progression is not prevented (Bhutto and Lutty, 2012).

Multimodal imaging in wAMD

The use of diagnostic imaging in the context of wAMD has allowed the definition of several pathology indicators that can be evaluated in a more objective and reproducible way compared with visual acuity (Sulzbacher et al., 2011). Multimodal imaging shows wAMD manifestations

clearly and provides information on the size, location, and extent of drusen, as well as the presence and activity of CNV (Mitchell et al., 2018).

The anatomic location of CNV determined by multimodal imaging is used to subclassify the vascular component of the disease process. Type 1 neovascularization arises when CNV proliferation occurs below the RPE, and corresponds to an occult CNV with a poorly defined pattern of leakage on FA. Type 2 neovascularization refers to CNV proliferation above the RPE in the subretinal space, and corresponds to classic CNV with intense fluorescein leakage. Type 3 neovascularization (or retinal angiomatous proliferation, i.e. RAP) occurs when the retinal circulation is involved, with an anastomosis between the choroidal and retinal circulations (Mitchell et al., 2018; Spaide et al., 2019).

FA remains the gold standard for the diagnosis and classification of CNV, as it allows the visualization of retinal vasculature and neovascular retinal/choroidal proliferations as well as its dynamic features, such as perfusion and exudation (Schmidt-Erfurth et al., 2014). ICGA can be used to identify the entire extension of the CNV lesion due to its capability to visualize the sub-RPE components of the CNV (Sulzbacher et al., 2011). Besides, ICGA allows a better identification of the neovascular network of type 1 CNV lesions and is also useful in the diagnosis of RAP and polypoidal choroidal vasculopathy (PCV), which is a subtype of type 1 CNV characterized by a large aneurysmal component. Both FA and ICGA are invasive and require dye injection (Gess et al., 2011).

OCT is a noninvasive imaging technique able to visualize structural changes of the neurosensory retina and the RPE through high-resolution cross-sectional (tomographic) images (B-scans). OCT has changed the diagnostic approach to wAMD. Current commercial OCT systems based on the spectral domain technology, i.e. spectral-domain OCT (SD-OCT), allow dense scanning of the macula with an improved axial resolution. SD-OCT is widely used to support the initial diagnosis of CNV obtained from FA and ICGA, as it allows to define the morphological features of the CNV complex, such as retinal thickening, and to detect early signs of CNV activity, such as intraretinal (IRF), subretinal (SRF) and under RPE (sub-RPE) fluid, intraretinal cystoid spaces and PED, as well as edema. Thus, through SD-OCT it is possible to qualitatively and quantitatively define these wAMD anatomical changes, as well as to measure the thickness of the retina. Moreover, SD-OCT scans performed at different time points with the same instrument can be compared over time to follow the progression/ regression of the lesions (Keane et al., 2012).

Recently, OCT Angiography (OCTA) has been introduced in clinical practice. OCTA is a non-invasive imaging modality that provides cross-sectional, three-dimensional and high-resolution imaging of the retinal and choroidal vasculature with micrometer-scale depth resolution. As SD-OCT, OCTA does not require any dye injection, thus is devoid of risk of side effects proper of classical FA and ICGA. OCTA allows an improved visualization of the choroid, resulting in a detailed visualization of the CNV, especially of the sub-RPE component. In addition, available OCTA software automatically analyze retinal layer scans at different depths, providing more detailed images compared with other imaging technique, including also SD-OCT (Coscas et al., 2019; Nikolopoulou et al., 2018).

Comparative studies have demonstrated that OCTA can detect CNV blood flow with the same sensitivity as FA, while is able to show the area of type 1 CNV lesions more precisely than

ICGA (Coscas et al., 2018). In routine practice, OCTA is still coupled with FA for the diagnosis and follow-up of wAMD. Besides, to date, no clinical trial has been designed with OCTA-based endpoints, therefore caution is necessarily required in taking treatment decisions based on OCTA alone (Nikolopoulou et al., 2018).

Based on the increased life expectancy and a growing negative impact of AMD environmental risk factors, AMD incidence is expected to continue rising (Wong et al., 2014). Therefore, early diagnosis and proper treatment are to be a major public health concern.

wAMD treatment

Improving or maintaining visual acuity is the main goal for wAMD treatment. Achieving this goal requires drying the affected retina through inhibiting new blood vessel growth and reducing the fluid leakage (Wykoff et al., 2018).

Vascular endothelial growth factor (VEGF) by increasing retinal vascular permeability and promoting neovascularization is a major contributor to CNV (Mitchell et al., 2018). The use of intravitreal (IVT) pharmacotherapy targeting VEGF has greatly improved visual outcomes and the prognosis for patients with wAMD, and has become established as the standard of care in wAMD treatment (Nguyen et al., 2020; Wykoff et al., 2018). Anti-VEGF treatments, such as ranibizumab 0.5 mg (Lucentis®) and aflibercept 2 mg (Eylea®), block all VEGF isoforms and have been shown to halt the growth of neovascular lesions and resolve retinal edema. Phase III clinical trials on ranibizumab and aflibercept demonstrated their comparable efficacy in maintaining or improving vision in patients with wAMD over up to 2 years. Moreover, as reported in the key clinical trials, the incidence of serious ocular adverse events, as well as treatment-related serious systemic events after injections of anti-VEGF agents was low (Schmidt-Erfurth et al., 2014; Wykoff et al., 2018).

The need for frequent injections can place a substantial burden on patients, as well as their caregivers, physician and the healthcare system, making patient adherence and monitoring difficult, which in turn has consequences for visual and anatomical outcomes. Indeed, long-term observational studies and clinical experiences have revealed that a substantial proportion of wAMD patients who begin treatment with anti-VEGF agents experience significant vision loss over periods of 3 to 8 years (Schmidt-Erfurth et al., 2014; Wykoff et al., 2018).

In an effort to lessen the treatment burden , increase treatment adherence and persistence and also to reduce costs associated with anti-VEGF treatment of wAMD, alternative dosing regimens, including *pro re nata* (PRN) or “as needed” and treat-and-extend (T&E), have been investigated. T&E treatment regimen, which allows to extend the treatment intervals usually by 2 weeks at a time if no disease activity is detected, has been approved in the labels of ranibizumab and aflibercept in Europe and many other countries (Wykoff et al., 2018).

Nevertheless, real-world studies indicate that relative under treatment of wAMD is very frequent and is associated with suboptimal outcomes. Further efforts are needed with regard to both diagnosis and treatment of wAMD in order to improve this unmet medical need. (Holz et al., 2014, 2015; Monés et al., 2020; Wykoff et al., 2018).

Brolucizumab

Brolucizumab 6 mg (Beovu®), is a newly marketed humanized single-chain antibody fragment (scFv) inhibitor of VEGF-A for the treatment of wAMD. Brolucizumab lower molecular weight (~26 kDa) allows for the administration of 6 mg of the compound in a single 50 µL IVT injection, which may prolong its therapeutic effect and enable better tissue penetration in the retina.

In two randomized, multicenter, double-masked, active-controlled, phase III studies (HAWK and HARRIER), wAMD patients on treatment with brolucizumab received three monthly injections followed by injections every 12 weeks (q12w), with the option of adjusting to every 8 weeks (q8w) dosing based on disease activity. The patients in the aflibercept arm were treated according to the approved schedule at that time. Brolucizumab was non-inferior to aflibercept in BCVA change from baseline to Week 48, with more than a half of brolucizumab-treated patient maintained exclusively on q12w dosing regimen. Moreover, brolucizumab was a more potent drying agent, with a significantly greater proportion of patients demonstrating an absence of IRF/SRF fluid and disease activity at both Week 16 (matched comparison) and Week 48 compared with aflibercept, as well as a significant reduction of central subfield thickness (CSFT) (Dugel et al., 2020). Both these advantages in anatomical parameters for brolucizumab and visual acuity gains observed in the first year were maintained in the second year. Safety was comparable between the treatment arms over 2 years (Nguyen et al., 2020).

Brolucizumab (Beovu®) has been recently approved in US and EU for the treatment of wAMD at the recommended dose of 6 mg, administered by IVT monthly injection for the first three doses, followed by IVT injections every 8 or 12 weeks, depending on the activity of the disease.

Since the first marketing authorization approval in October 2019 for the treatment of wAMD, adverse events of retinal vasculitis (RV) and/or retinal vascular occlusion (RVO), that may result in severe vision loss and typically in the presence of intraocular inflammation, have been reported from post-marketing experience with brolucizumab (Beovu). Results of the mechanistic study BASICHR0049 on blood samples from nAMD patients exposed to brolucizumab and having subsequently developed retinal vasculitis (RV) and/or retinal vascular occlusion (RVO), taken together with accumulated data from HAWK, HARRIER and MERLIN, regarding the association of treatment-emergent immunogenicity and IOI, indicate a causal link between the treatment-emergent immune reaction against brolucizumab and the brolucizumab-related retinal vasculitis and/or retinal vascular occlusion, typically in the presence of IOI. Considering the incidence of these events is uncommon, the overall risk/benefit assessment remains positive.

HAWK and HARRIER studies have proved that a careful early disease activity assessment based on OCT in the first months is crucial to determine patients' follow-up. Indeed, patients deemed suitable for a q12w treatment in the first q12w interval after the loading phase had a probability of remaining on q12w treatment up to Week 48 greater than 80% (Dugel et al., 2020). This further strengthens the relevance of assessing anatomical parameters in the evaluation of the therapeutic outcome and in helping the physician decide the appropriate therapeutic regimen for each patient.

Besides, lessening the treatment burden in wAMD for patients and healthcare providers remain a major challenge and an important unmet need (Monés et al., 2020). Innovative biomarkers

predictive of disease progression and treatment response might further help to achieve treatments which are better tailored to the desired therapeutic outcome for each patient and eventually to reduce the substantial monitoring burden during follow-up, thus possibly improving patient adherence and persistence to anti-VEGF therapy.

To the best of our knowledge, no clinical trial has prospectively investigated innovative early imaging parameters (OCTA and SD-OCT) at baseline and after the loading phase, which could predict the long-term clinical response to brolucizumab in wAMD patients, as measured by anatomical outcomes (fluid resolution).

Evidence from this phase IV study, along with pivotal trial data proving the superior efficacy of brolucizumab with regard to anatomical outcomes, could help the physicians in deciding which treatment regimen (q12w or q8w) would be more suitable for each patient treated with brolucizumab in order to achieve the therapeutic goal, i.e. fluid resolution.

1.2 Purpose

The purpose of this phase IV study is to identify innovative early imaging parameters as predictors of the long-term clinical response to brolucizumab in terms of fluid resolution in patients with wAMD with the purpose to evaluate their potential in supporting the treatment regimen choice (q12w or q8w).

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective The primary objective is to assess the predictive value of early anatomical parameters measured by multimodal imaging from Baseline to Week 16, in brolucizumab-treated participants with wAMD who present fluid resolution (i.e. absence of IRF and SRF) at Week 48 and have maintained the q12w treatment regimen up to Week 48 after the loading phase, defined also as fluid-free response (q12w fluid-free participants), compared with participants under a more frequent regimen and/or not fluid-free at Week 48.	**Endpoint(s) for primary objective** Early predictive factors of fluid-free response, which is defined as the absence of IRF and SRF (assessed by SD-OCT) at Week 48 in patients with a stable q12w treatment regimen up to Week 48 after the loading phase. The variables considered as potential predictive factors in the statistical model will be selected among the following qualitative and quantitative anatomical parameters: 1. Basal CNV lesion type, as assessed by SD-OCT at Baseline and FA, ICGA and CFP at Screening 2. Parameters assessed by OCTA at each visit from Baseline to Week 16, of which the main are presence/absence of branching vessels, peripheral anastomotic arcades, vascular loops and dark halo, and quantification of CNV flow size and vessel density 3. Parameters assessed by SD-OCT at each visit from Baseline to Week 16, of which the main are presence/absence of sub-RPE fluid,

Objective(s)	Endpoint(s)
	subretinal hyperreflective material (SHRM), outer retinal tubulation, status of the External Limiting Membrane (ELM) and measurement of central retinal thickness (CRT) and PED volume.
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
1. To evaluate the effect of brolucizumab on the evolution of qualitative and quantitative OCTA parameters of wAMD from Baseline to Week 48	1. Change in OCTA features assessed by qualitative (branching vessels, peripheral anastomotic arcades, vascular loops and dark halo) and quantitative criteria (CNV flow size, and vessel density) from Baseline up to Week 48
2. To evaluate the effect of brolucizumab on the evolution of qualitative and quantitative SD-OCT parameters of wAMD from Baseline to Week 48	2. Change in SD-OCT features assessed by qualitative (IRF, SRF, sub-RPE fluid, status of ELM, SHRM and outer retinal tubulation) and quantitative criteria (CRT and PED volume) from Baseline up to Week 48
3. To evaluate the effect of brolucizumab on the evolution of functional parameters of wAMD from Baseline to Week 48	3. Change in BCVA from Baseline up to Week 48
4. To evaluate the effect of brolucizumab on sustained dryness from Baseline to Week 48	4. Time to reach sustained dryness of the study eye, as defined by the absence of IRF and SRF for at least 2 consecutive visits and for at least 3 consecutive visits
	4. Cumulative incidence of sustained dryness of the study eye, i.e. the absence of IRF and SRF for at least 2 consecutive visits and for at least 3 consecutive visits
5. To evaluate the reasons underlying the Investigators' choice of brolucizumab treatment regimen (q21w or q8w) at Week 16	5. Determinants in the Investigator's choice of brolucizumab dosing regimen (q12w or q8w) at Week 16 (i.e. BCVA, IRF, SRF, sub-RPE fluid, presence of hemorrhages, CRT, OCTA anatomical parameters and/or 3-field CFP)
6. To evaluate anxiety/depression in patients with wAMD treated with brolucizumab	6. Change in Hospital Anxiety and Depression Scale (HADS) scores from Baseline to Week 48
7. To evaluate quality of life in patients with wAMD treated with brolucizumab	7. Change in EuroQol-5D-5L (EQ-5D-5L) scores from Baseline to Week 48
8. To assess the safety and tolerability of brolucizumab	8. Incidence of Ocular and Non-ocular AEs throughout the study

2.1 Primary estimands

The primary clinical question of interest is: what are the early anatomical parameters detectable by multimodal imaging techniques used for the diagnosis and monitoring of patients with

wAMD that could predict the long-term clinical response to brolucizumab in terms of fluid resolution with a stable q12w treatment regimen?

The justification for targeting this clinical question is that we will capture the early anatomical parameters that could predict long-term fluid resolution in patients with wAMD treated with brolucizumab every 12 weeks, after the initial loading phase. Further details can be found in Section 12.

The primary estimand is described by the following attributes:

1. Target population: male and female participants aged 50 years or older with untreated active subfoveal CNV secondary to wAMD in the study eye and with BCVA score greater than or equal to 23 letters at both Screening and Baseline. Further details about the population are provided in Section 5.
2. Primary variables: predictive factors of fluid-free response, which is defined as the absence of IRF and SRF at Week 48 in patients with a stable q12w treatment regimen up to Week 48. Qualitative and quantitative anatomical parameters measured by FA, ICGA and CFP at Screening, and SD-OCT and OCTA at each visit from Baseline to Week 16 will be included as potential predictive factors in the statistical model.
3. Treatment of interest: The investigational treatment brolucizumab 6 mg taken for the entire study duration with the q8w or q12w regimen. The protocol defines the use of allowed concomitant medications for the target population, as well as medications which are prohibited. Further details about the investigational treatment are provided in Section 6.
4. The summary measure is the odds ratio and/or beta estimates (fluid-free vs not fluid-free)

Detailed description of the primary estimand is provided in Section 12.4.

2.2 Secondary estimands

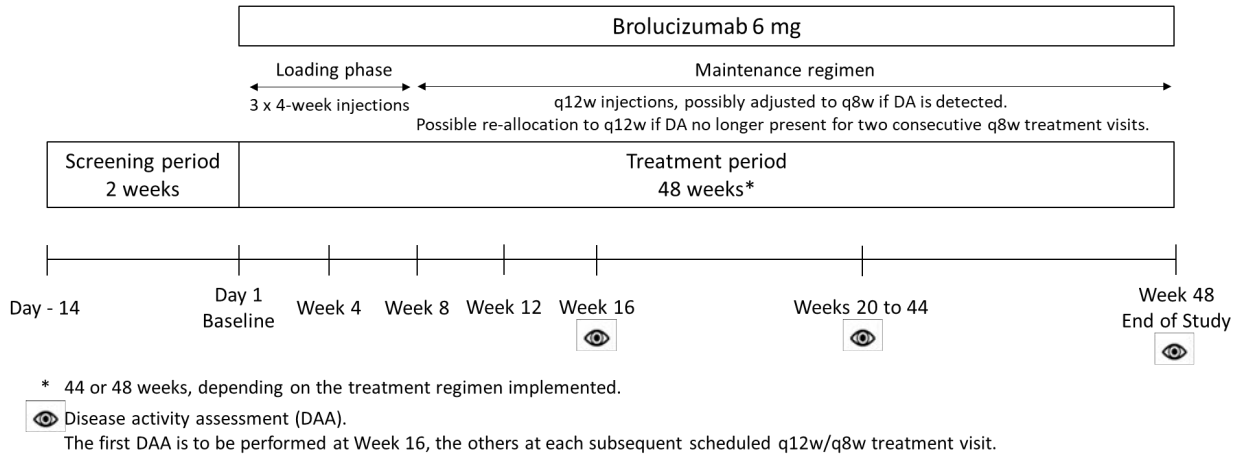
Not applicable.

3 Study design

This is a one-year, open-label, single arm, multicenter, phase IV study that will be conducted at approximately 30 centers in Italy. Patients with untreated active subfoveal CNV secondary to wAMD who provide signed informed consent and meet all eligibility criteria will be included in the study. Approximately 300 patients will be screened (12% screening failure rate expected) to enroll 263 evaluable participants. The duration of the study treatment for enrolled patient will be of maximum 48 weeks.

The study consists of a screening period of up to 2 weeks and a treatment period with brolucizumab from Baseline (Day 1) up to Week 48 (see Figure 3-1).

Figure 3-1 Study design



* 44 or 48 weeks, depending on the treatment regimen implemented.

Disease activity assessment (DAA).
The first DAA is to be performed at Week 16, the others at each subsequent scheduled q12w/q8w treatment visit.

Screening period: Day-14 to Day-1

A screening period of up to 2 weeks will be used to assess eligibility.

Patients who provide signed informed consent will undergo screening procedures to verify fulfilment of the study's inclusion/exclusion criteria. A BCVA assessment and a complete ophthalmic examination, which may include slit lamp exam, intraocular pressure (IOP) measurement and fundus exam will be performed on both eyes. SD-OCT, OCTA, FA, ICGA and 3-field color fundus photography (CFP) are to be performed on both eyes. The Investigator will also collect vital signs (blood pressure and pulse). Medical history, demographic features and prior/concomitant medications are also to be collected. A serum pregnancy test is to be performed in women of childbearing potential.

One-time re-screening of patients is allowed, except for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the patient. 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 re-screening 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 wAMD is not withheld in order for a patient to participate in the study.

Patients must have confirmed wAMD at Screening.

Treatment period: Day 1 to Week 48

At the Baseline visit (Day 1), after confirmation of eligibility, patients will be included and treated with intravitreal (IVT) brolucizumab at the dose of 6 mg. Only one eye could be treated in the study. Participants will receive three monthly loading doses of brolucizumab 6 mg at Baseline, Week 4 and Week 8, followed by a maintenance regimen every 12 weeks (q12w), which may be adjusted to a treatment regimen every 8 weeks (q8w) if disease activity (DA) in the study eye is detected according to Investigator's decision based on the disease activity assessments (DAAs) of visual and/or anatomical outcomes performed by the Investigator him/herself ("q12w/q8w regimen"). DA will be first assessed at Week 16 and then at each subsequent scheduled q12w/q8w treatment visit. In participants on q12w treatment regimen with DA occurrence at any of these visits, a q8w treatment regimen should be considered. If a

participant is adjusted to a q8w treatment regiment, he/she will subsequently be assessed at q8w treatment visits. In participants on q8w regimen without DA for two consecutive treatment visits, based on the Investigator's judgment, the re-allocation to a q12w treatment regimen should be considered. DAAs are to be performed by the Investigator based on visual acuity (BCVA) and/or 3-field CFP and/or one or more anatomical parameters assessed by SD-OCT and/or by OCTA, as per clinical practice. Of note, only those anatomical parameters that are instrumental to define DA in the Investigator's opinion will be recorded in the eCRF. All anatomical parameters collected by SD-OCT and OCTA throughout the study and by FA, ICGA (only for suspected PCV) and CFP at Screening and Week 48 (FA only) will be evaluated by an independent, treatment regimen-masked Central Reading Center (CRC) for the primary and secondary analyses at the end of the study. Of note, the Investigator will not be aware of the results of the CRC assessments during the study. For all participants, the last potential study treatment will be at the Week 44 visit or at the Week 48 visit, according to the different treatment regimen implemented.

A study visit schedule will be established at Baseline for all participants. The mandatory visits of the study during the treatment period for all participants are Baseline, Week 4, Week 8, Week 12 (no injection visit), Week 16 and Week 48. The timepoint of the other treatment visits will depend on the treatment regimen of each participant (q12w/q8w). BCVA assessment, SD-OCT, OCTA and 3-field CFP imaging are to be performed on the study eye at each assessment visit, as well as a urine pregnancy test in women of childbearing potential. FA and ICGA are to be performed at Week 48. Concomitant medications and any adverse events are to be recorded throughout the study. A complete ophthalmic examination, which may include slit lamp exam, fundus exam and IOP measurement and the collection of vital signs are to be performed at Baseline and at each subsequent visit by the Investigator. At each visit the Investigator have to exclude the presence of any active intraocular inflammation in the study eye. A complete ophthalmic examination is also to be performed at Week 48. Besides, IOP measurement is to be performed before and after each IVT injection. Patient's anxiety/depression and quality of life will be evaluated at Baseline and Week 48 through the Hospital Anxiety and Depression Scale (HADS) and the EuroQol-5D-5L (EQ-5D-5L), respectively. BCVA, SD-OCT, CFP, OCTA, FA, ICGA, ophthalmic examination and IOP measurement are also to be performed on the fellow eye at Week 48. No monitoring visits are planned between the injection visits. All efforts should be made to adhere to this study visit schedule within a ± 7-day window (except Baseline). For a given protocol visit (except Baseline), assessments can be performed on two consecutive days, provided both days are within the ± 7-day window. Treatment is intended to be administered on the day of study visit, or if this is not possible, within 3 days after the study visit at which the per-protocol assessments have taken place (except Baseline, in which case study treatment administration should occur within the next 24 hours). Two consecutive study treatments should be at least 21 days apart.

4 Rationale

4.1 Rationale for study design

This is a single-arm, non-randomized, open-label phase IV clinical trial aimed to identify innovative early imaging parameters that could predict the long-term clinical response to

brolucizumab, in terms of fluid resolution, in patients affected by wAMD with the purpose to evaluate their potential in supporting the treatment regimen choice (q12w or q8w) after the loading phase.

The safety and efficacy of brolucizumab has been recently demonstrated in two randomized, multicenter, double-masked, active controlled Phase III studies in wAMD patients (RTH258-C001 [HAWK] and RTH258-C002 [HARRIER]) up to 96 weeks, as described in Section 1.1. In these studies, anatomical changes were evaluated using SD-OCT, which relies on indirect parameters for the diagnosis and monitoring of active CNV.

Concurrently, research has led to a substantial development and/or improvement of cutting-edge imaging techniques in order to ensure the proper management of macular pathologies. The use of diagnostic imaging in the context of wAMD has allowed to define pathology indicators which can be evaluated in a more objective and reproducible manner, compared with visual acuity (VA).

In particular, OCTA has been widely introduced in ophthalmology clinical practice. OCTA is a diagnostic tool that allows the retinal and choroid vessels to be viewed dynamically. In OCTA, the contrast medium is the blood itself within capillaries, thus preventing the use of contrast medium to be injected intravenously and the risk of side effects proper of classical FA. In addition, available OCTA software automatically analyze retinal layer scans at different depths, providing more detailed images compared with less recent imaging techniques.
Several independent studies have been instrumental to understand and acknowledge the clinical relevance of OCTA for the qualitative and quantitative assessment of CNV lesions as an additional tool to evaluate the response to treatment in wAMD patients. This also provides promising evidence to suggest OCTA as relevant in treatment regimen decision, which generally relies only on the presence or absence of fluid on OCT B-scans.

A detailed multimodal imaging will be performed in this study to assess the predictive value of early anatomical parameters up to Week 16 for the long-term clinical response to brolucizumab in terms of fluid resolution and treatment regimen.

The basal type of CNV lesions assessed by Baseline SD-OCT and FA, ICGA and CFP at Screening and several SD-OCT and OCTA anatomical parameters evaluated from Baseline to Week 16 are to be considered as variables for the predictive model applied for the primary analysis. Moreover, brolucizumab response for the primary analysis is defined as the absence of IRF and SRF at Week 48, as hallmarks of wAMD pathology and signs of disease activity, in participants who have maintained the q12w regimen up to Week 48.

After the loading phase, participants are to be treated with a q12w regimen, with the possibility of adjusting to q8w based on disease activity. Disease activity will be assessed by the Investigator based on visual acuity and/or anatomical parameters and the first assessment is to be performed at Week 16, as recommended in the approved label. The possibility to switch back to q12w is foreseen when participants on the q8w regimen do not present disease activity for two consecutive visits, based on the Investigator’s judgment.

Besides, brolucizumab efficacy and safety have been consistently demonstrated in previous trials at the same dose and regimen (q12w/q8w) in comparison with aflibercept, as mainstay of treatment for wAMD, leading to the recent approval of brolucizumab for the treatment of wAMD in EU and US.

To reduce any bias due to unblinding the assessment of the anatomical parameters measured by FA, ICGA, CFP, SD-OCT and OCTA for the primary and secondary analysis of the study will be performed by an independent, treatment regimen-masked CRC. Moreover, the Investigator will not be aware of the results of the CRC assessments when he/she assesses disease activity, as per clinical practice.

4.2 Rationale for dose/regimen and duration of treatment

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

- The dose, regimen and route of administration of brolucizumab are as per European approved label (Beovu® SmPC, 2020).
- The study duration of 48 weeks allows to assess long-term efficacy and safety of this treatment regimen, as demonstrated in pivotal trials for registration of anti-VEGF treatments.
- 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.
- The route of administration is an intravitreal (IVT) injection as for all anti-VEGF drugs currently approved for the treatment of wAMD.
- Prefilled syringes (PFS) have been selected for the administration of study treatment in this study as this dosage form will be the one marketed in Italy.

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

Not applicable.

4.4 Purpose and timing of interim analyses

An interim analysis is planned after approximately 50% of participants planned to be enrolled have reached Week 16 in the study to obtain a preliminary evaluation of the clinical – functional and anatomical parameters (i.e. BCVA and/or IRF, SRF, sub-RPE fluid, hemorrhage and/or CRT and/or OCTA parameters and/or 3-field CFP) underlying the Investigators' choice of brolucizumab treatment regimen at Week 16, as secondary efficacy objective of the study.

4.5 Risks and benefits

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

Based on the results of phase III studies HAWK and HARRIER (Dugel et al., 2020), brolucizumab (Beovu®) has been recently approved in US and EU for the treatment of wAMD

at the recommended dose of 6 mg, administered by IVT monthly injection for the first three doses, followed by IVT injections every 8 or 12 weeks, depending on disease activity.

A total of 1088 patients, treated with brolucizumab, constituted the safety population in HAWK and HARRIER, with a cumulative 96-week exposure to brolucizumab and 730 patients treated with the recommended dose of 6 mg. Brolucizumab safety was comparable to aflibercept, with an overall incidence of adverse events balanced across all treatment groups in both HAWK and HARRIER.

For further details on safety information available for brolucizumab (Beovu®) treatment in wAMD, please refer to the Summary of Product Characteristics (Beovu® SmPC, 2020) and to the Investigator's Brochure (IB).

Women of child-bearing potential 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 outlined in the exclusion criteria (Section 5.2). If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Retinal vasculitis (RV) and/or vascular occlusion (RVO), typically in the presence of IOI have been reported following brolucizumab injection. These immune mediated adverse events may occur following the first intravitreal injection. Discontinuation of study treatment for brolucizumab is required in subjects who develop these events. In addition, subjects who experience IOI may be at risk of developing retinal vasculitis (RV) and/or retinal vascular occlusion (RVO) and should be closely monitored.

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).

Overall, brolucizumab was well tolerated in clinical studies with nAMD subjects when treatment interval is not less than every 8 weeks after the first 3 monthly initial doses (loading phase). The risk/benefit assessment for brolucizumab remains positive.

As regards efficacy, in addition to the non-inferior BCVA improvement, the lower probability of disease activity after the head-to-head comparison at Week 16, the greater reduction in CSFT and the lower proportion of patients with SRF and/or IRF through Week 48 for brolucizumab versus aflibercept in HAWK and HARRIER are anticipated to confer a longer duration of effect that will translate into a greater durability and longer injection intervals for brolucizumab 6 mg, with non-inferior efficacy (see Section 1.1 for more details). Of note, a reduced treatment and monitoring visit frequency will provide benefit to both subjects and caregivers/physicians. Thus, it seems safe to assume that the benefits of brolucizumab 6 mg treatment in wAMD outweigh the risks.

5 Study Population

The study population includes male and female participants aged 50 years or older diagnosed with active subfoveal CNV secondary to wAMD in the study eye, not treated previously with

any anti-VEGF drugs or investigational drugs (other than vitamin supplements) for this disease and able to comply with study procedures.

Assuming a 12% screening failure rate, approximately 300 patients will be screened and approximately 263 participants will be enrolled at approximately 30 sites in Italy. From Baseline, the expected duration of participation in the study is 48 weeks for each participant.

If both eyes are eligible as per the inclusion and exclusion criteria described below only one eye should be treated during the study, the eye with the worse visual acuity (BCVA) at Baseline will be selected as the study eye. If both eyes have the same BCVA, it is recommended to select the right eye as the study eye.

5.1 Inclusion criteria

The Investigator will assess the eligibility of the patient and the study eye at the Screening visit and confirm eligibility at Baseline. Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Male or female patients ≥ 50 years of age at Screening.
3. Active CNV secondary to AMD that affects 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) (or other imaging modalities) and sequelae of CNV, e.g. pigment epithelial detachment (PED), subretinal hemorrhage or sub-retinal pigment epithelium (sub-RPE) hemorrhage, blocked fluorescence, macular edema in the study eye at Screening.
4. Presence of intraretinal (IRF) and/or subretinal fluid (SRF) affecting the central subfield of the study eye as seen by SD-OCT in the study eye at Screening.
5. Best-corrected visual acuity (BCVA) score greater than or equal to 23 letters measured at 4-meters starting distance using Early Treatment Diabetic Retinopathy Study (EDTRS) visual acuity charts at both Screening and Baseline in the study eye.

5.2 Exclusion criteria

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

Ocular Conditions

1. Concomitant conditions or ocular disorders in the study eye at Screening or Baseline which, in the opinion of the Investigator, could prevent response to study treatment or may confound interpretation of study results, compromise visual acuity or require planned medical or surgical intervention during the course of the study.
2. Any active intraocular or periocular infection or active intraocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis) in study eye at Screening or Baseline.
3. Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication or according to Investigator's judgment at Screening or Baseline.

4. Presence of amblyopia, amaurosis or ocular disorders in the fellow eye with BCVA < 20/200 at Screening (except when due to conditions whose surgery may improve VA, e.g. cataract).
5. Atrophy or fibrosis involving the center of the fovea in the study eye, as assessed by color fundus photography at Screening.
6. The total area of fibrosis or subretinal blood affecting the foveal center point comprising ≥ 50% of the lesion area in the study eye at Screening.
7. Structural damage within 0.5 disc diameter of the center of the macula in the study eye, e.g. vitreomacular traction, epiretinal membrane, retinal pigment epithelium (RPE) rip/tear scar, laser burn, at the time of Screening that in the Investigator's opinion could preclude visual function improvement with treatment.
8. Current vitreous hemorrhage or history of vitreous hemorrhage in the study eye within 4 weeks prior to Screening.

Ocular treatment (study eye)

9. Previous treatment with any anti-VEGF drugs or investigational drugs (other than vitamin supplements) in the study eye at any time prior to Screening.
10. Previous use of intraocular or periocular steroids in the study eye within the 6-month period prior to Screening.
11. Macular laser photocoagulation (focal/grid) or photodynamic therapy (PDT) in the study eye at any time prior to Baseline and peripheral laser photocoagulation in the study eye within 3 months prior to Baseline.
12. Intraocular surgery in the study eye within 3 months prior to Baseline.
13. Vitreoretinal surgery in the study eye at any time prior to Baseline.
14. Aphakia with the absence of posterior capsule in the study eye.

Systemic conditions and treatments

15. Stroke or myocardial infarction in the 6-month period prior to Baseline.
16. End stage renal disease requiring dialysis or renal transplant.
17. Uncontrolled blood pressure defined as a systolic value ≥ 160 mmHg or diastolic value ≥ 100 mmHg at Screening or Baseline. (In case there is an elevated blood pressure measurement, it should be repeated after 20 minutes. If the repeat measurement is elevated, then the patient is not eligible to be enrolled into the study).
18. Systemic anti-VEGF therapy at any time.
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. History of hypersensitivity to any of the study drugs or their excipients or to drugs of similar classes, or clinically relevant sensitivity to fluorescein dye as assessed by the Investigator.
21. 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.
22. History of a medical condition (e.g. metabolic dysfunction disease with exception of type 1 or 2 diabetes mellitus, physical examination finding, or clinical laboratory finding) that, in

the judgment of the Investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product.

23. Use of systemic investigational drugs within 5 half-lives of baseline or within 30 days/until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations (observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary).

Other

24. Not interpretable OCTA and SD-OCT images according to Investigator's clinical judgment at Screening in the study eye
25. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG pregnancy test.
26. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant unless they are using highly effective methods of contraception during dosing of study drug administration and for 3 months after stopping the investigational medication.

    Effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Be aware that periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before Baseline. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to Baseline). For female participants in the study, the vasectomized male partner should be the sole partner for that participant.
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS).

    Women are considered post-menopausal and not of child-bearing 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 six 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 child-bearing potential.

6 Treatment

6.1 Study treatment

6.1.1 Investigational drug

Table 6-1 Investigational drug

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Brolucizumab 6 mg (Beovu® 120 mg/ml)	Solution for injection	Intravitreal use	Open label bulk supply; pre-filled syringes	Local

Brolucizumab will be provided in single use, sterile, pre-filled syringes. Each pre-filled syringe contains 19.8 mg brolucizumab in 0.165 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml solution containing 6 mg of brolucizumab.

Since the volume contained in the pre-filled syringe (0.165 ml) is greater than the recommended dose (0.05 ml), a portion of the volume contained in the pre-filled syringe must be discarded prior to administration. To expel the air bubble along with excess medicinal product, the plunger should be slowly depressed until the edge below the dome of the rubber stopper is aligned with the 0.05 ml dose mark (equivalent to 50 µl, i.e. 6 mg brolucizumab).

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

6.1.2 Additional study treatments

No control drug or other treatments beyond investigational drug are included in this trial.

6.1.3 Treatment arms/group

Eligible participants will be assigned at Baseline to the treatment with IVT brolucizumab 6 mg. Each participant will receive three monthly injections (at Baseline, Week 4 and Week 8), followed by a q12w or q8w treatment regimen, according to Investigator's decision upon the evaluation of disease activity based on visual and/or anatomical parameters at Week 16.

If DA is identified, at any scheduled visit following Week 16, the assignment of the participant on q12w regimen to a q8w regimen thereafter should be considered. If the participant on q8w regimen is DA-free for two consecutive treatment visits based on the Investigator's judgment, the re-allocation to a q12w regimen should be considered.

For all participants, the last potential study treatment will be at the Week 44 visit or at the Week 48 visit, according to the different treatment regimen implemented.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The Investigator has to instruct the participant to notify the study site about any new medications the participant takes after enrollment in the study. All medications, procedures, and

significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate page in the electronic Case Report Form (eCRF).

Each concomitant medication must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before enrolling a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant 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 wAMD 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 not to disturb the schedule for visits and treatments in the study eye. The fellow eye must be monitored according to routine practice and adverse events (AEs) captured in the eCRF.

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

If cataract surgery is necessary, attempt to schedule cataract surgery ≥ 7 days after the most recent study treatment. Study treatment may be resumed ≥ 14 days after cataract surgery, assuming an absence of surgically related complications.

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

If vitrectomy is necessary in the study eye, it should be attempted to schedule the surgery ≥ 14 days after the most recent study treatment. Study treatment may be given during vitrectomy surgery if deemed necessary according to investigator’s discretion.

If the subject is planning to receive a COVID-19 vaccine that is authorized by local regulation, it is recommended to receive the vaccine at least 7 days before or after the study treatment visit including Baseline (Day 1) visit.

6.2.2 Prohibited medication

Use of the treatments displayed in the table below are not allowed after the start of the study i.e., Screening. In addition, there are certain washout periods to be respected, as also outlined in the exclusion criteria (Section 5.2).

Table 6-2 Prohibited medication and procedures

Medication	Prohibition period	Action taken
Study Eye		
Any anti-VEGF drugs or investigational drugs, biologics or devices	Any time	Discontinue study treatment

Medication	Prohibition period	Action taken
Study Eye		
(other than vitamin supplements)		
Any periocular injection or intraocular administration of corticosteroids (except if needed as short term treatment of AE)	Any time	Discontinue study treatment (except if for treatment of AE)
Laser treatment for wAMD (except if needed as short-term treatment of AE)	Any time	Discontinue study treatment
Fellow eye		
Any investigational drug, biologic or device (other than vitamin supplements)	Any time	Discontinue study treatment
Systemic		
Anti-VEGF treatment	Any time	Discontinue study treatment
Any investigational drug, biologic or device (other than vitamin supplements)	Any time	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)	Any time	Discontinue study treatment

6.2.3 Rescue medication

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

In case of lack of efficacy with investigational drug for wAMD 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 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. The Participant No. consists of the Center Number

(Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available in the electronic data capture (EDC) system.

Participants who have been screen failures but are rescreened (see Section 8.1) will be assigned a new Participant No. if rescreening occurs beyond 14 days from the original screening date.

6.3.2 Treatment assignment, randomization

This is a single arm study; hence no randomization will be performed. All eligible participants are to be assigned to brolucizumab treatment at Baseline.

The Investigator will confirm that the participant has fulfilled all the inclusion/exclusion criteria in the source documents and the appropriate page on the eCRF. The Investigator will then assign the participant to treatment.

6.4 Treatment blinding

This is a single arm, open-label, phase IV study; thus, study participants, Investigators, study staff, sponsor clinical study team, field monitors and statisticians will all be unblinded to treatment (i.e. brolucizumab 6 mg) and treatment regimen (q12w or q8w).

An independent, treatment regimen-masked reading of SD-OCT, OCTA, FA, ICGA and CFP images collected at pre-defined timepoints (see Table 8-1, Section 8.3.2 and Section 8.3.3) for participants enrolled in the study will be performed at a Central Reading Centre (CRC).

Of note, the Investigator will not be aware of the results of the CRC assessments when he/she assesses disease activity throughout the study, as per clinical practice.

6.5 Dose escalation and dose modification

No study treatment dose adjustment is permitted.

Deviations to dose intervals during the initiation phase and/or dose adjustments during the whole study are not allowed.

Interruption of study treatment is allowed if warranted by an AE.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Registration of all visits in the eCRF is necessary. The date and time of all study treatment injections administered during the study and any deviations from the protocol treatment schedule will be captured 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 Investigator at each visit.

6.7 Preparation and dispensation

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

The study medication has a 2-part label (base plus tear-off label). A unique medication number is printed on each part of this label. Immediately before dispensing the package to the participant, the Investigator or his/her delegates will detach the outer part of the label from the package and affix it to the participant's source document.

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 secured location to which only the Investigator and designated site personnel have access. Upon receipt, the study treatment must be stored in a refrigerator (2°C - 8°C), keeping the pre-filled syringe in its sealed blister and in the outer carton in order to protect from light, according to the instructions specified on the labels and in the Summary of Product Characteristics (SmPC). Prior to use, the unopened blister may be kept at room temperature (below 25°C) for up to 24 hours (Beovu® SmPC, 2020).

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

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

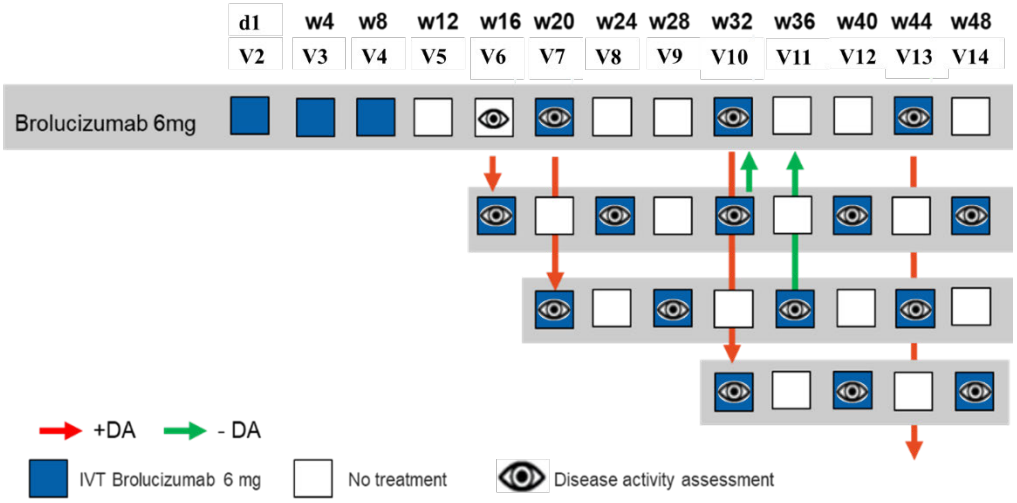
The Investigator or his/her delegates must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

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

6.7.2 Instruction for prescribing and taking study treatment

The study consists of a treatment period with brolucizumab from Baseline (Day 1) up to Week 48, as shown in Figure 6-1.

Figure 6-1 Treatment regimen



As per Beovu® SmPC, the recommended dose of 6 mg brolucizumab (0.05 ml solution) is to be administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses. Thereafter, the Investigator may individualize treatment intervals based on DA in the study eye as assessed by visual acuity and/or anatomical parameters (BCVA and/or IRF, SRF, sub-RPE fluid, hemorrhage, CRT and/or OCTA parameters and/or 3-field CFP). A first DA assessment is to be performed at Week 16, as recommended in Beovu® SmPC. In participants without DA, treatment every 12 weeks (q12w) should be considered. In patients with DA, treatment every 8 weeks (q8w) should be considered. DA will be first assessed at Week 16 and then at each subsequent scheduled q12w/q8w treatment visit. In participants on q12w regimen with DA at any of these visits, a q8w treatment regimen should be considered. In participants on q8w regimen without DA for two consecutive treatment visits in the opinion of the Investigator, the re-allocation to a q12w regimen should be considered.

Regardless of treatment administration, Baseline, Week 4, Week 8, Week 12, Week 16 and Week 48 visits are mandatory for all participants. The timepoints of the other treatment visits will depend on the treatment regimen of each participant (q12w/q8w). No monitoring visits are planned between the injection visits.

For all participants, the last potential study treatment will be at the Week 44 visit or at the Week 48 visit, according to the different treatment regimen implemented.

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

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

Type	Disease Activity Assessment	Treatment
Screening visit	No	No
Baseline (Day 1) visit	No	Yes
Week 4 and 8 visits	No	Yes
Week 12 visit	No	No

Type	Disease Activity Assessment	Treatment
Week 16 visit	Yes	Yes (if DA is present)
Treatment visits (every 8 or 12 weeks according to Investigator's decision)	Yes	Yes (every 8 or 12 weeks according to Investigator's decision)
Week 48 visit	Yes	Only if a treatment was planned at the visit, based on treatment regimen

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 (except for Baseline/Day 1, in which case study treatment administration should occur within the next 24 hours) or no later than within the visit window (± 7 days) as described in Section 3 and Section 8. When assessments and treatment take place on the same day, treatment must occur after completion of the efficacy assessments described in Section 8.3 and pre-injection safety measures (tonometry, slit lamp and fundus examination) described in Section 8.4.4. If study visit assessments and the corresponding treatment occur on separate days, a repeat safety check-up should be performed prior to treatment of the eye and results documented in the source documents. If any safety concern arises related to the study eye that, in the opinion of the Investigator, may be further impacted by the study treatment or injection procedure, treatment needs to be cancelled. IVT injection is contraindicated in subjects with active intraocular inflammation (IOI); therefore, the Investigators must verify that these conditions are not present in the study eye prior to every injection.

If any sign of IOI is present, then an IVT injection must not be performed. Additional ophthalmic examination and imaging should be performed to evaluate IOI (see Section 8.4.2). If IOI confirmed, subjects should be treated for IOI according to clinical practice and closely monitored since they may be at risk of developing retinal vasculitis and/or retinal vascular occlusion. If subject develops retinal vasculitis (RV) and/or retinal vascular occlusion (RO) based on the investigator's evaluation, the study treatment of brolucizumab must be discontinued.

Any adverse events must be recorded in the eCRF.

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

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participants' representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant 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 participant source documents.

Novartis will provide to Investigators in a separate document a proposed informed consent form to ensure that complies with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 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 to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the SmPC and the Core Data Sheet (CDS) for a marketed drug. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. As new information becomes available, informed consent will be updated and then must be discussed with the participant.

Women of childbearing potential 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.

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

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. All data must be entered in the eCRF in a timely manner (see Section 11.1).

A planned study visit schedule will be established at Baseline/Day 1 (first day of treatment) for all participants. All subsequent scheduled visits will be calculated based on the Day 1 visit date. The mandatory post-Baseline visits of the study are Week 4, Week 8, Week 12, Week 16 and Week 48. After Week 16, the treatment visit intervals will be determined by the Investigator, based on the patient's disease activity (see Section 6.7.2). All efforts should be made to adhere to all scheduled visits and assessments as outlined in the assessment schedule (Table 8-1).

A ± 7-day visit window is allowed, except for Baseline/Day 1, should the participant be unable to return per 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 treatment, i.e. two consecutive injections should be at least 21 days apart.

For a given protocol visit (except for Baseline), assessments can be performed on two consecutive days, provided both days are within the ± 7-day visit window.

Treatment is intended to be administered on the day of study visit, or if this is not possible, within 3 days after the study visit at which the per-protocol assessments have taken place (except Baseline, in which case study treatment administration should occur within the next 24 hours). 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. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed.

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.

Table 8-1 Assessment schedule

Period	Screening	Treatment						End of Study
Visit Name	**Screening***	**Baseline Day 1**	**W4**	**W8**	**W12**	**W16**	**Treatment visits**	**W48***
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7-13**	**14**
Weeks	**Up to 2 weeks**	**1**	**4**	**8**	**12**	**16**	**20 to 44[1]**	**48**
Obtain informed consent	X							
Demography	X							
Inclusion/ exclusion criteria	X	X						
Relevant medical history/current medical history	X							
Vital Signs[2, 3]	X	X	X	X	X	X	X	X
Prior/ Concomitant systemic medications	X	X	X	X	X	X	X	X
Prior/ Concomitant ocular medications	X	X	X	X	X	X	X	X
Serum β-hCG Pregnancy Test[4]	X							
Urine Pregnancy Test[4]		X	X	X	X	X	X	X
BCVA score (ETDRS)	X	X	X	X	X	X	X	X
IOP measurement[5]	X	X	X	X	X	X	X	X
Complete ophthalmic examination[2, 6]	X	X	X	X	X	X	X	X
SD-OCT[9]	X	X	X	X	X	X	X	X
OCTA	X	X	X	X	X	X	X	X
FA[9]	X							X
ICGA	X							X
Color Fundus Photography (CFP)[redacted]	X	X	X	X	X	X	X	X
EQ-5D-5L		X						X
HADS		X						X

Period	Screening	Treatment						End of Study
Visit Name	Screening*	Baseline Day 1	W4	W8	W12	W16	Treatment visits	W48*
Visit number	1	2	3	4	5	6	7-13	14
Weeks	Up to 2 weeks	1	4	8	12	16	20 to 44[1]	48
Disease Activity Assessment[7]						X	X	X
Study drug administration		X	X	X		X[8]	X[8]	X[8]
Adverse Events	X	X	X	X	X	X	X	X

X = assessment to be recorded in the clinical database or received electronically from a vendor

* At Screening and Week 48 the fellow eye will be assessed for BCVA, ophthalmic examination, IOP, SD-OCT, OCTA, CFP, FA and ICGA. For the other visits it will be assessed according to clinical practice

[1] Treatment visits will take place every 8 or 12 weeks starting from Visit 4 (Week 8), according to Investigator's decision at each assessment visit

[2] Vital signs collection and/or complete ophthalmic examination are to be performed at each visit. The Investigator have to exclude the presence of any active intraocular inflammation in the study eye.

[3] Vital signs include sitting blood pressure and pulse rate.

[4] Women of childbearing potential only. A positive urine test should be confirmed by a Serum β-hCG Pregnancy test.

[5] IOP measurement is to be performed prior and 30-60 minutes after each treatment IVT injection

[6] Complete ophthalmic examination include slit lamp exam, IOP measurement and fundus exam, for safety assessment before and after IVT. Pupil dilation optional according to local practice.

[7] Disease activity assessment to be performed by the Investigator based on BCVA and/or one or more anatomical parameters detected by SD-OCT among IRF, SRF, sub-RPE fluid, hemorrhage and CRT, and/or OCTA parameters and/or 3-field CFP, as per clinical practice. Of note, only which of these functional and/or anatomical parameters the Investigator considered to assess disease activity will be recorded in the eCRF.

[8] Treatment according to Investigator's decision on treatment regimen (q12w or q8w) based on disease activity assessment.

[redacted]

8.1 Screening

Screening

A screening period of up to 2 weeks will be used to assess patient eligibility. The screening period starts with the signing of the informed consent.

A BCVA assessment, as well as a complete ophthalmic examination, which may include slit-lamp exam, IOP measurement and fundus exam will be performed on both eyes. SD-OCT, OCTA, FA, ICGA and 3-field CFP are to be performed on both eyes and the diagnosis of active subfoveal CNV secondary to wAMD is to be confirmed in the study eye. The study Investigator will also collect vital signs (blood pressure and pulse). Medical history, demographic features and prior/concomitant medications are also to be collected. A serum pregnancy test is to be performed in women of childbearing potential.

One-time re-screening of patients is allowed, except for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the patient. 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 re-screening 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 wAMD is not withheld in order for a patient to participate in the study.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF page. The demographic information, informed consent, and Inclusion/Exclusion eCRF pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event (SAE) during the screening phase (see Section 10.1.3 for reporting details).

8.2 Participant demographics/other baseline characteristics

The following information will be collected/documented at Screening/Baseline visit for each participant:

- Age (Screening)
- Sex (Screening)
- Race/Ethnicity (Screening)
- Vital signs, i.e. sitting blood pressure (systolic and diastolic pressure in mmHg) and pulse rate (beats per minute) (Screening and Baseline). Of note, in case there is an elevated blood pressure measurement as specified in the exclusion criteria, at Screening, the blood pressure measurement should be repeated after 20 minutes. If the repeat measurement is elevated as specified in the exclusion criteria, then the patient is not eligible to be enrolled into the study.

- Pregnancy test results for all women of childbearing potential (Screening and Baseline)
- Visual acuity (BCVA) (Screening and Baseline)
- Complete ophthalmic examination (Screening and Baseline)
- Retinal imaging (SD-OCT, OCTA and 3-field CFP at Screening and Baseline; FA and ICGA at Screening)
- EQ-5D-5L questionnaire (Baseline)
- HADS questionnaire (Baseline)
- Prior/concomitant medications (all prescription medications, over-the-counter drugs and significant non-drug therapies must be documented. See Section 6.2.1 for further details) (Screening and Baseline)
- Medical history and current medical conditions (Screening)

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

8.3 Efficacy

The following assessments will be performed to assess the predictive value of early anatomical parameters measured by multimodal imaging at each visit from Baseline to Week 16 in q12w fluid-free participants (i.e. participants without IRF and SRF at Week 48 who have maintained a stable q12w treatment regimen up to Week 48 after the loading phase), as well as to evaluate the effect of brolucizumab on visual function, retinal structure, vascular leakage, quality of life and anxiety and depressive status:

- CNV lesion type assessed by FA, CFP and ICGA at Screening and SD-OCT at Baseline
- OCTA parameters, of which the main quantitative parameters are CNV flow size and vessel density and the main qualitative ones are branching vessels, peripheral anastomotic arcades, vascular loops and dark halo (from Baseline to Week 48)
- SD-OCT parameters, of which the main quantitative parameters are CRT and PED volume, and the main qualitative ones are IRF, SRF, sub-RPE fluid, status of the ELM, SHRM and outer retinal tubulation (from Baseline to Week 48)
- FA and ICGA (at Screening and Week 48)
- 3-field CFP (from Baseline to Week 48)
- BCVA with ETDRS-like charts at 4 meters (from Baseline to Week 48)
- EQ-5D-5L questionnaire (at Baseline and Week 48)
- HADS questionnaire (at Baseline and Week 48)

All efficacy assessments should be performed prior to any administration of study treatment.

8.3.1 Fluorescein angiography and indocyanine green angiography

Fluorescein angiography (FA) and indocyanine green angiography (ICGA) will be performed in both eyes at Screening and Week 48. All FA and ICGA images will be obtained by trained and study-certified site personnel at the study sites and evaluated by the Investigator according to his/her standard of clinical practice to confirm the diagnosis of wAMD at Screening. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study participants.

For the purpose of screening, FA and ICGA images from previous routine evaluations may be used as long as FA was performed within 3 days of the Screening visit using CRC-certified equipment and technician/Investigator.

A treatment regimen-masked Central Reading Centre (CRC) will be used in this study. The CRC will provide sites with a Study Manual and training materials for the specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software will be certified and validated by the CRC as specified in the Study Manual. FA and ICGA screening images and FA images at week 48 will be forwarded to the CRC for independent standardized analysis. The CRC data will be used for the evaluation of the objectives comprising the assessment of FA and ICGA parameters (i.e. to classify the type of CNV lesions) to ensure a standardized evaluation. Further details about all parameters to be evaluated by the CRC are reported in the CRC grading charter (a separate document). The CRC will create a database with the agreed variables as indicated in the CRC charter and will transfer the data from this database to Novartis/CRO for analysis.

Additional images will be taken in case of any signs of intraocular inflammation. Fluorescein angiography should be performed for safety evaluation as described in Section 8.4.2. and uploaded onto the CRC portal.

8.3.2 Optical coherence tomography

Spectral Domain Optical Coherence Tomography (SD-OCT) images will be obtained and assessed in the study eye at every study visit and in the fellow eye at Screening and at Week 48. Only SD-OCT machines can be used (i.e. no time-domain nor swept-source OCT).

These assessments will be performed by a trained technician or Investigator at the sites and should be performed after BCVA assessment and prior to any study drug administration. The SD-OCT machine used for an individual participant should not change for the duration of the study. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study participants.

The following main parameters will be qualitatively evaluated by SD-OCT:

- Intraretinal fluid (IRF), i.e. the fluid that accumulates within the neurosensory retina due to the disruption of the external limiting membrane (ELM)-photoreceptor complex in the outer retina by the active CNV membrane. On SD-OCT, diffuse retinal thickening and/or the formation of intraretinal cystoid spaces are indicative of the presence of IRF (Keane et al., 2012).

- Subretinal fluid (SRF), i.e. the fluid that commonly accumulates between the neurosensory retina and the RPE due to the profuse leakage from blood vessels of the CNV complex. On SD-OCT, SRF could be seen as hyporeflective or sparsely hyperreflective spaces between the retina and the RPE when the exudate is serous or contains fibrin or red blood cells, respectively (Keane et al., 2012).
- sub-retinal pigment epithelium (sub-RPE) fluid, i.e. the fluid that accumulates under the RPE, thus often leading to PEDs (Keane et al., 2012).
- Subretinal Hyperreflective Material (SHRM), i.e. a poorly defined, medium-to-hyperreflective mass between the neurosensory layers and the RPE on SD-OCT, which is indicative of the neurovascular membrane, particularly in type II CNV lesions, and of disciform scar formation (Keane et al., 2012).
- Outer retinal tubulation, i.e. branching tubular structures located in the outer nuclear layer of the retina, which seems to be indicative of a rearrangement of degenerating photoreceptors in a variety of retinal diseases, including wAMD. On SD-OCT, outer retinal tubulation appears as well-defined round or ovoid hyporeflective spaces with hyperreflective borders (Goldberg et al., 2013).
- The status of the ELM, as an indicator of retinal integrity (Oishi et al., 2010).

The following main parameters will be quantitatively evaluated by SD-OCT:

- Volume of Pigment-Epithelium Detachment (PEDs), i.e. irregularly elevated lesions produced by the growth of the choroidal neovascular membrane and the accumulation of fluid or material in the sub-RPE space. On SD-OCT, PEDs appear as broad elevations of the RPE band relative to Bruch's membrane (Keane et al., 2012).
- Central retinal thickness (CRT) measurement, as main quantitative morphological parameter of wAMD. The CRT evaluated in this study represents the average retinal thickness of the circular area within 1 mm diameter around the foveal center.

The Investigator will evaluate the SD-OCT images according to his/her standard of clinical practice to assess disease activity. The Investigator's assessed findings of both quantitative and qualitative parameters (i.e. IRF; SRF, sub-RPE fluid, hemorrhage and/or CRT) will not be captured in the eCRF but must be included in the source documents at the study site. Only parameters used by the Investigator to assess DA will be recorded in the eCRF.

The treatment regimen-masked CRC will provide sites with a Study Manual and training materials for the specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software will be certified and validated by the CRC as specified in the Study Manual. All SD-OCT images will be forwarded to the CRC for independent standardized analysis. The CRC data will be used for the evaluation of the objectives comprising the assessment of SD-OCT parameters to ensure a standardized evaluation. Further details about all qualitative and quantitative parameters to be evaluated by the CRC are reported in the CRC grading charter (a separate document). The CRC will create a database with the agreed variables as indicated in the CRC charter and will transfer the data from this database to Novartis/CRO for analysis.

Additional images will be taken in case of any signs of intraocular inflammation. OCT should be performed for safety evaluation as described in Section 8.4.2 and uploaded onto the CRC portal.

8.3.3 Optical coherence tomography angiography

Optical Coherence Tomography Angiography (OCTA) images will be obtained and assessed in the study eye at every study visit and in the fellow eye at Screening and Week 48.

These assessments will be performed by a trained technician or Investigator at the sites and should be performed after BCVA assessment and prior to any study drug administration. The OCTA machine used for an individual participant should not change for the duration of the study. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study participants.

The morphology of the CNV complex will be evaluated qualitatively by assessing by OCTA the following main parameters: presence/absence of branching vessels, peripheral anastomotic arcades, vascular loops and dark halo. The presence of tiny vessels branching from bigger vessels, peripheral anastomotic arcades at the vessel termini, vascular loops or dark halo (hypointense area considered as a region of choriocapillaris alteration, corresponding to local flow impairment) are indicative of an active CNV lesion (Al-Sheikh et al., 2018; Coscas et al., 2018; Darwish, 2017).

The following main parameters will be quantitatively evaluated by OCTA:

- CNV flow size, visualized by calculating the decorrelation of signal amplitude from consecutive B-scans, thus creating a contrast between static and non-static tissue, through an appropriate algorithm. To quantify the blood flow within the CNV, the CNV area and flow index were calculated from the 2D maximum projection outer retina CNV angiogram (Jia et al., 2014).
- vessel density of the lesion, calculated as a ratio of the area occupied by vessels to the total area of the lesion (Jia et al., 2014).

The Investigator will evaluate the OCTA images according to his/her standard of clinical practice to assess disease activity. The Investigator's assessed findings of both quantitative and qualitative parameters will not be captured in the eCRF but must be included in the source documents at the study site. Only parameters used by the Investigator to assess DA will be recorded in the eCRF.

The treatment regimen-masked CRC will provide sites with a Study Manual and training materials for the specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software will be certified and validated by the CRC as specified in the Study Manual. All OCTA images will be forwarded to the treatment regimen-masked CRC for independent standardized analysis. The CRC data will be used for the evaluation of the objectives comprising the assessment of OCTA parameters to ensure a standardized evaluation. Further details about all qualitative and quantitative parameters to be evaluated by the CRC are reported in the CRC grading charter (a separate document). The CRC will create a database with the agreed variables as indicated in the CRC charter and will transfer the data from this database to Novartis/CRO for analysis.

8.3.4 Color fundus photography

3-field color fundus photography (CFP) will be performed in the study eye at every study visit and in the fellow eye at Screening and Week 48. All 3-field color fundus photographic images will be obtained by trained and study-certified site personnel at the study sites and evaluated by the Investigator according to his/her standard of clinical practice to assess disease activity. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study participants.

A treatment regimen-masked Central Reading Centre (CRC) will be used in this study. The CRC will provide sites with a Study Manual and training materials for the specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software will be certified and validated by the CRC as specified in the Study Manual. CFP images at screening will be forwarded to the CRC for independent standardized analysis. The CRC data will be used for the evaluation of the objectives comprising the assessment of CFP parameters (i.e. to classify the type of CNV lesions) to ensure a standardized evaluation. Further details about all parameters to be evaluated by the CRC are reported in the CRC grading charter (a separate document). The CRC will create a database with the agreed variables as indicated in the CRC charter and will transfer the data from this database to Novartis/CRO for analysis.

[redacted] CFP (preferably wide-field or with peripheral sweeps) should be performed for safety evaluation as described in Section 8.4.2 and uploaded onto the CRC portal.

8.3.5 Best-Corrected Visual acuity

Visual acuity will be assessed in the study eye at every study visit and in the fellow eye at Screening and Week 48, using best correction determined from protocol refraction (BCVA). Visual acuity testing should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye. BCVA measurements will be taken in a sitting position using ETDRS–like visual acuity testing charts at an initial testing distance of 4 meters. The ETDRS chart has been established as the gold standard for objective VA measurement in clinical trials and consists of 14 rows of 5 letters each, for a total of 70 letters (Wykoff et al., 2018).

8.3.6 Disease activity assessments

The Investigator will perform a disease activity assessment (DAAs) on the study eye at Week 16 and at each subsequent scheduled q8w/q12w treatment visit. In participants on q12w treatment regimen with DA at any of these visits, a q8w treatment regimen should be considered. If a participant is adjusted to a q8w treatment regiment, he/she will subsequently be assessed at q8w treatment visits. In participants on q8w dosing regimen without signs of DA for two consecutive visits, based on the Investigator's judgment, the re-allocation to a q12w regimen should be considered. Of note, the Investigator will not be aware of the results of the CRC assessments at the time of performing each planned DAA.

DAAs are to be performed by the Investigator based on BCVA and/or one or more anatomical parameters detected by SD-OCT among IRF, SRF, sub-RPE fluid, hemorrhage, CRT and/or other OCTA parameters and/or 3-field CFP, as per clinical practice. The Investigator's assessed findings of both quantitative and qualitative SD-OCT and/or OCTA parameters will not be

captured in the eCRF but must be included in the source documents at the study site. Exclusively which of these parameters the Investigator considered instrumental to assess DA will be recorded in the eCRF.

8.3.7 Appropriateness of efficacy assessments

The use of BCVA as a measure of retinal function as well as SD-OCT images to analyze anatomical changes are standard assessments in this indication.

FA is still considered the gold standard for the diagnosis and classification of CNV lesions, whereas ICGA is a well-established procedure that helps to classify the type of lesion by identifying its entire extension. CFP is commonly used to inspect retinal pathology.

OCTA is an emerging valid non-dye imaging tool that has been widely introduced in ophthalmology clinical practice to detect the neovascular complex in wAMD. In routine practice, OCTA is still coupled with FA and other imaging techniques for the diagnosis and follow-up of wAMD.

The EQ-5D-5L questionnaire is one of the most widely used instruments for measuring health-related quality of life analysis, while the HADS questionnaire is one of the National Institute for Health and Care Excellence recommended tools for diagnosis of depression and anxiety.

8.4 Safety

Safety assessments will include complete ophthalmic examination, including IOP measurement prior and after each IVT injection, and vital signs, 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 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 Pregnancy

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Highly effective contraception, as summarized in the protocol's exclusion criteria (Section 5.2), is required for women of childbearing potential during dosing of study treatment and for 3 months after the final study injection.

A serum pregnancy test will be conducted for all women of childbearing potential to assess pregnancy before inclusion into the study at Screening visit and recorded on the eCRF. During the study, urine pregnancy testing will be performed at all visits. Of note, a positive urine test

should be confirmed by a serum pregnancy test. If the serum test is positive, the subject must discontinue study treatment of brolucizumab. Results of all pregnancy testing must be available as source documents.

8.4.2 Ophthalmic examination

A complete ophthalmic examination will be performed on the study eye at Screening, Baseline and Week 48 and may be performed at each in-between scheduled visit by the Investigator. At each visit the Investigator have to exclude the presence of any active intraocular inflammation in the study eye. This exam is also to be performed on the fellow eye at Screening and Week 48.

The ophthalmic exam may consist of the following:

- biomicroscopy (slit lamp examination) which includes the evaluation of the lids/lashes, conjunctiva, cornea, anterior chamber aqueous reaction (cell and flare), iris, lens and anterior part of the vitreous body will be completed at every (scheduled and unscheduled) visit. The results of the examination of either eye will 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.

- fundus (posterior segment) exam, which includes the evaluation of the vitreous, retina, macula, choroid, and optic nerve will be conducted at every scheduled and unscheduled visit by Investigator according to the clinical practice (fellow eye will be examined at the discretion of the investigator). Pupil dilation is to be performed at the discretion of the Investigator. An examination of the peripheral retina must also be performed, to ensure that the intravitreal injection can safely be performed as needed. Posterior segment examination must be performed carefully before each study treatment. The results of the examination including any abnormalities (e.g. vitreous cells/haze, retinal tear/detachment, hemorrhage and vascular occlusion, vasculitis, etc.) should be recorded in the source documents if appropriate. If there are any signs of IOI, vitreous cells and haze should be assessed using National Institutes of Health (NIH) grading system (Nussenblatt et al., 1985). The outcome of the examination will be documented in the source document (e.g., ophthalmic examination tool) and appropriate eCRF page as applicable. Any clinically significant abnormalities of either eye identified prior to signing the informed consent will be recorded on the medical history eCRF page, and on the adverse event page of the eCRF for any findings identified after signing the informed consent.

- intraocular pressure (IOP) measurement. Further details are reported in Section 8.4.3.

Results of these procedures will be recorded as appropriate in the source documents. Clinically significant abnormalities (as judged by the Investigator) should be recorded as an AE in the eCRF.

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. In case of unscheduled visits these additional assessments will be documented in the source and appropriate eCRF pages. These images are requested to be uploaded onto the CRC portal.

When IOI, retinal vasculitis, and/or retinal artery occlusion (RAO) is present or suspected during a visit (both scheduled and unscheduled), investigators must perform thorough ophthalmic examination, [redacted] These images are requested to be uploaded onto the CRC portal. If subject develops retinal vasculitis and/or retinal vascular occlusion based on the investigator's evaluation, the study treatment of brolucizumab must be discontinued. In addition, as some of the subjects who experience IOI may be at risk of developing retinal vasculitis and/or retinal vascular occlusion, the subject should be closely monitored and managed according to clinical practice.

8.4.3 IOP measurement

A measurement of IOP in the study eye will be conducted at each post-Screening visit when the treatment administration is foreseen (pre-dose and post-dose). In the fellow eye, IOP will be assessed at Screening and Week 48. The same method of tonometry should be used throughout the study for each participant. Treatment and close monitoring of IOP should be performed by the Investigator for any non-transient elevation in intraocular pressure ($\geq$ 25 mmHg). Intravitreal injection is not recommended unless normalization of the IOP has been achieved. Post-dose IOP should be assessed approximately within 60 minutes after injection and if $\geq$ 25 mmHg, assessment should be repeated until back to normal. Monitoring of optic nerve head perfusion after injection may be appropriate, at the discretion of the Investigator and/or according to local requirements/practices. Results of these procedures will be recorded as appropriate in the source documents. Clinically significant abnormalities (as judged by the Investigator) should be recorded as an AE in the eCRF.

8.4.4 Vital signs

Vital signs, i.e. sitting blood pressure (systolic and diastolic pressure in mmHg) and pulse rate (beats per minute) are to be collected at each scheduled visit. On days when study drug is administered, vital signs will be measured before administration of study medication.

Results of these procedures will be recorded as appropriate also in the source documents. Clinically significant abnormalities (as judged by the Investigator) should be recorded as an AE in the eCRF.

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population. If there are any signs of IOI, additional assessment will be performed as described in Section 8.4.2.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO)

The impact of brolucizumab treatment on patient quality of life and status of anxiety/depression will be assessed at Baseline and Week 48 by the EuroQoL five dimensions and five levels questionnaire (EQ-5D-5L) and the Hospital Anxiety and Depression Scale (HADS), respectively.

The participant must be given the questionnaires to be completed at the scheduled visit before any clinical assessments are conducted. Participant's refusal to complete all or any part of a PRO measures should be documented in the study data capture system and should not be captured as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

Completed questionnaires will be reviewed and examined by the Investigator for responses that may indicate potential AE or SAE, which should be confirmed and recorded into eCRF based on the Investigator's judgement (see Section 10.1.1 and Section 10.1.2 of the protocol).

EQ-5D-5L questionnaire

The EQ-5D-5L is a standardized widely used instrument for measuring generic health status. It comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels. i.e. no problems, slight problems, moderate problems, severe problems and extreme problems, corresponding to digit numbers ranging from 1 to 5. The EQ-5D-5L total score is determined through a Visual Analogue Scale (VAS) and ranges from 0 to 100 with higher scores indicative of a better health status.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a fourteen-item scale that generates ordinal data. Seven items relate to anxiety and seven relate to depression. This patient-reported outcome measure was specifically developed to avoid reliance on anxiety/depression aspects which are also common somatic symptoms of illness, such as fatigue and insomnia or hypersomnia.
Calculations of scores: each item is rated on a 4-point scale ('Yes, definitely', 'Yes, sometimes', 'No, not much' and 'No, not at all'). All items except items 7 and 10 are scored as 'Yes, definitely' = 3 to 'No, not at all' = 0. Items 7 and 10 are scored as 'Yes, definitely' = 0 to 'No, not at all' = 3. The HADS consists of two sub-scores: the HAD-A for anxiety and HAD-D for depression. Each sub-score ranges from 0 to 21 points: scores ≥11 indicate the presence of an anxious or depressive disorder, scores between 8-10 points are borderline abnormal, and scores ≤7 indicate that an anxious or depressive disorder is not present.

8.5.2 Assessments in the fellow eye

The following assessments will be performed for the fellow eye:

- At Screening: BCVA, ophthalmic examination, IOP, SD-OCT, OCTA, CFP, FA and ICGA. Images will be sent and stored by the CRC.

- At Week 48: BCVA, ophthalmic examination, IOP, SD-OCT, OCTA, CFP, FA and ICGA. Images will be sent and stored by the CRC.

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

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the Investigator.

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

Study treatment must be discontinued under the following circumstances:

- Participant decision
- Pregnancy (see Section 8.4.1 and Section 10.1.4)
- Use of prohibited treatment as per recommendations in Section 6.2.2
- Any situation in which study participation might result in a safety risk to the participant
- Subject develops a retinal vasculitis and/or a retinal vascular occlusion event in the brolucizumab arm
- Unsatisfactory therapeutic effect

If discontinuation of study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who prematurely discontinue study treatment for any reason, except for withdrawal of consent (refer to Section 9.1.2), should continue in the study with all the scheduled visits and assessments (except disease activity assessment, administration of study treatment, post-injection assessment and adherence to prohibited medication list) until Week 48, at the discretion of the Investigator or the participant. If a participant discontinues study treatment before Week 16 (visit 6), he/she will complete monthly visits until Week 16 (visit 6) and after Week 16 he/she will continue with bimonthly visits until Week 48.

Participants 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, participants should return for the Week 48 (end of study) assessments to be performed as indicated** in the Assessment Schedule (Table 8-1). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section.

This contact should preferably be done according to the study visit schedule. If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, 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

The Investigator must also register in the appropriate eCRF page the participant's discontinuation from study treatment.

9.1.1.1 Replacement policy

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

9.1.2 Withdrawal of informed consent

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

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

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

Where consent to the use of personal and coded data is not required in a certain country's legal framework, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

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 participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.1.3 Lost to follow-up

For participants 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 participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

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, but are not limited to:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development
- Practical reasons, including slow enrollment
- Regulatory or medical reasons

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. 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 participant's interests. The Investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their End of Study visit (Week 48) 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 participant 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

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign, symptom or disease) in a clinical investigation participant 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 participant and identifying adverse events.

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

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

Adverse events must be recorded 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: 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 or 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 will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
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 Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

   All adverse events 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

- participant hospitalized/participant'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

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

Adverse events should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last administration of study treatment.

Once an adverse event 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 SmPC and in the IB.

Abnormal test results constitute adverse events 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 test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from Baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

10.1.2 Serious adverse events

Any SAE is defined as any adverse event [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 participant 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 studied 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 participant'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 participant 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 participant 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 new 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 irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 4 weeks after the last study visit must be reported to Novartis Patient Safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site.

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

If the SAE is not previously documented in the SmPC and is thought to be related to the study treatment, a Chief Medical Office and 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 reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 4-week period after the last study visit (study discontinuation) should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. 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. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to brolucizumab with any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF page 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 Dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes (only data and time of injection)	Only if associated with an AE	Only if associated with an SAE

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

10.2 Additional Safety Monitoring

Not applicable.

11 Data Collection and Database management

11.1 Data collection

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

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

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should 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 investigational 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 investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

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

SD-OCT, OCTA, FA, ICGA and CFP images, appropriately anonymized from the Investigators, will be processed centrally by the Central Reading Center and the results will be sent electronically to the CRO working on behalf of Novartis. The Data management staff will review data received from the CRC for data structure and data completeness / accuracy as defined in the Data Transfer Specifications document.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis (or designated CRO) representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the Investigators and their staff. During the study, Novartis

employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis (or designated CRO) Clinical Research Associates organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The Investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments, including retinal images. All information on eCRFs must be traceable to these source documents in the participant's file. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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 participants will be disclosed.

12 Data analysis and statistical methods

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

All data will be listed and summarized as appropriate: continuous data will be summarized by mean, standard deviation (SD), median, minimum and maximum, Q1 and Q3; categorical data will be presented as absolute and relative frequencies. 95% confidence intervals will be provided as relevant.

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

Additional analysis may be also conducted to evaluate the impact of COVID-19 pandemic.

12.1 Analysis sets

The **Screened patient population** consists of all screened patients.

The **Full Analysis Set (FAS)** comprises all enrolled participants, i.e. participants who completed the Baseline visit.

The **Safety Set (SAF)** includes all FAS participants who received at least one dose of the study drug.

All statistical analyses are to be conducted on the Safety Set, if not differently specified.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics evaluated at Screening/Baseline will be listed and summarized descriptively for the FAS and Safety set.

Eye disease history will be summarized descriptively as appropriate (e.g. time from wAMD diagnosis, bilateral disease etc.).

Relevant medical histories and current medical conditions at Screening will be summarized by system organ class, preferred term and ongoing status.

12.3 Treatment

The Safety set will be used for the analyses below.

The duration of exposure to brolucizumab as number of IVT injections received from Baseline to Week 48 will be summarized by means of descriptive statistics. Furthermore, the number of participants at each injection category (e.g. 1 injection, 2 injections, etc.) from Baseline to Week 48 will be provided. All collected injection data will be listed.

The treatment regimen (q12w or 18w) will also be provided.

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

12.4 Analysis of the primary estimands

The primary aim of the study is to assess the predictive value of early anatomical parameters measured by multimodal imaging at each visit from Baseline to Week 16, in brolucizumab-treated participants with wAMD who present fluid resolution at Week 48 and have maintained the q12w treatment regimen up to Week 48 (i.e. q12w fluid-free participants), compared with participants on a q8w regimen and/or not fluid-free at Week 48.

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary estimand of the study is to identify the q12w fluid-free predictive factors.

A patient will be considered q12w fluid-free if does not present IRF and SRF at Week 48 and remains on the q12w regimen up to Week 48.

The following qualitative and quantitative anatomical parameters measured by FA, ICGA, CFP, SD-OCT and OCTA will be considered as potential predictive factors in the statistical model:

- Basal CNV lesion type, as assessed by SD-OCT, FA, ICGA and CFP at Screening
- Parameters assessed by OCTA from Baseline to Week 16, of which the main are presence/absence of branching vessels, peripheral anastomotic arcades, vascular loops and dark halo, and quantification of CNV flow size and vessel density
- Parameters assessed by SD-OCT from Baseline to Week 16, of which the main are presence/absence of sub-RPE fluid, SHRM, outer retinal tubulation and status of ELM, measurement of CRT and PED volume

The primary estimand of interest is described in Table 12-1 below, together with its key attributes. The estimand outlined below will be discussed in further details in the SAP.

Table 12-1 Primary estimand

Estimand definition	Analysis set	Use of data after intercurrent event (missing data imputation techniques)	Statistical methods
Proportion of q12 fluid-free participants	SAF	Participants who prematurely discontinued the study should be considered a not q12 fluid-free	Multivariable logistic regression model

12.4.2 Statistical model, hypothesis, and method of analysis

To test whether the above-mentioned anatomical parameters are predictors of response to brolucizumab in terms of fluid resolution and stable q12w regimen, participants within the Safety Set are to be divided in:

- q12w fluid-free participants, defined as participants who have maintained a stable q12w regimen up to Week 48 and are devoid of IRF and SRF at Week 48
- not q12w fluid-free participants, defined as participants who present IRF *or* SRF at Week 48 *or* have been on a q8w regimen at any time during the study *or* have dropped out at any time after Baseline

A Recursive Partitioning and Amalgamation (RECPAM) classification-tree analysis will be used to evaluate interactions between imaging measurements assessed by OCT, OCTA, FA, ICGA and CFP and to identify distinct and homogeneous subgroups of participants in terms of q12w fluid-free participants at Week 48.

This tree-based method integrates the advantages of main effects logistic regression and tree-growing techniques. At each partitioning step, the method chooses the covariate and its best binary split to maximize the difference in the outcome of interest. The algorithm stops when user-defined conditions (stopping rules) are met. To obtain more robust and stable splits, a permutation approach will be adopted to choose the best splitting variable. Global and local adjustment for possible confounders will be accounted for. Global variables will adjust the tree structure iteratively and add global coefficients to the model. Local variables will add different adjustment terms for any terminal node in a tree.

The RECPAM construction proceeds in the following three steps:

Step 1: Construction of a large tree.

Starting from the Safety Set (i.e. root node), the maximum dissimilarity between *q12w fluid-free patients* vs *non q12w fluid-free patients* for the Split Defining Statement (SDS) family (i.e. predictors variable) will be searched. This will identify the first branch of the tree and the corresponding tree. The same search will be performed recursively on the descendants of the root node, until a minimum node size specified by the user is reached. This defines the leaves of the larger tree.

Step 2: Pruning of the large tree and selection of the honest tree.

The best tree will be select considering jointly the two criteria: the Akaike Information Criterion (AIC) and the simultaneous significance levels (SLn). According to the minimum AIC principle

(Akaike, 1974), the honest tree should be the tree of the pruning sequence having the smallest AIC. This criterion is justified by the asymptotic equivalence of the minimum AIC model choice and leave-one-out cross validation. According to the SL approach, on the other hand, we should choose the smallest tree such that SLn is larger than a pre-fixed value, e.g. 0.05 or 0.01. Since the AIC sequence decreases, reaches a minimum and then increases with a characteristic jump in the increment, while SL sequence can only decrease but up to a point at which the SL drops rather abruptly, we will choose the point in which both curves show a characteristic elbow (Ciampi et al., 1995).

Step 3: Construction of the amalgamation tree and selection of the RECPAM classification.

For a given statistical significance α level, the leaves of the honest tree will be amalgamated successively until any couple of leaves is dissimilar at the nominal α level. This results in a sequence of nested partitions of the set of leaves of the honest tree, forming the amalgamation tree. The partition corresponding to the minimum AIC, is selected: it defines the RECPAM classification (Ciampi et al., 1991).

A multivariable logistic regression will then be applied to study the association between q12w fluid-free patients at Week 48 with different imaging parameters using the above-mentioned variables and the cut-off selected by the RECPAM analysis. FA, ICGA and CFP variables included in the model are measured at Screening, while OCTA and SD-OCT variables included in the model are assessed at Screening (only SD-OCT), Baseline and Weeks 4, 8, 12 and 16. The variables selection will be based on an automated stepwise selection.

12.4.3 Handling of remaining intercurrent events of primary estimand

As described in Table 12-1, participants who prematurely discontinued the study should be considered a not q12w fluid-free at Week 48.

12.4.4 Handling of missing values not related to intercurrent event

Imputation of missing values will be done following the Last Observation Carried Forward (LOCF) method mainly for the secondary endpoints. An observed approach will be also considered.

12.4.5 Sensitivity analyses for primary endpoint/estimand

A sensitivity analysis on the primary model will be performed using the LOCF approach in case of missing SD-OCT or OCTA evaluations between Week 4 and Week 16.

12.4.6 Supplementary analysis

Not applicable.

12.4.7 Supportive analyses

To investigate the robustness of the primary analysis with respect to a potential selection bias due to dropouts, the following approach will be used: a weighted multivariable logistic regression will be applied to provide a robust inferential procedure for the analysis of predictors of patients' responses in presence of missingness. Since excluding participants because of missing values could introduce a selection bias, in order to restore the complete-case analysis to its

original sample representation, each complete participant will be weighted for the inverse of his/her missingness probability (evaluated by means of a logistic regression considering all baseline available covariates and the dropouts during the one-year period as response variables) (Höfler et al., 2005).

Further details will be provided in the Statistical Analysis Plan (SAP).

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

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

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

To evaluate the effect of brolucizumab on the evolution of qualitative and quantitative OCTA parameters of wAMD from Baseline to Week 48

Summary statistics of each parameter assessed by OCTA, of which the main quantitative parameters are CNV flow size and vessel density, and the main qualitative ones are branching vessels, peripheral anastomotic arcades, vascular loops and dark halo, from Baseline up to Week 48 will be provided, including changes vs Baseline. Paired t-test or Wilcoxon signed rank test, based on data distribution, will be used to test the difference at each time point vs Baseline for continuous parameters. In case of a dichotomous parameter, a McNemar test will be used.

To evaluate the effect of brolucizumab on the evolution of qualitative and quantitative SD-OCT parameters of wAMD from Baseline to Week 48

Summary statistics of each parameter assessed by SD-OCT, of which the main quantitative parameters are CRT and PED volume, and the main qualitative ones are IRF, SRF, sub-RPE fluid, status of ELM, SHRM and outer retinal tubulation, from Baseline up to Week 48 will be provided, including changes vs Baseline.

Paired t-test or Wilcoxon signed rank test, based on data distribution, will be used to test the difference at each time point vs Baseline for continuous parameters. In case of a dichotomous parameter, a McNemar test will be used.

To evaluate the effect of brolucizumab on the evolution of functional parameters of wAMD from Baseline to Week 48

Summary statistics of BCVA from Baseline at each visit up to Week 48 as well as changes vs Baseline will be provided. Paired t-test or signed rank test, based on data distribution, will be used to test the difference at each time point vs Baseline.

Frequency of patients with an improvement of at least 5/10/15 letters or worsening will be also provided.

To evaluate the effect of brolucizumab on sustained dryness from Baseline to Week 48

- Time to reach sustained dryness of the study eye, as defined by the absence of IRF and SRF for at least 2/3 consecutive visits, will be descriptively summarized. Survival Kaplan-Meier curve will also be provided including summary estimates.

- Summary statistics of cumulative incidence of sustained dryness of the study eye will be provided by means of absolute and relative frequencies of participants with sustained dryness as defined above at each timepoint from Week 8 to Week 48. The binomial proportion and 95% confidence interval (CI) using the Clopper-Pearson method will also be provided.

To evaluate the reasons underlying the Investigators' choice of brolucizumab treatment regimen (q21w or q8w) at Week 16

The reasons underlying the Investigator's choice of brolucizumab dosing regimen (q12w or q8w) at Week 16 among BCVA and/or IRF, SRF, sub-RPE fluid, hemorrhage and/or CRT and/or OCTA parameters and/or 3-field CFP will be descriptively summarized. A multivariate logistic regression model will also be implemented in order to evaluate which of these factors are determinants for the selection of the dosing regimen at Week 16.

Further details will be provided in the Statistical Analysis Plan (SAP).

12.5.2 Safety endpoints

The safety set will be used for all safety analyses.

Safety summaries include only data from the on-treatment period. In particular, summary tables for adverse events (AEs) 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 study treatment to 30 days after the date of the last actual administration of the study treatment or the end of study, whichever is the latest.

Adverse events

All information obtained on adverse events will be summarized overall and listed by participant.

The number (and percentage) of participants with treatment-emergent adverse events (events started after the first dose of study medication) will be summarized in the following ways:

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

Separate summaries will be provided for study medication related treatment-emergent adverse events, death, serious treatment-emergent adverse events and other significant treatment-emergent adverse events leading to permanent treatment discontinuation.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

12.5.3 Patient reported outcomes

Quality of Life – EQ-5D-5L

Summary statistics of EuroQol-5D-5L (EQ-5D-5L) VAS scores at each time point as well as changes from Baseline will be provided. Paired t-test or signed rank test, based on data distribution, will be used to test the difference in VAS scores at Week 48 vs Baseline.

Hospital Anxiety and Depression Scale

Descriptive statistics of HAD-A and HAD-D score at each time point with changes vs Baseline will be provided. Paired t-test or signed rank test, based on data distribution, will be used to test the difference in HAD-A and HAD-D scores at Week 48 vs Baseline.

The sub-scores, HAD-A and HAD-D, will also be displayed per class (i.e. scores ≥11 indicate the presence of anxious or depressive disorders; scores between 8-10 points are borderline abnormal, and scores of ≤7 indicate that the disorder is not present) at each time point by means of a shift table.

In addition, the prevalence of anxiety and depression will be presented on the basis of the following three criteria: as per the score on the corresponding sub-scores of the HAD questionnaire, in terms of the treatment they are receiving for anxiety/depression, and according to both criteria.

12.6 Interim analyses

An interim analysis will be conducted when 50% of the participants planned to be enrolled have completed their Week 16 visit to evaluate the reasons underlying the Investigators' choice of brolucizumab treatment regimen at Week 16. The reasons underlying the Investigator's choice of brolucizumab dosing regimen (q12w or q8w) at Week 16 among BCVA and/or IRF, SRF, sub-RPE fluid, hemorrhage and/or CRT and/or OCTA parameters and/or 3-field CFP will be descriptively summarized. A multivariate logistic regression model will also be implemented in order to evaluate which of these factors are determinants for the selection of the dosing regimen.

12.7 Sample size calculation

12.7.1 Primary endpoint(s)

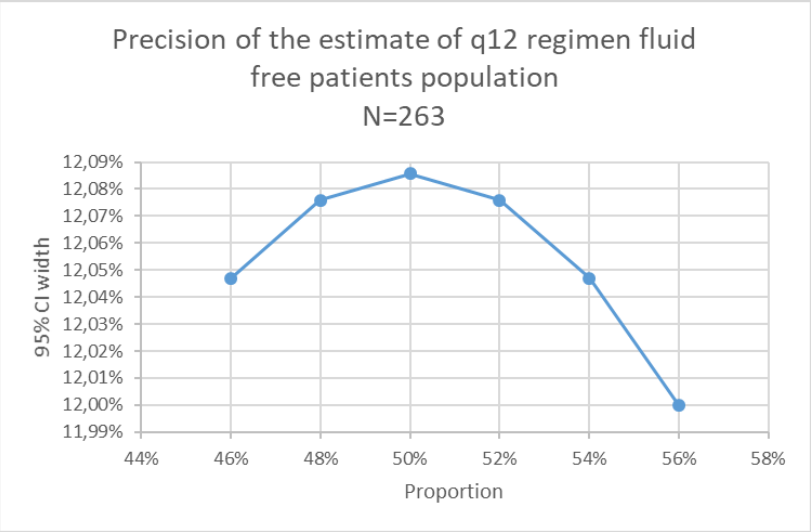
The sample size calculation is based on the assumption of an expected percentage of participants who have maintained the q12w regimen up to Week 48 equal to 56%, as derived from the HAWK study, and the hypothesis of a maximum percentage of not-fluid free participants out of these q12w-regimen participants at Week 48 equal to 18%. Therefore, the percentage of responders, defined as fluid-free participants who have maintained a q12w stable regimen up to Week 48, could range between 56% to 46%.

Considering a percentage of responders of 56% and a maximum width of the 95% confidence interval of 12%, 263 patients should be enrolled. Applying the rules of thumb, with 263 patients and a percentage of responders of 56%, a maximum number of 12 covariates can be included in the multivariate regression model (Harrell, 2015). As shown in Figure 12-1, the precision of the estimate remains stable around 12%, considering a percentage of responders ranging between 56% to 46%. Similar considerations can be made with a number of covariates that remains equal to 12.

Finally, to account for a screening failure rate of 12%, a total of approximately 300 participants will be screened in order to enroll 263 evaluable participants.

The sample size calculations were performed with Nquery 7.0.

Figure 12-1 Precision of the estimate scenario



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 Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the Investigator and IRB/IEC

Before initiating a trial, the Investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required

Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.). Results from the interim analyses may be published prior to study completion.

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

14.1 Protocol amendments

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

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

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this

study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Not applicable.

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Not applicable.

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Not applicable.