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RTH258

Clinical Trial Protocol CRTH258A2303 / NCT04005352

A 64-week, two-arm, randomized, double-masked, multi-center, phase IIIb study assessing the efficacy and safety of brolucizumab 6 mg compared to aflibercept 2 mg in a treat-to-control regimen in patients with neovascular age-related macular degeneration (TALON)

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AMD	Age-related Macular Degeneration
ANCOVA	Analysis of covariance
ANOVA	Analysis of Variance
BCVA	Best-corrected visual acuity
CFP	Color Fundus Photography
CFR	Code of Federal Regulation
CMO & PS	Chief Medical Office & Patient Safety
CNV	Choroidal Neovascularization
COVID-19	Coronavirus Disease 2019
CRC	Central Reading Center
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSFT	Central Subfield Thickness
DA	Disease Activity
DMC	Data Monitoring Committee
EDC	Electronic Data Capture
EOS	End-of-Study
EOT	End-of-Treatment
ETD	Early Treatment Discontinuation
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAS	Full Analysis Set
FIR	First Interpretable Results
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IOI	Intraocular Inflammation
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRF	Intraretinal Fluid
IRT	Interactive Response Technology
IVT	Intravitreal injection
LOCF	Last Observation Carried Forward
MedDRA	Medical dictionary for regulatory activities
nAMD	neovascular Age-related Macular Degeneration
NIH	National Institutes of Health
[redacted]	[redacted]

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PDT	Photodynamic Therapy
PPS	Per-Protocol Set
PFS	Prefilled Syringe
PRN	Pro re nata
PRO	Patient Reported Outcomes
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-OCT	Spectral Domain Optical Coherence Tomography
SOC	Standard Of Care
SRF	Subretinal Fluid
SUN	Standardization uveitis nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reactions
T&E	Treat-and-Extend
TtC	Treat-to-Control
USM	Urgent Safety Measure
VEGF	Vascular endothelial growth factor
VFQ25	Visual Function Questionnaire 25
YAG	Yttrium aluminum garnet

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
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.
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)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Masked/evaluating investigator	For the entire study duration and all study subjects, the masked/evaluating investigator is responsible for all aspects of the study (the conduct/supervision of all assessments and treatment decisions except the injection procedures and the safety assessment following the study drug injections).
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an Integration Response Technology (IRT) system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Patient	An individual with the condition of interest
Period	A subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
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.

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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.
Unmasked/treating investigator	For the entire study duration and all study subjects, the treating investigator only performs the treatment (injection active/sham) and assesses subject safety following the active/sham injections.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 3 (23-Sep-2021)

Amendment rationale

The purpose of this amendment is to include information on the gender imbalance in the reported rates of intraocular inflammation-related adverse events following brolucizumab treatment.

Changes to the protocol

- Section 4.5 Risk and benefits: Information added regarding the gender imbalance in the reported rates of intraocular inflammation-related adverse events following brolucizumab treatment.

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

[redacted]

Summary of previous amendments

Amendment 2 (13-Aug-2021)

Amendment rationale

The main reasons for the protocol amendment are:

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

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

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

To maintain masking, the new requirements apply to both treatment arms.

Changes to the protocol

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

Editorial changes and spelling corrections are done throughout the protocol.

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

- Section 1.1 Background: Language was added to indicate that the interval between two brolucizumab doses should not be shorter than 8 weeks beyond loading, and that the impact on the risk/benefit balance is considered to be low when patients are dosed ≥q8w after the loading phase. Clarified that treatment intervals after the initiation phase will range from 8 weeks to 16 weeks. In addition, the results of the mechanistic study BASICHR0049 of blood samples from nAMD patients exposed to brolucizumab and having subsequently developed RV and/or RO were added.
- Table 2-1 Objectives and related endpoints: Footnote was added to clarify analysis of 4-week treatment intervals.

[redacted]

- Section 3 Study design: Reduced visit window for Week 14 to ±7 days. Clarified that if disease activity is observed at Week 14/Week 16, then the study treatment will be administered at this visit and the further injections will be discontinued. Clarified the difference between study completion as per protocol versus early treatment discontinuation. Clarified that only during the loading phase injections should be at least 21 days apart.
- Figure 3-1 Study design: Updated the range for treatment intervals.
- Section 3 Study design; Section 4.1 Rationale for study design; Section 6.7.2 Instruction for prescribing and taking study treatment: Modified to clarify the shortest treatment interval in the TtC phase.
- Section 4.2 Rationale for dose/regimen and duration of treatment: Language added to provide background of the USM and impact on design.
- Section 4.5 Risks and Benefits: Added the three urgent safety measures related to adverse events observed in patients treated with brolucizumab from the MERLIN (CRTH258AUS04) study, the post marketing reports and the causal link (results of the mechanistic study BASICHR0049).
- Section 6.1.4 Treatment duration: Guidance added for subjects requiring injections every 4 weeks. Added a paragraph to clarify that subjects who prematurely discontinue from study treatment should continue in the study and should return 4 weeks after last treatment to perform assessments for early treatment discontinuation.
- Section 6.7.2 Instruction for prescribing and taking study treatment: Text added to show the treatment intervals allowed in the maintenance phase, following Week 16. In addition, changes made to clarify that subjects who require treatment every 4 weeks beyond the loading phase, should be discontinued from study treatment. A paragraph describing inspection visits for an interval extension from 4 weeks to 8 weeks was removed because this option will no longer apply in the study. Changes also made to update that if RV and/or RO is confirmed, subjects should be discontinued from study treatment. If only IOI (without RV and/or RO) is confirmed, the subject should be closely monitored and the investigator should evaluate the appropriateness of continuing further with study treatment. This has also been updated Table 6-3.
- Figure 6-1 Treatment regimen: Updated the range for treatment intervals.
- Table 6-3 Disease activity assessment and treatment occurrence according to visit type: Added newly implemented visit type “ETD”.
- Section 8: Visit schedule and assessments: Clarification added for visit windows for inspection visit at week 14. Removed a sentence that two consecutive injections should be at least 21 days apart as this is no longer applicable since in the maintenance phase, any subject who requires treatment every 4 weeks has to be discontinued from study treatment.
- Table 8-1 Assessment schedule: Columns added for early treatment discontinuation visits and for assessment visits after start of standard of care, including respective footnotes. In addition, footnotes #3 was updated to reflect the requirement to discontinue subjects from further treatment in case of disease activity at the inspection visit at Week 14; and a clarification was added in footnote #11 with respect to ophthalmic examinations and images. Updated the name of the ophthalmic examination where “and imaging” was added. Footnotes #12, #13, and #14 added with respect to ETD and EOS assessments.

[redacted]

- Section 8.3.2 Optical coherence tomography: Added the new visit for early treatment discontinuation.
- Section 8.4.2 Laboratory evaluations: Added a new visit for early treatment discontinuations.
- Section 9.1.1 Discontinuation of study treatment: Instructions were added for subjects who discontinue from study treatment early.
- Section 12 Data analysis and statistical methods: Language added to include analysis of impact of USM.
- Section 12.4.4 Sensitivity and supportive analyses: Sensitivity analysis added regarding impact of USM.

Other changes incorporated in this amendment:

- List of abbreviations: New abbreviations added in line with amendment 2.
- Protocol summary: Aligned with amendment 2.
- [redacted]
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action: Added guidance regarding SARS-CoV-2 vaccinations which should occur at least 7 days before or after the administration of study treatment.
- Section 8.4 Safety: Added a reference for monitoring, assessment and management of adverse events of inflammation, retinal vasculitis and/or retinal vascular occlusion.
- Section 8.4.4 Ophthalmic examination: Added "and imaging" to the header and to the related paragraph.
- Section 10 Safety monitoring and reporting: Consolidated the requirements for monitoring of adverse events of special interest that were already included in the previous version. Added the new requirement that if RV and/or RO is confirmed, subjects should be discontinued from study treatment. If only IOI (without RV and/or RO) is confirmed, the subject should be closely monitored and the investigator should evaluate the appropriateness of continuing further with study treatment.
- Section 10.1.3 SAE reporting: Clarified the timing for SAE reporting to Novartis as per latest protocol template.
- Section 12 Data analysis and statistical methods: Language modified to stipulate that analysis of the COVID-19 pandemic is planned.
- Table 12.1 Primary and supportive estimands: Added clarification that FAS data collected until the participant discontinued study treatment and started alternative treatment(s), will be included and that BCVA scores collected after subjects discontinued early from study treatment will not be analyzed. In addition, two sensitivity estimands were added to address the impact of the USM.
- Section 12.4.3 Handling of missing values/censoring/discontinuations: Modified to clarify the shortest treatment interval in the TtC phase (8 weeks instead of 4 weeks).
- Section 12.5.2 Safety endpoints: Clarifications added regarding clinically important vital signs and laboratory evaluations, and regarding adverse events of special interest.
- [redacted].

- Section 12.8.1 Primary endpoints: Clarification regarding sample size analyses.

Amendment 1 (02-Jun-2020)

Amendment Rationale

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

Changes to the protocol

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

- Section 1.1 Background: Information was added to describe new safety signal from post-marketing case reports and its impact on the benefit-risk balance.
- Section 6.2.2 Prohibited Medication: Restrictions in use of corticosteroids have been removed to provide flexibility using systemic steroids for the treatment of AEs at the investigator's discretion.
- Section 6.7.2 Instructions for prescribing and taking study treatment: Additional guidance was added to this section emphasizing that if any sign of intraocular inflammation is present, an IVT injection **must not** be performed and patients should be treated for IOI according to clinical practice.
- Additional examination and assessments included to fully characterize cases of intraocular inflammation were added in the following sections:
  - Table 8-1 Assessment schedule
  - Section 8.3.3 Color fundus photography [redacted]
  - Section 8.4.4 Ophthalmic Examination
  - Section 8.4.5 Appropriateness of safety measurements

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

- Section 5.2 Exclusion Criteria
- Section 6.2.2 Prohibited Medication
- Section 7 Informed Consent Procedures
- Section 8 Visit Schedule and Assessments
- Section 8.4 Safety
- Section 8.4.2 Laboratory evaluation
- Section 12 Data Analysis

Other changes incorporated in this amendment:

- Throughout the protocol: the ± 7-day window has been replaced by a ± 14-day window to allow for broader visit window to accommodate longer treatment intervals.
- Section 3 Study Design: changed to allow the assessments of the baseline visit to be performed on two consecutive days
- Figure 6-1 Removed the inspection visit during the second consecutive 16-week interval
- Section 6.1.1 Study Treatment: Introduced wording to include prefilled syringes in selected countries
- Section 6.4 Treatment masking: Language was added to clarify unmasked investigator/site personnel must not be switched to a masked role at any time after randomization.
- Section 6.7.2 Instruction for Prescribing and Taking Study Treatment: Language regarding the injection procedure was added replacing reference to an applicable manual.

[redacted]

- Section 8.4.3 Pregnancy: Additional serum pregnancy testing was included to confirm positive urine testing outcome.
- Section 8.4.4 Ophthalmic examination: Added instructions for the patients in case of symptoms of inflammation.
- Section 10.1.3 SAE Reporting: Clarification of the SAE reporting period
- Section 10.2.1 Data Monitoring Committee: Language was added to introduce program level Data Monitoring Committee.
- Section 12.1 Analysis Sets: Modified to include importance of Estimands per ICH E9(R1) guidance.
- Section 15 References: Added two references
- List of Abbreviations

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

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

IRBs/IECs

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

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

[redacted]

Protocol summary

Protocol number	CRTH258A2303
Full Title	A 64-week, two-arm, randomized, double-masked, multi-center, phase IIIb study assessing the efficacy and safety of brolucizumab 6 mg compared to aflibercept 2 mg in a treat-to-control regimen in patients with neovascular age-related macular degeneration (TALON)
Brief title	Study assessing the efficacy and safety of brolucizumab vs aflibercept in a treat-to-control regimen in patients with neovascular age-related macular degeneration
Sponsor and Clinical Phase	Novartis Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate the efficacy and safety of brolucizumab used in a Treat-to-Control (TtC) regimen for the treatment of patients with neovascular age-related macular degeneration (nAMD) with the objective to evaluate the potential to reduce treatment frequencies
Primary Objective(s)	To demonstrate that brolucizumab is superior to aflibercept with respect to the duration of treatment intervals at Week 32 To demonstrate that brolucizumab is non-inferior to aflibercept with respect to average change in best corrected visual acuity (BCVA) from baseline at Weeks 28 and 32
Secondary Objectives	1. To evaluate the durability of brolucizumab relative to aflibercept 2. To evaluate the functional outcomes with brolucizumab relative to aflibercept 3. To evaluate the anatomical outcomes with brolucizumab relative to aflibercept 4. To evaluate the effect of brolucizumab relative to aflibercept on Patient-Reported Outcomes (PRO) 5. To assess the safety and tolerability of brolucizumab relative to aflibercept
Study design	The study is a 64-week, randomized, double-masked, multi-center, active-controlled, two-arm study in patients with nAMD. Patients will be randomized in a 1:1 ratio to one of the two treatment arms: • Brolucizumab 6 mg: 3 x 4-week injections and one 8-week injection, followed by Treat-to-Control treatment from Week 16 up to Week 60/62. • Aflibercept 2 mg: 3 x 4-week injections and one 8-week injection, followed by Treat-to-Control treatment from Week 16 up to Week 60/62. In both treatment arms, treatment intervals after the initiation phase will be either 8 weeks, 12 weeks, or 16 weeks. More frequent injections, i.e., treatment intervals of <8 weeks are not allowed.
Population	Approximately 962 adult patients will be screened (28% screening failure rate expected) and approximately 692 (346 per arm) patients will be randomized in a 1:1 ratio in approximately 200 centers worldwide. The maximum study duration for one subject is 66 weeks, including screening and post-treatment follow-up.

[redacted]

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 who are treatment naive • Active choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) that affects the central subfield, including retinal angiomatous proliferation (RAP) with a CNV component, confirmed by presence of active leakage from CNV seen by fluorescein angiography (FA) (or other imaging modalities) and sequelae of CNV, e.g. pigment epithelial detachment (PED), subretinal or sub-retinal pigment epithelium (sub-RPE) hemorrhage, blocked fluorescence, macular edema (study eye) • Presence of intraretinal fluid (IRF) or subretinal fluid (SRF) that affects the central subfield, as seen by Spectral Domain Optical Coherence Tomography (SD-OCT) (study eye) • Best-corrected visual acuity (BCVA) score between 83 and 38 letters, inclusive, at an initial testing distance of 4 meters, using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts (approximately Snellen equivalent of 20/25 to 20/200) at both screening and baseline visit (study eye)
Key Exclusion criteria	• Concomitant ocular conditions/disorders 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 first 12-month study period, structural damage of the fovea, atrophy or fibrosis at the center of the fovea (study eye) • 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 which can lead to improved visual acuity (VA) after surgery, e.g. cataract) • Ocular treatments: previous treatment with any anti-vascular endothelial growth factor (VEGF) drugs or investigational drugs, intraocular or periocular steroids, macular laser photocoagulation, photodynamic therapy (PDT), vitreoretinal surgery, intraocular surgery (study eye) • Stroke or myocardial infarction during the 6-month period prior to baseline • Systemic anti-VEGF therapy at any time.
Study treatment	Brolucizumab 6 mg/0.05 mL Aflibercept 2 mg/0.05 mL
Efficacy assessments	BCVA using ETDRS-like charts SD-OCT Color Fundus Photography (CFP) Fluorescein Angiography (FA) National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) vision-related quality of life instrument

[redacted]

Key safety assessments	Monitoring of Adverse Events (AE) Ophthalmic examinations and imaging Vital signs Laboratory assessments (hematology, clinical chemistry, urinalysis) Pregnancy testing
[redacted]	
Data analysis	In order to test the superiority of brolucizumab compared to aflibercept in terms of the distribution of the last treatment interval with no disease activity (q4w, q8w, and q12w) up to Week 32, a one-sided Wilcoxon test for 2 ordered multinomial distribution with type I error of $\alpha = 0.025$ will be considered. To test the non-inferiority of brolucizumab compared to aflibercept in terms of average BVCA change from baseline at Week 28 and Week 32, a two-sided 95% confidence interval for the treatment difference will be derived from an analysis of variance (ANOVA) model with treatment arm, baseline BCVA categories and age categories as fixed effects. In order to demonstrate non-inferiority with respect to average BCVA change from baseline at Week 28 and Week 32, the lower limit of the two-sided 95% confidence interval for the treatment difference (brolucizumab – aflibercept) must be greater than -4 letters, representing the non-inferiority margin. Furthermore, the respective one-sided P-value for BCVA non-inferiority assessed at significance level of 0.025 will be provided. 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. The interim database lock for the primary analyses will be conducted when all ongoing subjects have completed their Week 32 visit. Subjects will remain in the study and will continue to receive masked treatment through the planned study duration of 64 weeks, to allow for further evaluation of efficacy and safety. Additional analyses are planned to evaluate the impact of the coronavirus disease 2019 (COVID-19) pandemic and the q4w urgent safety measures on the primary and selected secondary endpoints.
Key words	Neovascular age-related macular degeneration, anti-VEGF, choroidal neovascularization, individualized treatment

[redacted]

1 Introduction

1.1 Background

Age-related macular degeneration (AMD) is a leading cause of severe vision loss in people, affecting 11.6% to 18.5% of individuals between 60 and 69 years old and 31.6% to 45.3% of individuals between 80 and 84 years old in North America, Europe, and Oceania (Wong et al 2014). Genetic, environmental and health factors play an important role in the pathogenesis of the disease.

AMD is classified into 2 clinical subtypes: the non-neovascular (atrophic) or dry form, and the neovascular (exudative) or wet form (Ferris et al 1984, Lim et al 2012, Miller 2013). Neovascular AMD (nAMD) is characterized by the growth of abnormal new blood vessels (neovascularization) under the retinal pigment epithelium (RPE) or sub-retinal space from the subjacent choroid, termed choroidal neovascularization (CNV) (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. This damage to the retina 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). Although the neovascular form of the disease is only present in about 10 % of all AMD cases, it accounted for approximately 90 % of the severe vision loss from AMD prior to the introduction of antivascular endothelial growth factor (anti-VEGF) treatments (Ferris 1983).

Anti-VEGF in nAMD

Vascular endothelial growth factor (VEGF) has been shown to be elevated in patients with nAMD and is thought to play a key role in the neovascularization process (Spilsbury et al 2000). The use of intravitreal injection (IVT) pharmacotherapy targeting VEGF has significantly improved visual outcomes in patients with nAMD (Bloch et al 2012, Campbell et al 2012). Anti-VEGF treatments, such as ranibizumab (Lucentis®) and aflibercept (Eylea®), inhibit VEGF signaling pathways and have been shown to halt the growth of neovascular lesions and resolve retinal edema. Intravitreal administration of anti-VEGF treatments is the current standard of care in nAMD. They have considerably reduced the incidence of blindness and severe vision loss and revolutionized outcomes for patients with nAMD (Freund et al 2013, Holz et al 2014).

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). Although the PRN treatment regimen is able to reduce the frequency and overall cost of treatment in nAMD, it remains relatively inconvenient for patients because frequent follow-up is still required to ensure comparable visual outcomes to monthly dosing (Busbee et al 2013, Holz et al 2015, Li et al 2016, Holz et al 2017, Koh et al 2017).

Treat-and-Extend treatment regimen

Typically, Treat-and-Extend (T&E) treatment regimen includes a loading phase of monthly injections, followed by a maintenance phase during which injection interval is progressively prolonged if there is no disease activity, primarily determined by optical coherence tomography

[redacted]

(OCT) and visual acuity assessment, or shortened if disease recurs. The T&E treatment regimen aims at identifying optimal individual injection intervals to minimize the number of injections and reduce visit burden while maintaining the vision gains obtained at the end of the loading phase during the maintenance phase.

The TREX-AMD, TREND and CANTREAT studies compared a T&E regimen with a 2-week interval adjustment after 2 or 3 monthly injections of ranibizumab to monthly ranibizumab injections in patients with nAMD. Patients in the T&E regimen arms received on average 2 to 3 fewer injections than those treated monthly after 1 year, for similar mean BCVA gains and comparable safety profile between arms (Wykoff et al 2015, Silva et al 2018, Kertes et al 2019). In the first year of the ARIES study (Mitchell et al 2018), nAMD patients received 3 monthly injections of aflibercept and another injection 8 weeks thereafter, followed by either a T&E regimen with a 2-week adjustment or injections every 8 weeks (q8w). Vision changes from Week 16 to Week 52 were comparable for both regimens, with a mean of 0.8 fewer injection with the T&E regimen. In the head-to-head RIVAL study, aflibercept and ranibizumab administered in an identical T&E regimen based on a 2-week interval adjustment after 3 monthly injections produced similar visual improvements at 1 year after a mean of 9.7 injections in both arms (Gillies et al 2019). Less than 25% of the patients reached the maximal interval of 12 weeks at 12 months. The Japanese ALTAIR study (Ohji et al 2018) compared two T&E regimens of aflibercept using either 2-week or 4-week adjustments, with the treatment intervals from 8 weeks to 16 weeks, after 3 monthly injections and another injection 8 weeks thereafter. BCVA improved from baseline by 9.0 and 8.4 letters at Week 52, and 7.6 and 6.1 letters at Week 96, for the 2-week and 4-week adjustment arms, respectively. About 25 % of patients were maintained on a 8-week interval until Week 96, whereas the last interval at Week 96 was 16 weeks for 41.5% to 46.3% of the patients. The overall safety profile of IVT aflibercept was consistent with previous studies.

T&E treatment regimen has been approved in the labels of ranibizumab 0.5 mg (Lucentis®) and aflibercept 2 mg (Eylea®) in Europe and many other countries. For instance, Eylea® SmPC indicates that after 3 monthly doses and the next dose two months thereafter, the treatment interval may be maintained at 2 months or further extended using a T&E dosing regimen by 2- or 4-weekly increments.

The T&E treatment paradigm has come in a variety of regimens. Whereas most T&E regimens entail extending or shortening the injection interval based on absence or presence of disease activity, the Treat-to-Control (TtC) regimen emphasizes sustained disease control to determine the optimal treatment interval for each patient rather than solely adjusting treatment intervals. For instance, it allows patients that may not benefit from treatment interval extension to be temporarily or lastingly maintained on a treatment interval.

While T&E regimens have been associated with a reduction in treatment and visit burdens in nAMD, the number of visits remain relatively high for most patients as the average number of injections in the studies range from 8 to 10.1 in the first 12 months and from 14.1 to 18.6 in the first 2 years (Wykoff et al 2015, DeCroos et al 2017, Wykoff et al 2017, Guymer et al 2018, Silva et al 2018, Ohji et al 2018, Gillies et al 2019, Kertes et al 2019). There still is a need for highly effective treatments that prolong intervals between injections and further reduce treatment burden, while maintaining vision gains.

[redacted]

Brolucizumab

Brolucizumab (RTH258, formerly known as ESBA1008), is a humanized single-chain antibody fragment (scFv) inhibitor of VEGF-A with a molecular weight of ~26 kDa. Brolucizumab 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 is designed for ophthalmic use and is administered by IVT injection. In this setting, the smaller molecular size of the scFv is expected to have advantages over immunoglobulin G antibodies and larger antibody fragments due to the delivery of a higher molar dose (i.e. VEGF binding equivalents per mg protein), which may prolong the therapeutic effect and enable better tissue penetration at the retina.

In two large Phase III pivotal studies (RTH258-C001 [HAWK] and RTH258-C002 [HARRIER]), nAMD patients received brolucizumab every 12 weeks (q12w), with the option of adjusting to a q8w dosing interval based on disease activity, or aflibercept q8w, after three monthly loading doses. Brolucizumab was non-inferior to aflibercept with regards to change from Baseline in BCVA at Week 48, with over half of the subjects in the brolucizumab 6 mg arm maintained exclusively on the q12w dosing interval (56% in HAWK and 51% in HARRIER). The visual acuity gains observed in the first year were maintained in the second year. Significantly fewer patients in the brolucizumab 6 mg arm had disease activity at Week 16 in a head-to-head comparison based on a matching dosing intervals, with a relative decrease of 30% ($P = 0.0022$) versus aflibercept. Significantly fewer patients on brolucizumab had intraretinal fluid (IRF) and/or subretinal fluid (SRF), with a 35% and 33% reduction relative to aflibercept at Week 16 ($P < 0.001$ for both) in HAWK and HARRIER, respectively, and a 31% and 41% reduction relative to aflibercept at Week 48 in HAWK and HARRIER, respectively ($P < 0.0001$ for both). Brolucizumab 6 mg achieved superior reductions in central subfield thickness (CSFT) versus aflibercept in both the matched dosing and maintenance phases ($P = 0.0016$ and $P = 0.0023$ at Week 16 and Week 48, respectively, in HAWK; $P < 0.0001$ at both Week 16 and Week 48 in HARRIER). These advantages for brolucizumab were maintained in the second year. Safety was comparable between the treatment arms over 2 years.

Since the initial marketing authorization approval in Oct-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 of blood samples from nAMD patients exposed to brolucizumab and having subsequently developed Retinal Vasculitis (RV) and/or Retinal Vascular Occlusion (RO), taken together with accumulated data of the association of treatment-emergent immunogenicity and intraocular inflammation (IOI) indicate a causal link between the treatment-emergent immune reaction against brolucizumab and the brolucizumab-related “retinal vasculitis and/or retinal vascular occlusion, 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 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

[redacted]

loading phase and when patients who develop RV and/or RO are discontinued from further treatment with brolucizumab.

Summary

The T&E regimen is an effective approach associated with a reduction in anti-VEGF treatment and visit burdens for patients with nAMD. There remains a need for medicines with longer therapeutic durability that could support more efficient T&E strategy by enabling faster interval extensions, e.g. by 4 weeks, and longer treatment interval, e.g. 16 weeks. The efficacy profile of brolucizumab in nAMD patients points to a potential for brolucizumab to be associated with longer treatment intervals, and thus fewer visits, than aflibercept in a Treat-to-Control regimen, with comparable visual outcomes, based on the following highlights from HAWK and HARRIER:

- the superior anatomical outcomes vs aflibercept in the matching dose comparison,
- the more pronounced reduction in CSFT over time,
- the visual outcomes similar to aflibercept over time, with more than 50% of the patients on q12w at year 1.

The TALON study intends to complement the current clinical dataset on brolucizumab by generating new evidence based on the T&E concept prevalent in the current management of patients with nAMD. It will be comparing the efficacy and safety of brolucizumab and aflibercept administered in an identical 4-week-adjustment Treat-to-Control regimen with treatment intervals from 8 to 16 weeks after the initial three consecutive monthly injections and one treatment interval extension by 4 weeks from Week 8 to Week 16 ("initiation phase"). Subjects requiring injections every 4 weeks after the initiation phase will be discontinued from further study treatment.

1.2 Purpose

The purpose of this study is to demonstrate the superiority of brolucizumab compared with aflibercept in terms of durability and the non-inferiority of brolucizumab compared to aflibercept in terms of visual outcomes in an identical Treat-to-Control (TtC) regimen in patients with neovascular age-related macular degeneration (nAMD).

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that brolucizumab is superior to aflibercept with respect to the duration of treatment intervals at Week 32	• Distribution of the last interval with no disease activity up to Week 32 (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks*)
• To demonstrate that brolucizumab is non-inferior to aflibercept with respect to average change in BCVA from baseline at Weeks 28 and 32	• Average change in BCVA from baseline at Weeks 28 and 32

[redacted]

Objective(s)	Endpoint(s)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the durability of brolucizumab relative to aflibercept	• Distribution of the last interval with no disease activity up to Week 64 (if there was disease activity, the last interval will be shortened by 4 weeks down to a minimum of 4 weeks*) • Distribution of the maximal intervals with no disease activity up to Week 64 • Proportion of patients with no disease activity at Weeks 14 and 16 • Time from the last loading injection to the first visit with no disease activity
• To evaluate the functional outcomes with brolucizumab relative to aflibercept	• Average change in BCVA from baseline at Weeks 60 and 64 • Occurrence of BCVA improvements of ≥ 10 and ≥ 15 letters from baseline at Week 32, Week 64, and at the last injection visit • Occurrence of BCVA ≥ 69 letters at Week 32, at Week 64, and at the last injection visit
• To evaluate the anatomical outcomes with brolucizumab relative to aflibercept	• Average change from baseline in CSFT as assessed by SD-OCT at Weeks 28 and 32 • Average change from baseline in CSFT as assessed by SD-OCT at Weeks 60 and 64 • Number of visits with presence of IRF and/or SRF, and sub-RPE fluid in the central subfield, as assessed by SD-OCT at Weeks 28 and 32 • Number of visits with presence of IRF and/or SRF, and sub-RPE fluid in the central subfield as assessed by SD-OCT at Weeks 60 and 64
• To evaluate the effect of brolucizumab relative to aflibercept on Patient-Reported Outcomes (PRO)	• Change in Visual Function Questionnnaire-25 (VFQ-25) total and subscale scores from baseline at Weeks 32 and 64
• To assess the safety and tolerability of brolucizumab relative to aflibercept	• Incidence of Ocular and Non-ocular AEs up to Week 64
[redacted]	

* Subjects who will be assigned to a 4-week interval will be analyzed in the q4w category, but discontinued from further study treatment.

[redacted]

3 Study design

The study is a 64-week randomized, double-masked, multi-center, active-controlled, two-arm study in patients with nAMD who have not previously received anti-VEGF treatment.

Patients who consent will undergo screening assessments to evaluate their eligibility based on the inclusion and exclusion criteria. Patients who meet all the inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio to one of two treatment arms:

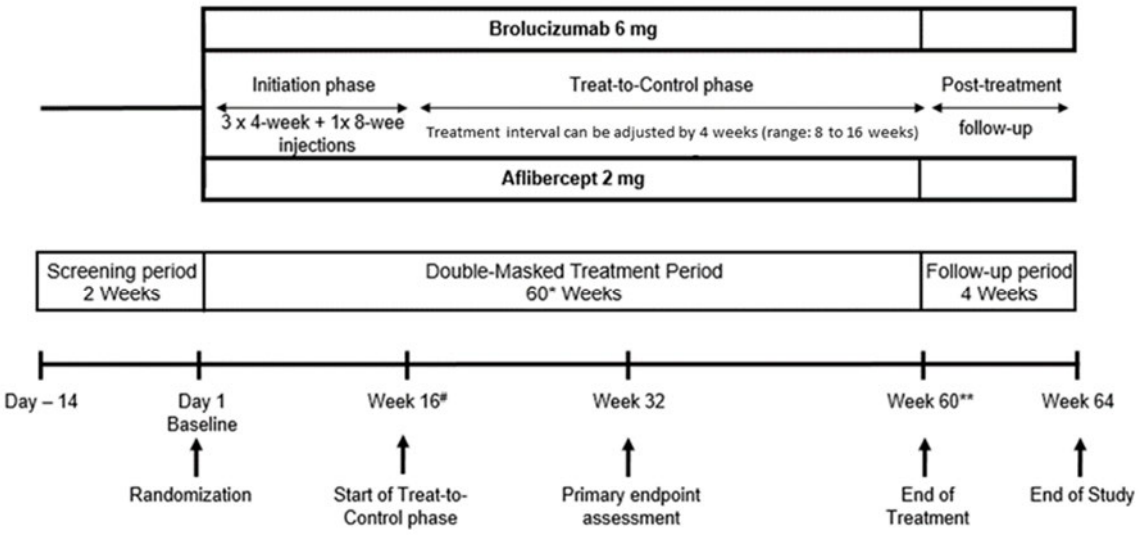
- Brolucizumab 6 mg: 3 x 4-week injections and one 8-week injection, followed by Treat-to-Control treatment from Week 16 up to Week 60/62.
- Aflibercept 2 mg: 3 x 4-week injections and one 8-week injection, followed by Treat-to-Control treatment from Week 16 up to Week 60/62.

Approximately 962 adult patients will be screened (28% screening failure rate expected) and approximately 692 (346 per arm, 10% drop-out rate expected) patients will be randomized in a 1:1 ratio in approximately 200 centers worldwide. The maximum study duration for one subject is 66 weeks, including screening and post-treatment follow-up.

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

- Screening period: from Day -14 to Baseline
- Double-masked treatment period: from Baseline (Day 1) to Week 60/62
- Post-treatment follow-up period: from Week 60/62 to Week 64.

Figure 3-1 Study design



Week 14 if inspection visit
Depending on visit schedules:
* 62 weeks
** Week 62

Screening period: Day-14 to Day-1

[redacted]

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

One time reassessment 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.

Patients must have confirmed nAMD at screening.

Double-masked treatment period: Day 1 to Week 60/62

After confirmation of eligibility, patients will be randomized in a 1:1 ratio to one of the two treatment arms. A study visit schedule will be established at the time of randomization for all patients (Figure 6-1). All efforts should be made to adhere to this study visit schedule within a ±14 day window (±7 days at visit Week 14). For a given protocol visit assessments can be performed on two consecutive days, provided both days are within the 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 when the per-protocol assessments will have taken place (except Baseline/Day1, in which case study treatment administration should occur within the next 24 hours).

The baseline visit is defined as Baseline/Day 1. For all patients, the last potential study treatment will be at the Week 60 visit or at the Week 62 visit if the patients will have received the study treatment at an odd number of inspection visits (see below). The initiation phase starts on Day 1 and ends on Week 16. TtC regimen starts on Week 16 until end of treatment (Week 60/62).

Patients will receive three consecutive injections every 4 weeks at Baseline, Weeks 4 and 8 (loading phase), which should be at least 21 days apart. The injection interval will then be extended by 4 weeks to a 8-week interval to Week 16. From Week 16, based on investigator's judgment of visual and/or anatomic outcomes, the injection interval can be further extended by 4 weeks at a time, if there is no disease activity, as provided in the guidance to the investigators, e.g. no change in visual acuity and in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.). If disease activity recurs, the injection interval should be shortened accordingly by 4 weeks at a time or to a minimal interval of 8 weeks. The injection interval can also be maintained if the investigator deems that the patient will not benefit from injection interval extension. Patients who require study treatment every 4 weeks after the initiation phase (Week 14/Week 16) will be discontinued from further study treatment at the next visit.

At the investigator's discretion, an inspection visit 6 weeks after the last injection can be performed when the injection interval is extended from 4 weeks to 8 weeks, i.e., after the 3rd injection at Week 8. If there is no disease activity in the study eye at the inspection visit, as assessed by the masked investigator, no treatment is administered at this inspection visit; the next visit and injection will take place 2 weeks later, i.e. 8 weeks after the previous study treatment. If disease activity is observed by the masked investigator in the study eye at the inspection visit at Week 14, the study treatment will be administered by the unmasked investigator, and the subject will be discontinued from further study treatment at the next visit. Inspection visits 10 weeks and 14 weeks after the last injection can be performed when the

[redacted]

injection interval is extended from 8 weeks to 12 weeks, and from 12 weeks to 16 weeks, respectively (see Section 6.7.2).

Post-treatment follow-up period: Week 60/62 to Week 64

For all patients completing the study as per protocol, the End-of-Study (EOS) assessment will be performed at Week 64 (± 21 days), four weeks (± 14 days) following their last possible study treatment administration (Week 60/62).

Subjects withdrawn from the study prior to study completion will be asked to return for an early discontinuation (EOS) visit, four weeks (± 14 days) following their last study treatment administration (End-of-Treatment, EOT). For early treatment discontinuations (ETD) refer to Section 9.1.1.

4 Rationale

4.1 Rationale for study design

This study is designed as a randomized, double-masked, multi-center, active-controlled, two-arm study to demonstrate the safety and efficacy of brolucizumab 6 mg compared to the active comparator, aflibercept, used in an identical Treat-to-Control regimen, a modified Treat-and-Extend regimen (see Section 1.1).

The anti-VEGFs, e.g. aflibercept and ranibizumab, are the mainstay of treatment for nAMD (Schmidt-Erfurth et al 2007; Schmidt-Erfurth et al 2014). Hence, aflibercept will be used as an active comparator in the present study.

Co-primary efficacy endpoints based on treatment interval and BCVA were chosen to evaluate the benefits of treatment in terms of treatment durability and functional outcome, respectively:

- Treatment intervals may be extended, reduced, or maintained, based on the evaluation of disease activity by masked investigators. Superiority testing related to the distribution of the last interval with no disease activity up to Week 32 will be carried out. If there is disease activity during the last interval up to Week 32, the last interval will be shortened by 4 weeks down to a minimum of 8 weeks.
- The co-primary efficacy endpoint based on BCVA (ETDRS letters, measured at 4 meters) will also be assessed by masked personnel. Non-inferiority testing related to the co-primary efficacy parameter BCVA will be based on a margin of 4 letters. 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 > 5 letters would be considered as clinically relevant regardless of the underlying disease. A non-inferiority margin of 4 letters for the endpoint change from baseline in BCVA is well established and considered clinically relevant in the indication of nAMD (FVF4579g - HARBOR, RTH258-C001 - HAWK and RTH258-C002 - HARRIER studies) and was also applied in diabetic macular edema (CRFB002D2304 - RETAIN study).
- The co-primary endpoint will be assessed as average change from baseline in BCVA at Week 28/30 and Week 32. In the Treat-to-Control phase, patients will receive injections at

[redacted]

different intervals. Patients with longer treatment intervals may receive their last injection far earlier before the fixed assessment time point than those with shorter treatment intervals. 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 2 time points 4 weeks apart will mitigate this potential bias.

Masked treatment for approximately 60 weeks of treatment, including 44 weeks of Treat-to-Control regimen, allows evaluation of the long-term safety and efficacy of brolucizumab compared to aflibercept in an identical Treat-to-Control regimen in nAMD.

The following will apply to ensure masking is maintained:

- To fulfil the double-masking requirement, the study site will have masked and unmasked staff to perform the masked and unmasked study assessments/procedures accordingly.
- Disease activity assessment and decision on next treatment interval will be made by the masked investigator for both arms and at each visit during the Treat-to-Control phase, including Week 16 (or the first optional inspection visit Week 14, at the discretion of the masked investigator).

4.2 Rationale for dose/regimen and duration of treatment

The dose and regimen for brolucizumab and aflibercept 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 III 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 Treat-to-Control phase to reduce the treatment burden (see Section 1.1).
- Current evidence from large ranibizumab studies in nAMD (CRF002A2411 - TREND, CRF002ACA06 - CAN-TREAT, CRF002AAU15 - FLUID, CRF002AAU17 - RIVAL studies) indicates that the Treat-and-Extend regimen is an efficient regimen which is clinically comparable to monthly injections in improving visual acuity while reducing the number of visits and treatments (see Section 1.1).
- In the aforementioned studies, Treat-and-Extend regimens with treatment intervals between 4 and 12 weeks were found to be effective and safe. Recently, treatment intervals were extended to the maximum interval of 16 weeks as early as Week 40 for some Japanese patients with nAMD treated with aflibercept 2 mg in a Treat-and-Extend regimen where treatment intervals could be every 4-week adjusted based on disease activity, following 3 consecutive 4-week injections and a 8-week injection (Ohji et al 2018). There is no evidence yet about the safety and efficacy of intervals longer than 12 weeks with brolucizumab. However, one could expect that patients could also be effectively and safely injected with brolucizumab 6 mg at 16-week intervals, as brolucizumab 6 mg dosed q12w/q8w was superior to aflibercept 2 mg dosed q8w in terms of fluid control and suppression of disease activity as seen in RTH258-C001 - HAWK and RTH258-C002 - HARRIER.

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- CRTH258AUS04 (MERLIN) is a two-year, multicenter, randomized, double masked, Phase IIIa study evaluating brolucizumab 6 mg q4w versus aflibercept 2 mg q4w in patients with nAMD with persistent fluid. Review of the 52-week FIR led to an urgent safety communication based on an increased incidence of intraocular inflammation (IOI) and related adverse events including retinal vasculitis (RV), and retinal vascular occlusion (RO) in patients with q4w dosing with brolucizumab beyond the "loading phase". IOI including RV, and RO were reported at a higher frequency in brolucizumab 6 mg q4w when compared to aflibercept 2 mg q4w (IOI: 9.3% vs 4.5% of which RV: 0.8% vs 0.0%; RO: 2.0% vs 0.0%, respectively). Accordingly, the CRTH258A2303 protocol is being amended 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 64 weeks allows for two complete 16-week intervals to assess long-term efficacy and safety of this Treat-to-Control regimen.

4.3 Rationale for choice of control drug

Aflibercept 2 mg (Eylea®) is an established standard of care for nAMD and has been chosen as an active comparator that is approved across many countries.

4.4 Purpose and timing of interim analyses

The primary analysis will be conducted when all ongoing subjects have completed their Week 32 visit. Subjects will remain in the study and will continue to receive masked treatment through the planned study duration of 64 weeks, to allow for further evaluation of efficacy and safety. Treatment masking of individual subjects will remain in effect for all subjects, masked investigators and selected staff from the Sponsor who have access to the patient data and have contact with investigators until the final database lock has occurred.

4.5 Risks and benefits

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 8.4.4 and Section 10.

Adverse events (AEs) of retinal vasculitis and/or retinal vascular occlusion have occurred since the Oct-2019 marketing authorization approval for brolucizumab (Beovu®) in the treatment of nAMD. These AEs may result in severe vision loss and typically in the presence of intraocular inflammation. 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).

Results of the mechanistic study BASICHR0049 of blood samples from nAMD patients exposed to brolucizumab and having subsequently developed Retinal Vasculitis (RV) and/or Retinal Vascular Occlusion (RO) taken together with accumulated data of the association of treatment-emergent immunogenicity and intraocular inflammation (IOI) indicate a causal link between the treatment-emergent immune reaction against brolucizumab and the brolucizumab-

[redacted]

related “retinal vasculitis and/or retinal vascular occlusion, 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 USM (CRTH258AUS04 FIR), the brolucizumab dosing interval should not be less than 8 weeks beyond the loading period.

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.

Aflibercept, an approved inhibitor of VEGF-A, has consistently demonstrated efficacy in VEGF-driven retinal pathologies, including nAMD, with benefits outweighing the risks.

In both Phase III studies (HAWK, 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, 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 that will translate into greater durability and longer injection intervals for brolucizumab 6 mg, with non-inferior efficacy. 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).

[redacted]

5 Population

The study population will be male and female patients ≥ 50 years old diagnosed with active choroidal neovascularization (CNV) secondary to AMD, not treated previously for this disease and able to comply with study or follow-up procedures.

Assuming a 28% screen failure rate, approximately 962 adult patients will be screened and approximately 692 (346 per arm, 10% dropout rate expected) patients will be randomized in a 1:1 ratio in approximately 200 centers worldwide.

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. 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 CNV secondary to AMD that affects the central subfield, including retinal angiomatous proliferation (RAP) with a CNV component, confirmed by presence of active leakage from CNV seen by fluorescein angiography (or other imaging modalities) and sequelae of CNV, e.g. pigment epithelial detachment (PED), subretinal or sub-retinal pigment epithelium (sub-RPE) hemorrhage, blocked fluorescence, macular edema.
4. Presence of intraretinal fluid (IRF) or subretinal fluid (SRF) that affects the central subfield, as seen by SD-OCT.
5. BCVA score must be ≤ 83 and ≥ 38 letters at an initial distance of 4 meters starting distance using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity charts (approximately Snellen equivalent of 20/25 to 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 first 12-month study period.
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.

[redacted]

4. Presence of amblyopia, amaurosis or ocular disorders in the fellow eye with BCVA < 20/200 at screening (except when due to conditions whose surgery may improve VA, e.g. cataract).
5. Atrophy or fibrosis involving the center of the fovea in the study eye, as assessed by color fundus photography.
6. The total area of fibrosis or subretinal blood affecting the foveal center point comprising ≥ 50% of the lesion area in the study eye.
7. 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. Previous treatment with any anti-VEGF drugs or investigational drugs in the study eye at any time prior to baseline.
9. Previous use of intraocular or periocular steroids in study eye within the 6-month period prior to baseline.
10. Macular laser photocoagulation (focal/grid) or photodynamic therapy (PDT) in the study eye at any time prior to baseline and peripheral laser photocoagulation in the study eye within 3 months prior to baseline.
11. Intraocular surgery in the study eye within 3 months prior to baseline.
12. Vitreoretinal surgery in the study eye at any time prior to baseline.
13. Aphakia with the absence of posterior capsule in the study eye.

Systemic conditions or treatments:

14. Stroke or myocardial infarction during the 6-month period prior to baseline.
15. End stage renal disease requiring dialysis or renal transplant.
16. 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).
17. Systemic anti-VEGF therapy at any time.
18. Systemic medications known to be toxic to the lens, retina or optic nerve (e.g. deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol) used during the 6 month period prior to baseline except temporary use for COVID-19 treatment.
19. 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.
20. 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.
21. History of a medical condition (e.g. metabolic dysfunction disease with exception of type 1 or 2 diabetes mellitus, physical examination finding, or clinical laboratory finding) that, in the judgment of the investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product.

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

Other:

23. 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.
24. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unl**ess** 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 before taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

    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.

[redacted]

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational and comparator drugs

Investigational/ Comparator Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor
Brolucizumab 6 mg (RTH258 6 mg/0.05 mL)	Solution for injection	Intravitreal use	Glass vials or pre-filled syringe	Global
Aflibercept 2 mg/0.05 mL	Solution for injection	Intravitreal use	Glass vials or pre-filled syringe	Global

Brolucizumab will be provided in a single use, sterile glass vial, or may be provided in prefilled syringe (PFS) (in selected countries), containing sufficient brolucizumab to deliver a 6 mg dose when administering a volume of 0.05 mL.

Aflibercept will be provided in a single use, sterile glass vial, or may be provided in prefilled syringe (in selected countries) containing sufficient aflibercept to deliver a 2 mg dose when administering a volume of 0.05 mL.

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

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

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug is 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: 3 x 4-week injections and one 8-week injection, followed by Treat-to-Control treatment from Week 16 up to Week 60/62
- Aflibercept 2 mg: 3 x 4-week injections and one 8-week injection, followed by Treat-to-Control treatment from Week 16 up to Week 60/62

6.1.4 Treatment duration

The planned duration of treatment is 60 weeks (62 weeks for the patients who may have received study treatment at an odd number of inspection visits). 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.

After the initiation phase (Week 14/Week 16), study treatment will also be discontinued for patients who require injections every 4 weeks.

[redacted]

If retinal vasculitis, and/or retinal vascular occlusion is confirmed, subjects must be discontinued from study treatment.

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

6.2 Other 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 enrollment in the study. 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 on the appropriate Electronic Case Report Forms (eCRFs).

Each concomitant medication must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis 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

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.

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

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

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

[redacted]

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed after screening.

Table 6-2 Prohibited medications and procedures

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

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

6.2.3 Rescue medication

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

In case of lack of efficacy with 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.

[redacted]

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.) 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 (4 digit number for Center No. as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it (3 digit number for Subject No.), 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.

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

6.3.2 Treatment assignment, randomization

All screened subjects must be added to the Interactive Response Technology (IRT) system. At the Baseline Visit/Day 1 all eligible subjects will be randomized via IRT to 1 of the treatment arms in a ratio of 1:1.

The unmasked investigator or his/her delegate will contact the IRT after receiving confirmation from the masked investigator that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the study treatment packages (each containing 1 vial) to be dispensed to the subject. The randomization number will not be communicated to subject or site users.

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 subject randomization list will be produced using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

The intent of masking is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. Bias could arise from the influence that the knowledge of a specific treatment assignment may have on the recruitment and allocation of subjects, their subsequent care, the assessment of endpoints, the handling of withdrawals, and so on. The essential aim of masking, therefore, is to prevent identification of the treatments by the investigator, subject, and others associated with the conduct of the study until all such opportunities for bias are no longer present.

[redacted]

This study will be double-masked, with subjects randomized to be treated with brolucizumab 6 mg or aflibercept 2 mg. The sponsor clinical study team will be masked to treatment assignments until the Week 32 Interim Database Lock for the primary analysis and will be unmasked once the Week 32 Interim Database Lock for primary endpoints is reached. However, masking to the original treatment assignment will be maintained at the site level (patients, masked study site personnel, masked monitors) until the end of the study.

Unmasking of investigators and site personnel directly involved in the conduct of the study will only occur in case of subject emergencies (see Section 6.6.2), and then at the time of the final analysis, at the conclusion of the study (see Section 4.4 and Section 11.2).

In the event of a medical emergency or an adverse event (AE) during the study where the knowledge of subject treatment is required (e.g. in case of Suspected Unexpected Serious Adverse Reaction (SUSAR)), an investigator will have the ability to unmask the treatment assignment for a specific subject. The investigator should notify the Sponsor prior to unmasking a subject, if there is sufficient time. Further, the Sponsor must be informed whenever the randomization code is broken and be informed about the reasons for unmasking.

Each site must have both masked and unmasked investigators available. The investigator who performs the injection will be unmasked to the treatments as will any other site personnel who have been delegated responsibility for working with the investigational product. The unmasked site personnel and unmasked injecting investigator must not perform BCVA assessments, complete ophthalmic examination, disease stability assessments or administer the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25). Also, the unmasked site personnel and unmasked injecting physician must not perform assessment of any ocular or non-ocular safety parameters, or assess causality of AEs for subjects during the course of the study.

The unmasked investigator/site personnel should, however, assess the subject's functional vision (e.g. finger counting) and may perform other safety assessments as needed immediately following injection.
Once the designated roles are determined, the unmasked investigator/site personnel must not be switched at any time after randomization to masked role. Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this masked study.

Treatment masking of individual subjects will remain intact until the database lock has occurred by ensuring that randomization data are kept strictly confidential until the time of unmasking and will not be accessible by anyone else involved in the study except the unmasked/treating investigator. During and after Database Locks at Week 32 and Week 64, the masked personnel at site and subjects will remain masked to the treatment assignment until the conclusion of the study.

Unmasked monitors will be available to perform study medication accountability and to deal with study issues involving the unmasked investigator or unmasked site staff.

An independent, masked review of color fundus photography (CFP), [redacted] images collected at pre-defined time-points (see Section 8.3.2 and Section 8.3.3) for subjects enrolled in the study will be performed at a Central Reading Center (CRC).

[redacted]

6.5 Dose escalation and dose modification

No study treatment dose modification is allowed.

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

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

6.6 Additional treatment guidance

6.6.1 Treatment compliance

IRT needs to be accessed by unmasked study personnel at every visit. Registration of all visits in the IRT system is necessary and when treatment is warranted, IRT will provide a medication (kit) number to administer the assigned investigational product to the subject. 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 unmasked study personnel or by unmasked 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 unmasked field monitor at each visit using vial counts and information provided by the pharmacist or by the unmasked study personnel.

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the IRT system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken. If the treatment code needs to be broken in the interest of subject safety, the investigator is encouraged to contact an appropriate Sponsor representative prior to unmasking if there is sufficient time.

It is the unmasked or masked investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- name (if available)
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unmasking can be performed at any time.

[redacted]

The appropriate personnel from the site and Sponsor will assess whether study treatment should be discontinued for any subject whose treatment code has been broken for any reason.

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). For both brolucizumab and aflibercept, the study drug packaging has a 2-part label (base plus tear-off label). A unique medication number is printed on each part of this label, which corresponds to one of the treatment arms. Unmasked study personnel will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the medication kit to the subject, unmasked study personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

6.7.1 Handling of study treatment

Study treatment must be received by a designated unmasked person at the study site, handled and stored safely and properly and kept in a secured location to which only the unmasked investigator and designated site personnel have access. Upon receipt, all study treatment must be registered in the IRT system and 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 Country Organization 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 but no information about the subject except for the medication number.

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

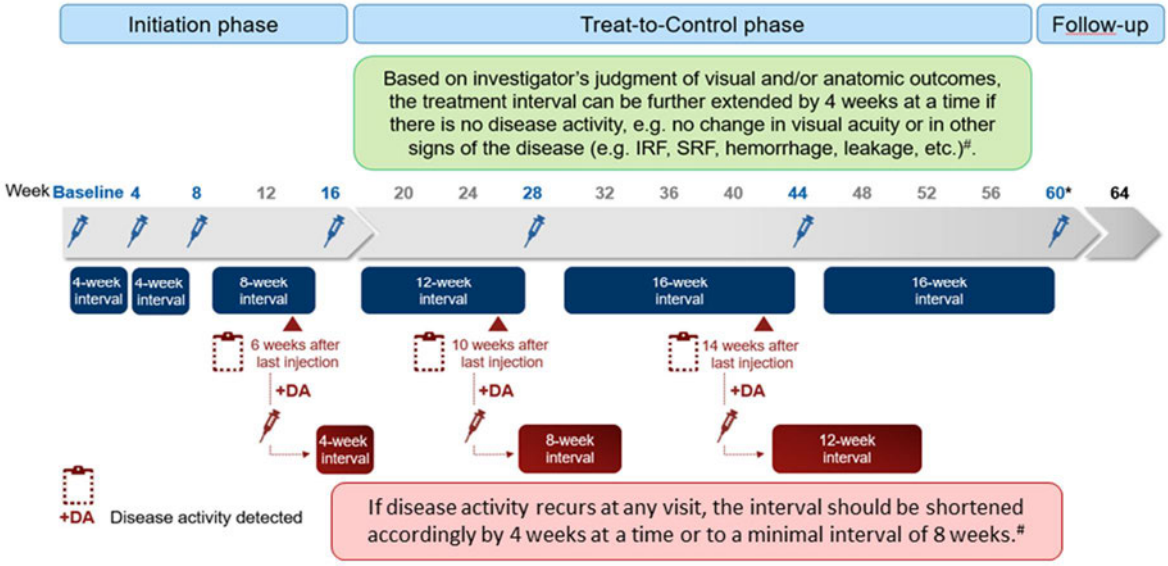
6.7.2 Instruction for prescribing and taking study treatment

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT system

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

[redacted]

Figure 6-1 Treatment regimen



The treatment interval can also be maintained if the investigator deems that the patient will not benefit from treatment interval extension
* Week 62, depending on visit schedule

Initiation Phase

In the initiation phase, treatment with either brolucizumab 6 mg or aflibercept 2 mg will occur every 4 weeks for 3 consecutive injections (baseline, Weeks 4 and 8). The injection interval will then be extended by 4 weeks to Week 16.

At the investigator's discretion, an inspection visit at Week 14, i.e. 6 weeks after the 3rd injection, can be performed. If there is no disease activity in the study eye at Week 14 as assessed by the masked investigator, no treatment will be administered at the inspection visit; the next visit and treatment will take place at Week 16. If disease activity is observed by the masked investigator in the study eye at Week 14, the study treatment will be administered by the unmasked investigator, and the subject will be discontinued from further study treatment at the next visit.

Treat-to-Control (TtC) Phase

The TtC phase starts at Week 16 and is defined as follows:

- Following Week 16, treatment intervals will be either 8 weeks, 12 weeks, or 16 weeks. A subject must be discontinued from further study treatment if treatment is required more frequently, i.e., every 4 weeks.
- The assessment of disease activity is performed at each visit by the masked investigator.
- Based on investigator's judgment of visual and/or anatomic outcomes, the treatment interval can be extended by 4 weeks at a time, if there is no disease activity, i.e. no change in visual acuity and in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.).

[redacted]

- If disease activity recurs, the interval should be shortened accordingly by 4 weeks at a time or to a minimal interval of 8 weeks.
- The treatment interval can also be maintained if the investigator deems that the patient will not benefit from treatment interval extension.
- Inspection visits 10 weeks after the last injection can be performed at the investigator's discretion when the injection interval is extended from 8 weeks to 12 weeks. If there is no disease activity in the study eye at the inspection visit as assessed by the masked investigator, the study treatment will not be administered; the next visit and injection will take place 2 weeks later, i.e. 12 weeks after the previous study treatment. If disease activity is observed by the masked investigator in the study eye at the inspection visit, the study treatment will be administered by the unmasked investigator; the injection interval will be reduced to 8 weeks and the next injection visit will be 8 weeks after the inspection visit.
- Similarly, inspection visits 14 weeks after the last injection can be performed at the investigator's discretion when the injection interval is extended from 12 weeks to 16 weeks, respectively. If there is no disease activity in the study eye at the inspection visit as assessed by the masked investigator, the study treatment will not be administered; the next visit and injection will take place 2 weeks later, i.e. 16 weeks after the previous study treatment. If disease activity is observed by the masked investigator in the study eye at the inspection visit, the study treatment will be administered by the unmasked investigator; the injection interval will be reduced to 12 weeks and the next injection visit will be 12 weeks after the inspection visit.
- Regardless of treatment administration, Week 28, Week 32, and Week 60 visits are mandatory. Patients who will receive study treatment at an inspection visit may also have a study visit at Week 30 or 62; for these patients, the Week 30 or 62 visit will take place in lieu of the visit at Week 28 or 60 (unless this visit is inspection visits), respectively.
- The last potential study treatment may be administered at the Week 60 visit (or at the Week 62 visit for the patients who will have received study treatment at an odd number of inspection visits).
- A disease activity assessment will also be performed at the Week 64/EOS visit; however, no study treatment will be administered.

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

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

Type	Study Period or Phase	Disease Activity Assessment	Treatment
Screening visit	Screening	Yes	No
Baseline (Day 1) visit	Initiation phase	Yes	Yes
Week 4 and 8 visits	Initiation phase	No	Yes
Treatment visits	Treat-to-Control phase	Yes	Yes

[redacted]

Type	Study Period or Phase	Disease Activity Assessment	Treatment
Inspection visits (optional)	Treat-to-Control phase	Yes	Based on DA, as per the masked investigator's judgment
Week 28/30*, 32, and 60/62* visits	Treat-to-Control phase	Yes	Only if a treatment was planned at the visit
ETD visit, and EOS visit (Week 64)	Follow-up	Yes	No

* depending on visit schedule

Brolucizumab or aflibercept should be administered in the study eye on the day of the study visit or, if this is not possible, within 3 days after the occurrence of the study visit (except for Baseline/Day 1, in which case study treatment administration should occur within the next 24 hours) or no later than within the visit window (±14 days) as described in Section 3 and Section 8. When assessments and treatments take place on the same day, treatment must occur after completion of the efficacy assessments described in Section 8.3 and pre-injection safety measures (tonometry, slit lamp and fundus examinations) described in Section 8.4.4. If study visit assessments and the corresponding treatment occur on separate days, a repeat safety check-up should be performed prior to treatment of the eye and results documented in the source documents. If any safety concern arises related to the study eye that, in the opinion of the investigator, may be further impacted by the study treatment or injection procedure, treatment needs to be cancelled. IVT injection is contraindicated in subjects with active intraocular 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. Any adverse events must be recorded in the eCRF.

If any signs of intraocular inflammation is present, then an IVT injection **must not** be performed. Additional ophthalmic examination and imaging should be performed to evaluate IOI (see Section 8.4.4).

If retinal vasculitis, and/or retinal vascular occlusion is confirmed, subjects should be discontinued from study treatment. In addition, subjects who experience IOI only (without RV and/or RO) may be at risk of developing retinal vasculitis and/or retinal vascular occlusion and should be closely monitored and the investigator should evaluate the appropriateness of continuing further with study treatment.

The assessment of the masked/evaluating investigator will be passed to the unmasked/treating investigator or delegate in order to be entered in the IRT system. The IVT injection procedure for brolucizumab and aflibercept including aseptic and antimicrobial requirements, will be performed according to local clinical practice. IVT injection will be performed by the unmasked investigator. All kits of study treatment assigned by the IRT will be recorded in the IRT system.

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

[redacted]

7 Informed consent procedures

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

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol) 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 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 (IN) 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.

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 of the assessments and indicates with an “X” the visits when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation. All data must be entered in the eCRF in a timely

[redacted]

manner (see Section 11.1). The assessments indicated with an "S" to be recorded in the source documentation only.

A planned study visit schedule will be established at Baseline/Day 1, randomization (first day of treatment) for all subjects. All post-baseline and/or subsequent scheduled visits will be calculated based on the Day 1 visit date. During the TtC phase, from Week 16 to Week 60/62, the treatment visit intervals will be determined by the masked 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 ± 14-day visit window is allowed, except for Baseline/Day 1, the inspection visit at Week 14 (± 7-day visit window), and the Week 64 visit (± 21-day visit window), should the subject be unable to return per scheduled visit. All efforts should be made to revert back to the planned visit schedule taking into consideration the restrictions on the minimum treatment interval for the study medications (brolucizumab or aflibercept).

For a given protocol visit assessments can be performed on 2 consecutive days in which both days must occur within the visit window.

Treatment is intended to be administered on the day of study visit, or if this is not possible, within 3 days after the study visit at which the per-protocol assessments took place (except Baseline/Day 1, in which case study treatment administration should occur within the next 24 hours). For all visits, efficacy assessments (Section 8.3) and safety assessments (Section 8.4) should be performed prior to any administration of study treatment.

Missed or rescheduled visits should not lead to automatic discontinuation. 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 EOS final visit will be performed.

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

[redacted]

Table 8-1 Assessment Schedule

Period	Screening	Initiation phase			Treat-to-Control phase					Follow-up			
Visit Name	**Screening**	**Baseline Visit 1**	**W4**	**W8**	**W16**[2]	**n**[3]	**W28**[4]	**W32**	**n**[3]	**W60/EOT**[5]	**ETD**[12]	**W64/EOS**[13]	**m**[14]
Visit Numbers[1]	**1**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**190**	
Weeks	**-2 to -1**	**1**	**4**	**8**	**16**	**18 to 26**	**28**	**32**	**34 to 58**	**60**		**64**	
Informed consent	X												
Inclusion / Exclusion criteria	X	X											
Demography	X												
Medical history/current medical conditions	X												
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[6]	S	S	S	S	S	S	S	S	S	S	S	S	
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X							X			X	X	
Clinical chemistry	X							X			X	X	
Urinalysis	X							X			X	X	
VFQ-25		X						X			X	X	
BCVA score (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Intraocular Pressure (IOP)	X	X	X	X	X	X	X	X	X	X	X	X	
SD-OCT[11]	X	X	X	X	X	X	X	X	X	X	X	X	
CFP[11]	X							X			X	X	

[redacted]

[redacted]

Period	Screening	Initiation phase			Treat-to-Control phase					Follow-up			
Visit Name	**Screening**	**Baseline Visit 1**	**W4**	**W8**	**W16[2]**	**n[3]**	**W28[4]**	**W32**	**n[3]**	**W60/EOT[5]**	**ETD[12]**	**W64/EOS[13]**	**m[14]**
Visit Numbers[1]	**1**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**190**	
Weeks	**-2 to -1**	**1**	**4**	**8**	**16**	**18 to 26**	**28**	**32**	**34 to 58**	**60**		**64**	
Randomization		X											
Disease activity assessment					X	X	X	X	X	X	X	X	
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	
Ophthalmic examination and imaging [9,11]	S	S	S	S	S	S	S	S	S	S	S	S	
Study drug or comparator IVT		X	X	X	X	X	X[10]	X[10]	X	X[10]			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] The number of weeks between visits will vary depending on the disease stability and length of intervals between injections as determined by disease activity assessment. Study treatment at the optional inspection visits (6 weeks after the last injection when the interval is extended from 4 weeks to 8 weeks, 10 weeks after the last injection when the interval is extended from 8 weeks to 12 weeks, and 14 weeks from the last injection when the interval is extended from 12 weeks to 16 weeks) is at the discretion of the investigator based on disease activity assessment.
[3] At the investigator's discretion, an inspection visit may be performed at Week 14. If there is no disease activity in the study eye at Week 14, the next visit and treatment will take place at Week 16. If disease activity is observed in the study eye, the study treatment will be administered and the subject will be discontinued from further study treatment.
[4] Patients may have a study visit at Week 30; in this case, the Week 30 visit will take place in lieu of the Week 28 visit, unless the Week 28 visit is an inspection visit.
[5] Week 60 is the last visit when study treatment may be administered. End-of-Treatment visit will take place on Week 62 in lieu of Week 60 for the patients who have a study visit on Week 62, unless the Week 60 visit is an inspection visit.
[6] A serum pregnancy test must be performed on all women of child-bearing potential at screening and Week 64/EOS. Additional urine tests should be performed prior to each IVT.
[7] Vital signs include sitting blood pressure and pulse rate.
[redacted]
[9] May include visual acuity check, slit lamp examination, fundus examination, optic nerve perfusion, and tonometry, for safety assessment before and after IVT.
[10] Study treatments on the mandatory Week 28/30, Week 32, and Week 60/62 visits only if required based on treatment interval.
[11] Additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation, retinal vasculitis, and/or retinal vascular occlusion.

[redacted]

Period	Screening	Initiation phase			Treat-to-Control phase					Follow-up			
Visit Name	**Screening**	**Baseline Visit 1**	**W4**	**W8**	**W16**[2]	**n**[3]	**W28**[4]	**W32**	**n**[3]	**W60/EOT**[5]	**ETD**[12]	**W64/EOS**[13]	**m**[14]
Visit Numbers[1]	**1**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**190**	
Weeks	**-2 to -1**	**1**	**4**	**8**	**16**	**18 to 26**	**28**	**32**	**34 to 58**	**60**		**64**	

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

[13] The week 64 EOS assessments only apply to subjects who completed the study per protocol. The assessments are not required for subjects who have undergone ETD assessments and continued in the study without study treatment.

[14] For subjects who continue in the study after ETD and up to Week 64 (end of study) while subject is on standard of care. Additional safety assessments and imaging can also be performed if required, as per investigators discretion. In addition, after ETD, subjects are not required to attend the mandatory visits at Week 28/Week 32, and Week 60/Week 62. The last visit should be at week 64. This can occur at any time point.

[redacted]

8.1 Screening

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

[redacted]

One time reassessment of subjects is allowed, **except** for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the subject. 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 subject to participate in the study.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and who are 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, inclusion/exclusion and disposition eCRF 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 (SAE) during the screening phase (**see Section 10.1.3 for reporting details**). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. If the subject is not eligible to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

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:

- Age
- Sex
- Race/Ethnicity
- Vital signs
- Study eye
- Visual acuity
- Choroidal neovascularization characteristics
- Intraocular pressure
- Ophthalmic examinations
- Retinal imaging

[redacted]

- Laboratory test results
- VFQ-25 questionnaire
- Concomitant medications
- Medical history and current medical conditions

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

8.3 Efficacy

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

- Best-corrected visual acuity with ETDRS-like charts at an initial testing distance of 4 meters
- Anatomical retinal evaluation of SD-OCT images
- Color Fundus Photography [redacted]

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, Week 32 and Week 64/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 material, are provided in the applicable manual. Certification of the assessment procedures and assessors will occur prior to any evaluation of study subjects.

Subjects at sites in some Asian countries will undergo BCVA testing using numerical charts rather than letter charts. Therefore, all references in the protocol to changes in letters read will be changes in numbers in these countries.

8.3.2 Optical coherence tomography

Spectral Domain Optical Coherence Tomography (SD-OCT) images will be obtained and assessed in the study eye at every study visit and in the fellow eye at the screening, Week 32 and Week 64/EOS visits. Only SD-OCT machines can be used (i.e. no time-domain nor swept-source OCT).

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

[redacted]

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

[redacted]

The masked investigator will evaluate the images according to their standard of clinical practice and may use any of the SD-OCT [redacted] imaging findings to inform his/her decision for treatment. However, their assessed findings of both quantitative and qualitative parameters will not be captured in the eCRF but must be included in the source documentation at the study site.

A CRC will be used in this study. The CRC will provide sites with a Study Manual and training materials for the specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software will be certified and validated by the CRC as specified in the Study Manual. All SD-OCT [redacted] images will be obtained by trained and study-certified site personnel at the study sites. SD-OCT images captured at baseline, Weeks 28/30, 32, 60/62, ETD, Week 64/EOS [redacted] will be forwarded to the CRC for independent standardized analysis. All SD-OCT [redacted] images will also be forwarded to Novartis or Contract Research Organization (CRO) for storage.

The CRC will create a database with the agreed variables as indicated in the CRC grading charter (a separate document) and will transfer the data from this database to Novartis for analysis. The CRC data will be used for the evaluation of the objectives having SD-OCT [redacted] parameters 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 [redacted]

Color fundus photography (CFP) will be performed in both eyes at the screening, Week 32 and Week 64/EOS visits. [redacted] In case of premature discontinuation from the study, there is no need to repeat the CFP [redacted] if there was a CFP [redacted] performed within the previous 12 weeks, **except if there is significant disease worsening, in the opinion of the investigator**.

The masked investigator will evaluate the images according to their standard of clinical practice and may use any of the CFP [redacted] imaging findings to inform his/her decision for treatment. However, their assessed findings of both quantitative and qualitative parameters will not be captured in the eCRF but must be included in the source documentation at the study site.

The CRC will provide sites with a Study Manual and training materials for the specified study ocular images. Before any study images are obtained, site personnel, test images, systems and

[redacted]

software will be certified and validated by the CRC as specified in the Study Manual. All CFP [redacted] images will be obtained by trained and study-certified site personnel at the study sites and forwarded to the CRC for independent standardized analysis and to Novartis or a CRO for storage.

The CRC will create a database with the agreed variables as indicated in the CRC grading charter (a separate document) and will transfer the data from this database to Novartis for analysis. The CRC data will be used for the evaluation of the objectives having CFP [redacted] parameters and their change over time as endpoints 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. [redacted], Color fundus photography [redacted] (preferably wide-field or with peripheral sweeps) should be performed for safety evaluation as described in Section 8.4.4

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.

[redacted]

8.4 Safety

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

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

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

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

8.4.1 Vital sign assessments

Vital signs include assessment of sitting blood pressure (systolic and diastolic pressure in mmHg) and pulse rate (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

[redacted]

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.

8.4.2 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected at screening, Week 32, ETD, and Week 64/EOS visits. Details on the collections, shipment of the samples and reporting of the results by the central laboratory are provided to investigators in the central laboratory manual.

Clinically significant abnormalities must be recorded in the relevant section of the medical history, current medical conditions or adverse event eCRF page as appropriate.

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 8-2 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute and percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and quantitative platelet count
Clinical chemistry	**Serum biochemistry tests** Serum electrolytes (sodium, potassium, chloride, phosphorus, calcium, magnesium), uric acid, urea nitrogen, creatinine, albumin, glucose, total protein, total bilirubin and direct bilirubin, serum glutamic oxaloacetic transaminase (SGOT)/ aspartate aminotransferase (AST), serum glutamic pyruvic transaminase (SGPT)/ alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) **Additional chemistry tests**: Lipids panel - triglycerides (TG), low-density lipoproteins (LDL), high-density lipoproteins (HDL), total cholesterol (TC)
Urinalysis	Dipstick measurements for specific gravity, pH, protein, glucose, ketones, bilirubin, nitrite, leucocyte and urine occult blood

8.4.3 Pregnancy

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

Highly effective contraception is required for women of child-bearing potential during the study drug administration and for 3 months after stopping the investigational and comparator medications.

A **serum** pregnancy test will be conducted for all women of child-bearing potential to assess pregnancy before inclusion into the study at Screening visit, and then at Week 64/EOS visit. 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

[redacted]

pregnancy test must be performed for confirmation; if the serum test is positive, the subject should discontinue study medication. Results of all pregnancy testing must be available as source documentation.

8.4.4 Ophthalmic examination and imaging

The ophthalmic exam will consist of the following:

- **Intraocular pressure** (IOP) will be assessed in the study eye, pre-dose and post-dose at 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, Week 32 and Week 64/EOS visit. 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 (≥ 25 mmHg). Intravitreal injection is not recommended unless normalization of the IOP has been achieved. Post-dose IOP should be assessed within 60 minutes after injection and if ≥ 25 mmHg, assessment should be repeated until back to normal. Monitoring of 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 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 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 optional according to local practices.

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

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

[redacted]

Imaging: When IOI, retinal vasculitis, and/or RO (Retinal Vascular Occlusion) is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and will conduct [redacted] 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.

8.4.5 Appropriateness of safety measurements

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

If there are any signs of IOI, additional assessments will be performed as described in Section 8.4.4.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

8.5.1.1 Patient Reported Outcomes (PRO)

The impact of brolucizumab on patient visual function will also be assessed by a visual function questionnaire using the National Eye Institute VFQ-25 which is a validated instrument that has been used in many studies of patients with nAMD. The VFQ-25 was developed to address the need to measure a patient's subjective assessment of vision-related Quality of Life (Mangione et al 2001). This is part of the 51-item NEI-VFQ which was developed based on feedback from patients to measure vision-targeted functioning and the impact of vision problems on Health-Related Quality of Life across a number of common eye conditions. This allowed the developers to identify the content areas and aspects of visual disability that were most important and relevant to AMD patients. At baseline and Weeks 32 and 64, the VFQ-25 will be completed and captured by masked site staff on behalf of the patients, at sites where local language versions are available, validated, and approved by the IEC/IRB. All these questionnaires should be completed before patients see the study physician where applicable. A detailed training manual relating to the administrative procedures of the questionnaires will be provided to the sites. Completed questionnaires will be reviewed and examined by the masked/evaluating investigator for responses that may indicate potential AE or SAE, which should be confirmed and recorded into eCRF based on the judgement of the evaluating investigator (see Section 10.1.1 and Section 10.1.2 of the protocol).

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.

[redacted]

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 subject if he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject requires treatment on a q4w interval after the initiation phase (Week 14/Week16), i.e., after the three monthly injections at Baseline, Week 4, and Week 8, followed by the first interval extension
- Subject develops retinal vasculitis and/or retinal vascular occlusion
- Subject/guardian decision
- Pregnancy (see Section 8.4.3 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
- Following emergency unmasking (see Section 6.6.2).

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

- The investigator must contact the IRT to register the subject’s discontinuation from study treatment.
- The investigator should make a reasonable effort to understand and document the primary reason for the subject’s premature discontinuation of study treatment using 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. Subjects should return 4 weeks after last study treatment to perform the assessments for early treatment discontinuation (ETD). Please refer to Table 8-1.
- After these assessments are performed, patient can be switched to standard of care (SOC) anti-VEGF IVT as per investigators discretion. IVT injection is contraindicated in 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.
- After premature study treatment discontinuation, at a minimum till week 64, 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

[redacted]

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

- Dosing of SOC and follow-up visits as per investigators discretion. Subjects are not required to attend the mandatory visits at Week 28/Week 32 and Week 60/Week 62.

- 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. EOS visit assessments on Table 8-1 do not need to be repeated at week 64 for patients on standard of care as they would have been performed as ETD assessment prior to standard of care switch.
- 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.

In the event that premature study treatment discontinuation occurs because treatment code has been broken, please refer to Section 6.6.2.

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

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

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

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

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

The investigator must contact the IRT to register the subject's withdrawal of consent.

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

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

[redacted]

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For the United States of America: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For the European Union and the Rest of the World: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

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 the 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 investigator or Sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their 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.

[redacted]

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

- Instruct the patient to contact the site for any changes in vision or any symptoms of inflammation between scheduled visits (refer to the optional patient brochure). Every effort should be made to bring the subject for immediate examination.
- Close patient monitoring and thorough examination of the eye should be done to detect potential signs of inflammation (Section 8.4.4).
- When IOI, retinal vasculitis, and/or retinal vascular occlusion is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and will conduct [redacted] color fundus photography (preferably wide-field or with peripheral sweeps). The images are requested to be uploaded onto the CRC portal.
- If any signs of intraocular inflammation is present, an IVT injection must not be performed. Therefore investigators must verify that these conditions are not present in the study eye prior to every injection.
- Subjects who experience intraocular inflammation only (without RV and/or RO) may be at risk of developing retinal vasculitis and/or retinal vascular occlusion and should be closely monitored. The investigator should carefully evaluate the appropriateness of continuing further with study treatment.
- If retinal vasculitis and/or retinal vascular occlusion is confirmed, subjects should be discontinued from study treatment.
- Participants should be treated for these events promptly according to clinical practice.

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

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An 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 may also be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

[redacted]

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

a) the severity grade

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

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 SAE (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
- subject hospitalized/subject's hospitalization prolonged (see Section 10.1.2 for definition of SAE)

f) its outcome:

- not recovered/not resolved;
- recovered/resolved;
- recovered/resolved with sequelae;
- fatal or unknown.

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

[redacted]

visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

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

Abnormal 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

[redacted]

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 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

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

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

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

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

[redacted]

Pregnancy should be recorded and reported by the investigator to the Novartis CMO & PS Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to brolucizumab (investigational treatment) and/or aflibercept 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, subject or consumer (European Medicines Agency definition).

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

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

The RTH258 program level Data Monitoring Committee (DMC) will monitor ocular safety. DMC will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

11 Data Collection and Database management

11.1 Data collection

Designated masked 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.

[redacted]

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 investigative site.

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

11.2 Database management and quality control

Novartis (or designated CRO) personnel will review the data entered by investigative staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigative site via the EDC system. Designated masked investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

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

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis. Color fundus photographs, [redacted] will be processed centrally by the Central Reading Center and the results will be sent electronically to Novartis. VFQ-25 data will be processed centrally by a designated vendor and the results will be sent electronically to Novartis. The Data management staff will review data received from the central reading center and central labs. Data Review will be done for data structure and data completeness / accuracy as defined in Vendor Data Transfer Specifications.

Randomization codes and data about all study treatments dispensed to the subject and all dosage changes will be tracked and managed using an Interactive Response Technology (IRT). The system will be supplied by a vendor who will also manage the database. The IRT data will be sent electronically to Novartis.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined at Week 32 before the Interim Database Lock for the primary analysis and at the conclusion of the study. Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unmasked and made available for data analysis. However, masking to the original treatment assignment will be maintained at the site level (patients, masked study site personnel, masked monitors) after the Week 32 Interim Database Lock until the end of the study (see Section 6.4). Any changes to the database after that time can only be made after written agreement by Novartis development management.

[redacted]

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. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis (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, [redacted]), and the results of any other tests or assessments. All information on eCRFs 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 eCRFs 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

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

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

Additional analysesare planned to evaluate the impact of COVID-19 pandemic and the urgent safety measures.

12.1 Analysis sets

The **Randomized Analysis Set** consists of all randomized subjects.

The **Full Analysis Set (FAS)** comprises all subjects to whom study treatment has been assigned by randomization. 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

[redacted]

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.

The **Per-Protocol Set (PPS)** is a subset of subjects of the Full Analysis Set with protocol deviation with impact. The list of protocol deviations criteria will be provided in a separate document.

However, when assessing the robustness of the overall efficacy conclusions, considerations will be given to the analysis based on the primary estimand using FAS and the supplementary estimands (refer to Table 12-1) using PPS, i.e. similar conclusions on non-inferiority based on both estimands are expected. Inconsistencies in the results will be examined and discussed in the CSR.

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, n, 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 histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment arm.

The last available assessment on or prior to randomization (assignment of study treatments, i.e. brolucizumab/aflibercept) is taken as “baseline” assessment.

12.3 Treatments

The Safety set will be used for the analyses below.

The extent of exposure to study treatments as number of injections from baseline to Week 64 will be descriptively summarized by treatment arm. Furthermore, number of subjects at each injection category (e.g. 1 injection, 2 injections, etc.) from baseline to Week 64 by treatment arm will be provided. 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 arm.

12.4 Analysis of the primary endpoint(s)

The primary objective of this study is:

- To demonstrate that brolucizumab is superior to aflibercept with respect to the duration of treatment intervals at Week 32; AND
- To demonstrate that brolucizumab is non-inferior to aflibercept with respect to average change in BCVA from baseline at Weeks 28 and 32.

12.4.1 Definition of primary endpoint(s)

The co-primary endpoint of this study is:

[redacted]

- Distribution (proportion of patients) of last interval with no disease activity up to Week 32 (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks); AND
- Average change in BCVA from baseline at Week 28 and Week 32.

Both criteria in the co-primary endpoint must be met to satisfy the primary objective of this study.

12.4.2 Statistical model, hypothesis, and method of analysis

To test the superiority of brolucizumab vs aflibercept in terms of the distribution of the last interval with no disease activity (q4w, q8w, and q12w) up to Week 32, a one-sided Wilcoxon test for 2 ordered multinomial distribution with type I error of $\alpha = 0.025$ will be considered. Specifically, the Wilcoxon test will assess the following hypothesis:

H0: brolucizumab and aflibercept interval distributions are equal, vs

H1: brolucizumab interval distribution is stochastically larger than aflibercept interval distribution.

The number (%) of patients in q4w, q8w, and q12w at Week 32 together with the respective P-value of the Wilcoxon test will be provided. The Wilcoxon test statistic is equivalent to the score statistic for testing global treatment difference in interval distributions from the proportional odds cumulative logistic model (Natarajan et al 2012).

To test the non-inferiority of brolucizumab compared to aflibercept in terms of average change in BCVA from baseline at Week 28 and Week 32, a two-sided 95% confidence interval for the treatment difference will be derived from an analysis of variance (ANOVA) model with treatment arm, baseline BCVA categories and age categories as fixed effects. The baseline BCVA and age categories will be specified in the SAP. In order to demonstrate non-inferiority of average change in BCVA from baseline at Week 28 and Week 32, the lower limit of the two-sided 95% confidence interval for the treatment difference (brolucizumab – aflibercept) must be greater than -4 letters representing the non-inferiority margin. Furthermore, the respective one-sided P-value for non-inferiority in terms of change in BCVA assessed at significance level of 0.025 will be provided.

Upon significance of both non-inferiority of average change in BCVA from baseline at Week 28 and Week 32 and superiority of distribution of the last interval without disease activity up to Week 32, the primary objectives of this study will be satisfied.

The FAS will be used as primary population to analyze the co-primary endpoints.

12.4.3 Handling of missing values/censoring/discontinuations

The imputation of missing data will be handled by defining the estimand framework. The primary estimands are described by the following four attributes:

1. The **target population** is defined by the study inclusion and exclusion criteria. The protocol defines the use of allowed concomitant medications for this target population, as well as medications which are prohibited.
2. The **co-primary variable 1** is proportion of patients in q4w, q8w, and q12w intervals (interval distribution) at last interval with no disease activity up to Week 32 (if there was

[redacted]

disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 8 weeks). The **co-primary variable 2** is average of change in BCVA from baseline at Week 28 and Week 32.

3. The **intercurrent event** describes how events that occur after randomization are captured when assessing the co-primary variables. Post-randomization events of interest in this study are assessed as:
   1. Discontinuation of study treatments
   2. Treatment interruption
4. The **summary measure**s are the P-values of the hypothesis testings to demonstrate superiority of brolucizumab compared to aflibercept in terms of interval distribution at Week 32 as per the co-primary variable 1 AND to demonstrate non-inferiority of brolucizumab compared to aflibercept with respect to average of change in BCVA from baseline at Week 28 and Week 32, as per the co-primary variable 2.

The primary estimands and other supportive estimands of interest are described in Table 12-1 below, together with their key attributes. The estimands outlined below will be discussed in further detail in the SAP.

Table 12-1 Primary and supportive estimands

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Primary estimand 1 (interval distribution)	Proportion of patients in q4w, q8w, q12w intervals at the last treatment interval with no disease activity assessed at Week 32	FAS	Before Week 16 (initiation phase): q4w From Week 16 included (TtC phase): last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	*Last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	Superiority testing using a one-sided Wilcoxon test

[redacted]

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Primary estimand 2 (change in BCVA)	Average BCVA change from baseline at Week 28 and Week 32	FAS, FAS data collected until the participant discontinued study treatment and started alternative treatment(s), will be included. BCVA scores collected after subjects discontinued early from study treatment will not be analyzed	LOCF	LOCF	Analysis of variance (ANOVA) model including terms for treatment arm (factor), baseline BCVA categories and age categories
Supportive estimand 1 (interval distribution)	Proportion of patients in q4w, q8w, q12w intervals at the last treatment interval with no disease activity assessed at Week 32; excluding patients with protocol deviations with impact as per definition of PPS	PPS**	Before Week 16 (initiation phase): q4w From Week 16 included (TtC phase): last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	*Last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	Superiority testing using a one-sided Wilcoxon test

[redacted]

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Supportive estimand 2 (change in BCVA)	Average BCVA change from baseline at Week 28 and Week 32; excluding patients with protocol deviations with impact as per definition of PPS	PPS** PPS** data collected until the participant discontinued study treatment and started alternative treatment(s), will be included. BCVA scores collected after subjects discontinued early from study treatment will not be analyzed	LOCF	LOCF	Analysis of variance (ANOVA) model including terms for treatment arm (factor), baseline BCVA categories and age categories
Sensitivity to primary estimand 1 (interval distribution)	Proportion of patients in (q4w, q8w, q12w) at the last treatment interval with no disease activity assessed at Week 32	FAS	Before Week 16 (initiation phase): q4w From Week 16 included (TtC phase): last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	*Last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	Cumulative logistic model with the proportional odds assumption

[redacted]

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Sensitivity to primary estimand 2 (change in BCVA)	Average BCVA change from baseline at Week 28 and Week 32	FAS, FAS data collected until the participant discontinued study treatment and started alternative treatment(s), will be included. BCVA scores collected after subjects discontinued early from study treatment will not be analyzed	LOCF	LOCF	Analysis of covariance (ANCOVA) model including terms for treatment arm (factor), baseline BCVA (as continuous variable) and age (as continuous variable)
Sensitivity to primary estimand 2 (proportion in q12w)	Proportion of patients in q12w at the last treatment interval with no disease activity assessed at Week 32	FAS	Before Week 16 (initiation phase): q4w; From Week 16 included (TtC phase): last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	*Last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	Logistic model

[redacted]

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Sensitivity to primary estimand 3 (proportion in q12w)	Proportion of patients in q12w at the last interval with no disease activity assessed at Week 32	PPS**	Before Week 16 (initiation phase): q4w; From Week 16 included (TtC phase): last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	Last interval with no disease activity (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks)	Logistic model

LOCF: Last Observation Carried Forward
*: If the duration of the last interval falls within the following ranges of [q4w, q8w) or [q8w, q12w) or ≥ q12w then the floor value of these ranges i.e. q4w, q8w, or q12w, respectively, will be used for imputation.
**: Patients who take prohibited concomitant medication are already excluded from PPS as taking prohibited medication is considered a protocol deviation with impact.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

As a sensitivity analysis for the superiority of brolucizumab compared to aflibercept with respect to the last interval distribution with no disease activity (q4w, q8w, and q12w) at Week 32 using a parametric method, a cumulative logistic model with consideration of the proportional odds assumption will be performed based on FAS (Table 12-1). The point estimate of the odds ratio of making response at or below any category of interval distribution between aflibercept and brolucizumab obtained from the model, the respective 95% confidence interval of the odds ratio and the P-value of the treatment effect in this model using the likelihood ratio test assessed at one-sided significance level of 0.025 will also be provided. In case the proportional odds assumption test is significant, the non-proportional odds assumption might be considered.

As a sensitivity analysis for the non-inferiority of brolucizumab compared to aflibercept with respect to average change in BCVA from baseline at Week 28 and Week 32, analysis of covariance (ANCOVA) including independent variables of treatment arm (factor), age

[redacted]

(continuous variable) and baseline BCVA (continuous variable) will be provided (Table 12-1). Other covariates may also be specified in the SAP.

Supportive analyses

As a supportive analysis, the analysis of the co-primary endpoints will be repeated based on PPS (Table 12-1).

All aforementioned missing data handling approaches will be applied for this supportive analysis too.

Sensitivity estimand in exposed and non-exposed to the urgent safety measures: As a sensitivity analysis for the superiority of brolucizumab compared to aflibercept with respect to the last interval distribution with no disease activity at Week 32, the proportion of subjects with 12-week intervals as the last interval with no disease activity at Week 32 is compared before and after the urgent safety measures were introduced. The analyses are performed in FAS and PPS based on the Binomial test of proportions and the logistic regression model with adjustments for the baseline age and BCVA.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoint(s)

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

To evaluate the durability of brolucizumab relative to aflibercept

- Distribution of the last interval with no disease activity up to Week 64 (if there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks) will be provided.
- Distribution of the maximal interval with no disease activity up to Week 64 will be provided.
- Number (%) of patients with no disease activity at Weeks 14 and 16 will be provided. In addition, 95% CI will also be provided.
- Time from last loading injection to first visit with no disease activity will be descriptively summarized and Kaplan-Meier plots per treatment arm will be provided.

The FAS will be used to analyze durability outcomes.

To evaluate the functional outcomes of brolucizumab relative to aflibercept

- Summary statistics of average change in BCVA from baseline at Week 60 and Week 64 per treatment arm will be provided.
- Number (%) of patients with occurrence of BCVA improvements of ≥ 10, and ≥ 15 letters from baseline at Week 32, Week 64 and the last injection visit per treatment arm will be provided.
- Number (%) of patients with occurrence of BCVA ≥ 69 letters at Week 32, Week 64 and the last injection visit per treatment arm will be provided.

The FAS will be used to analyze functional outcomes.

To evaluate the anatomical outcomes with brolucizumab relative to aflibercept

[redacted]

- Average change in CSFT from baseline as assessed by SD-OCT at Weeks 28 and 32 per treatment arm will be provided.
- Average change in CSFT from baseline as assessed by SD-OCT at Weeks 60 and 64 per treatment arm will be provided.
- Number (%) of patients with presence of IRF and/or SRF and sub-RPE fluid in the central subfield, as assessed by SD-OCT at Weeks 28 and 32, by number of visits (0, 1, 2 visits) per treatment arm will be provided.
- Number (%) of patients with presence of IRF and/or, SRF, and sub-RPE fluid in the central subfield, as assessed by SD-OCT at Weeks 60 and 64, by number of visits (0, 1, 2 visits) per treatment arm will be provided.

The FAS will be used to analyze anatomical outcomes.

12.5.2 Safety endpoints

The safety set will be used for all safety analyses.

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

To assess the safety and tolerability of brolucizumab relative to aflibercept

- Incidence of ocular and non-ocular AEs up to Week 64 per treatment arm will be provided.

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment arm.

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 will be provided. In particular, summary tables for adverse events of special interest (AESIs) will summarize only on-treatment events, with a start date during the on-treatment period. 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

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

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 double-masked 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.

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

The number (%) of subjects with adverse events of special interest will be summarized by treatment, primary system organ class and preferred term.

[redacted]

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

Vital signs

Clinically relevant abnormalities in vital signs data will be listed by treatment arm, subject, and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

Abnormal laboratory values of potential clinical importance including hematology, laboratory data will be listed by treatment arm, subject, and visit/time and if normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

12.5.3 Patient reported outcomes

The secondary objective and endpoint for PRO in this study is as follows:

To evaluate the effect of brolucizumab relative to aflibercept on PRO

- VFQ-25 change from baseline at Week 32 and 64 in total and subscale scores per treatment arm will be provided.

The FAS will be used to analyze PRO outcomes.

[redacted]

12.7 Interim analyses

The primary analyses will be conducted when all ongoing subjects have completed their Week 32 visit. Subjects will remain in the study and will continue to receive masked treatment through the planned study duration of 64 weeks, to allow for further evaluation of efficacy and safety.

The analyses of the co-primary endpoints and other selected efficacy/safety variables up to Week 32 will be described in a separate interim analyses SAP. The primary analysis will be performed by unmasking of selected staff from the Sponsor (Section 6.4) who are not involved in the direct conduct of the trial.

Treatment masking of individual subjects will remain intact for all subjects, masked investigators and selected staff from the Sponsor who have contact with subjects or investigators until the final database lock has occurred.

[redacted]

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size calculation is based on the co-primary endpoint of the distribution of the last interval with no disease activity up to Week 32 and average change in BCVA from baseline at Weeks 28 and 32 using the following assumptions derived from the HAWK and HARRIER studies. The sample size analyses were performed before the urgent safety measures were introduced.

- expected interval distribution for aflibercept 2 mg and brolucizumab 6 mg (Table 12-2)

Table 12-2 Expected interval distribution for aflibercept 2 mg and brolucizumab 6 mg

Treatment	4w	8w	12w
Aflibercept	20%	35%	45%
Brolucizumab	13%	32%	55%

- common standard deviation of change in BCVA from baseline of 13 letters for both brolucizumab and aflibercept.

In order to calculate the sample size for the co-primary endpoint of:

1. Superiority of brolucizumab over aflibercept in terms of interval distribution; AND
2. Non-inferiority of brolucizumab compared to aflibercept in terms of average change in BCVA from baseline at Week 28 and Week 32.

Two one-sided tests each with $\alpha = 0.025$ and power of 80% are conducted.

For superiority of the interval distribution, a one-sided Wilcoxon test for comparing two ordered multinomial populations (H0: brolucizumab and aflibercept interval distribution are equal, vs H1: brolucizumab interval distribution is larger than aflibercept interval distribution) is performed which results in a sample size of 622 patients.

Secondly, for non-inferiority of average change in BCVA from baseline, a one-sided T-test assuming equal means with non-inferiority margin of 4 letters and a common standard deviation of 13 letters is performed which provides a sample size of 334 patients.

As in this co-primary endpoint, both superiority in terms of interval distribution and non-inferiority in terms of change in BCVA from baseline must be met, the maximum sample size of two hypothesis testings, i.e. 622, is considered. With the sample size of 622 patients, an overall power of 77.5% for the co-primary endpoint is obtained (97% re-calculated power for non-inferiority in terms of BCVA).

Finally, to take into account loss to follow-up of 10%, the required sample size of the study will be 692 patients, who will be randomized to each treatment arm in a 1:1 ratio (346 patients in each treatment arm).

The sample size calculations were performed using StatXact 9.0 and PASS 11.

[redacted]

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 International Council on Harmonization (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.). Results from the interim analyses may be published prior to study completion.

Publications will be developed based on guidance provided by the Sponsor and the TALON Steering committee.

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.

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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.

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