NOVARTIS

Novartis Research and Development

RTH258/brolucizumab

Clinical Trial Protocol CRTH258A2303E1/ NCT04597632

A 56-week phase IIIb/IV, open-label, one-arm extension study to assess the efficacy and safety of brolucizumab 6 mg in a Treat-to-Control regimen with maximum treatment intervals up to 20 weeks for the treatment of patients with neovascular age-related macular degeneration who have completed the CRTH258A2303 (TALON) study

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List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
ANOVA	Analysis of Variance
BCVA	Best Corrected Visual Acuity
CDP	Clinical Development Plan
CFP	Color Fundus Photography
CFR	Code of Federal Regulation
CI	Confidence Interval
CMO&PS	Chief Medical Office and Patient Safety
CNV	Choroidal Neovascularization
CRC	Central Reading Center
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSFT	Central Subfield Thickness
DA	Disease Activity
eCRF	electronic Case Report/Record Form
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 Analyses Set
FIR	First Interpretable Results
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IOI	Intraocular Inflammation
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRF	Intraretinal Fluid
IRT	Interactive Response Technology
IVT	Intravitreal injection
LOCF	Last observation carried forward
MedDRA	Medical dictionary for regulatory activities

MMRM	Mixed Model for Repeated Measures
mg	milligram(s)
mL	milliliter(s)
nAMD	neovascular Age-related Macular Degeneration
OCT	Optical Coherence Tomography
PDT	Photodynamic Therapy
PPS	Per Protocol Set
PRN	Pro Re Nata (as needed)
q12w	Every 12 weeks
q16w	Every 16 weeks
q20w	Every 20 weeks
q4w	Every 4 weeks
q8w	Every 8 weeks
QMS	Quality Management System
RO	Retinal Vascular Occlusion
RPE	Retinal Pigment Epithelium
RV	Retinal Vasculitis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
scFV	single-chain antibody fragment
SD	Standard Deviation
SD-OCT	Spectral Domain Ocular Coherence Tomography
SOC	Standard of Care
SOP	Standard Operation Procedures
SRF	Subretinal Fluid
SUSAR	Suspected Unexpected Serious Adverse Reaction
T&E	Treat-and-Extend
TtC	Treat-to-Control
USM	Urgent Safety Measures
VEGF	Vascular Endothelial Growth Factor

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time.
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained.
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study.
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy).
Participant	A trial participant (can be a healthy volunteer or a patient).
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized participant.
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study.

Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant.
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy.
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data.

Amendment 2 (20-Oct-2021)

Amendment rationale

The main purpose of this amendment is to reduce the sample size for this study.

The initial sample size calculation for this open-label, one arm extension study was mainly based on the assumption that all eligible subjects completing the core study could be enrolled. Following the USM dated 27-May-2021, subjects requiring study treatment every 4 weeks will be discontinued, therefore, the originally planned number of subjects transitioning from the core study into the extension study will be reduced. Consequently, the sample size was re-assessed with the focus on the estimation of subjects who will be on a q20w interval. This estimation can be achieved with acceptable precision with a sample size of 250. The study objectives will still be assessed with the revised sample size.

In addition, information was included on the gender imbalance in the reported rates of intraocular inflammation-related adverse events following brolucizumab treatment.

Changes to the protocol

- Protocol summary: Aligned with amendment 2.
- Section 3 Study design: Changed the number of participants to be enrolled from approximately 622 to 250. In addition, removed stipulation for minimum time interval between two injections of 21 days as a 4-week interval is no longer an option.
- 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.
- Section 5 Study population: Changed the number of participants to be enrolled from approximately 622 at 190 sites to 250 at 60 sites.
- Section 6.7.2 Instruction for prescribing and taking study treatment, and Section 10 Safety monitoring and reporting: For consistency, in the sentence “If retinal vasculitis and/or retinal vascular occlusion is confirmed, subjects should be discontinued from study treatment.”, replaced “should” with “must”.
- Section 9.1.2 Withdrawal of informed consent: Section was replaced with updated language based on latest protocol template.
- Section 10 Safety monitoring and reporting: For consistency, incorporated the mandatory safety phone call required two weeks after the first injection (defined in Table 8-2) in the consolidated list for safety monitoring.
- Section 10.1.3 SAE reporting: Clarified the timing for SAE reporting to Novartis as per latest protocol template.
- Section 12.8 Sample size calculation: Section updated to implement the sample size reduction from 622 down to approximately 250 participants expected to be enrolled into the extension study.
- Minor editorial changes (e.g. typographical mistakes, grammatical changes, rewording) to improve flow and consistency have been made throughout the protocol.

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.

Summary of previous amendments

Amendment 1 (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.

Changes to 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. In sub-section "CRTH258A2303 study (TALON)", clarified that, in the core study, the treatment intervals after the initiation phase with 3 monthly injections at Baseline, Week 4, and Week 8 will range from 8 weeks to 16 weeks, and that subjects requiring injections every 4 weeks after the loading phase will be discontinued from further study treatment. In addition, the results of the mechanistic study BASICHR0049 of blood samples from nAMD patients exposed to brolucizumab and having subsequently developed RV and/or RO were added.
- Section 2.1 Primary estimands, and Table 2-1 Objectives and related endpoints: Text added to clarify analysis of 4-week treatment intervals.

- Section 3 Study design: Changes were made to clarify the minimal treatment interval and the requirement to discontinue from study treatment if subjects require treatment every 4 weeks beyond the loading phase. Reference to Section 9.1.1 added regarding early treatment discontinuation.
- Figure 3-1 Study design: Updated the range for treatment intervals.
- Section 4.1 Rationale for study design: Modified to clarify the shortest treatment interval
- Section 4.2 Rationale for dose/regimen and duration of treatment: Language added to provide background of the USM.
- 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 5.2 Exclusion criteria: Added criteria to exclude subjects who require anti-VEGF IVT injections every 4 weeks.
- 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 6.2.1.1 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 6.7.2 Instruction for prescribing and taking study treatment: Changes were made to clarify the requirement to discontinue from study treatment if subjects require treatment every 4 weeks. Changes also made to update that if RV and/or RO is confirmed, subjects must 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.
- Figure 6-1 Treatment regimen: Updated to update the range for treatment intervals.
- Table 8-1 Assessment schedule: Columns added for assessment visits after start of standard of care and for early treatment discontinuation visits, including respective footnotes.
- Section 9.1.1 Study treatment discontinuation and study discontinuation: Clarification and instructions were added for subjects who discontinue from study treatment early.
- 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 must 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.
- Table 12-1 Primary and sensitivity estimands: Clarification added regarding BCVA scores collected after start of standard of care. The estimands are re-ordered to match the order in the Table 2-1. In addition, sensitivity estimands are added regarding the proportion of q12w.

- Section 12.4.5 Sensitivity analyses for primary endpoint/estimand: Sensitivity analysis added regarding USM. Added MMRM abbreviation.

Other changes incorporated in this amendment:

- List of abbreviations: New abbreviations added in line with amendment 1.
- Protocol summary: Aligned with amendment 1.
- Section 2 Objectives and endpoints: Revised to make it clear that the baseline being referred to is that of the extension study and not the core study baseline. The prefix extension is added before the word “baseline”. There are no changes in the end-points or the primary analysis. The same prefix ”extension” will be added for the CSFT and OCT end-points with no changes made to the analyses.
- Section 6.3.1 Participant numbering: Updated section on participant numbering, because participant IDs in EDC may be different in IRT.
- Section 6.7.2 Instruction for prescribing and taking study treatment. Changes made to update that if 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 investigator should evaluate the appropriateness of continuing further with study treatment. This has been updated in several sections.
- Section 7 Informed consent procedures: Removed text to align with Investigator Brochure and ICF. Section 8 Visit schedule and assessments: Clarification added for visit windows.
- Table 8-1 Assessment schedule and Table 8-2 Safety assessments: Updated the visit window for mandatory safety phone call timing. The timing is changed from one week to two weeks and the window from +7 days to +14 days. Reason being that the median time of onset of AESI’s is about 21 days (as per Novartis Pharmacovigilance data) and therefore expanding the time frame may be more appropriate for picking up AE’s.
- Section 8.4 Safety: Added a reference for monitoring, assessment and management of adverse events of inflammation, retinal vasculitis and/or retinal vascular occlusion. Also added imaging as key safety assessment. This change has been made in multiple sections of the protocol.
- 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 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 10.1.4 Pregnancy reporting: Clarification added regarding follow-up during pregnancy and after childbirth.
- Section 12.5.1 Correction of typographical error, and Section 12.5.2 Safety endpoints: Removed “by treatment” because only one treatment arm in the study, and clarified that clinically relevant abnormalities in vital signs will be listed.
- Section 12.8 Sample size calculation: Clarification regarding sample size analyses.

Protocol summary

Protocol number	CRTH258A2303E1
Full Title	A 56-week, phase IIIb/IV, open-label, one-arm extension study to assess the efficacy and safety of brolucizumab 6 mg in a Treat-to-Control regimen with maximum treatment intervals up to 20 weeks for the treatment of patients with neovascular age-related macular degeneration who have completed the CRTH258A2303 (TALON) study
Brief title	An extension study assessing the efficacy and safety of brolucizumab in a Treat-to-Control regimen in patients with neovascular age-related macular degeneration who have completed the CRTH258A2303 (TALON) study
Sponsor and Clinical Phase	Novartis Phase IIIb/IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate the efficacy and safety of brolucizumab used in a Treat-to-Control regimen for treatment of patients with neovascular age-related macular degeneration with the objective to assess the potential for long durability up to 20 weeks
Primary Objective(s)	To evaluate the extended durability of brolucizumab in a Treat-to-Control regimen assessed as duration of the last interval with no disease activity up to Week 56. To evaluate the functional outcomes of brolucizumab in a Treat-to-Control regimen assessed as average change of best corrected visual acuity from the extension baseline at week 52 and week 56
Secondary Objectives	To evaluate the anatomical outcomes of brolucizumab in all patients and per randomized arm in the core study - assessed by central subfield thickness and number of visits with presence of intra-retinal fluid and/or sub-retinal fluid, and sub-retinal pigment epithelium fluid in the central subfield, as seen by spectral domain ocular coherence tomography at Week 52 and Week 56 To assess the durability of brolucizumab in all patients and/or per randomized arm in the core study - measured as duration of last interval and maximum interval with no disease activity up to week 56, as well as change of the duration of last interval with no disease activity between extension baseline and Week 56 To assess the functional outcomes of brolucizumab per randomized arm in the core study by measuring change of best corrected visual acuity from extension baseline to week 52 and week 56 To assess the safety of brolucizumab – measured as occurrence of ocular and non-ocular adverse events up to week 56
Study design	This is a 56-week, one-arm, open-label, multi-center extension study where all patients are to be treated with brolucizumab up to week 52 in a Treat-to-Control regimen with treatment intervals from 8 weeks up to maximum 20 weeks
Study population	Approximately 250 of the subjects who have completed the CRTH258A2303 (TALON) study are expected to be enrolled in approximately 60 sites worldwide

Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study • The participant has successfully completed the TALON core study at the week 64 visit (End of Study)
Key Exclusion criteria	• Participant has a medical condition or personal circumstance which precludes study participation or compliance with study procedures, as assessed by the Investigator • Participant has discontinued study treatment in the core study • Anti-VEGF treatment is futile in the study eye, in the investigator's opinion • 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
Study treatment	Brolucizumab 6 mg/0.05 mL
Efficacy assessments	• Best corrected visual acuity using ETDRS-like charts • Spectral Domain Optical Coherence Tomography • Color Fundus Photography
Key safety assessments	• Monitoring of adverse events • Ophthalmic examinations and imaging • Vital signs (pulse and blood pressure) • Pregnancy testing
Other assessments	Ocular Coherence Tomography Angiography
Data analysis	The primary analyses will be conducted in the full analyses set with missing data imputed based on the last observation carried forward method. Duration of the last interval with no disease activity up to Week 56 will be estimated using proportions with two-sided 95% Binomial Confidence Intervals and simultaneous Confidence Intervals obtained based on Goodman method (1965). The change in best corrected visual acuity from extension baseline at Week 52 and Week 56 will be estimated based on an analysis of covariance model with baseline best corrected visual acuity and age. The estimates of the change in best corrected visual acuity will be accompanied by two-sided 95% Confidence Intervals. Additional analysis is planned to evaluate the impact of the 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

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). Intravitreal administration of anti-VEGF treatments is the current standard of care in nAMD.

Treat-and-Extend treatment regimen

Typically, a Treat-and-Extend (T&E) treatment regimen includes a loading phase of monthly injections, followed by a maintenance phase during which the injection interval is progressively prolonged if there is no disease activity (DA), primarily determined by optical coherence tomography (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. T&E treatment regimen has been approved in the labels of anti-VEGF treatments, such as ranibizumab (Lucentis®) and aflibercept (Eylea®) in Europe and many other countries. The 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 DA, 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 AMD, the number of visits remain relatively high for most patients as the average number of injections in Lucentis® and Eylea® studies range from 8 to 10.1 in the first 12 months and from 10.4 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, Gillies et al 2019, Kertes et al 2019, Ohji et al 2020).

There still is a need for highly effective treatments that prolong intervals between injections and further reduce treatment burden, while maintaining vision gains.

Brolucizumab

Brolucizumab (RTH258, ESBA1008, AL-86810), is a humanized single-chain antibody fragment (scFv) with a molecular weight of ~26 kilodalton (kDa) which inhibits VEGF-A binding to its receptors VEGFR1 and VEGFR2. Brolucizumab is administered by intravitreal injection and has been approved by the US Food and Drug Administration on 7 Oct 2019 and many other countries (e.g. EU countries, Australia, Japan and Canada) subsequently, for the treatment of nAMD.

The efficacy and safety of brolucizumab in subjects with nAMD has been demonstrated in two 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 DA, 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 participants in the brolucizumab 6 mg arm maintained exclusively on the q12w dosing interval (56% in HAWK and 51% in HARRIER). Significantly fewer patients in the brolucizumab 6 mg arm had DA 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). These advantages for brolucizumab were maintained in the second year. Safety was comparable between the treatment arms over 2 years.

Since the first marketing authorization approval in October 2019 for the treatment of nAMD, adverse events of retinal vasculitis and/or retinal vascular occlusion, that may result in severe vision loss and typically in the presence of intraocular inflammation, have been reported from post-marketing experience with brolucizumab (Beovu®).

Results of the mechanistic study BASICHR0049 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 loading phase and when patients who develop RV and/or RO are discontinued from further treatment with brolucizumab.

For further details, please refer to the investigator brochure (IB) or package insert whichever is applicable.

CRTH258A2303 study (TALON)

There is an ongoing study CRTH258A2303 (TALON) which 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 three monthly injections at Baseline, Week 4, and Week 8 (loading phase), followed by an identical 4-week-adjustment Treat-to-Control regimen with treatment intervals from 8 to 16 weeks. Subjects requiring injections every 4 weeks after the loading phase will be discontinued from further study treatment.

This study, CRTH258A2303E1, is an extension study of the CRTH258A2303 (TALON) study, aiming at gathering additional long-term efficacy and safety evidence about brolucizumab in a TtC treatment regimen with treatment intervals further extended up to 20 weeks in nAMD. It intends to contribute to the growing clinical dataset of brolucizumab by generating supplementary evidence on treatment safety, efficacy, and durability in nAMD.

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of brolucizumab used in a Treat-to-Control (TtC) regimen with maximum treatment intervals up to 20 weeks for the treatment of patients with neovascular age-related macular degeneration (nAMD) who have completed the CRTH258A2303 study (TALON).

In addition, switch data from aflibercept to brolucizumab is collected.

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 evaluate the extended durability of brolucizumab in a TtC regimen with respect to the duration of treatment intervals at Week 56	• Duration of the last interval with no DA up to Week 56
• To evaluate the functional outcomes of brolucizumab in a TtC regimen with respect	• Change in BCVA from extension baseline at Week 52 and Week 56

Objective(s)	Endpoint(s)
to average change in BCVA at Week 52 and Week 56	
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the anatomical outcomes of brolucizumab in all patients and per randomized arm in the core study	• Change in CSFT from extension baseline to Week 52 and Week 56 Number of visits with presence of IRF and/or SRF, and sub-RPE fluid in the central subfield, as assessed by SD-OCT at Week 52 and Week 56
• To assess the durability of brolucizumab in all patients and/or per randomized arm in the core study	• Duration of the last interval with no DA up to Week 56 Duration of the maximal intervals with no DA up to Week 56 Change of the duration of last interval with no DA between extension baseline and Week 56
• To assess the functional outcomes of brolucizumab per randomized arm in the core study	• Change in BCVA from extension baseline to Week 52 and Week 56
• To assess the safety of brolucizumab	• Occurrence of Ocular and Non-ocular AEs up to Week 56
[redacted]	

2.1 Primary estimands

There are two primary clinical questions of interest: 1. what is the effect of brolucizumab 6 mg on treatment interval extension? and 2. what is the effect of brolucizumab 6 mg on visual acuity change in a TtC regimen with maximum treatment intervals up to 20 weeks after treatment in patients with nAMD who have completed the CRTH258A2303 study?

These two effects were targeted to estimate the effect of brolucizumab in a TtC regimen with maximum treatment intervals up to 20 weeks without breaking masking of the CRTH258A2303 study (TALON).

The primary estimand is described by the following attributes:

1. Population: participants who have completed the CRTH258A2303 study (TALON) irrespective of the study treatment received in the core study. Further details about the population are provided in Section 5.

2. The co-primary variable 1 is change in BCVA from extension baseline at Week 52 and Week 56, i.e. the average change in BCVA from extension Baseline to Week 52 and Week 56. The co-primary variable 2 is the duration of the last interval with no DA up to Week 56, i.e. the proportion of participants in q4w, q8w, q12w, q16w and q20w intervals (interval distribution) at last interval with no DA up to Week 56 (subjects who will be assigned to a 4-week interval will be analyzed as such, but discontinued from further study treatment).

3. Treatment of interest: brolucizumab 6 mg will be taken for the entire study duration. Further details about the investigational drug are provided in Section 6.

Handling of remaining intercurrent events:

- Study treatment discontinuation: For the co-primary endpoint of change in BCVA, a hypothetical treatment strategy will be applied to estimate the treatment effect under the hypothetical assumption that the patient would not start an alternative anti-VEGF treatment (i.e. standard of care therapy) on the study eye. For the co-primary endpoint of duration of treatment interval, a 'while on treatment strategy' will be applied as disease stability assessment will not be performed after the patient discontinued treatment.
- Study treatment interruption: For both the co-primary endpoints, a treatment policy strategy will be applied.

The summary measure for the co-primary variable 1 is the interval distribution, and for the co-primary variable 2 is the least square means.

2.2 Secondary estimands

Not applicable

3 Study design

This study is a 56-week, open-label, one-arm extension study in participants who have completed the CRTH258A2303 study (TALON).

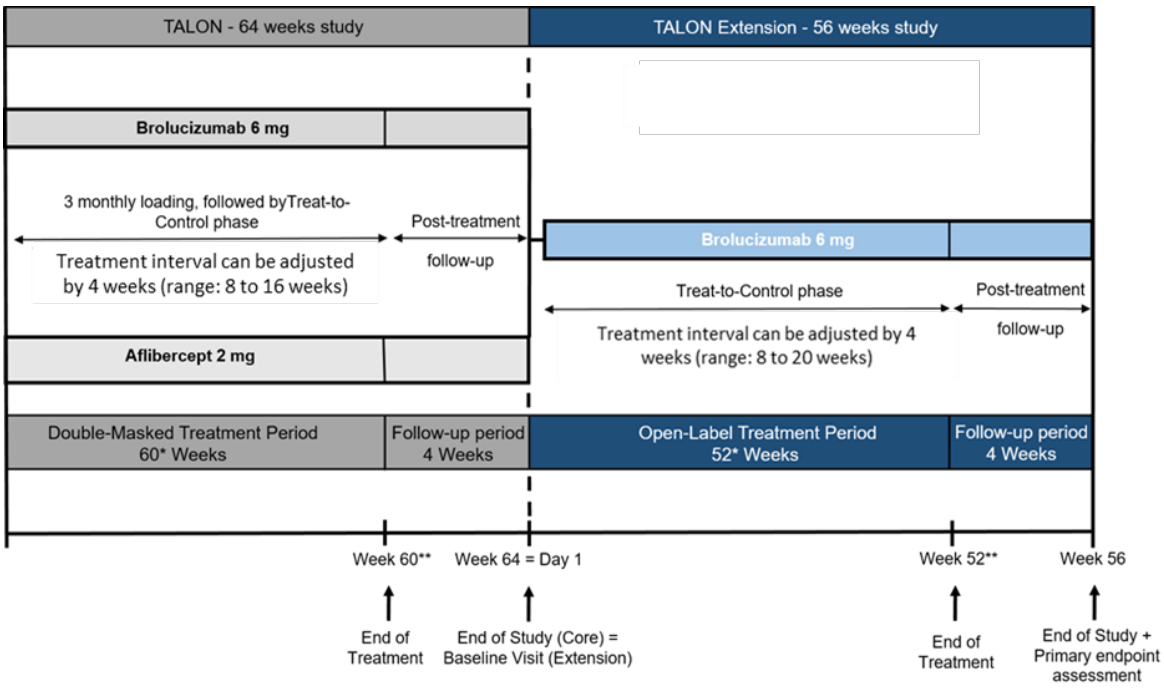
Participants who consent and meet all the inclusion and none of the exclusion criteria will be enrolled into this extension study and receive brolucizumab 6 mg in a TtC regimen, irrespective of the treatment received in the core study.

Approximately 250 participants from the core study will enter the extension study. The maximum study duration for a participant is 56 weeks, including post-treatment follow-up.

There will be two periods in this study, see Figure 3-1:

- Treat-to-Control treatment period: from Baseline (Day 1) to Week 52
- Post-treatment follow-up period: from Week 52 to Week 56.

Figure 3-1 Study design



Depending on visit schedules:
* 62 weeks (core) / 54 weeks (extension) ** Week 62 (core) / Week 54 (extension)

Baseline visit: Day 1

Participants should sign informed consent no later than the Week 64 (EOS) visit of the core study. Baseline visit for the extension study (extension baseline) should occur on the same day as the Week 64 (EOS) visit of the core study. Participants will be assessed on inclusion and exclusion criteria of the extension study at the baseline visit.

The study eye will be the same eye that received brolucizumab or aflibercept treatment in the core study.

Treat-to-Control treatment period: Day 1 to Week 52

All efforts should be made to adhere to the study visit schedule within a ±14day window (baseline visit should occur on the same day as the Week 64 (EOS) visit of the core study). For a given study visit, assessments can be performed on 2 consecutive days provided both days occur within the visit window. Study treatment is intended to be administered on the day of the study visit, or, if this is not possible, within 3 days after the assessments have taken place.

The first injection visit in the extension study will be based on the planned treatment interval as decided by the investigator at the last injection visit of the core study. The treatment interval can then be extended by 4 weeks at a time based on the investigator's judgment of visual and/or anatomic outcomes, as per guidance provided, for example, no change in visual acuity and in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.). Patients who have the last injection interval with no DA of q16w in the core study should be injected at another q16w

interval before start to extend intervals in the extension study. The maximal treatment interval is 20 weeks.

The injection interval can also be maintained if the investigator deems that the patient will not benefit from injection interval extension.

The interval should be shortened by 4 weeks at a time if DA recurs (to a minimal interval of 8 weeks).

The investigators have options to plan for an inspection visit when the treatment intervals are extended. Further details are provided in Section 6.7.2.

For all participants, the last potential study treatment will be at the Week 52 visit. Participants who will receive a study treatment at an inspection visit may have a study visit at Week 54. For those participants, the Week 54 visit will take place in lieu of the visit at Week 52.

Post-treatment follow-up period: Week 52 to Week 56

For all participants completing the study, the EOS (Week 56 ±21 days) assessments will be performed 4 weeks after the last treatment administration (Week 52/54).

Participants withdrawn from the study prior to study completion within less than 4 weeks after the last study treatment will be asked to return for an EOS visit, 4 weeks (±14 days) following their last study treatment administration (EOT). For early treatment discontinuations (ETD) refer to Section 9.1.1.

4 Rationale

4.1 Rationale for study design

The primary research interest is to assess the durability and functional outcome of brolucizumab treatment effect with treatment intervals up to 20 weeks, in all the eligible participants who will have completed the CRTH258A2303 (TALON) study, which compared the efficacy and safety of brolucizumab and aflibercept administered in the same TtC regimen with the treatment intervals from 8 to 16 weeks. Hence, this study is designed as an open-label, one-arm study. And the treatment interval adjustment will continue from the last treatment interval in the CRTH258A2303 (TALON) study, i.e. q8w, q12w and q16w, with an additional treatment interval of 20 weeks added in the extension 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 DA by investigators. The distribution of the last interval with no DA up to Week 56 will be analyzed. If there is DA during the last interval up to Week 56, 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) will also be assessed. 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 co-primary endpoint will be assessed as average change from the extension baseline in BCVA at Week 52 and Week 56. In the TtC phase, patients will receive injections at 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 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 two time points 4 weeks apart will mitigate this potential bias.

Approximately 52 weeks of treatment in a TtC regimen, allows up to two consecutive q20w intervals and the evaluation of the long-term safety and efficacy of brolucizumab.

4.2 Rationale for dose/regimen and duration of treatment

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

- Brolucizumab is well tolerated at a dose of 6 mg administered three times every four weeks during the loading phase, based on the previous clinical Phase III program in which 1088 participants 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 TtC phase to reduce the treatment burden (see Section 1.1).
- In a recent Treat and Extend study, 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 DA, following 3 consecutive 4-week injections and a 8-week injection (Ohji et al 2020). 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 DA as seen in RTH258-C001 - HAWK and RTH258-C002 - HARRIER. Hence, the treatment interval range in the ongoing CRTH258A2303 (TALON) study is from 4 to 16 weeks for brolucizumab and aflibercept.
- Evidence from ranibizumab study in nAMD (CRFB002A2413 – SUSTAIN) showed that 20.5% of patients did not receive any additional dose during a PRN phase (re-treatment criteria were guided by VA and OCT variables) for periods lasting up to eight months. It indicates that some patients may not need frequent injections. These patients may benefit from brolucizumab 6 mg administered at 20-week intervals as in the current study.
- 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 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 protocol was amended to discontinue subjects from study treatment who require treatment every 4 weeks during the extension study.

- The route of administration is an intravitreal injection as for all anti-VEGF treatments currently approved for the treatment of nAMD.
- Study duration of 56 weeks allows two consecutive 20-week intervals to assess long-term efficacy and safety of brolucizumab in a TtC regimen.

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

Not applicable

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable

4.5 Risks and benefits

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring described in Section 6.7.2, Section 8.4 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-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 participant will not reliably comply, they should not be entered or continue in the study.

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 participants 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.

5 Study population

The study population will be adult male and female patients who have completed the CRTH258A2303 study (TALON) with the EOS visit at Week 64 and able to comply with study procedures.

Approximately 250 participants are expected to be enrolled in approximately 60 sites worldwide.

The study eye will be the same eye that received brolucizumab or aflibercept study treatment in the core study.

5.1 Inclusion criteria

The investigator will assess the eligibility of the participant and the study eye at the baseline visit and confirm eligibility for the extension study. Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.

2. The participant has successfully completed the TALON core study, as defined by providing assessments at the Week 64 visit (EOS) of the core study.

5.2 Exclusion criteria

Patients fulfilling any of the following criteria at study entry are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Participant has a medical condition or personal circumstance which precludes study participation or compliance with study procedures, as assessed by the Investigator.

2. Participant has discontinued study treatment in the core study.

3. Anti-VEGF treatment is futile in the study eye, in the investigator's opinion.

4. 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.

5. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the study drug administration and for 3 months after stopping the investigational medication. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). 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 baseline). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
- 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.

6. Subject requires study treatment every 4 weeks.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Brolucizumab 6 mg (RTH258 6 mg/0.05 mL)	Solution for injection	Intravitreal use	Prefilled syringes / Glass vials	Global

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

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

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

All eligible participants will receive brolucizumab 6 mg TtC treatment from baseline to Week 52.

6.1.4 Treatment duration

The planned duration of treatment is 52 weeks (54 weeks for the participants who may have received study treatment at an odd number of inspection visits). Discontinuation of study treatment for a participant occurs when study drug is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

Study treatment will also be discontinued for patients who require injections every 4 weeks.

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).

6.2 Other treatment(s)

6.2.1 Concomitant therapy

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

Concomitant medications which are ongoing at the time of the Week 64 (EOS) visit in the core study must be recorded, and entries in the extension study database should match those in the core study database as appropriate.

Each concomitant drug must be individually assessed against the prohibited medication Table 6-2. If in doubt, the investigator should contact the Novartis medical monitor before enrolling a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Fellow eyes

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

Study eyes

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.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed from the Week 64 (EOS) visit of the core study.

Table 6-2 Prohibited medications and procedures

Medication	Prohibition period	Action taken
Study Eye		
Any periocular injection or intraocular administration of corticosteroids (except if needed as a 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

Medication	Prohibition period	Action taken
Any investigational drug, biologic or device	Anytime	Discontinue study treatment
Medications known to be toxic to the lens, retina or optic nerve, including ethambutol, chloroquine/hydroxychloroquine, deferoxamine, phenothiazines and tamoxifen (except temporary use for COVID-19 treatment)	Anytime	Discontinue study treatment
Fellow eye		
investigational drug, biological, device	Anytime	None

6.2.3 Rescue medication

There will be no rescue medication for nAMD in the study eye. In case of lack of efficacy with the investigational drug for nAMD and if the investigator deems it is in the best interest of the participant 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 9.1.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant 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.

6.3.2 Treatment assignment, randomization

All participants will be treated with brolucizumab, no randomization will be performed in this study.

IRT will be used to assign kit numbers for each treatment occasion, in order to manage study drug supply at site level.

6.4 Treatment blinding

Treatment will be open to participants, investigators/site personnel, sponsor clinical trial team (CTT) and monitors while randomization data from the core study will be kept strictly

confidential for participants, investigators/site personnel, sponsor CTT and monitors until database lock.

Should there be a reasonable need to unmask the core study treatment before the database lock of this extension study, investigator shall contact Novartis.

6.5 Dose escalation and dose modification

Investigational treatment dose adjustment is not permitted. 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 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 investigational product to the participant. The date and time of all study treatment injections administered during the study and any deviations from the protocol treatment schedule will be captured by the study personnel or by field monitor on the appropriate study treatment dispensing form.

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

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational drugs Section 6.1. A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be registered in the IRT system and stored according to the instructions specified on the labels and in the Investigator's Brochure.

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

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

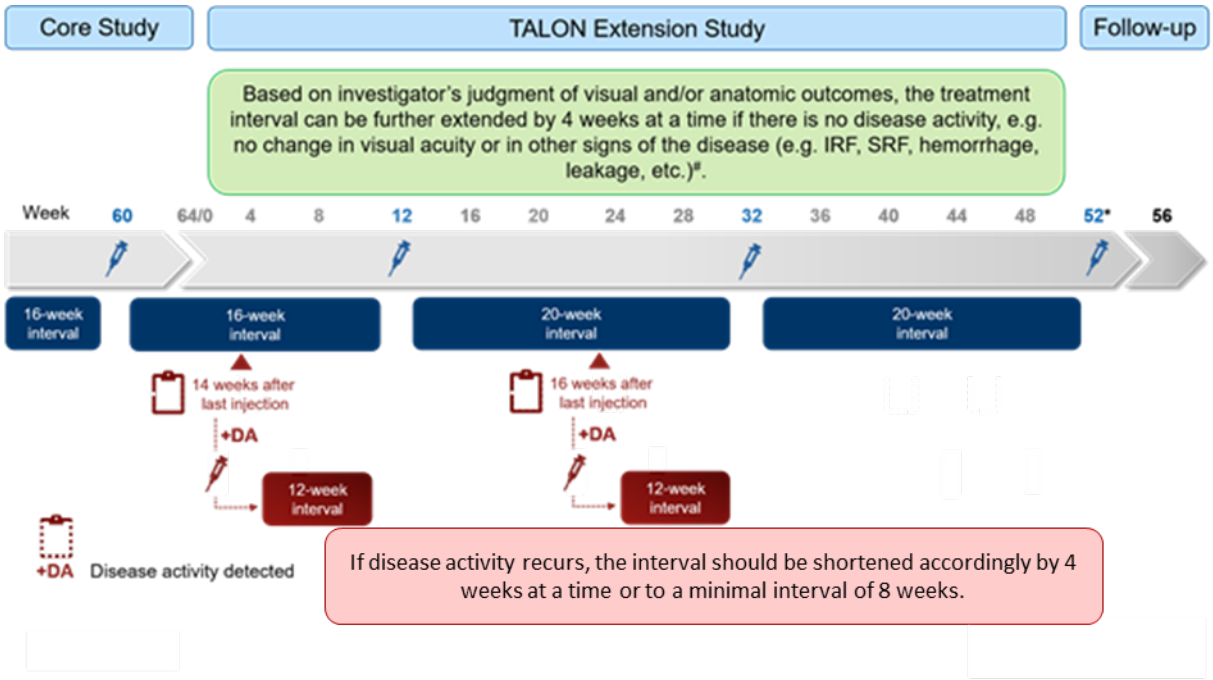
The investigator/site personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

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

6.7.2 Instruction for prescribing and taking study treatment

There will be only one treatment phase in the extension study which is similar to the TtC phase of the core study and is defined as follows:

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 54, depending on visit schedule

Treat-to-Control treatment phase (Baseline/Day 1 to Week 52):

Treatment intervals will be either 8 weeks, 12 weeks, 16 weeks, or 20 weeks. A subject must be discontinued from further study treatment if treatment is required every 4 weeks.

The participant will receive the first injection based on the next planned injection interval decided by the investigator at the last injection visit of the core study. For example, if a participant has the last injection visit at Week 60 of the core study, and the next planned injection interval is a q12w interval, the first injection visit for this participant will be planned at Week 8 of the extension study (12 weeks from Week 60 of the core study).

At each injection visit, DA should be assessed using anatomic and functional outcomes (e.g. SD-OCT, BCVA, etc.). Based on investigator's judgment of visual and/or anatomic outcomes, the treatment interval can be further extended by 4 weeks at a time, if there is no DA, i.e. no change in visual acuity and in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.).

Participants whose last injection interval in the core study is q16w and are without DA should be injected at another q16w interval in the extension study before extending to q20w in the extension study.

The treatment interval can also be maintained if the investigator deems the participant will not benefit from treatment interval extension.

If DA recurs, the interval should be shortened accordingly by 4 weeks at a time, to a minimal interval of 8 weeks.

When the investigator decides to extend the treatment interval from 16 to 20 weeks, the investigator has the option to plan for an inspection visit 4 weeks before the next treatment visit (i.e. 16 weeks after the last treatment visit) to assess DA. If the study eye has no DA at the inspection visit, the participant will not receive study treatment at the inspection visit but 4 weeks later. If the investigator observes DA in the study eye at the inspection visit, the participant will receive study treatment at this visit. The treatment interval will then be reduced by 4 weeks and the next study treatment visit will be planned 12 weeks after the inspection visit.

When the investigator decides to extend the treatment interval from 8 to 12 weeks, the investigator has the option to plan for an inspection visit 2 weeks before the next treatment visit (i.e. 10 weeks after the last treatment visit) to assess DA. If the study eye has no DA at the inspection visit, the participant will not receive study treatment at the inspection visit but 2 weeks later. If the investigator observes DA in the study eye at the inspection visit, the participant will receive study treatment at the inspection visit. The next treatment interval will be reduced to 8 weeks. The same optional inspection visit 2 weeks earlier than the next treatment visit will be offered, when the investigator decides to extend the treatment interval from 12 to 16 weeks. If the study eye has no DA at the inspection visit, the participant will not receive study treatment at the inspection visit but 2 weeks later. If DA is observed in the study eye at the inspection visit, the participant will receive study treatment at the inspection visit. The next treatment interval will be reduced to 12 weeks. If the patient requires a reduction of the treatment interval down to 4 weeks, the patient will receive an injection at the visit, but will be discontinued from further study treatment at the next visit.

Regardless of treatment administration, Week 52 and Week 56 visits are mandatory. Participants who will receive study treatment at an inspection visit may also have a study visit

at Week 54; for these participants, the Week 54 visit will take place in lieu of the visit at Week 52 (unless this visit is inspection visit), respectively.

The last potential study treatment may be administered at the Week 52 visit (or at the Week 54 visit for the participants who will have received study treatment at an odd number of inspection visits).

DA assessments will be recorded in the IRT system by the investigator or his/her delegate.

A DA assessment will also be performed at the Week 56/EOS visit; however, no study treatment will be administered.

The different types of study visits are summarized in Table 6-3 with a description of when DA assessments and treatments take place.

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

Type	Study Period	DA Assessment	Treatment
Baseline visit	TtC-Phase	Yes	Only if treatment was planned according to the individual TtC regimen of the core study
Treatment visits	TtC-Phase	Yes	Yes
Inspection visits (optional)	TtC-Phase	Yes	Based on DA, as per investigator`s judgement
Week 52/54*	TtC-Phase	Yes	Only if treatment was planned according to the individual TtC regimen
ETD visit and EOS visit (Week 56)	Follow-Up	Yes	No

Brolucizumab should be administered in the study eye on the day of the study visit, or, if this is not possible, within 3 days after the occurrence of the study visit (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. If study visit assessments and the corresponding treatment occur on separate days, a repeat safety checkup should be performed prior to treatment of the eye and results should be 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 participants with active intraocular or periocular infections and in participants 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 sign of intraocular inflammation (IOI) is present, then an IVT injection **must not** be performed. Additional ophthalmic examination and imaging should be performed to evaluate IOI, see Section 8.4 .

If retinal vasculitis, and/or retinal vascular occlusion is confirmed, subjects must 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 IVT injection procedure, including aseptic and antimicrobial requirements, will be performed according to local clinical practice.

7 Informed consent procedures

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

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

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

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) and/or Core Data Sheet (CDS) for countries where brolucizumab is in the market. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study.

- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment.

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements.

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

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

As new information becomes available, informed consent to be updated and then must be discussed with the participant.

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 participant 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” or “S” the visits when they are performed. All data obtained from these assessments must be supported in the participant’s source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule Table 8-1 or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, the adverse event and concomitant medications should be recorded on the CRF.

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

Table 8-1 Assessment Schedule

Period	**Treat-to-Control phase**			**Follow-up**		
Visit Name	**Baseline Visit 1**	**n[2]**	**W52/EOT[3]**	**ETD[10]**	**W56/EOS[11]**	**m[12]**
Visit Numbers[1]	**1**	**110**	**120**	**130**	**130**	
Weeks	**1**	**2 to 50**	**52**		**56**	
Informed consent	X					
Inclusion / Exclusion criteria	X					
Demography	X[4]					
Medical history/current medical conditions	X					
Prior/concomitant medication	X	X	X	X	X	X
Pregnancy Test	S[4]	S	S	S	S	
Vital signs (sitting pulse and blood pressure)	X[4]	X	X	X	X	
BCVA score (ETDRS)	X[4]	X	X	X	X	X
Intraocular Pressure (IOP)	X[4]	X	X	X	X	
Ophthalmic examination [5,6]	X	X	X	X	X	
CFP[6]	X[4]	X	X	X	X	
Fluorescein Angiography[6]	X[4]					
SD-OCT[6]	X[4]	X	X	X	X	
OCT Angiography [6,7]	X[4]	X	X	X	X	
Disease activity assessment	X[4]	X	X	X	X	
Contact IRT	X	X	X	X	X	
Study drug administration[8]	X	X	X			
Telephone follow-up post injection[9]	X after 1st injection					
Adverse Events	X	X	X	X	X	X

Period	Treat-to-Control phase			Follow-up		
Visit Name	Baseline Visit 1	n[2]	W52/EOT[3]	ETD[10]	W56/EOS[11]	m[12]
Visit Numbers[1]	1	110	120	130	130	
Weeks	1	2 to 50	52		56	

[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 (10 weeks after the last injection when the interval is extended from 8 weeks to 12 weeks, 14 weeks from the last injection when the interval is extended from 12 weeks to 16 weeks, and 16 weeks when the interval is extended from 16 to 20 weeks) is at the discretion of the investigator based on disease activity assessment.
[3] Week 52 is the last visit when study treatment may be administered. End-of-Treatment visit will take place on Week 54 in lieu of Week 52 for the participants who have a planned injection visit on Week 54, unless the Week 52 visit is an inspection visit with injection administered.
[4] Assessments at the Week 64 (EOS) visit of the core study will be used as the baseline.
[5] May include visual acuity check, optic nerve perfusion, and tonometry, for safety assessment before and after IVT, as well as slit lamp examination, fundus examination before IVT. In case of an ocular AE, the assessments shall be recorded in the eCRF.
[6] Additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion.
[7] OCT Angiography will only be performed at a subset of sites.
[8] Study treatments are dependent on disease activity assessments and latest treatment interval.
[9] A telephone follow-up on safety should be performed two weeks after the first injection (a window for the phone call is +14 days). From the second injection onwards, similar phone calls should be made at investigator's discretion per local practice.

[10] ETD: Early treatment discontinuation applies to subjects who discontinue early from study treatment and continue in the study. This can occur at any time point. The assessments should be performed 4 weeks after the last injection of study drug. For visits conducted after ETD and up to Week 56 (end of study), while subject is on standard of care, only BCVA, new/any concomitant medications, and/or adverse events/ serious adverse events have to be recorded. 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 visit at Week 52.

[11] The 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.

[12] For subjects who continue in the study after ETD and up to Week 56 (end of study) while subject is on standard of care. This can occur at any time point. 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 52. The last visit should be at week 56.

8.1 Screening

8.1.1 Information to be collected on screening failures

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

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition Case Report Form.

8.2 Participant demographics/other baseline characteristics

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

Assessments performed at the Week 64 (EOS) visit of the core study will serve as the baseline for this extension study.

The following information will be documented at baseline visit for each enrolled participant:

- Age
- Sex
- Race/Ethnicity
- Vital signs
- Study eye
- Visual acuity
- Intraocular pressure
- Ophthalmic examinations
- Retinal imaging
- Prior/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 on visual function, retinal structure and vascular leakage:

- Best-corrected visual acuity with ETDRS-like charts

- Anatomical retinal evaluation of SD-OCT images
- Color Fundus Photography

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

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 baseline and Week 56/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 participants.

Participants 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 baseline and Week 56/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. Investigators will evaluate the SD-OCT images to assess the status of disease stability. The SD-OCT machine used for an individual participant should not change for the duration of the study.

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.

In addition to the standard SD-OCT assessment, at sites that have the applicable equipment, OCT angiography should be performed at each visit in the study eye. If OCT angiography was not assessed at baseline of the study, then it should not be introduced at later visits. OCT angiography will be used to identify or confirm the presence of CNV and its evolution.

The investigator will evaluate the images according to their standard of clinical practice and may use any of the SD-OCT and OCT angiography if available - 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 and OCT angiography images will be obtained by trained and study-certified site personnel at the study sites. All SD-OCT and OCT angiography

images will be forwarded to the CRC for independent standardized analysis, and 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 and OCT angiography 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 and fluorescein angiography

Color fundus photography (CFP) will be performed in the study eye at each scheduled injection visit, and in the fellow eye at baseline and Week 56/EOS visits.

Fluorescein angiography (FA) will be performed in both eyes at baseline (captured at EOS of the core study) visit. FA may be performed at other visits at the investigator's discretion.

Additional images will be taken in case of any signs of intraocular inflammation. OCT, CFP and FA (preferably wide-field or with peripheral sweeps) should be performed for safety evaluation, see Table 8-2.

The investigator will evaluate the images according to their standard of clinical practice and may use any of the CFP 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.

All images, from scheduled and unscheduled visits, must be sent to the Central Reading Center (CRC). 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 CFP and FA 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 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.

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.

8.4 Safety

Safety assessments will include vital signs, ophthalmic examinations, imaging and local laboratory evaluation (as per investigators' discretion) as well as monitoring and recording type, frequency, and severity for all AEs.

If the COVID-19 pandemic limits or prevents on-site study visits, phone calls or virtual contacts should be conducted for safety monitoring and discussion of the participant´s health status, until the participant can again visit the site.

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 AE Section 10.1.

Safety assessments are specified below:

Table 8-2 Safety assessments

Assessment	Specification
Vital signs	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. 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.
Ophthalmic exam and additional safety measures	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 baseline and Week 56/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.

Assessment	Specification
	Anterior biomicroscopy (slit lamp examination) will be completed pre-dose at every scheduled and unscheduled visit to examine the anterior segment structures of the study eye (e.g., eyelids/lashes, conjunctiva, cornea, anterior chamber, iris, lens and anterior part of the vitreous). The fellow eye will be examined at baseline for eligibility, and at other visits at the discretion of the investigator. The results of the examination of either eye will be recorded in the source documents. Slit lamp examination must be carefully performed before each study treatment. If there are any signs of IOI, severity of anterior chamber cells and flare should be assessed according to the standardization of 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 baseline 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. Clinically significant abnormal findings from slit lamp or ophthalmoscopy observations should be recorded as an AE in the eCRF.

Assessment	Specification
	A phone call two weeks after the first injection (a window for the phone call is +14 days) must be made to check whether there are any changes in vision or any symptoms of intraocular inflammation. It should be documented in the source document and eCRF. From the second injection onwards, similar phone calls should be made at investigator's discretion per local practice. In addition, **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 participant for immediate examination.** **Imaging:** When IOI, retinal vasculitis, and/or retinal vascular occlusion is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and conduct OCT, fluorescein angiography and color fundus photography (preferably wide-field or with peripheral sweeps). These additional assessments will be documented in the source and appropriate eCRF pages as applicable. The images are requested to be uploaded onto the CRC portal. Site visits for safety assessments (unscheduled visits) also can be made at any time during follow-up as needed.

No central laboratory will support the study. However, investigators may at their discretion request laboratory tests, which should be performed by a local laboratory.

8.4.1 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have urine pregnancy testing. Urine pregnancy testing will be performed at the site before anti-VEGF injections at every visit. If a urine test is positive after inclusion in the study, a serum pregnancy test must be performed for confirmation; if the serum test is positive, the participant should discontinue study medication. Additional pregnancy testing might be performed if requested by local requirements.

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.2 Appropriateness of safety measurements

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

If there are any signs of IOI, additional assessment will be performed as described in Table 8-2 and Section 10.

8.5 Additional assessments

No additional tests will be performed on participants entered into this study.

9 Study discontinuation and completion

9.1 Discontinuation and completion

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

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

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

9.1.1 Study treatment discontinuation and study discontinuation

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

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

Study treatment must be discontinued under the following circumstances:

- Subject requires treatment on a q4w interval
- Subject develops retinal vasculitis and/or retinal vascular occlusion
- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the participant

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

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' Section 9.1.2). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the Lost to follow-up Section 9.1.3. This contact should preferably be done according to the study visit schedule.

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

After premature study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events
- BCVA

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

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

Subjects must return 4 weeks after last study treatment to perform the Early Treatment Discontinuation (ETD). ETD assessments should be performed before start of standard of care treatment.

- 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.
- Dosing of SOC and follow-up visits as per investigators discretion. Subjects are not required to attend the mandatory visit at Week 52. The last visit should be at Week 56.

9.1.2 Withdrawal of informed consent

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

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

and

- No longer wishes to receive study treatment

and

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

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

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

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

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

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

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

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

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

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

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

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their 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 participant may receive standard of care or other treatments, at the discretion of the investigator and/or referring physician, if needed.

10 Safety monitoring and reporting

Subjects should be closely monitored for adverse events.

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

- A phone call two weeks after the first injection (window: +14 days) must be made to check whether there are any changes in vision or any symptoms of intraocular inflammation. From the second injection onwards, similar phone calls should be made at investigator's discretion per local practice (Table 8-2).
- 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 (Table 8-2).
- When IOI, retinal vasculitis, and/or retinal vascular occlusion is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and will conduct OCT, fluorescein angiography and color fundus photography (preferably wide-field or with peripheral sweeps). The images are requested to be uploaded onto the CRC portal.
- If any sign 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 must be discontinued from study treatment.
- Participants should be treated for these events promptly according to clinical practice.

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 clinical

investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

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

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

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

1. The severity grade:
- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. Its outcome

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

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 for at least 30 days following the last dose of study treatment.

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (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 participant with the underlying disease.

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 participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant’s general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant 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 obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). 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 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

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up until birth and one year after childbirth to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment with any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	No	No

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

Not applicable.

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

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

Dates of visits and data about study treatments dispensed to the participant, will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated 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 participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data

may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

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

12 Data analysis and statistical methods

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

Continuous variables will be summarized for the measured values at each visit and change from the baseline values using the number of observations, mean, standard deviation, quartiles, minimum and maximum. Categorical variables will be summarized with counts and percent in each category. Endpoints characterizing TtC regimen will be presented together with two-sided 95% Confidence Intervals (CI). When appropriate, two-sided p-values will be presented as a descriptive statistics.

All the endpoints, including the primary endpoint, are defined with respect to the study eye.

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

In addition to the statistical methods outlined below, further details will be described in the statistical analyses plan (SAP).

12.1 Analysis sets

The following analyses sets are defined:

The Enrolled Analysis Set (EAS) includes all participants who signed ICF and are assigned participant numbers. This analyses set will be used to summarize disposition of participants and pre-treatment adverse events.

The Full Analysis Set (FAS) comprises all participants who received at least one dose of study treatment in the extension study. This set will serve as the primary analyses set for all efficacy and safety analyses.

The Per-Protocol Set (PPS) is a subset of participants of the FAS with no protocol deviation with impact in the core study or the extension. The list of protocol deviations criteria will be provided in a separate document.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively in all participants for all analyses sets.

Medical history (ocular and non-ocular) will be tabulated by system organ class.

Relevant medications and procedures will be summarized using number and percentage by ATC class and preferred term according to the WHO Drug Reference list dictionary in all sets, and also listed by ocular and non-ocular events. Other relevant baseline information will be listed and summarized with descriptive statistics as appropriate.

12.3 Treatments

The FAS will be used for the analyses described below.

[redacted]

The duration to the treatment exposure will be summarized descriptively by counts and percentage of participants in 4-week, 8-week, 12-week, 16-week and 20-week intervals at each visit. Frequency of selected treatment patterns will be shown.

Percentages of participants who completed the study as per protocol without treatment discontinuation and interruptions will be summarized in all participants up to Week 56, and within the treatment intervals.

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 ATC classification system in all participants up to Week 56.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary objectives of the study are:

- To evaluate the extended durability of brolucizumab in a TtC regimen with respect to the duration of treatment intervals up to Week 56
- To evaluate the functional outcomes of brolucizumab in a TtC regimen with respect to average change in BCVA at Week 52 and Week 56, i.e. change from the extension baseline to the average of Week 52 and Week 56

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

The primary endpoints of the study are:

- Duration of the last interval with no DA up to Week 56
- Change in BCVA from extension baseline at Week 52 and Week 56

Primary estimands along with the sensitivity estimands are in Table 12-1.

Table 12-1 Primary and sensitivity estimands

Endpoint	Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (including missing data strategy)
Duration of last interval with no DA	Primary estimand 1	Duration of the last interval with no DA, i.e. distribution of the last interval with no DA up to Week 56, i.e. proportion of participants in last interval with no DA that is 4/8/12/16/20-week intervals	FAS	*Last interval with no DA up to Week 56	Two-sided 95% Confidence Interval of proportions. If there was DA, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks

Endpoint	Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (including missing data strategy)
Change in BCVA	Primary estimand 2	Change in BCVA from extension Baseline at Week 52 and Week 56, i.e. the average difference in BCVA from extension Baseline over the period Week 52 through Week 56	FAS	All data collected until the participant discontinued study treatment and started SOC treatment(s) will be included.	Two-sided 95% Confidence Interval obtained from ANCOVA with age at the baseline categories and BCVA at the baseline categories with (LOCF) imputation / replacement for missing data (e.g data unavailable due to lost to follow-up) / censored data (e.g. data unavailable due to use of alternative anti-VEGF)

Endpoint	Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (including missing data strategy)
Duration of last interval with no DA excluding participants with protocol deviations with impact	Sensitivity estimand 1.1	Duration of the last interval with no DA up to Week 56, i.e. distribution of the last interval with no DA up to Week 56, i.e. proportion of participants in last interval with no DA that is 4/8/12/16/20-week intervals, excluding participants with protocol deviations with impact as per PPS	**PPS	*Last interval with no DA up to Week 56	Two-sided 95% Confidence Interval of proportions. If there was DA, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks

Endpoint	Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (including missing data strategy)
Change in BCVA excluding participants with protocol deviations with impact	Sensitivity estimand 2.1	Change in BCVA from extension Baseline at Week 52 and Week 56, i.e. the average difference in BCVA from extension Baseline over the period Week 52 through Week 56; excluding participants with protocol deviations with impact as per definition of PPS	**PPS	All data collected until the participant discontinued study treatment and started alternative treatment(s), will be included.	Two-sided 95% Confidence Interval obtained from ANCOVA with age at the baseline categories and BCVA at the baseline categories and with (LOCF) imputation / replacement for missing data (e.g data unavailable due to lost to follow-up) / censored data (e.g. data unavailable due to use of alternative anti-VEGF).

Endpoint	Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (including missing data strategy)
Duration of last interval with no DA excluding participants with protocol deviations with impact either in the core study or in the extension study	Sensitivity estimand 1.2	Duration of the last interval with no DA up to Week 56, i.e. distribution of the last interval with no DA up to Week 56, i.e. proportion of participants in last interval with no DA that is 4/8/12/16/20-week intervals, excluding participants with protocol deviations with impact either in the core or in the extension as per PPS	**PPS	*Last interval with no DA up to Week 56	Two-sided 95% Confidence Interval of proportions. If there was DA, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks

Endpoint	Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (including missing data strategy)
Change in BCVA excluding participants with protocol deviations with impact either in the core study, or in the extension study	Sensitivity estimand 2.2	Change in BCVA from extension Baseline at Week 52 and Week 56, i.e. the average difference in BCVA from extension Baseline over the period Week 52 through Week 56; excluding participants with protocol deviations with impact either in the core study or in the extension study as per definition of PPS	**PPS	All data collected until the participant discontinued study treatment and started standard of care (SOC) treatment(s), will be included.	Two-sided 95% Confidence Interval obtained from ANCOVA with age at the baseline categories and BCVA at the baseline categories variables with (LOCF) imputation / replacement for missing data (e.g data unavailable due to lost to follow-up) / censored data (e.g. data unavailable due to use of alternative anti-VEGF).
Proportion of participants with at least 16-weeks duration of last interval with no disease activity	Sensitivity estimand 1.3	Proportion of participants in last interval with no disease activity that is at least16-weeks intervals up to Week 56	FAS	*Last interval with no disease activity up to Week 56	Two-sided 95% Confidence Interval of proportions. If there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks

Endpoint	Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (including missing data strategy)
Change in BCVA	Sensitivity estimand 2.3	Change in BCVA from extension Baseline at Week 52 and Week 56, i.e. the average difference in BCVA from extension Baseline over the period Week 52 through Week 56	FAS	All data collected until the participant discontinued study treatment and started SOC treatment(s) will be included.	Two-sided 95% Confidence Interval obtained based on mixed effects models with age at the baseline categories and BCVA at the baseline categories
Proportion of participants with at least 16-weeks duration of last interval with no disease activity excluding participants with important protocol deviations	Sensitivity estimand 1.4	Proportion of participants in last interval with no disease activity that is at least 16-weeks intervals at Week 56, excluding participants with important protocol deviations as per PPS	PPS**	*Last interval with no disease activity up to Week 56	Two-sided 95% Confidence Interval of proportions. If there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks

Endpoint	Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (including missing data strategy)
Proportion of participants with at least 16-weeks duration of the last interval with no disease activity excluding participants with important protocol deviations either in the core study or in the extension study	Sensitivity estimand 1.5	Proportion of participants in last interval with no disease activity that is at least 16-weeks intervals, excluding participants with important protocol deviations either in the core or in the extension as per PPS	PPS**	*Last interval with no disease activity up to Week 56	Two-sided 95% Confidence Interval of proportions. If there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks

*: If the duration of the last interval falls within the following ranges of [q4w, q8w) or [q8w, q12w), [q12w, q16w), [q16w, q20w) or ≥ q20w then the floor value of these ranges i.e. q4w, q8w, q12w, q16w, q20w, respectively, will be used for imputation.

**: Patients who take prohibited concomitant medication are already excluded from PPS as taking prohibited medication is considered a deviation with impact.

12.4.2 Statistical model, hypothesis, and method of analysis

The average change in BCVA from extension baseline at Week 52 and Week 56 will be estimated in Analyses of Covariance (ANCOVA) with baseline age categories and baseline BCVA categories. The estimate of BCVA change will be accompanied by 95% CI.

The distribution of the last interval with no DA up to Week 56 will be described based on counts and proportions of participants at 4-week, 8-week, 12-week, 16-week, and 20-week intervals. The proportions will be accompanied by 95% Confidence Intervals (CI).

12.4.3 Handling of remaining intercurrent events of primary estimand

In case of an intercurrent event, i.e. treatment interruption or discontinuation, the treatment interval will be defined as the last interval with no DA. If there was DA at the last interval, the last interval will be shortened by 4 weeks down to a minimum of 4 weeks.

Missing BCVA data due to intercurrent events, i.e. treatment interruption or discontinuation, will be imputed using last observation carried forward (LOCF) method. Observed values from both scheduled and unscheduled visits will be used for the LOCF imputation.

For participants who discontinue treatment but continue in the study, the BCVA data will be censored at the time the participant started Standard of Care treatment in the study eye.

12.4.4 Handling of missing values not related to intercurrent event

In case of a missing visit for reasons other than specified in Section 12.4.3, the treatment interval will be defined as the last interval with no DA. If there was DA at the last interval, the last interval will be shortened by 4 weeks down to a minimum of 4 weeks.

Missing BCVA values for reasons other than specified in Section 12.4.3 will also be imputed using LOCF method.

12.4.5 Sensitivity analyses for primary endpoint/estimand

Sensitivity analyses to examine robustness with respect to protocol deviations will be performed based on the PPS.

Sensitivity analyses will be performed in a subset excluding participants with protocol deviations with impact either in the core study, or in the extension study.

To evaluate robustness of the analyses based on the LOCF method, sensitivity analyses will be performed on the observed data in the FAS and mixed models for repeated measures (MMRM).

Sensitivity estimands in exposed and non-exposed to the urgent safety measures: As a sensitivity analyses, the proportion of participants with at least 16-weeks as the last interval with no disease activity at Week 56 will be estimated in pre- and post- the urgent safety measures were introduced. The estimates of proportions will be accompanied by 95% CI obtained using Goodman (1965). The analyses will be performed FAS and PPS (excluding participants with important protocol deviations in the extension study and either in the core study or in the extension study).

12.5 Analysis of secondary endpoints/estimands

12.5.1 Efficacy and/or pharmacodynamic endpoint(s)

FAS will be used to analyze durability, functional and anatomical outcomes.

To evaluate the anatomical outcomes of brolucizumab in all patients and per randomized arm in the core study

- Change in CSFT from extension baseline to Week 52 and Week 56
- Number of visits with presence of IRF and/or SRF, and sub-RPE fluid in the central subfield as assessed by SD-OCT at Week 52 and Week 56

To assess the durability of brolucizumab in all patients and/or per randomized arm in the core study

- Duration of the last interval with no DA up to Week 56
- Duration of the maximal intervals with no DA up to Week 56
- Change of the duration of last interval with no DA between extension baseline and Week 56

To assess the functional outcomes of brolucizumab per randomized arm in the core study

- Change in BCVA from extension baseline to Week 52 and Week 56

Counts and proportions for the endpoints describing durability, tolerability and anatomical outcomes (i.e. number of visits with presence of IRF and/or SRF) will be accompanied by two-sided 95% CI inferred based on binomial distribution for each endpoint and two-sided 95% simultaneous CIs inferred using the Goodman method (Goodman 1965).The Goodman method is used for obtaining simultaneous confidence intervals (might be better than single binomial confidence intervals) for the parameters of a multinominal distribution, for example for a multinomial endpoint (4-week interval, 8-week interval, 12-week interval, 16-week interval, and 20-week interval). These analyses will be performed for all participants.

For the analyses of functional and anatomical outcome (i.e. change in CSFT) the 95% CI will be inferred based on ANOVA analyses.

12.5.2 Safety endpoints

The following endpoints assess the safety of brolucizumab

- Occurrence of Ocular and Non-ocular AEs up to Week 56

For all safety analyses, the FAS will be used. All listings and tables will be presented in all participants.

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 (AEs) 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

Treatment emergent AEs are defined as AEs which start on or after the time of the first injection of study treatment in this extension study and until the patient exits the study. AEs which start prior to the date/time of the first injection of study treatment in this extension study will be listed only. Treatment emergent AEs occurring during the last 6 months of the core study, for the same set of participants included in the extension study safety set will be presented. All treatment emergent SAEs/AEs as documented in the core study will be listed as medical history.

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

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

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

The number (and proportion) of participants with adverse events of special interest will be summarized.

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

Adverse events which will be counted for a specific treatment period (i.e. baseline to Week 52) are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period.

Vital signs

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

12.7 Interim analyses

There is no interim analysis planned for the study.

12.8 Sample size calculation

It is planned to enroll approximately 250 participants in the extension study.

The below described simulation studies were conducted before the USM were introduced.

With a standard deviation of the change in BCVA of 13, the 95% Confidence Interval (CI) of the change is estimated to be (-2.1, 0.13) assuming the observed change is -1.

Table 12-2 shows the distribution of duration as estimated based on simulation studies along with precision as estimated based on the simulations. Table 12-3 shows width of 95% CI as estimated based on a sample size (number of participants completing the extension study) varying from 503 to 100. The numbers are chosen based on assuming that 90% / 80% / 70% / etc. of participants from the core study enter the extension and also assuming that 10% / 20 % / 30 % / etc of participants drop out reaching EOS of the extension. Similarly, Table 12-4 shows 95% CI for the estimate in the change in BCVA, assuming that the observed change is -1 and the standard deviation of the change is 13.

For example, when the number of participants completing the extension study decreases from 503 to 250, width of the 95% CI increases from 5.8% to 8.3% for the estimated proportion of 12.7% participants being on the 16-weeks interval; and from 6.9% to 9.8% for the estimated proportion of 19.4% of participants being on 20-weeks intervals. With the same reduction in the sample size, the 95% CI for the estimated change in BCVA goes from (-2.1, 0.14) to (-2.6, 0.62).

Table 12-2 Duration of intervals as estimated based on simulation studies

Interval duration	**4-weeks**	**8-weeks**	**12-weeks**	**16-weeks**	**20-weeks**
Frequency (SD as assessed by simulations)	8.6% (1.7%)	30.2% (1.9%)	29.2% (2.3%)	12.7% (1.7%)	19.4% (2.4%)

Table 12-3 Duration of intervals as estimated based on simulation studies and width of 95% Confidence Interval

Duration of the treatment interval	4-weeks	8-weeks	12-weeks	16-weeks	20-weeks
Frequency (SD from simulations)	8.6% (1.7%)	30.2% (1.9%)	29.2% (2.3%)	12.7% (1.7%)	19.4% (2.4%)
N of participants completing the extension study	**Width of 95% Confidence Interval**				
503	4.9%	8.0%	7.9%	5.8%	6.9%
447	5.2%	8.5%	8.4%	6.2%	7.3%
391	5.6%	9.1%	9.0%	6.6%	7.8%
447	5.2%	8.5%	8.4%	6.2%	7.3%
398	5.5%	9.0%	8.9%	6.5%	7.8%
348	5.9%	9.6%	9.6%	7.0%	8.3%
391	5.6%	6.6%	9.0%	6.6%	7.8%
348	5.9%	9.6%	9.6%	7.0%	8.3%
304	6.3%	10.3%	10.2%	7.5%	8.9%
250	7%	11.4%	11.3%	8.3%	9.8%

200	8.3%	13.1%	13.0%	9.7%	11.4%
170	9.0%	14.3%	14.2%	10.6%	12.4%
150	9.6%	15.2%	15.1%	11.3%	13.2%
120	10.9%	17.1%	16.9%	12.7%	14.9%
100	12.0%	18.8%	18.6%	14.0%	16.3%

Table 12-4 95% Confidence Interval for BCVA change assuming SD of the change is 13.

N of participants completing the extension study	95% Confidence Interval of BCVA change assuming the observed change is -1.
503	(-2.1, 0.14)
447	(-2.2, 0.21)
391	(-2.3, 0.29)
447	(-2.2, 0.21)
398	(-2.3, 0.28)
348	(-2.4, 0.37)
391	(-2.3, 0.29)
348	(-2.4, 0.37)
304	(-2.5, 0.47)
250	(-2.6, 0.62)
200	(-2.8, 0.81)
170	(-3.0, 0.97)
150	(-3.1, 1.1)
120	(-3.4, 1.4)
100	(-3.6, 1.6)

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and

procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by

Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

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

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

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

15 References

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16 Appendices

Not applicable