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Novartis Research and Development

[RTH258/brolucizumab]

Clinical Trial Protocol CRTH258ADE01 / NCT04679935

A 52-week, two arm, randomized, open-label, multicenter study assessing the efficacy and safety of two different brolucizumab 6 mg dosing regimens for patients with suboptimal anatomically controlled neovascular age-related macular degeneration (FALCON)

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List of abbreviations

[redacted]	[redacted]
AE	Adverse Event
AMD	Age-related Macular Degeneration
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CFP	Color Fundus Photography
CMO	Chief Medical Office
CNV	Choroidal Neovascularization
COVID-19	Coronavirus Disease 2019
CRC	Central Reading Center
CRF	Case Report Form
CRO	Contract Research Organization
CSFT	Central Subfield Thickness
CTT	Clinical Trial Team
DA	Disease Activity
DAA	Disease Activity Assessment
DMC	Data Monitoring Committee
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End-of-Study
EOT	End-of-Treatment
eSource	Electronic Source
ETDRS	Early Treatment Diabetic Retinophathy Study
FA	Fluorescein Angiography
FAS	Full Analysis Set
FCP	Fundus-Controlled Perimetry
FDA	Food and Drug Administration
FIR	First Interpretable Results
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
h	Hour
hCG	Human Chorionic Gonadotropin
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
IOI	Intraocular Inflammation
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRF	Intraretinal Fluid
IUD	Intrauterine Device

IUS	Intrauterine System
IVT	Intravitreal Injection
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
nAMD	Neovascular Age-related Macular Degeneration
NIH	National Institutes of Health
OCT	Optical Coherence Tomography
PD	Protocol Deviation
PDT	Photodynamic Therapy
PED	Pigment Epithelial Detachment
PFS	Pre-filled Syringe
PPS	Per-protocol Set
PRN	*pro re nata*
PS	Patient Safety
PT	Preferred Term
q4w	every 4 weeks
q6w	every 6 weeks
q8w	every 8 weeks
q10w	every 10 weeks
q12w	every 12 weeks
QMS	Quality Management System
RAO	Retinal Artery Occlusion
RAP	Retinal Angiomatous Proliferation
RAS	Randomized Analysis Set
RO	Retinal Vascular Occlusion
RPE	Retinal Pigment Epithelium
RV	Retinal Vasculitis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
scFv	Single-chain Antibody Fragment
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SOC	System Organ Class
SRF	Subretinal Fluid
SUN	Standardization Uveitis Nomenclature
sub-RPE	Sub-Retinal Pigment Epithelium
SUSAR	Suspected Unexpected Serious Adverse Reaction
T&E	Treat-and-Extend
USM	Urgent Safety Measures
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WoC	Withdrawal of Consent
YAG	Yttrium Aluminum Garnet

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Dosage	Dose of the study treatment given to the subject 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 subject (including follow-up)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
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
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Patient	An individual with the condition of interest for the study
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
Premature subject withdrawal	Point/time when the subject 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.
Randomization number	A unique identifier assigned to each randomized subject
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 subject 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 subject

Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s).
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date.
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
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.

Amendment 2 30-Nov-2022

Amendment rationale from protocol version 01

The main reasons for the protocol amendment are:

Due to the slow enrollment the feasibility of this trial has been reconsidered. The first patient was recruited in July 2021. So far, only 47 out of 490 anticipated patients (9.6%) could be enrolled within 16 months.

Several actions were taken to improve the recruitment rate: the protocol was amended in February 2022 to broaden the inclusion criteria; regular study newsletters, investigator meetings and monitor visits to inform the sites, opening of further sites.

Despite these actions, the sites could not find enough patients matching the inclusion and exclusion criteria. Novartis also requested an actual recruitment forecast by the sites which confirms that this population cannot be recruited in any reasonable time. In combination with the low recruitment rate achieved so far, it is very unlikely that the number of patients required to determine the primary endpoint will be enrolled within a reasonable time. Therefore, this amendment is driven by feasibility reasons.

The aim of this amendment is to prematurely discontinue study recruitment due to feasibility reasons (slow enrollment) and allow all randomized patients to stay in the study and continue their treatment until week 52. Reason for the treatment continuation is that brolucizumab is an approved marketed product for the treatment of nAMD in the countries where the study is running. Moreover, with continuation in the study, we will be able to collect the full data sets for all patients that are already randomized and evaluate the data in a descriptive manner. The primary endpoint hypothesis can no longer be addressed, but our goal is to at least provide insights on whether pretreated nAMD patients need loading with three monthly brolucizumab injections and put the results of our descriptive analysis into context together with current and future literature on how to treat patients who had an unsatisfactory response to other anti-VEGF treatments.

The premature discontinuation of recruitment will become effective with approval of this protocol amendment by the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. From this time point on, no further patients can be recruited, but the trial will continue for all already randomized patients.

Changes to the protocol

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

Editorial changes and spelling corrections are done throughout the protocol. Other minor clarifications and corrections were made where applicable.

- Protocol summary: The patient number was changed from planned 490 to expected 50 randomized patients. It was clarified that the primary objective can no longer be addressed and all analyses will be performed in a purely descriptive manner due to the reduced sample size. Accordingly, the primary objective has been revised from demonstrating non-inferiority to assessing the difference in BCVA between the two study arms.

- Section 1.2 Purpose: The study purpose has been revised since the primary objective cannot be analyzed as initially planned.
- Section 2 Objectives and endpoints: It was clarified that the primary endpoint can no longer be addressed and all analyses will be performed in a purely descriptive manner. The primary endpoint was changed from demonstrating non-inferiority to evaluate the difference in BCVA between the two study arms.
- Section 3 Study design: The patient number was changed from 490 to approximately 50 patients which will be randomized in a 1:1 ratio in approximately 33 centers.
- Section 4.1 Rationale for study design: The study design rationale was updated to reflect that the initially planned primary objective can no longer be reached.
- Section 12.4 Analysis of the primary endpoint: It was clarified that the primary endpoint can no longer be addressed and all endpoints will be analyzed in a purely descriptive manner, non-inferiority testing will be omitted. No sensitivity or supportive analysis for the primary endpoint will be carried out.
- Section 12.8 Sample size calculation: It was clarified that the initial recruitment number cannot be achieved due to the slow recruitment rate and the enrollment will be prematurely discontinued when this protocol amendment becomes effective, expecting a total of about 50 patients to be enrolled. As a consequence, all analyses will be performed in a purely descriptive manner. Based on an expected sample size of 25 patients per group, a precision in terms of the width of the respective 95% confidence interval for the difference in change from baseline of the visual acuity of +/- 7,21 can be achieved.

IRBs/IECs

A copy of this amended protocol will be submitted 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, which will be updated by the sponsor and submitted to the IRB/IEC and Health Authority approval according to local regulations prior to implementation.

Amendment 1 18-Nov-2021

Amendment rationale

The main reasons for the protocol amendment are:

(1) To implement the Urgent Safety Measures (USM) described in 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).

(2) The safety sections were updated throughout the protocol including updating the risks and benefits section and creating a new section under safety monitoring to consolidate all the information regarding the risk mitigation into one section in the protocol. Furthermore, it was clarified that treatment intervals of < 8 weeks are not allowed after the initiation phase.

(3) 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.

(4) The list of inclusion and exclusion criteria has been updated to better reflect the patient population in real-world clinical practice. In addition, the criteria for disease activity assessment have been clarified.

Changes to the protocol

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

Editorial changes and spelling corrections are done throughout the protocol. Other minor clarifications and corrections were made where applicable.

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

- Section 1.1 Background: Information added to describe the Urgent Safety Measures
- Section 4.2 Rationale for dose/regimen and duration of treatment: Language added to provide background of the USM
- Section 4.5 Risk and benefits: Information added to describe USM from the MERLIN (CRTH258AUS04) study and results of the mechanistic study BASICHR0049 and additional information on gender imbalance on IOI following brolucizumab treatment
- Section 6.1.4 Treatment duration: Guidance added for subjects requiring injections every 4 weeks and patients with IOI, RV and/or RO
- Section 8.4 Safety: Guidance for COVID-19 remote assessments was updated to reflect that study treatment cannot be administered without an on-site study visit
- Section 8.4.2 Pregnancy and assessment of fertility: Requirement that treatment must be discontinued for pregnant woman was added

- Section 8.4.3 Ophthalmic examination: Requirement of treatment discontinuation for brolucizumab was added if subject developed IOI, RV and/or RO
- Section 9.1.1 Discontinuation of study treatment: the following circumstances were added and instructions were given for switch to standard of care:
  - Unsatisfactory therapeutic effect, e.g. a subject requires injections more frequently than every 8 weeks after the loading phase (week 8, loading arm) or baseline (non-loading arm)
  - Subjects develop IOI, RV and/or RO
- Section 10 Safety monitoring and reporting: Consolidated the requirements for monitoring of adverse events. Added the new requirement that if IOI, RV and/or RO is confirmed, subjects should be discontinued from study treatment.
- Section 10.1.3 SAE reporting: Clarified the timing for SAE reporting to Novartis as per latest protocol template and extended reporting to 60 days after the last administration of study treatment.

Other changes incorporated in this amendment

- The glossary of terms was updated to the latest template wording
- Section 1.2 Purpose: the wording to describe the study purpose was updated
- Section 3 Study Design: the instructions for disease activity assessment and treatment regimen adjustment were updated for clarification purposes
- Section 5.1 Inclusion criteria: The list of inclusion criteria was updated to better reflect the patient population in real-world clinical practice.
- Section 5.2 Exclusion criteria: The list of exclusion criteria was updated to better reflect the patient population in real-world clinical practice.
- 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
- Section 6.3.2 Treatment assignment, randomization: Figure 6-1 Screening and randomization procedure was updated into a colored image.
- Section 6.7.2 Instruction for prescribing and taking study treatment: the instructions for disease activity assessment and treatment regimen adjustment, Figure 6-2 Treatment regimen and Figure 6-3 Examples for treatment regimen adjustments were updated for clarification purposes
- Section 8 Visit schedule and assessments: legend of Table 8-1 assessment schedule was updated for better comprehensibility
- Section 9.1.2 Withdrawal of informed consent: Clarified the definition of Withdrawal of Consent (WoC)

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, which will be updated by the sponsor and submitted to the IRB/IEC for approval according to local regulations prior to implementation.

Protocol summary

Protocol number	CRTH258ADE01
Full Title	A 52-week, two arm, randomized, open-label, multicenter study assessing the efficacy and safety of two different brolucizumab 6 mg dosing regimens for patients with suboptimal anatomically controlled neovascular age-related macular degeneration (FALCON)
Brief title	Study assessing efficacy and safety of two different brolucizumab regimens for pretreated patients with neovascular age-related macular degeneration
Sponsor and Clinical Phase	Novartis Pharma GmbH Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to evaluate the efficacy and safety of two different brolucizumab regimens for pretreated patients with neovascular age-related macular degeneration. The study shall provide contributive information as to whether nAMD patients who showed an unsatisfactory response to previous anti-VEGF treatments (i.e. residual or recurrent fluid despite continuous anti-VEGF treatment), need loading with three monthly brolucizumab 6 mg injections or whether they can immediately receive brolucizumab treatment every 12 weeks. Our goal is to provide insights to support the medical practice and put the results of our descriptive analysis into context together with current and future literature on how to initiate treatment for pretreated patients who had an unsatisfactory response to other anti-VEGF treatments and to evaluate interval prolongation compared to previous treatment.
Primary Objective(s)	The study will evaluate the difference in BCVA change from baseline for brolucizumab 6 mg with one (initial) injection followed by treatment every 12 weeks as compared to brolucizumab 6 mg with three monthly loading injections followed by treatment every 12 weeks. As a consequence of Amendment 2, the assumed patient number necessary for analysis of the primary objective will not be achieved. Therefore, the primary endpoint and all analyses will now be performed in a purely descriptive manner. With 25 patients per group, a precision in terms of the width of the respective 95% confidence interval for the difference in change from baseline of the visual acuity of +/- 7,21 can be achieved.
Secondary Objectives	• To evaluate treatment interval prolongation compared to previous treatment • To estimate the proportions of patients maintained at every 12 weeks treatment frequency in the two brolucizumab groups • To evaluate the functional outcomes comparing the two brolucizumab groups • To evaluate the anatomical outcomes comparing the two brolucizumab groups • To evaluate the safety and tolerability of brolucizumab
Study design	The study is a 52-week, randomized, open-label, multi-center, two-arm study in patients with nAMD. Consenting patients will participate in a screening period, lasting up to 14 days. Eligible patients will be randomized in a 1:1 ratio to one of the two treatment arms:

	1. Brolucizumab 6 mg **"loading arm"**: 3 x 4-weekly initial injections followed by an injection every 12 weeks 2. Brolucizumab 6 mg "**non-loading arm**": one initial injection followed by an injection every 12 weeks In both study arms, treatment intervals after the initiation phase will be either 8 weeks or 12 weeks depending on disease activity status. More frequent injections, i.e., treatment intervals of < 8 weeks are not allowed after the initiation phase.
Population	490 randomized patients ≥50 years of age with visual impairment due to neovascular age-related macular degeneration had initially been targeted. According to Amendment 2 for premature discontinuation of recruitment, the planned sample size will not be achieved, expecting a total of approximately 50 patients to be recruited by the time of approval of Amendment 2.
Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study • Male or female patients ≥50 years of age at screening • Active choroidal neovascularization (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 and sequelae of CNV, e.g. pigment epithelial detachment (PED), subretinal or sub-retinal pigment epithelium (sub-RPE) hemorrhage, blocked fluorescence, macular edema (intraretinal fluid (IRF) and/or subretinal fluid (SRF) and/or sub-retinal pigment epithelium (sub-RPE) fluid that affects the central subfield, as seen by Spectral Domain Optical Coherence Tomography (SD-OCT)) at screening, as confirmed by central reading center (study eye). If active CNV according to the above explained activity criteria is not detectable in screening image data (no IRF and no SRF), presence of residual and/or recurrent fluid (IRF and/or SRF) within the last 6 months before baseline visit is also considered eligible. In this case, historical images must be submitted for analysis by the central reading center. • Pretreatment with any anti-VEGF drug for a maximum of five years (60 months). Patients should have shown functional and/or anatomical treatment response to the pretreatment(s), prior to participating in this study. • The treatment initiation phase with the current anti-VEGF must have been completed for at least 6 months with continuous treatment in a ≥ q4w to ≤ q12w injection interval (±2-day window, i.e. 26 to 86 days inclusive) before the baseline visit. At least 4 weeks (minimum 26 days) must have passed between the last anti-VEGF pretreatment and baseline. • BCVA score must be ≤ 83 and ≥ 38 letters at 4 meters starting distance using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity charts (approximately Snellen equivalent of 20/25 and 20/200), at both screening and baseline
Key Exclusion criteria	• Concomitant conditions or ocular disorders in the study eye at screening or baseline which could, in the opinion of the investigator, prevent response to study treatment or may confound interpretation of study results, compromise visual acuity or require planned medical or surgical intervention during the 52-week study period, atrophy or fibrosis at the center of the fovea as confirmed by central reading center or structural damage of the fovea (study eye) • Treatment with anti-VEGF drugs for > 5 years

	• Any active intraocular or periocular infection or active intraocular inflammation, at screening or baseline (study eye) • Uncontrolled glaucoma defined as intraocular pressure (IOP) > 25 mmHg on medication, or according to investigator's judgment, at screening or baseline (study eye) • 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) • Ocular treatments: pretreatment with brolucizumab at any time in the study eye, previous treatment with investigational drugs in the last 6 months, intraocular or periocular steroids at any time, macular laser photocoagulation or photodynamic therapy at any time, peripheral laser photocoagulation within 3 months prior to baseline, intraocular surgery within 3 months prior to baseline, vitreoretinal surgery at any time, aphakia with the absence of posterior capsule (study eye) • Stroke or myocardial infarction during the 6-month period prior to baseline • Systemic anti-VEGF therapy during the 3-month period prior to baseline
Study treatment	Brolucizumab 6 mg/0.05 mL
Efficacy assessments	• BCVA testing using ETDRS charts, anatomical markers on SD-OCT, Color Fundus photography (CFP) and Fluorescein angiography (FA)
Key safety assessments	• Monitoring of adverse events • Standard ophthalmic examinations and imaging • Vital signs (blood pressure, heart rate) • Pregnancy testing
Other assessments	[redacted] • Whole blood collection via venipuncture
Data analysis	The difference of brolucizumab "non-loading" compared to brolucizumab "loading" in terms of mean change in BCVA from baseline to mean of visits at week 40 to week 52 will be evaluated using descriptive statistics. Summary statistics will be presented by treatment arm unless otherwise specified. For continuous variables, summary statistics will generally include: n, mean, standard deviation, median, minimum and maximum. For categorical variables, these will generally include: n and percentage in each category.
Key words	Neovascular age-related macular degeneration, anti-VEGF, choroidal neovascularization, brolucizumab, loading vs. non-loading

1 Introduction

1.1 Background

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in people over the age of 65 in the United States and other Western countries (Rein et al., 2009). The neovascular, exudative or wet form of AMD (nAMD) is characterized by the growth of abnormal new blood vessels (neovascularization) under the retinal pigment epithelium (RPE) from the choroid into the retina (Ferris et al., 1984). These newly formed vessels have an increased likelihood to leak blood and serum, damaging the retina by stimulating inflammation and scar tissue formation which results in progressive, severe, and irreversible vision loss (Shah and Del Priore, 2007, Shah and Del Priore, 2009). Without treatment, most affected eyes will have poor central vision (20/200) within 12 months (Blinder et al., 2003).

Vascular endothelial growth factor (VEGF) was identified to play a key role in the neovascularization process (Spilsbury et al., 2000). The use of intravitreal injection pharmacotherapy targeting VEGF, such as ranibizumab (Lucentis®) and aflibercept (Eylea®), has significantly improved visual outcomes in patients with nAMD (Bloch et al., 2012, Campbell et al., 2012) and has been shown to halt the growth of neovascular lesions and resolve retinal edema, which raised anti-VEGF treatments to current standard of care in nAMD.

Brolucizumab

Brolucizumab is a humanized single-chain antibody fragment (scFv), binding to VEGF-A with high affinity. It works by binding to the receptor binding site of the VEGF-A molecule, thereby preventing the interaction of VEGF-A with its receptors VEGFR1 and VEGFR2 on the surface of endothelial cells (Escher et al., 2015). Brolucizumab has a molecular weight of ~26 kDa which allows a delivery of a high molar dose via intravitreal injection. A 6 mg dose of brolucizumab delivers a molar dose which is approximately 11 and 22 times higher than aflibercept 2 mg and ranibizumab 0.5 mg, respectively. Higher molar doses are expected to lead to longer presence of relevant drug levels in the eye. In addition, a low molecular weight and high concentration gradient between the vitreous and the retina may increase drug distribution to the target site of action, supporting effective control of anatomical disease activity and has therefore the potential to show superior outcomes.

Brolucizumab has been approved for treatment of nAMD by more than 70 health authorities globally, e.g. the Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Swissmedic. It was tested in two large phase 3 trials and found to be efficacious and safe when compared to aflibercept in patients with nAMD (HAWK and HARRIER). Brolucizumab demonstrated non-inferiority to aflibercept in mean change in best-corrected visual acuity (BCVA) from baseline to week 48 in both trials. Treatment of treatment-naive patients was started with three monthly brolucizumab injections (loading phase), followed by treatment every 12 weeks (q12w). If disease activity was identified during the study, patients were assigned to treatment every 8 weeks (q8w) and stayed on the q8w interval until the end of study. After one year of treatment, the primary endpoint was met with change of BCVA from baseline being non-inferior with more than 50 % of patients (56 % in HAWK, 51 % in HARRIER) were being maintained on a q12w dosing interval following the loading phase through week 48 in the brolucizumab arm vs. the aflibercept arm (fixed q8w treatment frequency). The visual acuity gains observed in the first year were maintained in the second

year. In addition, in these phase 3 trials brolucizumab demonstrated superior anatomical outcomes vs. aflibercept. Significantly fewer patients on brolucizumab had intraretinal fluid (IRF) and/or subretinal fluid (SRF) and brolucizumab achieved superior reductions in central subfield thickness (CSFT) versus aflibercept. These superior anatomic outcomes for brolucizumab were maintained in the second year. Brolucizumab safety was comparable to aflibercept, with the overall incidence of adverse events balanced across all treatment groups in both studies.

Since the first marketing authorization approval in October 2019 for the treatment of nAMD, adverse events of retinal vasculitis and/or retinal vascular occlusion, 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 and/or retinal vascular occlusion, taken together with accumulated data from HAWK, HARRIER and MERLIN, regarding the association of treatment-emergent immunogenicity and intraocular inflammation (IOI), indicate a causal link between the treatment-emergent immune reaction against brolucizumab and the brolucizumab-related retinal vasculitis (RV) and/or retinal vascular occlusion (RO), typically in the presence of IOI. This finding supports the requirement to discontinue treatment with brolucizumab in patients who develop events of RV and/or RO.

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

These impacts on the risk/benefit balance of the product are considered to be low and the overall risk/benefit assessment remains positive, when patients are dosed at q8w or longer after the loading phase and when patients who develop RV and/or RO are discontinued from further treatment with brolucizumab.

Current standard therapy regimens

Currently marketed anti-VEGF treatments typically start with a loading phase of 3 monthly doses, followed by maintenance dosing, either with fixed (e.g. every 4 or 8 weeks) or individualized treatment intervals, based on *pro re nata* (PRN) or Treat-and-Extend (T&E) concepts (Wykoff et al., 2018).

In ranibizumab and aflibercept trials, in both interventional (e.g. TREND (Silva et al., 2018), ALTAIR (Bayer Vital Gmbh, 2019) and real life studies (prospective non-interventional trials, e.g. OCEAN (Voegeler and Mueller, 2017), a number of patients still showed persistent fluid when extended to q6w or longer treatment intervals, although initial functional and anatomical response after the loading phase (three initial injections) was seen. The German Retina Society recommends that switching to another anti-VEGF drug may be considered if an inadequate morphological effect is observed after the initial three series or follow-up therapies. In several case series it was shown that after a change of the drug, a further visual stabilization could be achieved with a simultaneous reduction of the morphological lesion activity criteria (Retinologische Gesellschaft, 2014).

For these patients, a presumably more effective and longer lasting anti-VEGF agent like brolucizumab may lead to optimized fluid, and disease control i.e. sustained functional and anatomical response, respectively; which overall might result in improved patient care (e.g. less frequent visits, reduced treatment burden). Often the switch is initiated with a loading phase of three monthly doses, as described above for treatment naïve patients. However, a clear recommendation and scientific evidence is missing and it is unclear how to optimally initiate the change to brolucizumab treatment subsequent to an unsatisfactory anti-VEGF treatment response.

Summary

Ranibizumab, aflibercept and brolucizumab all inhibit the activity of VEGF-A and all have demonstrated efficacy in the treatment of patients with nAMD. However, under ranibizumab and aflibercept, a number of patients have still shown persistent fluid when extended to q6w or longer treatment intervals. Since brolucizumab showed superior anatomical outcomes and longer durability in HAWK & HARRIER, these findings support the evaluation of brolucizumab also in pretreated patients.

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of two different brolucizumab 6 mg treatment regimens for pretreated patients with suboptimal anatomically controlled nAMD. We aim to evaluate whether nAMD patients who showed an unsatisfactory response to previous anti-VEGF treatments (i.e. residual or recurrent fluid despite continuous anti-VEGF treatment), can immediately go to a q12w regimen when treatment is initiated with brolucizumab 6mg, or need loading with three monthly brolucizumab 6 mg injections. Our goal is to provide insights to support the medical practice and put the results of our descriptive analysis into context together with current and future literature on how to treat patients who had an unsatisfactory response to other anti-VEGF treatments.

2 Objectives and endpoints

As a consequence of Amendment 2, the assumed patient number necessary for analysis of the primary objective will not be achieved. Therefore, the primary endpoint and all analyses will now be performed in a purely descriptive manner.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the difference in brolucizumab 6 mg with one (initial) injection followed by q12w maintenance as compared to brolucizumab 6 mg with 3x q4w loading injections followed by q12w maintenance	• Mean change in BCVA from baseline to mean of visits at week 40 to week 52
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**

Objective(s)	Endpoint(s)
• To evaluate treatment interval prolongation compared to previous treatment	• Mean treatment interval (overall as well as per study group comparing treatment intervals from baseline to week 52 in the study vs. 24 weeks to baseline prior to enrollment) • Rate of patients (overall and per group) with prolonged interval compared to mean treatment interval in last 24 weeks prior to enrollment
• To estimate the proportions of patients maintained at q12w treatment frequency in the two brolucizumab groups	• Comparison of proportions of patients maintained at a q12w interval at week 52 between the two arms • Distributions of patients at q8w/q12w intervals from baseline to week 52
• To evaluate the functional outcomes comparing the two brolucizumab groups	• Average change in BCVA from baseline to week 52 • Proportions of patients with BCVA improvements of ≥5, ≥ 10, and ≥ 15 letters from baseline to week 52 • Proportions of patients with BCVA ≥ 69 letters at week 52 • Mean change in BCVA from baseline to mean of visits at week 16 to week 28
• To evaluate the anatomical outcomes comparing the two brolucizumab groups	• Change from baseline in CST as assessed by SD-OCT per visit up to week 52 • Absence of IRF, SRF, and sub-RPE fluid as assessed by SD-OCT per visit up to week 52 • Presence of active CNV leakage as assessed by fluorescein angiography at week 52
• To evaluate the safety and tolerability of brolucizumab	• Incidence of ocular and non-ocular AEs up to week 52

[redacted]

3 Study design

This study is a 52-week randomized, open-label, multi-center, two arm study for pretreated patients with suboptimal anatomically controlled nAMD. Patients who consent will be screened whether they meet all the inclusion and none of the exclusion criteria to evaluate eligibility. After confirmation of eligibility, patients will be randomized in a 1:1 ratio to one of the two treatment arms:

- Brolucizumab 6 mg **"loading arm"**: 3 x 4-weekly initial injections followed by an injection every 12 weeks;
- Brolucizumab 6 mg **"non-loading arm"**: one initial injection followed by an injection every 12 weeks

The initial plan was to screen approximately 598 adult patients (18 % screening failure rate expected) and randomize approximately 490 patients (245 per arm, 10 % drop-out rate expected) in a 1:1 ratio in approximately 65 centers. According to Amendment 2 for premature discontinuation of recruitment, the planned sample size will not be achieved, expecting a total of approximately 50 patients to be recruited by the time of approval of Amendment 2 (25 per arm, in approximately 33 centers).

The maximum study duration for one subject is 54 weeks, including the screening period and post-treatment follow-up.

There will be three periods in this study (see Figure 3-1 and Figure 6-2):

- Screening period: from day -14 to baseline
- Open-label treatment period: from baseline (day 1) to week 48
- Post-treatment follow-up period: from week 48 to week 52

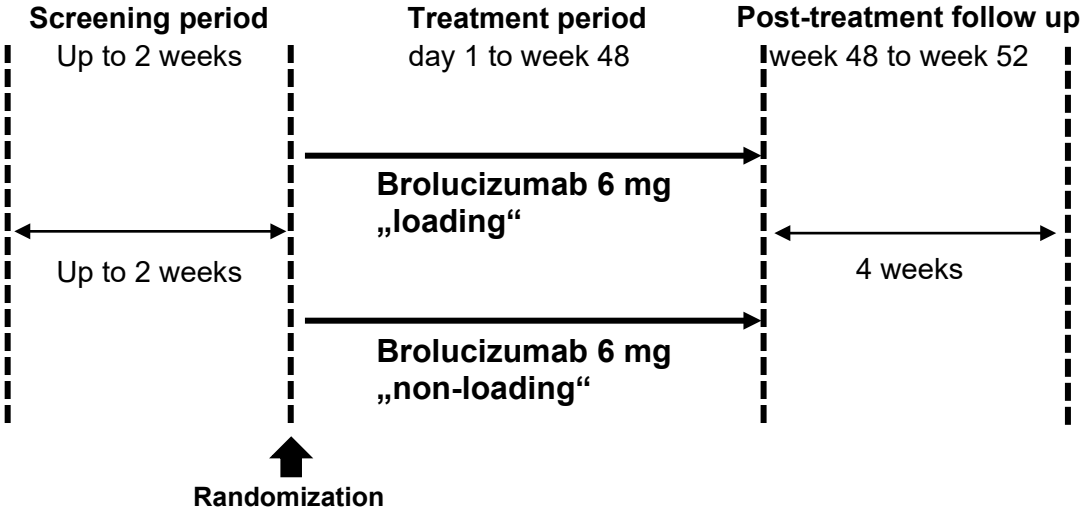

Figure 3-1 Study design

1. Screening period: Day -14 to day -1

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

One-time rescreening 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 rescreening is to occur beyond 14 days from the original screening visit date, then all screening procedures must be repeated. Medical judgment should be exercised to ensure that treatment of nAMD is not withheld in order for a patient to participate in the study.

2. Open-label treatment period: Day 1 to week 48

After confirmation of eligibility, patients will be randomized in a 1:1 ratio to one of the treatment arms.

Only one eye will be selected as study eye and treated with study medication.

The baseline visit is defined as day 1/visit 1, and end of treatment visit as visit 13 (week 48).

A study visit schedule will be established at the time of randomization for all patients with study visits scheduled every 4 weeks. All efforts should be made to adhere to this study visit schedule ±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 when the per-protocol assessments took place. In addition, for a given protocol visit, assessments can be performed in two consecutive days.

In the "loading arm", patients will receive three consecutive injections every 4 weeks at baseline, weeks 4 and 8, which should be at least 21 days apart, followed by an injection every 12 weeks. In the "non-loading arm", patients will receive one initial injection followed by an injection every 12 weeks. For both study arms: The assessment of disease activity will be performed 8 and 12 weeks after the previous injection. If disease activity is identified by the investigator for the first time at any visit after / from week 8 respectively, patients should stay on a q12w dosing, if the decline in BCVA is clinically non-significant (BCVA loss ≤ 4 ETDRS letters) compared to the previous visit. If after / from week 8, a BCVA-loss of ≥ 5 ETDRS letters appears compared to the previous visit or disease activity is identified for a second time based on the investigator's judgment of visual and/or anatomic outcomes and signs of disease activity, patients must be assigned to q8w dosing. One attempt of interval re-extension from q8w to q12w treatment will be allowed based on the investigator's judgement if no disease activity (DA) is detected during the subsequent visit(s). If the patient shows significant DA at any visit after the re-extension attempt, injection intervals will be fixed to q8w until the end of the study. The disease activity decision should be based on the BCVA loss criteria (BCVA loss ≤ 4 ETDRS letters and BCVA-loss of ≥ 5 ETDRS compared to the previous visit) and beyond that on investigator's judgement of visual and/or anatomic outcomes and signs of disease activity (e.g. IRF, SRF, hemorrhage, leakage, visual acuity loss over time etc.).

Patients who require injections more frequently than every 8 weeks after the loading phase (week 8, loading arm) or baseline (non-loading arm) will be discontinued from further study treatment.

3. Post-treatment follow-up period: Week 48 to week 52

For all patients, the last study assessment will be performed at week 52.

Patients withdrawn from the study prior to study completion will be asked to return for an early discontinuation visit (EOS / visit 14), four weeks (±7 days) following their last study visit (see Section 9).

4 Rationale

4.1 Rationale for study design

This study is designed as a randomized, open-label, multi-center, two-arm parallel study to assess the efficacy and safety of two different brolucizumab 6 mg regimen for pretreated patients with suboptimal anatomically controlled nAMD.

The primary efficacy endpoint based on BCVA was chosen to evaluate the benefits of treatment in terms of functional outcome. Non-inferiority testing was intended originally related to the primary efficacy parameter BCVA change from baseline. However, due to feasibility reasons, purely descriptive analyses will be performed. Historically, the change from baseline in BCVA at a selected time point is considered appropriate as the primary efficacy endpoint in confirmatory nAMD studies, based on the evidence available from existing anti-VEGF treatments in nAMD (e.g. ranibizumab, aflibercept). The BCVA assessment has its own variability and generally in the clinical practice a change of BCVA $\geq$ 5 letters would be considered as clinically relevant regardless of the underlying disease.

The BCVA will be evaluated as the mean change from baseline to mean of visits at week 40 to 52 due to the fact, that patients will receive injections at different intervals and timepoints. Patients in the loading arm on a q12w treatment interval may receive their last injection at week 44, whereas patient in the non-loading arm on a q12w treatment interval may receive their last injection at week 48. Shifting from q12w to a q8w treatment regime will also lead to differences in treatment schedule. A difference in the time since the last injection between both arms may affect BCVA gain and could introduce a bias on BCVA gain if measured at a single fixed assessment time point. Averaging change in BCVA from baseline at four time points 12 weeks apart will mitigate this potential bias.

4.2 Rationale for dose/regimen and duration of treatment

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

- Brolucizumab is well tolerated at a dose of 6 mg administered three times every four weeks during the loading phase based on the previous clinical phase 3 program in which 1088 subjects with nAMD received brolucizumab (RTH258-C001 - HAWK and RTH258-C002 - HARRIER). The nAMD study results regarding q12w/q8w maintenance dosing interval support stretching the interval between injections during the maintenance-phase to reduce the treatment burden (see Section 1.1).
- CRTH258AUS04 (MERLIN) is a two-year, multicenter, randomized, double masked, phase IIIa study evaluating brolucizumab 6 mg q4w versus aflibercept 2 mg q4w in patients with nAMD with persistent fluid. Review of the 52-week FIR led to an urgent safety communication based on an increased incidence of intraocular inflammation (IOI) and related adverse events including retinal vasculitis (RV), and retinal vascular occlusion (RO) in patients with q4w dosing with brolucizumab beyond the “loading phase”. IOI including RV, and RO were reported at a higher frequency in brolucizumab 6 mg q4w when compared to aflibercept 2 mg q4w (IOI: 9.3% vs. 4.5% of which RV: 0.8% vs. 0.0%, RO: 2.0% vs. 0.0%, respectively). Therefore, the protocol contains the note to discontinue subjects from study treatment who require treatment every 4 weeks.

- The route of administration is an intravitreal injection as for all anti-VEGF treatments currently approved for the treatment of nAMD.
- Study duration of 52 weeks allows for one initial injection followed by four complete 12-week intervals to evaluate effect of non-loading on long-term efficacy and safety.

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

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable. No formal interim analysis will be performed.

4.5 Risks and benefits

Ranibizumab and aflibercept (both approved inhibitors of VEGF-A) have consistently demonstrated efficacy in VEGF-driven retinal pathologies, including nAMD, with benefits outweighing the risks and are considered standard of care for treatment of nAMD patients.

In both phase 3 studies (HAWK and HARRIER) in nAMD, brolucizumab demonstrated non-inferiority to aflibercept in mean change in BCVA from baseline to week 48. These results were achieved while a majority of subjects on brolucizumab 6 mg – 56% in HAWK and 51% in HARRIER – were maintained on a q12w dosing interval following the loading phase through week 48, i.e. with a reduced treatment frequency compared to aflibercept. Brolucizumab safety was comparable to aflibercept, with the overall incidence of adverse events balanced across all treatment groups in both studies.

The lower probability of disease activity after the head-to-head comparison at week 16, the greater reduction in CSFT through week 48 and the lower proportion of patients with SRF and/or IRF at the majority of visits through week 48 for brolucizumab 6 mg versus aflibercept 2 mg in HAWK and HARRIER are anticipated to confer a longer duration of effect. This might translate into greater durability and longer injection intervals for brolucizumab 6 mg, with non-inferior efficacy. The potential superior anatomical results and a reduced treatment and monitoring visit frequency will provide benefit to subjects and caregivers/physicians. Further details of the known and potential risks and benefits associated with brolucizumab are presented in the Investigator's Brochure (IB).

Since until now only treatment-naive patients have been investigated with brolucizumab 6.0 mg treatment, this study will give insights on treatment response in pretreated patients. With the presumed longer lasting efficacy of brolucizumab the treatment burden also for pretreated patients might be reduced.

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring described in Section 6.7.2, Section 8.4.3 and Section 10.

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. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Intravitreal injections, including those with brolucizumab, have been associated with endophthalmitis and retinal detachments. Acute intraocular pressure (IOP) increases have also been reported.

Intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion may occur following the first intravitreal injection with brolucizumab and at any time of treatment. These events were observed more frequently early on during treatment.

[redacted]

Patients with a medical history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with brolucizumab are at risk of developing retinal vasculitis and/or retinal vascular occlusion and should be closely monitored.

In patients developing intraocular inflammation (IOI), including retinal vasculitis and/or retinal vascular occlusion, treatment with brolucizumab in the FALCON study should be discontinued and the events should be promptly managed.

In addition, based on USM (CRTH258AUS04 FIR), the brolucizumab dosing interval should not be less than 8 weeks beyond the loading period.

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). A higher incidence was also observed in Japanese patients.

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 profile for brolucizumab remains positive.

5 Population

The study population will be male and female patients ≥50 years old diagnosed with active choroidal neovascularization (CNV) secondary to AMD, treated previously for this disease and able to comply with study or follow-up procedures.

If both eyes are eligible as per the inclusion and exclusion criteria described below, the eye with the worse visual acuity should be selected for study eye, unless the investigator deems it more appropriate to select the eye with better visual acuity, based on medical reasons or local ethical requirements.

5.1 Inclusion criteria

The investigator will assess the eligibility of the patient and the study eye at the screening visit and confirm eligibility prior to randomization. Before enrollment, morphological eligibility must be confirmed by the central reading center as part of the screening period. Subjects 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.

Study eye:

3. Active choroidal neovascularization (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 and sequelae of CNV, e.g. pigment epithelial detachment (PED), subretinal or sub-retinal pigment epithelium (sub-RPE) hemorrhage, blocked fluorescence, macular edema (intraretinal fluid (IRF) and/or subretinal fluid (SRF) and/or sub-retinal pigment epithelium (sub-RPE) fluid that affects the central subfield, as seen by SD-OCT) at screening as confirmed by central reading center. If active CNV according to the above explained activity criteria is not detectable in screening image data (no IRF and no SRF), presence of residual and/or recurrent fluid (IRF and / or SRF) within the last 6 months before baseline visit is also considered eligible. In this case, historical images must be submitted for analysis by the central reading center.
4. Pretreatment with any anti-VEGF drug for a maximum of five years (60 months). Patients should have shown functional and/or anatomical treatment response to the pretreatment(s), prior to participating in this study.
5. The treatment initiation phase with the current anti-VEGF must have been completed for at least 6 months with continuous treatment in a ≥ q4w to ≤ q12w injection interval (±2-day window, i.e., 26 to 86 days inclusive) before the baseline visit. At least 4 weeks (minimum 26 days) must have passed between the last anti-VEGF pretreatment and baseline.
6. BCVA score must be ≤ 83 and ≥ 38 letters at 4 meters starting distance using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity charts (approximately Snellen equivalent of 20/25 and 20/200), at both screening and baseline.

5.2 Exclusion criteria

Subjects 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 could, in the opinion of the investigator, prevent response to study treatment or may confound interpretation of study results, compromise visual acuity or require planned medical or surgical intervention during the 52-week study period (e.g. structural damage of the fovea, vitreous hemorrhage, retinal vein occlusion, retinal detachment, macular hole, choroidal neovascularization unrelated to age-related macular degeneration, diabetic retinopathy (except mild non-proliferative) and diabetic macular edema).

2. Any active intraocular or periocular infection or active intraocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis, uveitis) 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 confirmed by central reading center.
6. The total area of fibrosis or subretinal blood affecting the foveal center point comprising ≥ 50% of the lesion area as well as chronic cystic lesions in the study eye as confirmed by central reading center.
7. Structural damage within 0.5 disc diameter of the center of the macula in the study eye, e.g. vitreomacular traction, epiretinal membrane, scar, laser burn, at the time of screening that in the investigator's opinion could preclude visual function improvement with treatment.

Ocular treatments:

8. Treatment with any anti-VEGF drug for > 5 years in the study eye.
9. Pretreatment with brolucizumab at any time in the study eye.
10. Previous treatment with investigational drugs in the last 6 months in the study eye.
11. Previous use of intraocular or periocular steroids (non-topical) in study eye.
12. Macular laser photocoagulation (focal/grid) or photodynamic therapy in the study eye at any time prior to baseline and peripheral laser photocoagulation in the study eye within 3 months prior to baseline.
13. Intraocular surgery in the study eye within 3 months prior to baseline.
14. Vitreoretinal surgery in the study eye at any time prior to baseline.
15. Aphakia with the absence of posterior capsule in the study eye.

Systemic conditions or treatments:

16. Stroke or myocardial infarction during the 6-month period prior to baseline.
17. End stage renal disease requiring dialysis or renal transplant.
18. 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).
19. Systemic anti-VEGF therapy during the 3-month period prior to baseline.

20. 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 Coronavirus SARS-CoV-2 (COVID-19) treatment.
21. 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.
22. 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.
23. History of a medical condition (e.g. metabolic dysfunction disease with exception of controlled 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.

Other:

24. Patients on an investigational drug, biologic, or participated in a device study shorter than 5 half lives of the respective investigational drug, or < 30 days, or until the expected pharmacological effect has returned to baseline, whichever is longer.
25. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) pregnancy test.
26. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during the study drug administration and for 3 months after stopping the investigational medication. Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. 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 screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), 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.

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 ago. 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.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational drug

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Brolucizumab / RTH258 120mg/ml	Solution for injection	Intravitreal use	pre-filled syringe	local

The investigational treatment used in this study is brolucizumab 6 mg/0.05 mL. Brolucizumab is formulated as a sterile solution aseptically filled in a sterile syringe for single use containing sufficient brolucizumab to deliver a 6 mg dose when administering a volume of 0.05 mL. The content of the study drug pre-filled syringe must **not** be split. Brolucizumab will be packed according to local legal requirements.

The storage conditions will be described on the package and follow the current recommendations of the manufacturer. Study medication should not be stored together with commercial brolucizumab to avoid mix up.

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

6.1.2 Additional study treatments

No other treatment beyond investigational drug are included in this trial.

6.1.3 Treatment arms/group

Eligible subjects will be randomly assigned at Baseline to one of the following two treatment arms in a 1:1 ratio:

- Brolucizumab 6 mg **"loading arm"**: 3 x 4-weekly initial injections followed by an injection every 12 weeks (q12w maintenance)
- Brolucizumab 6 mg **"non-loading arm"**: one initial injection followed by an injection every 12 weeks (q12w maintenance)

6.1.4 Treatment duration

The planned duration of treatment is maximum 48 weeks and determined by the treatment arm and q12w/q8w maintenance, respectively. Discontinuation of study treatment for a subject occurs when study drug is stopped earlier than the protocol planned duration and can be initiated by either the subject or the investigator.

Study treatment will also be discontinued for patients who require injections more frequently than every 8 weeks after the loading phase (week 8, loading arm) or baseline (non-loading arm).

In patients developing intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion, treatment with brolucizumab in the FALCON study should be discontinued and the events should be promptly managed.

Subjects who prematurely discontinue study treatment for any reason except for withdrawal of consent should continue in the study and carry out the scheduled visits and assessments, at the discretion of the subject and investigator.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator must instruct the subject to notify the study site about any new medications the subject takes after signing the study informed consent. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded in the appropriate Case Report Forms.

Each concomitant drug/procedure must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the sponsor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact the sponsor to determine if the subject should continue to take study treatment or should discontinue study treatment but still continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Fellow eye

During the study, standard of care or other treatments according to the investigator's practice for nAMD and other diseases in the fellow eye are permitted at any time and must be recorded in the appropriate eCRF page. Treatment of the fellow eye must be scheduled in a way 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.

Study eye

Administration of topical ocular corticosteroids in the study eye is allowed during the study. Corticosteroids administered via intra-nasal, inhaled, intra-articular or non-extensive dermal route (< 20% total body surface area) are also permitted during the study. For other routes of corticosteroid administration, refer to Section 6.2.2.If cataract surgery is necessary and cannot be postponed until end of study, 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 perfomed ≥ 7 days prior to the scheduled study visit.

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

6.2.2 Prohibited medication

Use of the treatments displayed in the below table (Table 6-2) are not allowed after screening.

Table 6-2 Prohibited medications and procedures

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

Standard of care or other treatments according to the investigator's practice for nAMD and other diseases in the fellow eye are permitted at any time and must be recorded in the appropriate eCRF page.

6.2.3 Rescue medication

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

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

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No., three digits), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No., four digits) (as assigned by the sponsor to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available in the electronic data capture (EDC) system.

Once assigned to a patient, the patient number will not be reused for another patient. Subjects who have been screen failures but are rescreened (see Section 8.1) will be assigned a new Subject No. if rescreening occurs beyond 14 days from the original screening date.

If the patient fails to be randomized for any reason, the reason for not being randomized will be entered on the Screening Log, and the Demography eCRF should be completed.

6.3.2 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of the sponsor using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. Randomization codes will be assigned by the eCRF. The randomization codes should be requested only after receiving the positive feedback from the reading center (via the eCRF) and central lab (female patients, if applicable) that the patient in screening is eligible to be included in the study as described in Figure 6-1.

Randomization codes and data about all study drug injected to the patient's eye will be tracked in the eCRF.

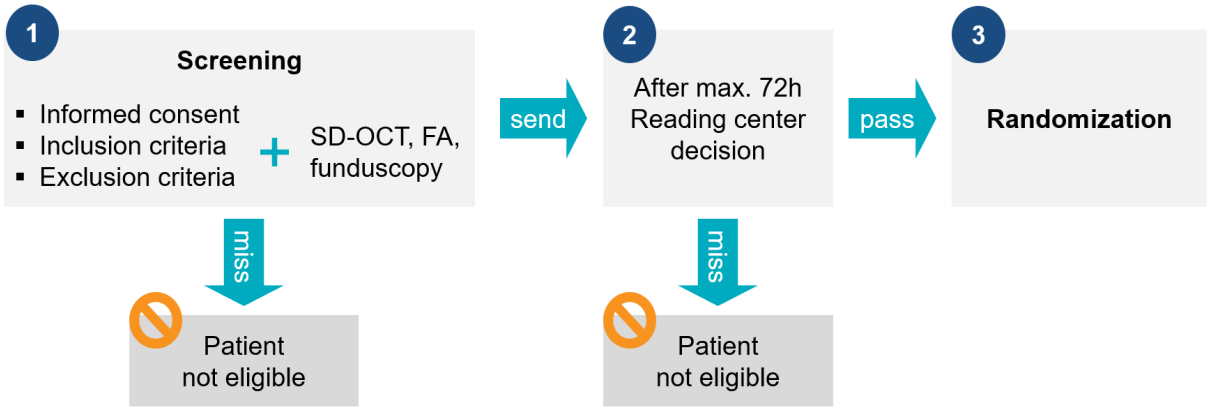

Figure 6-1 Screening and randomization procedure

6.4 Treatment blinding

Treatment will be open to subjects, investigator staff, persons performing the assessments, and the clinical trial team (CTT). The central reading center (CRC) will be blind to the identity of the treatment from the time of randomization until database lock.

6.5 Dose escalation and dose modification

No study treatment dose modification is allowed.

Deviations from 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

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

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

6.7 Preparation and dispensation

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

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, all study treatment must be stored according to the instructions specified on the labels and in the IB. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment.

The study personnel 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 the 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 study personnel will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.2 Instruction for prescribing and taking study treatment

There will be two different treatment regimens (see Figure 6-2) for IVT injections with different timing for brolucizumab "loading" and "non-loading" treatment arms:

- **Brolucizumab 6 mg "loading**": Treatment with brolucizumab will be initiated with three loading injections every 4 weeks for three consecutive injections (baseline, weeks 4 and 8). From week 8 onwards, patients will be scheduled to receive one injection of brolucizumab 6 mg every 12 weeks.
- **Brolucizumab 6 mg "non-loading":** Treatment with brolucizumab will be initiated with one single injection (baseline). From baseline onwards, patients will be scheduled to receive one injection of brolucizumab 6 mg every 12 weeks.

For both study arms:

- The assessment of disease activity will be performed 8 and 12 weeks after the previous injection.
- If disease activity is identified by the investigator for the first time at any visit after / from week 8 respectively, patients should stay on a q12w dosing, if the decline in BCVA is clinically non-significant (BCVA loss ≤ 4 ETDRS letters) compared to the previous visit.
- If after / from week 8, a BCVA-loss of ≥ 5 ETDRS letters appears compared to the previous visit or disease activity is identified for a second time based on the investigator's judgement of visual and/or anatomic outcomes and signs of disease activity*, patients must be assigned to q8w dosing.
- One attempt of re-extension to q12w will be allowed based on the investigator's judgement if no disease activity (DA) is detected during the subsequent visit(s).
- If the patient shows significant DA after the re-extension attempt, injection intervals will be fixed to q8w until the end of the study

- *The disease activity decision should be based on the BCVA loss criterium (BCVA loss ≥ 5 ETDRS letters or ≤ 4 ETDRS letters compared to the previous visit) and beyond that on investigator's judgment of visual and/or anatomic outcomes and signs of disease activity (e.g. IRF, SRF, hemorrhage, leakage, visual acuity loss over time etc.).

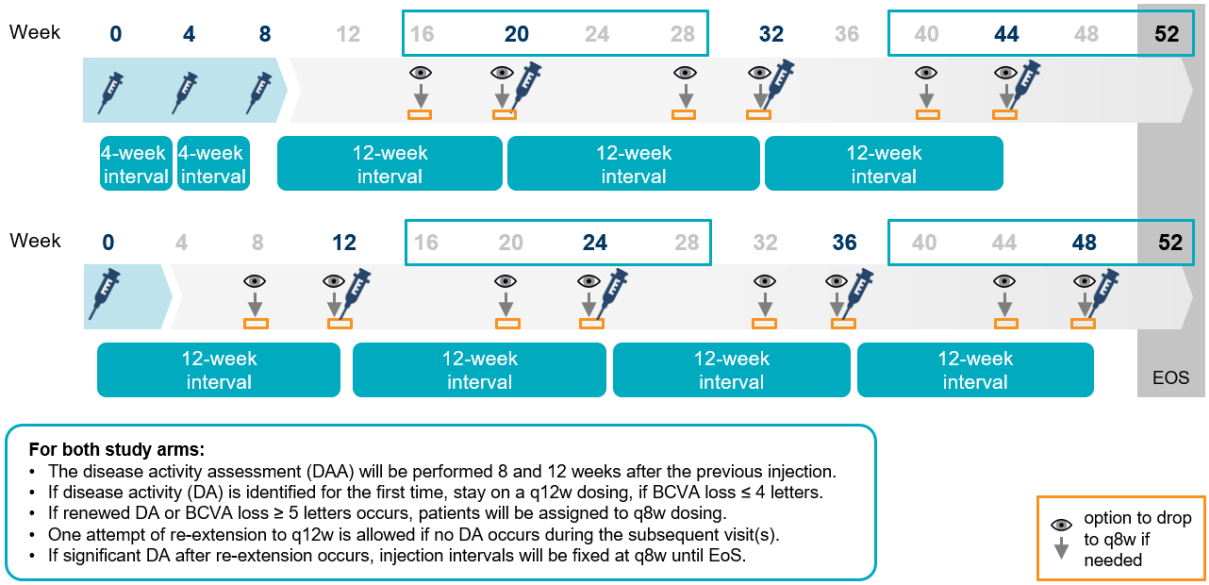

Figure 6-2 Treatment regimen

Evaluation of Disease Activity (DA):

The concept of the brolucizumab q12w/q8w regimen is to allocate patients according to their individual treatment needs to either a q12w or a q8w treatment schedule. The initial schedule is q12w and a patient will remain on q12w as long as the investigator does not identify nAMD disease activity which in his opinion requires more frequent anti-VEGF treatment (BCVA-loss of ≥ 5 ETDRS letters compared to the previous visit or disease activity is identified for a second time based on the investigator's judgement of visual and/or anatomic outcomes).

In case of BCVA-loss of ≥ 5 ETDRS letters compared to the previous visit, the patient must be switched to a q8w regimen. Beyond the BCVA loss criteria, the assessment of the DA is at the discretion of the investigator and should be made based on changes in vision and anatomical parameters (e.g. IRF, SRF, hemorrhage, leakage, vision loss over time etc.) with reference to the patients' disease status. Figure 6-3 shows three examples for regimen adjustments for the loading arm (examples 1-3) and non-loading arm (examples 4-6), respectively.

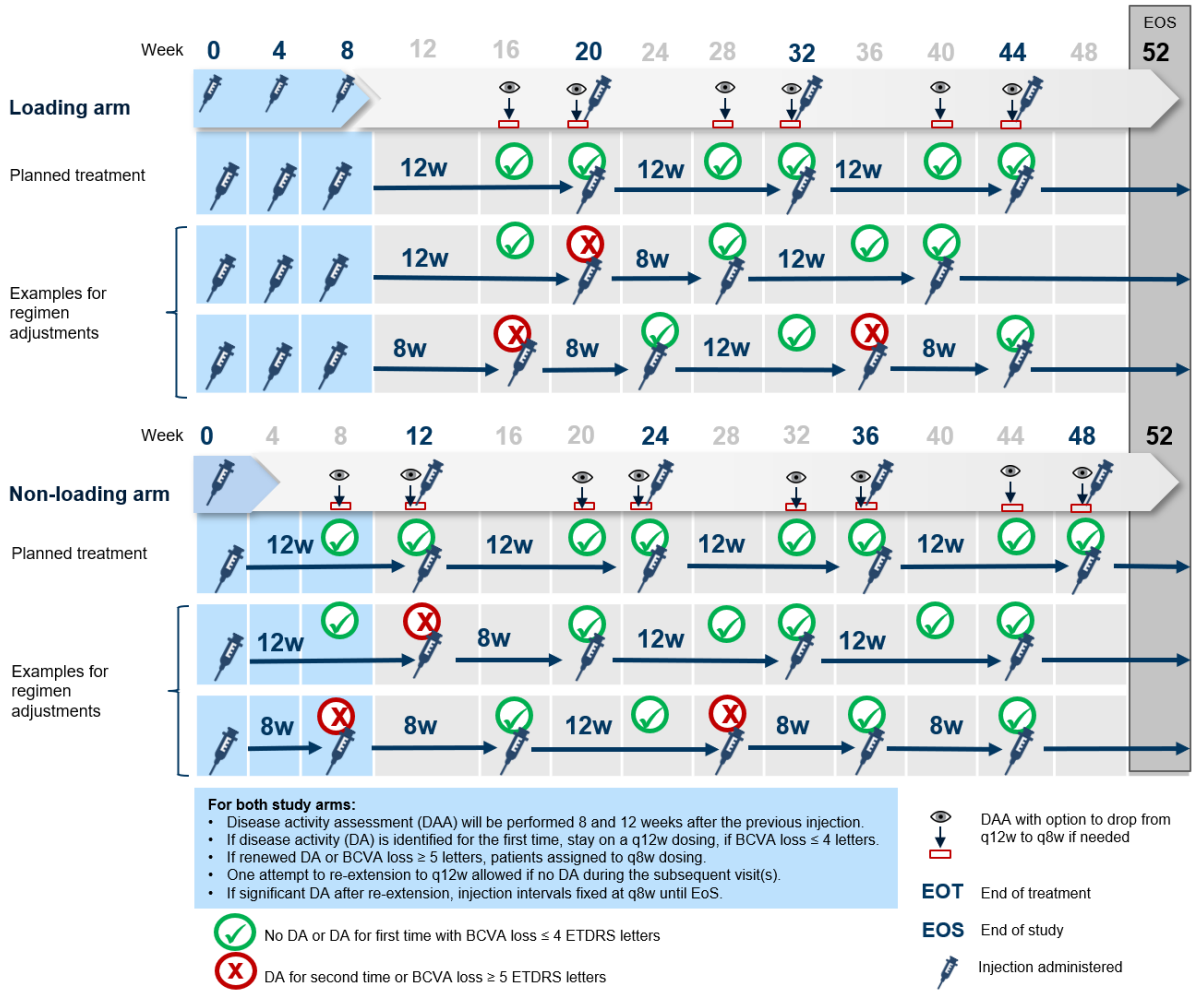

Figure 6-3 Examples for treatment regimen adjustments

Brolucizumab should be administered in the study eye on the day of the study visit or, if this is not possible, within 3 days after the occurrence of the study visit or no later than within the visit window (±7 days) as described in Section 3 and Section 8. Every effort should be made to ensure that the subject adheres to the visit/treatment schedule.

When assessments and treatments take place on the same day, treatment must occur after completion of the efficacy assessments described in Section 8.3 and pre-injection safety measures (tonometry, slit lamp and fundus examinations) described in Section 8.4.3. If study visit assessments and the corresponding treatment occur on separate days, a repeat safety checkup 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.

Brolucizumab administration

The IVT injection procedure for brolucizumab including aseptic and antimicrobial requirements, will be performed according to local clinical practice. IVT injection is contraindicated in

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

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

In patients developing intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion, treatment with brolucizumab in the FALCON study should be discontinued and the events should be promptly managed.

7 Informed consent procedures

Eligible subjects may only be included in the study after signing Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved informed consent.

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

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

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

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 for the duration of the study and for 3 months after stopping the investigational medication.

If there is any question that the patient will not reliably comply, they must not be entered in the study.

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

During the COVID-19 pandemic that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial

participant and person obtaining informed consent, etc.). Remote informed consent should be appropriately documented and confirmed by way of standard informed consent procedures at the earliest opportunity when the subject will be back at the trial sites.

8 Visit schedule and assessments

The assessment schedule (Table 8-1) lists all the assessments when they are performed (indicated with an "X"). All data obtained from these assessments must be supported in the subject's source documentation. All data must be entered in the eCRF in a timely manner (see Section 11.1).

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1). All post-baseline and/or subsequent scheduled visits will be calculated based on the day 1 visit date. From baseline on, patients will visit the site every 4 weeks. From baseline (non-loading arm) or week 8 (loading arm) to week 52, the treatment intervals will be set to q12w / q8w 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/day1 and the week 52 visit (± 21-day visit window), should the subject be unable to return per scheduled visit. For a given protocol visit, assessments can be performed on two consecutive days in which both days must occur 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 took place. 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. Subjects 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. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

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

Visit Name	Screening	Baseline	Treatment Period (w)													Comment
Visit Number	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14 / EOS	
Week (w) / Day (d)	-2w to -1d	Day 1	4	8	12	16	20	24	28	32	36	40	44	48	52	
Informed Consent	X															[redacted]
Inclusion/Exclusion Criteria	X	X														
Demography	X															
Medical history/ current medical conditions / nAMD history	X															b = bilateral
Randomization		X														
Injection RTH258 – 1 initial injection in non-loading arm[1]		X			X			X			X			X		* = assessment of disease activity will be performed 8 and 12 weeks after the previous injection
Injection RTH258 – 3 initial injections in loading arm[1]		X	X	X			X			X			X			1 = if disease activity is identified by the investigator for the first time, patients will stay on a q12w dosing, if the decline in BCVA is clinically non-significant (BCVA loss ≤ 4 ETDRS letters). If renewed disease activity is identified or BCVA-loss of ≥ 5 ETDRS letters appears, patients will be assigned to q8w dosing. One attempt to re-extension to q12w will be allowed based on the investigator's judgement if no disease activity is detected during the subsequent visit(s). If the patient shows significant DA after the re-extension attempt, injection intervals will be fixed at q8w until the end of the study (see Section 6.7.2)
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum β-hCG Pregnancy Test	X															
Urine Pregnancy Test		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Best-Corrected Visual Acuity	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	
Intraocular pressure (IOP)	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	
Ophthalmic Exam[2]	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	
SD-OCT[2]	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	
[redacted]																
Color Fundus Photography[2]	X[b]														X[b]	
Fluorescein Angiography[2]	X[b]														X[b]	
Disease Activity Assessment				X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	
[redacted]																

Visit Name	Screening	Baseline	Treatment Period (w)													Comment
Visit Number	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14 / EOS	
Week (w) / Day (d)	-2w to -1d	Day 1	4	8	12	16	20	24	28	32	36	40	44	48	52	
[redacted]																2 = additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion
																[redacted]

8.1 Screening

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

For the purpose of screening, fluorescein angiography (FA) images from a previous **routine** evaluation may be used as long as FA was performed within 7 days of the screening visit using CRC-certified equipment and technician/investigator.

One-time rescreening 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 rescreening is to occur beyond 14 days from the original screening visit date, then the subject must be reconsented and all screening procedures must be repeated. Medical judgment should be exercised to ensure that treatment of nAMD is not withheld in order for a patient to participate in the study.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible prior to randomization 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 pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see Section 10.1.3 for reporting details). SAE data, informed consent, and inclusion/exclusion data are recorded on the eCRF. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

Subjects who are randomized and fail to start treatment, e.g. subjects randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Subject demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

The following information will be collected/documented at screening/baseline visit for each randomized subject:

- Year of birth/ age
- Gender
- Race
- Vital signs
- Study eye
- Visual acuity
- Choroidal neovascularization characteristics

- Intraocular pressure
- Ophthalmic examinations
- Retinal imaging
- Laboratory test results (pregnancy test)
- Prior/concomitant medications; anti-VEGF pretreatment (24 weeks to baseline prior to enrollment)
- Medical history (including possible underlying inflammation and autoimmune disease), nAMD history and current medication conditions

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

8.3 Efficacy

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

- Best-corrected visual acuity with ETDRS-like charts at 4 meters
- Anatomical retinal evaluation of SD-OCT images
- Color Fundus Photography and vascular leakage evaluation by Fluorescein angiography

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

8.3.1 Visual acuity

Visual acuity will be assessed in the study eye at every study visit and in the fellow eye at the screening and week 52/EOS visits using best correction determined from protocol refraction (BCVA). 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 details of the refraction technique and VA testing, as well as training materials, are provided in the applicable manual. Certification of the assessment procedures and assessors will occur prior to any evaluation of study patients.

8.3.2 SD-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 the screening and week 52 / EOS visits. The central reading center (CRC) will check screening images (SD-OCT, FP, FA) for eligibility of patients within 72 hours of image upload. Only after patients are deemed eligible by the CRC, they may be randomized if all other in/exclusion criteria are met.

SD-OCT assessments will be performed by trained technician or investigator at the sites and should be performed **after** BCVA assessment and **prior** to any study drug administration. The investigator will evaluate the SD-OCT images to assess the status of disease activity. The SD-OCT machine used for an individual patient should not change for the duration of the study.

[redacted]

The images will be reviewed by a CRC to ensure a standardized evaluation. For further procedural details the investigator should refer to the applicable manual provided by the CRC.

8.3.3 Color fundus photography and fluorescein angiography

Color fundus photography (CFP) and fluorescein angiography (FA) will be performed in both eyes at the screening and week 52/EOS visits. CFP and FA may be performed at other visits at the investigator's discretion. For the purpose of screening, FA images from a previous routine evaluation may be used as long as FA was performed within 7 days of the screening visit using CRC-certified equipment and technician/investigator. In case of premature discontinuation from the study, there is no need to repeat the CFP and FA if there was a CFP and FA performed within the previous 12 weeks, except if there is significant disease worsening, in the opinion of the investigator.

These assessments will be performed by trained personnel at the sites. The images will be reviewed by a CRC to ensure a standardized evaluation. For further procedural details the investigator should refer to the applicable manual provided by the CRC.

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

8.3.4 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 and are required for a comparative evaluation of this trial with the existing evidence from previous trials.

Color fundus photography (CFP) is used to inspect retinal pathology.

Fluorescein angiography (FA) is also an established procedure that helps to classify the type of lesion and is used to assess vascular leakage.

8.4 Safety

Safety assessments will include vital signs, ophthalmic examinations and imaging, and laboratory evaluation (pregnancy testing) as wells as monitoring and recording type, frequency, and severity for all AEs.

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 participants to visit the site again.

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

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

Table 8-2 Assessments & Specifications

Assessment	Specification
Vital signs	Vital signs include assessment of blood pressure (systolic and diastolic pressure in mmHg, sitting position) and pulse (beats per minute) and will be collected at all visits. In case there is an elevated blood pressure measurement as specified in the exclusion criteria, at the screening and baseline visits, the blood pressure measurement should be repeated after 20 minutes. If the repeat measurement is elevated as specified in the exclusion criteria, then the subject is not eligible to be enrolled into the study. On days when study drug is administered, vital signs will be measured **before** administration of study medication. The results will be recorded in the eCRF.
Height and weight	Height in centimeters (cm) and body weight (to the nearest kilogram (kg), in indoor clothing but without shoes) will be measured at screening only. The results will be recorded in the eCRF.

8.4.1 Laboratory evaluations

No specific mandatory laboratory evaluations for safety assessment will be performed except serum pregnancy testing (see Section 8.4.2 for details). Details on the collection, shipment of the samples for pregnancy testing and reporting of the results by the central laboratory are provided to investigators in the laboratory manual.

If the COVID-19 pandemic limits or prevents on-site study visits, the collection of samples may be modified by Novartis if applicable and if modified, will be communicated to the Investigator.

Table 8-3 Laboratory assessments

Test Category	Test Name
Pregnancy test	Serum pregnancy test will be performed at screening, Urine pregnancy test will be performed at all other visits (Section 8.4.2)

8.4.2 Pregnancy and assessments of fertility

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 is required for women of child-bearing potential during the study drug administration and for 3 months after stopping the investigational medication.

A **serum** pregnancy test will be conducted for all women of child-bearing potential to assess pregnancy before inclusion into the study at the screening visit. If the serum pregnancy test is inconclusive, the leftover sample will be used to conduct a FSH (Follicle Stimulating Hormone) test to confirm the child-bearing potential.

During the study, **urine** pregnancy testing will be performed at visits when serum pregnancy testing will not be conducted. If a urine test is positive after inclusion in the study, a serum pregnancy test must be performed for confirmation; if the serum test is positive, the subject must discontinue study treatment with brolucizumab. Results of all pregnancy testing must be available as source documentation.

8.4.3 Ophthalmic examination and imaging

The ophthalmic exam will consist of the following:

- **Intraocular pressure** will be assessed in the study eye, pre-dose and post-dose and at every scheduled visit. The same method of tonometry has to be used through the whole study. In the fellow eye IOP will be assessed at screening and week 52 / EOS visits. The values recorded in mmHg for either eye will be entered into the eCRF. Treatment and close monitoring of IOP should be performed by the investigator for any non-transient elevation in intraocular pressure ($\geq$ 25 mmHg). Intravitreal injection is not recommended unless normalization of the IOP has been achieved. Post-dose IOP should be assessed within 60 minutes after injection and if $\geq$ 25 mmHg, assessment should be repeated until back to normal. Monitoring of 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, and if the findings constitute an AE, it should be recorded in the eCRF.
- **Anterior biomicroscopy (slit lamp examination)** will be completed at every (scheduled and unscheduled) visit to examine the anterior segment structures (e.g., eyelids/lashes, conjunctiva, cornea, anterior chamber, iris, lens and anterior part of the vitreous) of the study eye (fellow eye will be examined at screening and on discretion of the investigator). The outcome of the examination will be recorded in the source documents. Slit lamp examination must be carefully performed before each study treatment. If there are any signs of intraocular inflammation (IOI), severity of anterior chamber cells and flare should be assessed according to the standardization uveitis nomenclature (SUN) working group grading system (Jabs et al., 2005). The test results will be recorded in the source documents (e.g., ophthalmic examination tool) and captured in the appropriate eCRF as applicable.
- **Posterior segment (indirect fundus) examination** will be conducted by the investigator at the screening visit for both eyes. An examination of the peripheral retina must also be conducted to ensure that the intravitreal injection can safely be performed. Posterior segment examination must be performed carefully after pupil dilation before each study treatment. The results of the examination including any abnormalities (e.g. vitreous cells/haze, retinal tear/detachment, hemorrhage and vascular occlusion, vasculitis, etc.) should be recorded in the source documents. If there are any signs of IOI, vitreous cells and haze should be assessed using National Institutes of Health (NIH) grading system (Nussenblatt et al., 1985). The outcome of the examination will be documented in the source document (e.g., ophthalmic examination tool) and appropriate eCRF page as applicable.

Pupil dilation for slit lamp examination and indirect ophthalmoscopy is recommended.

Clinically significant abnormalities of either eye will be recorded on the medical/ocular history page before baseline and on the adverse event page of the eCRF for any findings identified after baseline.

Instruct the patient to contact the site for any changes in vision or any symptoms of inflammation between scheduled visits. Every effort should be made to bring the subject for immediate examination.

Imaging: When intraocular inflammation, retinal vasculitis, and/or retinal artery occlusion (RAO) is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and will conduct OCT, fluorescein angiography and color fundus photography (preferably wide-field or with peripheral sweeps). These additional assessments will be documented in the source and appropriate eCRF pages as applicable. The images are requested to be uploaded onto the CRC portal. In patients developing intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion, treatment with brolucizumab in the FALCON study should be discontinued and the events should be promptly managed.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

If there are any signs of IOI, additional assessment will be performed as described in Section 8.4.3.

9 Study discontinuation and completion

9.1 Discontinuation

The investigator should discontinue study treatment for a given subject and/or withdraw the subject from the study if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

A subject will be considered to have completed the study when the subject has completed the last visit planned in the protocol.

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

9.1.1 Discontinuation of study treatment

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

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

Study treatment must be discontinued under the following circumstances:

- Subject decision
- Pregnancy (see Section 8.4.2 and Section 10.1.4)
- Use of prohibited treatment (see Section 6.2.2)
- Any situation in which continuation with study treatment might result in a safety risk to the subject
- Unsatisfactory therapeutic effect, e.g. a subject requires injections more frequently than every 8 weeks after the loading phase (week 8, loading arm) or baseline (non-loading arm).
- Subjects develop intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information on the appropriate eCRF page.

Subjects 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 stability assessment, administration of study treatment, post-injection assessment and adherence to prohibited medication list) until EOS. These patients can be switched to standard of care anti-VEGF IVT as per investigator's discretion. Any IVT injection is contraindicated in subjects with active intraocular or periocular infections and in subjects with active intraocular inflammation; therefore, the investigators must verify that these conditions are not present in the study eye prior to every injection.

Subjects 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, subjects should return for the EOS visit assessments to be performed as scheduled** in Table 8-1.

If a subject fails to return for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed (see Section 9.1.3).

If the subject cannot or is unwilling to return at any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After premature 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
- BCVA

9.1.1.1 Replacement policy

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

9.1.2 Withdrawal of informed consent

Withdrawal of consent/opposition to use data/biological samples occurs 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 their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their 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).

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

9.1.3 Lost to follow-up

For subjects 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 subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 Early study termination by the sponsor

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

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

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests. The sponsor (as applicable by local law) will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

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

After study completion the subject 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

Subjects should be closely monitored for adverse events.

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

- Instruct the patient to contact the site immediately for any changes in vision or any symptoms of inflammation independently of scheduled visits (refer to the optional patient brochure). Every effort should be made to bring the subject for immediate (< 12 hours) examination including on weekends and public holidays.
- Close patient monitoring and thorough examination of the eye should be done to detect potential signs of inflammation (Section 8.4.3).
- Patients with a medical history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with brolucizumab are at risk of developing retinal vasculitis and/or retinal vascular occlusion and should be closely monitored.
- When IOI, retinal vasculitis, and/or retinal vascular occlusion is present or suspected during any visit, investigators must perform thorough dilated pupil ophthalmic examination, and will conduct OCT, fluorescein angiography and color fundus photography (preferably wide-field or with peripheral sweeps). The images are requested to be uploaded onto the CRC portal.

- If any signs of intraocular inflammation are present, an IVT injection must not be performed. Therefore, investigators must verify that these conditions are not present in the study eye prior to every injection.
- In patients developing intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion, treatment with brolucizumab in the FALCON study should be discontinued and the events should be promptly managed.

For additional information related to safety assessments refer to Section 6.7.2 and Section 8.4.3.

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 (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject 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 subject 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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, or other assessments.

Adverse events must be recorded in the appropriate eCRF capturing AEs 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):

a) the severity AE 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

b) 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 treatment arms, not on a single subject

c) its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported

d) whether it constitutes a serious adverse event (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met

e) action taken with the 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
- patient hospitalized/patient's hospitalization prolonged (see Section 10.1.2 for definition of SAE)

f) its outcome:

- not recovered / not resolved;
- recovered / resolved;
- recovering / resolving
- resolved / resolved with sequelae;
- fatal or unknown

g) localization (study eye, fellow eye, systemic)

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

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

Adverse event monitoring should be continued until 30 days (safety follow-up) after the last administration of study treatment (EOT).

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.

Abnormal laboratory values or 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 abnormal laboratory values or 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 subjects with the underlying disease. Investigators have the responsibility for managing the safety of individual subjects and identifying adverse events.

10.1.2 Serious adverse events

An 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 subject 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 subject'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 subject 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 subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

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

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

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

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until the last study visit or 60 days after the last administration

of study treatment whichever is later must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Following this study period, SAEs considered by the investigator to be causal related to study treatment should be reported to Novartis safety. 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 immediately, without undue delay, but under no circumstances later than 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 Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis Patient Safety 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.

10.1.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy 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 Patient Safety. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment with any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

Misuse/ abuse of the study drug by the patient is not applicable to this study as IVT injection is performed by the investigator.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record in the eCRF and in the Dispensing Log at the study site,

irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

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

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes (date 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 (eCRF). 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 subject 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 personnel (or designated CRO) will review the data entered by investigative staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the 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 will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse

events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of the sponsor using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. Randomization codes will be assigned by the eCRF. Randomization codes and data about all study drug dispensed to the patient will be tracked in the eCRFs.

The occurrence of relevant protocol deviations will be determined. Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

Laboratory samples and images (Color fundus photographs, fluorescein angiograms, and SD-OCT images) will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

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. eCRF) 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 subject 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 subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, retinal images (CFP, FA, SD-OCT), and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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 CRFs are performed according to the

study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The primary safety and efficacy analysis will be conducted on all subject data at the time the trial ends. This analysis will be performed once all patients completed their final visits or terminated the study prematurely.

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

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

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

12.1 Analysis sets

The **Randomized Analysis Set (RAS)** consists of all randomized subjects.

The **Full Analysis Set (FAS)** comprises all subjects who receive at least one IVT injection of the study treatment. The FAS will serve as the primary analysis set for all efficacy analyses. According to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The **Safety Set** includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

Relevant protocol deviations and their potential impact on the analysis will be assessed and adequately documented / processed before database lock.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment arm for the FAS and Safety set.

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

Relevant medical history and current medical conditions at baseline will be summarized separately by system organ class (SOC) and preferred term, by treatment arm.

Other relevant baseline information will be listed and summarized with descriptive statistics as appropriate.

12.3 Treatments

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

The duration of exposure to the investigational drug as number of injections from baseline to EOS/week 52 will be summarized by means of descriptive statistics using the safety set. All collected injection data will be listed.

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, by treatment group.

12.4 Analysis of the primary endpoint(s)

The primary objective of this study is to evaluate descriptively the difference of brolucizumab 6 mg with one (initial) injection followed by q12w maintenance and brolucizumab 6 mg with 3x q4w loading injections followed by q12w maintenance with respect to the change in BCVA from baseline to mean of visits at week 40 to week 52.

12.4.1 Definition of primary endpoint(s)

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

The population will be male and female patients ≥50 years old diagnosed with active choroidal neovascularization (CNV) secondary to AMD and treated previously for this disease, who will be switched to brolucizumab at baseline.

Variable of interest: primary endpoint is the change in BCVA from baseline to mean of visits at week 40 to week 52; irrespective of adherence to treatment, i.e. the treatment policy.

Intervention effect: effect of brolucizumab "non-loading arm" versus " loading arm" after 52 weeks regardless of adherence to randomized treatment.

Summary measure: Difference in means

12.4.2 Statistical model, hypothesis, and method of analysis

The analysis of the primary endpoint will be perfomed in a purely descriptive manner and non-inferiority testing will be omitted. To evaluate the outcome in terms of mean change in BCVA from baseline to mean of visits at week 40 through week 52, a two-sided 95% confidence interval for the treatment difference will be derived from a mixed model with repeated measures (MMRM) model with factors treatment arm, baseline BCVA and age. Details will be specified in the respective SAP.

The FAS will be used to analyze the primary endpoint.

12.4.3 Handling of missing values/censoring/discontinuations

As a primary approach, retrieved data will be included, irrespective of intercurrent events such as prohibited medication or treatment interruption or discontinuation (treatment policy, difference in all randomized patients). Details will be specified in the respective SAP. For

statistical analyses of continuous parameters, missing data in case of lost to follow-up will be accounted for in a mixed model for repeated measures (MMRM) assuming data after loss to follow-up are missing at random (MAR), and assuming almost all data will be retrieved. Thus, every effort must be made to follow-up on patients after treatment discontinuation up to end of study.

12.4.4 Sensitivity and supportive analyses

Not applicable.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoints

The secondary efficacy objectives and endpoints of this study are listed in Table 2-1.

Secondary endpoints will be analyzed using adequate descriptive statistics.

For continuous variables, summary statistics will generally include: n, mean, standard deviation, median, minimum and maximum. Treatment group comparisons may include confidence intervals and group differences together with the respective confidence intervals.

The secondary endpoint "Mean change in BCVA from baseline to mean of visits week 16 to week 28" will be analyzed analogous to the primary endpoint analysis.

For categorical variables, these will generally include: n and percentage in each category.

Rates and percentages will be presented for binary variables.

For the endpoints "rate of patients (overall and per group) with prolonged interval compared to mean treatment interval in last -24 weeks prior to enrollment" and "proportions of patients maintained at a q12w interval at week 52" a logistic regression model will be fitted.

[redacted]

12.5.2 Safety endpoints

The secondary safety objective and endpoint of this study is as follows:

To evaluate the safety and tolerability of brolucizumab

- Incidence of ocular and non-ocular AEs up to week 52

There are no formal safety hypotheses in this study. For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment arm.

Safety endpoints are based on the variables from safety assessments which include:

- Extent of exposure
- Adverse events
- Ophthalmic examinations

- Vital signs

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

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

Adverse events

A treatment-emergent adverse event is defined as any adverse event that develops after initiation of the study treatment or any event already present that worsens following exposure to the study treatment. Only treatment-emergent adverse events will be presented in the summary tables.

All information obtained on adverse events will be displayed by treatment arm and subject.

The number (%) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, standardized MedDRA Query (SMQ) and preferred term.

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

Adverse events will be coded using the MedDRA dictionary and presented by system organ class (SOC) and preferred term (PT). Treatment-emergent AEs will be analyzed based on the number and percentage of patients with at least one AE in the category of interest. Separate presentations will be provided related to ocular events in the study eye and fellow eye and systemic events. Additional summaries will be provided by severity and causality (separately assessed for the injection procedure and the drug). Serious adverse events and adverse events leading to discontinuation of study treatment will also be summarized separately.

Ophthalmic examinations

Pre-injection IOP measurements will be presented descriptively (absolute values and change from baseline). Post-injection IOP measurements will be listed.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

[redacted]

12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

12.8.1 Primary endpoint

Due to feasibility reasons, resulting in a substantial delay in recruitment, as described above, with Amendment 2 the recruitment will be prematurely discontinued. A final number of approximately 50 patients is expected to be recruited by the time of approval of the amendment.

As a consequence, all analyses will be performed and interpreted in a purely descriptive manner.

Based on an expected sample size of 25 patients per group, and an assumed common standard deviation of 13 letters, a precision in terms of the width of the respective 95% confidence interval for the difference in change from baseline of the visual acuity of +/- 7,21 can be achieved. Taking into account the current number of patients of (for 23 patients per group), the precision in terms of the half width of the 95% confidence interval would be 7,51.

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, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. 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.).

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 subjects 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 subject 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 subject 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.

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16 Appendices

Not applicable.