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RTH258

Clinical Trial Protocol CRTH258B2305 / NCT03917472

A 12-Month, 2-Arm, Randomized, Double-Masked, Multicenter Phase III Study Assessing the Efficacy and Safety of Brolucizumab every 4 weeks versus Aflibercept every 4 weeks in Adult Patients with Visual Impairment due to Diabetic Macular Edema (KINGFISHER)

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List of abbreviations

ADA	anti-drug antibody
AE	adverse event
ANOVA	analysis of variance
AR	Analysis Restriction
BCVA	Best-corrected visual acuity
CFR	Code of Federal Regulation
CI	confidence interval
CMO	Chief Medical Office
CNV	Choroidal neovascularization
CO	country organization
COVID-19	Coronavirus disease 2019
COA	Clinical Outcome Assessment
CP	Color fundus photography
CRA	Clinical Research Associate
CRC	Central Reading Center
CRO	Contract Research Organization
CSFT	Central subfield thickness
DM	Diabetes mellitus
DMC	Data Monitoring Committee
DME	Diabetic macular edema
DR	Diabetic retinopathy
[redacted]	[redacted]
DRSS	Diabetic retinopathy severity scale
EC	Ethics committee
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
ESI	adverse event of special interest
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EudraCT	European Clinical Trials Database
FA	fluorescein angiography
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Global Clinical Supply
HbA1c	Hemoglobin A1c
hCG	human chorionic gonadotropin
IB	Investigator's Brochure
ICF	informed consent form

[redacted]

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator notification
IOI	Intraocular inflammation
IOP	Intraocular pressure
IP	Investigational Product
IRB	Institutional Review Board
IRF	Intraretinal fluid
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	intrauterine system
IVT	Intravitreal
kDA	kiloDaltons
LOCF	Last observation carried forward
MedDRA	Medical dictionary for regulatory activities
nAb	Neutralizing antibody
nAMD	Neovascular age-related macular degeneration
NIH	National Institutes of Health
NIM	Non-inferiority margin
OCT	Optical coherence tomography
PD	Protocol Deviation
PDR	Proliferative diabetic retinopathy
PFS	Pre-filled syringe
PK	pharmacokinetic(s)
PPS	Per Protocol Set/Protocol analysis set
PS	Patient Safety
q12w	every 12 weeks
q4w	every 4 weeks
q8w	every 8 weeks
QMS	Quality Management System
RAS	Randomized Analysis Set
RAO	Retinal artery occlusion
RoW	Rest of World
RVO	retinal vein occlusion
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
scFv	single-chain fragment variable
SD	standard deviation
SD-OCT	Spectral domain optical coherence tomography
SMQ	Standardized MedDRA Query

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SOC	System Organ Class
SRF	Subretinal fluid
SUN	Standardization uveitis nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFQ	Trial Feedback Questionnaire
US	United States
VA	Visual acuity
VEGF	Vascular endothelial growth factor
WHO	World Health Organization
YAG	yttrium aluminum garnet

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Biological samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
Investigational drug/treatment	The drug whose properties are being tested in the study
Masked/evaluating investigator	For the entire study duration and all study patients, the masked/evaluating investigator is responsible for all aspects of the study (the conduct/supervision of all assessments and treatment decisions except the injection procedures and the safety assessment following the injection)
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Patient ID	A unique number assigned to each patient upon signing the informed consent
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who 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
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures

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Study treatment discontinuation	When the subject 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
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Unmasked/treating investigator	For the entire study duration and all study patients, the treating investigator only performs the treatment (injection active) and assesses patient safety following the injections
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Visual acuity assessor	For the entire study duration and all study patients, the visual acuity assessor (which could be a masked/evaluating investigator) performs the BCVA assessment and is masked to the assigned treatment
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

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Amendment 1 (08-June-2020)

Amendment rationale

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

Changes to the protocol

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

- Section 1.1 Background: Information was added to describe new safety signal from post-marketing case reports.
- Section 6.7.2 Instructions for prescribing and taking study treatment: Additional guidance was added to this section emphasizing that if any sign of intraocular inflammation is present, an IVT injection **must not** be performed and patients should be treated for IOI according to clinical practice.
- Additional examination and assessments included to fully characterize cases of intraocular inflammation were made in the following sections:
  - Table 8-1 Assessment schedule
  - Section 8.3.3 Color fundus photography and fluorescein angiography
  - Section 8.4.3 Ophthalmic Examination
  - Section 8.4.4 Appropriateness of safety measurements

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

- Section 6.2.2 Prohibited medication
- Section 7 Informed consent procedures
- Section 8 Visit Schedule and Assessments
- Section 8.4 Safety
- Section 8.4.1 Laboratory evaluations
- Section 12 Data Analysis and statistical methods

Other changes incorporated in this amendment:

- Section 6.1.1 Investigational and control drugs.
- Section 6.4 Treatment masking: Language was added to clarify unmasked investigator/site personnel must not be switched to a masked role at any time after randomization.
- Section 8 Visit schedule and assessments: addition of visit windows except for Baseline visit.
- Section 8.4.3 Ophthalmic examination: clarification on the use of same method for IOP measurement and timing for post-injection IOP measurement.

[redacted]

- Section 8.5.2 Anti-drug antibodies (immunogenicity).
- Section 10.1.3 SAE reporting: clarification of the SAE reporting period.
- Section 10.2.1 Data Monitoring Committee: Language was added to introduce program level DMC.
- Section 12 Analysis sets and statistical methods: Language was adapted to clarify primary and supplementary estimands and analyses based on estimands.
- Section 15 References
- List of Abbreviations

Other minor clarifications were made where applicable. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

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

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

[redacted]

Protocol summary

Protocol number	CRTH258B2305
Full Title	A 12-Month, 2-Arm, Randomized, Double-Masked, Multicenter Phase III Study Assessing the Efficacy and Safety of Brolucizumab every 4 weeks versus Aflibercept every 4 weeks in Adult Patients with Visual Impairment due to Diabetic Macular Edema (KINGFISHER)
Brief title	Efficacy and Safety of Brolucizumab every 4 weeks versus Aflibercept every 4 weeks in Adult Patients with Visual Impairment Due to Diabetic Macular Edema (DME)
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the efficacy and safety of brolucizumab dosed every 4 weeks versus aflibercept dosed every 4 weeks (q4w) in the treatment of patients with visual impairment due to DME.
Primary Objective	To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the change in visual acuity from baseline compared to Week 52.
Secondary Objectives	• To assess the effect of brolucizumab compared with aflibercept with respect to anatomical outcomes • To assess the effect of brolucizumab compared with aflibercept with respect to visual acuity (VA) • To assess the effect of brolucizumab relative to aflibercept on the status of Diabetic Retinopathy (DR) • To assess the safety and tolerability of brolucizumab compared with aflibercept • To assess the immunogenicity of brolucizumab
[redacted]	
Study design	This study is a multi-center, randomized, double masked, parallel group study in subjects with visual impairment due to DME. Subjects who meet all the inclusion and none of the exclusion criteria will be randomized in a 2:1 ratio to one of two treatment arms • Brolucizumab 6 mg: treatment every 4 weeks up to and including Visit 13 (Week 48) • Aflibercept 2 mg: treatment every 4 weeks up to and including Visit 13 (Week 48)
Population	Approximately 619 adult patients will be screened (20% screening failure rate expected) so that approximately 495 patients will be randomized in a 2:1 ratio (330 in brolucizumab arm, 165 in aflibercept arm, 9% dropout rate expected) in approximately 115 centers worldwide. The study duration is 52 weeks, including follow-up. The study includes both naive patients and those who previously received anti-vascular endothelial growth factor (VEGF) therapies.

[redacted]

Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study. • Patients ≥ 18 years of age at baseline. • Patients with type 1 or type 2 diabetes mellitus (DM) and Hemoglobin A1c (HbA1c) ≤ 12% at screening. • Study eye Visual impairment due to DME with: • Best-corrected visual acuity (BCVA) score between 73 and 23 letters, inclusive, using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts at an initial testing distance of 4 meters (approximate Snellen equivalent of 20/40 to 20/320) at both screening and baseline. • DME involving the center of the macula, with Central Subfield Thickness (CSFT) ≥ 320 µm on Spectral Domain Optical Coherence Tomography (SD-OCT) at screening.
Key Exclusion criteria	*Ocular conditions* • High-risk proliferative diabetic retinopathy (PDR) in the study eye as per investigator assessment at both screening and baseline • Concomitant conditions or ocular disorders in the study eye at screening or baseline which may, in the opinion of the investigator, confound interpretation of study results, compromise visual acuity or require medical or surgical intervention during the 12-month study period (eg, structural damage of the fovea, vitreous hemorrhage, retinal detachment, vitreomacular traction, macular hole, retinal vein/arterial occlusion, neovascularization of iris or choroidal neovascularization (CNV) of any cause). • Any active intraocular or periocular infection or active intraocular inflammation in the either eye at screening or baseline. • Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication, or according to investigator's judgment at screening or baseline • Presence of amblyopia, amaurosis or ocular disorders in the fellow eye with BCVA <20/200 at screening (except when due to conditions whose surgery may improve VA, eg, cataract) *Ocular treatments* • Use of anti-VEGF therapies, intraocular surgery or laser photocoagulation (macular or panretinal) in the study eye during the 3-month period prior to baseline • Use of intraocular corticosteroids including dexamethasone intravitreal implant (Ozurdex) in the study eye during the 6-month period prior to baseline, and use of fluocinolone acetonide intravitreal (IVT) implant (Iluvien) at any time prior to baseline • Prior investigational drugs in either eye, vitreoretinal surgery in the study eye at any time prior to baseline
Study treatment	Brolucizumab 6 mg/0.05 mL Aflibercept 2 mg/0.05 mL
Efficacy assessments	• Best-corrected visual acuity using ETDRS-like charts • Spectral-Domain Optical Coherence Tomography (SD-OCT) • 7-field stereo Color Fundus Photography (CP)

[redacted]

Key safety assessments	• Monitoring of Adverse Events (AEs) • Ophthalmic examinations • Physical examinations • Vital signs • Laboratory assessments (hematology, HbA1c, clinical chemistry, urinalysis) • Pregnancy testing
Other assessments	• Retinal imaging (Fluorescein Angiography (FA), [redacted] • Anti-drugs antibodies (Immnunogenicity)
Data Analysis	**Primary objective and estimand** The objective related to the primary endpoint is to demonstrate non-inferiority of brolucizumab versus aflibercept with respect to the change from baseline in BCVA at Week 52, assuming a non-inferiority margin (NIM) of 4 ETDRS letters. The primary estimand associated with the primary objective is defined as the between-treatment difference in change from baseline in BCVA at Week 52, excluding the effect of relevant DME prohibited medication(s) applied to the study eye. **Analysis populations** The analysis set for the primary estimand is the Full Analysis Set (FAS), which comprises all randomized subjects who receive at least one IVT injection of the study treatment. Subjects in the FAS will be analyzed according to the treatment assigned to them at randomization **Statistical model and analysis** Based on the FAS, the hypothesis of non-inferiority will be tested via an analysis of variance (ANOVA) model. The model will include treatment, baseline BCVA (≤ 34, > 34 letters) and age category (< 65, ≥ 65) as factors. Additional factors may also be included as appropriate, as well as interactions between treatment and factors of interest. The two-sided 95% confidence interval (CI) for the least square mean difference (brolucizumab - aflibercept) at Week 52 will be presented. Non-inferiority will be considered established if the lower limit of the corresponding 95% CI is greater than -4 letters. **Sample size justification** Subjects will be randomized to the brolucizumab and aflibercept arms in a ratio of 2:1. A total sample size of 357 subjects (238 on the brolucizumab arm vs 119 on the aflibercept arm) will allow assessment of non-inferiority (using a NIM of 4 letters) of brolucizumab 6 mg versus aflibercept 2 mg with respect to the change from baseline in BCVA at Week 52. Assuming equal means and a common standard deviation (SD) of 11 letters, for a NIM of 4 letters and a two−sided alpha level of 0.05, there is 90% power to reject the null hypothesis that brolucizumab is inferior to aflibercept. To ensure that at least 300 patients are treated with brolucizumab 6 mg on a fixed every 4 weeks (q4w) regimen, the total sample size will be increased to 450 subjects total (300 on the brolucizumab arm vs 150 on the aflibercept arm). This results in a statistical power for assessing non-inferiority of 95%

[redacted]

Key words	Diabetic Macular Edema, intravitreal injection, brolucizumab, aflibercept, double-masked

[redacted]

1 Introduction

1.1 Background

Diabetes mellitus (DM) is the most common endocrine disease in developed countries, with prevalence estimates ranging between 2% to 5% of the world population. Diabetic retinopathy (DR) and diabetic macular edema (DME) are common microvascular complications in patients with diabetes and may have a debilitating impact on visual acuity (VA), eventually leading to blindness. DME is a frequent manifestation of DR (Lee et al 2015) and is the major cause of vision loss in patients with DR.

Available therapies

The current treatment options for patients with DME are intravitreal (IVT) treatment of anti-vascular endothelial growth factor (VEGF), corticosteroids, corticosteroid implants, or laser photocoagulation. The favorable efficacy and safety profile of anti-VEGF therapies has placed these as first-line treatment. Corticosteroids are typically used as a second-line treatment and focal/grid laser photocoagulation remains a therapeutic option, but with a lower expected benefit compared with steroid and anti-VEGF therapies.

For anti-VEGF agents like ranibizumab or aflibercept, a favorable benefit-risk ratio was demonstrated versus the previous standard of care (laser photocoagulation) in large Phase III programs that consequently led to their approval for the treatment of DME (Ziemssen et al 2017; Korobelnik et al 2014). Anti-VEGF treatment led to clinically relevant improvements of best-corrected visual acuity (BCVA), resolution of macular edema and decreased severity of diabetic retinopathy. However, despite the treatment success of existing anti-VEGFs, there remains a need for further treatment options to improve response rate and/or reduce use and injection frequency in patients with DME (Virgili et al 2014; Agarwal et al 2015; Sivaprasad and Oyetunde 2016).

Brolucizumab

Brolucizumab, formerly known as RTH258, is a humanized single-chain fragment variable (scFv), binding to VEGF-A (ie, interfering with activation of VEGF-R1 and R2 on endothelial cells) with a molecular weight of ~26 Kilodaltons (kDa) that is being developed for the treatment of neovascular age-related macular degeneration (nAMD), DME, and macular edema associated with retinal vein occlusion (RVO).

Development of brolucizumab initially focused on the nAMD indication. In two Phase III studies in patients with nAMD, brolucizumab ((3 mg and/or 6 mg) every 8 weeks (q8w)/every 12 weeks (q12w) after three monthly loading doses) was non-inferior to aflibercept [(2 mg) q8w after three monthly loading doses] for the change from baseline in BCVA at Week 48. Furthermore, brolucizumab was shown to be long acting, with over 50% of patients maintained on a q12w regimen at 48 Weeks. Brolucizumab has been shown to be efficacious and safe for use as chronic therapy, and addresses the unmet medical need of enhanced durability and reduced treatment and monitoring burden compared with available therapy.

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

[redacted]

post-marketing experience with brolucizumab (Beovu®). Considering these events, the overall risk/benefit assessment remains positive.

Brolucizumab for diabetic macular edema

Two pivotal, two-year, randomized, double masked, multi-center Phase III studies of brolucizumab are ongoing in patients with DME: CRTH258B2301 (KESTREL) and CRTH258B2302 (KITE). Based on the positive nAMD results for the q12w/q8w regimen, KESTREL and KITE are designed to evaluate the potential of reducing the treatment and monitoring burden for patients and caregivers with a q6w loading regimen for brolucizumab followed by q12w/q8w maintenance phase compared to aflibercept administered as per current label (q4w loading followed by q8w maintenance).

Although it is important for physicians and patients to optimize and individualize the treatment strategy while reducing treatment burden, previous studies with anti-VEGF therapies suggest that some patients may need continuous dosing as frequently as every 4 weeks to improve and maintain functional and anatomical outcomes.

- The two-year results for protocol T comparing multiple anti-VEGF therapies for the treatment of DME indicated that some patients required over 11 injections in the first year of treatment (Wells et al 2016).
- Post-hoc analyses from large anti-VEGF studies in DME identified a subset of patients with limited response to initial q4w (monthly) injections who benefitted from continued q4w therapy (ie, delayed responders). These patients may need up to one year of intensive treatment to obtain comparable outcomes to early responders (Bressler et al 2016; Pieramici et al 2016; Pieramici et al 2018).
- In the 148-Week results from the VISTA and VIVID studies, although the aflibercept q8w regimen provided, on average, comparable visual and anatomical improvements as the q4w regimen, the observed fluctuations of central subfield thickness (CSFT) in the q8w arm suggest a suboptimal anatomical outcome.

The reasons for individual variability of clinical response and treatment need in DME patients observed in clinical trials have been investigated in a number of studies. Although controversial, these studies suggest that baseline characteristics such as visual acuity, CSFT, glycated hemoglobin (HbA1c), and severity of diabetic retinopathy may affect functional and anatomical improvements after anti-VEGF treatment (Bansal et al 2015; Staurenghi et al 2018; Bressler et al 2019). The open-label extension study of the RISE and RIDE trials reported that individual treatment need, as measured by injection, frequency, ranges from 0 to 13 in one year (Wykoff et al 2016). The authors suggest that duration of diabetes and DME, central foveal thickness, area of fluorescein leakage, HbA1c and severity of diabetic retinopathy may be related to injection frequency. Recent data from real world evidence studies suggests that DME patients tend to receive fewer injections and achieve poorer outcomes in terms of visual acuity compared to those patients in the large clinical studies (Ciulla et al 2018).

In conclusion, the available evidence suggests that there is a subset of DME patients who may benefit from more frequent anti-VEGF injections to achieve rapid response with optimal functional and anatomical outcomes.

[redacted]

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of brolucizumab dosed every 4 weeks versus aflibercept dosed every 4 weeks in the treatment of patients with visual impairment due to DME.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the change in visual acuity from baseline up to Week 52	• Change from baseline in BCVA at Week 52
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the effect of brolucizumab compared with aflibercept with respect to anatomical outcomes	• Change from baseline in CSFT at each post-baseline visit • Proportion of study eyes with fluid-free macula at each post-baseline visit • Proportion of study eyes with absence of DME (CSFT < 280 µm) at each post-baseline visit • Time to first fluid-free macula • Time to first absence of DME (CSFT < 280 µm)
• To assess the effect of brolucizumab compared with aflibercept with respect to visual acuity	• Change from baseline in BCVA at each post-baseline visit • Proportion of study eyes with gain in BCVA of 5/10/15 letters or more at each post-baseline visit compared to baseline
• To assess the effect of brolucizumab relative to aflibercept on the status of Diabetic Retinopathy	• Change from baseline in ETDRS Diabetic Retinopathy Severity Scale (DRSS) score at Week 12, Week 24 and Week 52
• To assess the safety and tolerability of brolucizumab compared with aflibercept	• Incidence of ocular and non-ocular Adverse Events (AEs)
• To assess the immunogenicity of brolucizumab	• Anti-drug antibody (ADA) measurement

[redacted]

[redacted]

[redacted]

3 Study design

This is a multi-center, randomized, double-masked, parallel group study in subjects with visual impairment due to DME. Subjects who consent will undergo screening assessments to evaluate their eligibility based on the inclusion and exclusion criteria. Subjects who meet all the inclusion and none of the exclusion criteria will be randomized in a 2:1 ratio to one of two treatment arms:

- Brolucizumab 6 mg: treatment every 4 weeks up to and including Visit 13 (Week 48)
- Aflibercept 2 mg: treatment every 4 weeks up to and including Visit 13 (Week 48)

Approximately 619 adult patients will be screened (20% screening failure rate expected) so that approximately 495 patients will be randomized in a 2:1 ratio (330 in brolucizumab arm, 165 in aflibercept arm, 9% dropout rate expected) in approximately 115 centers worldwide. The study duration is 52 weeks, including follow-up.

All participants will have study visits every 4 weeks through Week 52. The primary analysis will be performed at the End of Study (EOS) visit, Visit 14 (Week 52) (Figure 3-1) (further details can be found in Section 5 and Section 8.1).

Screening Period

Patients will be screened for enrollment into the treatment period at the Screening Visit. The screening period may last up to 14 days prior to administration of the first dose of study treatment, dependent upon confirmation of the patient meeting eligibility criteria.

Treatment Period

Subjects meeting eligibility criteria will enter the treatment period and be randomized in a 2:1 ratio into one of the two treatment arms at the Baseline visit: brolucizumab 6 mg or aflibercept 2 mg.

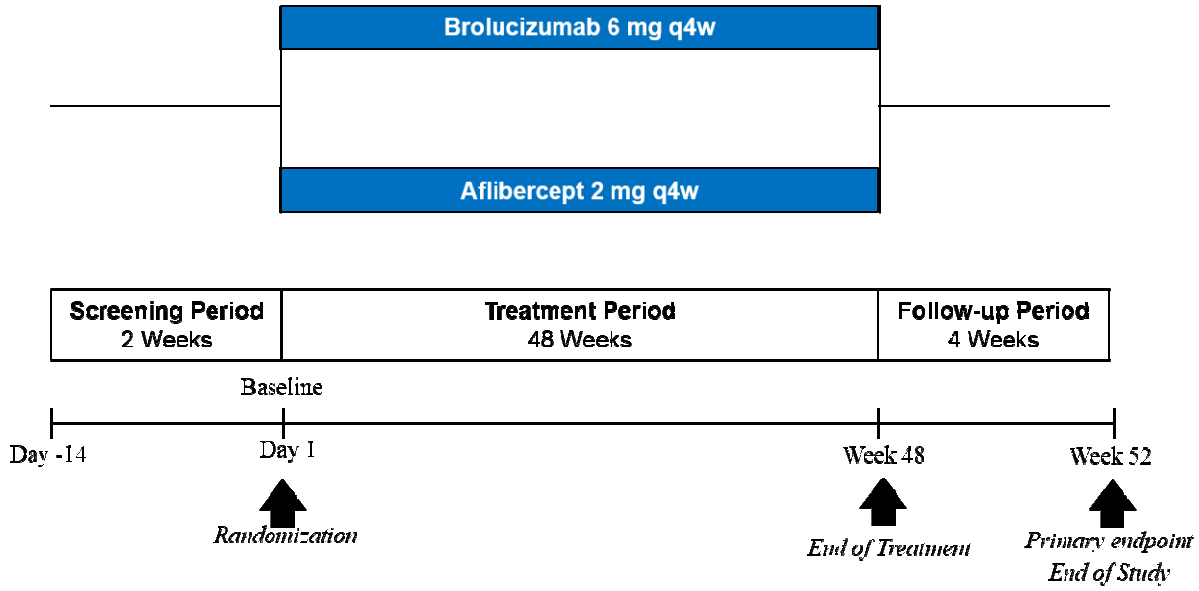
Follow-up period

For all subjects, the last study assessment will be performed at the Week 52/EOS visit (Visit 14), four weeks after the last study treatment in this study.

Subjects withdrawn from the study prior to study completion will be asked to return, if possible, for an early discontinuation (EOS) visit, four weeks following their last study treatment administration.

[redacted]

Figure 3-1 Study design



q4w= every 4 weeks

4 Rationale

4.1 Rationale for study design

This study is designed as a randomized, double-masked, multicenter, active controlled prospective study to evaluate if brolucizumab 6 mg dosed q4w is safe and effective in the treatment of DME patients.

Based on Food and Drug Administration (FDA)'s Guidance for Industry: Premarketing Risk Assessment (FDA 2005) a 2:1 randomization ratio is chosen to ensure that approximately 300 subjects are randomized into the brolucizumab arm.

To ensure masking is maintained, the investigational site will have both masked and unmasked staff to perform the masked and unmasked study assessments/procedures accordingly.

4.2 Rationale for dose/regimen and duration of treatment

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

- In the Phase III brolucizumab studies in nAMD CRTH258A2301 (HAWK) and CRTH258A2302 (HARRIER), brolucizumab 3 mg and/or 6 mg doses showed efficacy and safety profiles comparable to aflibercept with numerical advantages related to efficacy for the 6 mg dose.
- In the HAWK and HARRIER studies, brolucizumab (6 mg) was well tolerated when administered at a q4w regimen during the loading phase (12 weeks).

[redacted]

- Previous studies suggest that for some DME patients, frequent dosing (ie, q4w) with anti-VEGF therapy may be necessary to improve and maintain functional and anatomical outcomes (see Section 1.1 for details).
- Aflibercept is applied as per the current approved label for DME.

Route of administration is via intravitreal injection as for all anti-VEGF therapies currently approved for the treatment of DME.

The study duration of approximately 1 year is adequate to assess the efficacy and safety of brolucizumab 6 mg dosed in a q4w regimen.

The current study design will provide efficacy and safety data of brolucizumab 6 mg on a q4w regimen to enable physicians to treat an individual patient as frequently as needed in order to achieve maximum efficacy outcomes.

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

Aflibercept 2 mg is an established standard of care option in the treatment of DME and has been chosen as the comparator for this study due to the approved dose and posology of aflibercept (EYLEA®) for the targeted indication.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable

4.5 Risks and benefits

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

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Ranibizumab and aflibercept (both approved inhibitors of VEGF-A) have consistently demonstrated efficacy in VEGF-driven retinal pathologies, including DME, with benefits outweighing the risks. Assuming a corresponding class-effect, it is justified to expect that brolucizumab (having the same mode of action (MoA) as ranibizumab and aflibercept) will likewise be efficacious and have a similar safety profile in the DME indication. In both Phase III studies in nAMD (HAWK, HARRIER), brolucizumab demonstrated non-inferiority to aflibercept in mean change from baseline in BCVA at Week 48. The visual acuity gains observed in the first year were maintained in the second year.

Overall, brolucizumab was well tolerated in Phase I, II, and III clinical studies in nAMD, with an ocular and non-ocular safety profile similar to ranibizumab and aflibercept.

Further details of the known and potential risks and benefits associated with brolucizumab are presented in the Investigator's Brochure (IB).

[redacted]

5 Population

The study population will consist of male and female patients with type 1 or type 2 diabetes mellitus and diagnosed with visual impairment due to DME. Approximately 619 patients are expected to be screened (20% screening failure rate expected) with approximately 495 patients expected to be randomized at approximately 115 sites. The study will include both patients who are naive and patients who previously received anti-VEGF therapy. In addition, this study will allow patients with HbA1c ≤ 12% and patients with mild or moderate proliferative diabetic retinopathy, characteristics which may be associated with the need for frequent anti-VEGF therapy.

5.1 Inclusion criteria

1. Signed informed consent must be obtained prior to participation in the study.
2. Patients ≥18 years of age at baseline.
3. Patients with type 1 or type 2 diabetes mellitus and HbA1c ≤ 12% at screening.
4. *Study eye*

   Visual impairment due to DME with:

   - BCVA score between 73 and 23 letters, inclusive, using ETDRS visual acuity testing charts at an initial testing distance of 4 meters (approximate Snellen equivalent of 20/40 to 20/320) at both screening and baseline.
   - DME involving the center of the macula, with CSFT ≥ 320 μm on SD-OCT at screening.

   If both eyes are eligible, the eye with the worse visual acuity will be selected for study eye. However, the investigator may select the eye with better visual acuity, based on medical reasons or local ethical requirements.

5.2 Exclusion criteria

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

Ocular conditions

1. High-risk proliferative diabetic retinopathy (PDR) in the study eye as per investigator assessment at both screening and baseline.
2. Concomitant conditions or ocular disorders in the study eye which may, in the opinion of the investigator, confound interpretation of study results, compromise visual acuity or require medical or surgical intervention during the 12-month study period (eg, structural damage of the fovea, vitreous hemorrhage, retinal detachment, vitreomacular traction, macular hole, retinal vein/arterial occlusion, neovascularization of iris or choroidal neovascularization of any cause) at screening or baseline.
3. Any active intraocular or periocular infection or active intraocular inflammation (eg, infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis, uveitis) in either eye at screening or baseline.
4. Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication, or according to investigator's judgment at screening or baseline

[redacted]

5. Presence of amblyopia, amaurosis or ocular disorders in the fellow eye with BCVA <20/200 at screening (except when due to conditions whose surgery may improve VA, eg, cataract)

Ocular treatments

6. Use of anti-VEGF therapies in the study eye during the 3-month period prior to baseline
7. Use of intraocular corticosteroids including dexamethasone intravitreal implant (Ozurdex) in the study eye during the 6-month period prior to baseline, and use of fluocinolone acetonide intravitreal implant (Iluvien) at any time prior to baseline.
8. Intraocular surgery or laser photocoagulation (macular or panretinal) in the study eye during the 3-month period prior to baseline
9. Prior investigational drugs in either eye at any time prior to baseline
10. Vitreoretinal surgery in the study eye at any time prior to baseline
11. Aphakia with the absence of posterior capsule in the study eye

Systemic conditions or treatments

12. Use of systemic corticosteroids for 30 or more consecutive days within 90 days prior to baseline, with the exception of low stable doses of corticosteroids (defined as ≤ 10 mg prednisolone or equivalent dose used for 90 days or more); Inhaled, nasal or dermal steroids are permitted.
13. Stroke or myocardial infarction during the 6-month period prior to baseline
14. End stage renal disease requiring dialysis or renal transplant
15. Systemic anti-VEGF therapy at any time prior to baseline
16. Systemic medications known to be toxic to the lens, retina or optic nerve (eg, deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol) used during the 6-month period prior to baseline
17. Uncontrolled blood pressure defined as a systolic value ≥180 mmHg or diastolic value ≥100 mmHg at screening or baseline (In case there is an elevated blood pressure measurement, it should be repeated after 20 minutes. If the repeat measurement is elevated, then the patient is not eligible to be enrolled into the study).
18. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar classes, or clinically relevant sensitivity to fluorescein dye as assessed by the investigator
19. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
20. History of a medical condition (eg, metabolic dysfunction disease with exception of type 1 or 2 diabetes mellitus, physical examination finding, or clinical laboratory finding) that, in the judgment of the investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product
21. Use of systemic investigational drugs within 5 half-lives of baseline (or within 30 days /until the expected pharmacodynamic effect has returned to baseline, whichever is longer) or longer if required by local regulations (observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary)

[redacted]

Other

22. 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
23. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the study drug administration and for 3 months after stopping the investigational medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

    In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

    Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg, 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 childbearing potential.

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

[redacted]

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

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

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

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

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

6.1.2 Treatment arms/group

Eligible subjects will be randomly assigned at Visit 1/Baseline to one of the following two masked treatment arms in a ratio of 2:1.

- Brolucizumab 6 mg injected every 4 weeks up to and including Visit 13 (Week 48).
- Aflibercept 2 mg injected every 4 weeks up to and including Visit 13 (Week 48).

6.1.3 Treatment duration

The planned total duration of study treatment is 48 weeks with a 4-week follow up period.

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

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

[redacted]

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject is enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate electronic Case Report Forms (eCRFs). Each concomitant drug or procedure must be individually assessed against all exclusion criteria/prohibited medications and procedures. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.1.1 Permitted concomitant therapy

Panretinal photocoagulation is permitted at any time during the study as deemed necessary by the investigator (eg, when diabetic retinopathy progresses into high risk PDR) and the patient can continue the study treatment.

If needed, administration of topical ocular corticosteroids in the study eye is allowed during the study. If cataract surgery or yttrium aluminum garnet (YAG) laser is necessary in the study eye, it should be scheduled in a way not to disturb the schedule for study treatment.

During the study, if the fellow eye develops visual impairment due to DME or other disease, it may also be treated with standard of care at the discretion of the investigator, as well as other treatments according to clinical practice. Fellow eye treatment will be captured in the eCRF. The fellow eye must be monitored according to routine practice and AEs captured in the eCRF.

6.2.2 Prohibited medication

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

Table 6-2 Prohibited medications/procedures

Medication / Procedures	Prohibition period	Action taken
Study eye		
Intra- or periocular corticosteroids (except if needed as short term treatment of AE)	Any time	Discontinue study treatment (except if for treatment of AE)
Anti-VEGF therapy other than assigned study treatment	Any time	Discontinue study treatment
Laser photocoagulation (focal/grid)	Any time	Continuation of study treatment at the investigator's discretion
Any investigational drug, biologic or device	Any time	Discontinue study treatment

[redacted]

Medication / Procedures	Prohibition period	Action taken
Fellow eye		
Investigational treatment	Any time	Continuation of study treatment in the study eye at the investigator's discretion
Systemic		
Systemic corticosteroids for 30 or more consecutive days (low stable doses of corticosteroids [defined as ≤10 mg prednisolone or equivalent dose], inhaled, nasal, or dermal steroids are permitted)	Any time	Discontinue study treatment
Anti-VEGF therapy	Any time	Discontinue study treatment
Any investigational drug, biologic or device (with the exception of over-the counter vitamins, supplements or diets)	Any time	Discontinue study treatment
Medications toxic to the lens, retina or optic nerve (except temporary use for COVID-19 treatment)	Any time	Discontinue study treatment

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

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject signs the ICF 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 investigational 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 ICF, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

Interactive Response Technology (IRT) will be used for dispensing medication during the treatment period, and all screened subjects must be added to IRT.

At Baseline/Day 1, all eligible subjects will be randomized via IRT to one of the treatment arms in a ratio of 2:1. The randomization will be stratified by the following baseline BCVA scores: ≤34 letters read and >34 letters read. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the study treatment packages (each containing one vial) to be dispensed to the subject.

[redacted]

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. The IRT provider will produce a subject randomization list using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

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

6.4 Treatment masking

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

This study will be double-masked, with subjects randomized to be treated with brolucizumab 6 mg or aflibercept 2 mg. All masked members of the Study Team will be masked to treatment assignments until database lock. Sponsor personnel who have access to treatment codes (eg, bioanalysts) will not divulge the codes to subjects, investigators, site staff or other Sponsor personnel.

Unmasking of investigators and personnel directly involved in the conduct of the study will only occur in case of patient emergencies (Section 6.6.2), and then at the time of the final analysis (Section 12), at the conclusion of the study.

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

Each site must have both masked and unmasked investigators available. The investigator who performs the injection will be unmasked to the treatments as will any other site personnel who have been delegated responsibility for working with the investigational product (IP). Only the masked site personnel and masked investigator perform BCVA, complete ophthalmic examination, ophthalmic imaging assessments and administer the Trial Feedback Questionnaire (TFQ). Also, the masked investigator/site personnel assess ocular and non-ocular safety parameters, and determine causality of AEs for subjects during the course of the study except for an event reported immediately following IVT injection. The unmasked investigator/site personnel should assess subject safety immediately following injection.

[redacted]

Once the designated roles are determined, the unmasked investigator/site personnel must not be switched at any time after randomization to a masked role. Every effort must be made to limit the number of unmasked site personnel to ensure the integrity of this masked study.

Treatment masking of individual subjects will remain intact until the database lock has occurred by ensuring: randomization data are kept strictly confidential until the time of unmasking and will not be accessible by anyone else involved in the study except the unmasked investigator and unmasked site staff.

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

An independent, masked review of color fundus photography, fluorescein angiography, SD-OCT [redacted] for patients enrolled in the study will be performed at a Central Reading Center (CRC).

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments are not permitted.

Study treatment can be interrupted if warranted due to an AE.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Every time the study treatment is to be administered, IRT needs to be accessed by unmasked site personnel for the medication (kit) number. The date and time of all study treatment injections administered during the study and any deviations from the protocol treatment schedule will be captured by the unmasked site personnel or by the unmasked field monitor on the appropriate study treatment dispensing form.

Exposure to the study treatment will be based on the number of injections administered. The unmasked field monitor will assess compliance with the study treatment at each visit using vial counts and information provided by the pharmacist or by the unmasked site personnel.

6.6.2 Emergency breaking of assigned treatment code

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

[redacted]

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

- protocol number
- study drug name
- subject number

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

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under Section 6.1.1. The study medication has a 2-part label (base plus tear-off label). A unique medication number is printed on the study medication label. Unmasked site personnel will identify the study drug kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the medication kit to the subject, unmasked site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

6.7.1 Handling of study treatment

Study treatment must be received by a designated unmasked person at the study site, handled and stored safely and properly, and kept in a secured location to which only the unmasked investigator and unmasked site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (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 subject except for the medication number.

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

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

6.7.2 Instruction for prescribing and taking study treatment

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

Treatment Period

Arm 1: Brolucizumab 6 mg q4 weeks

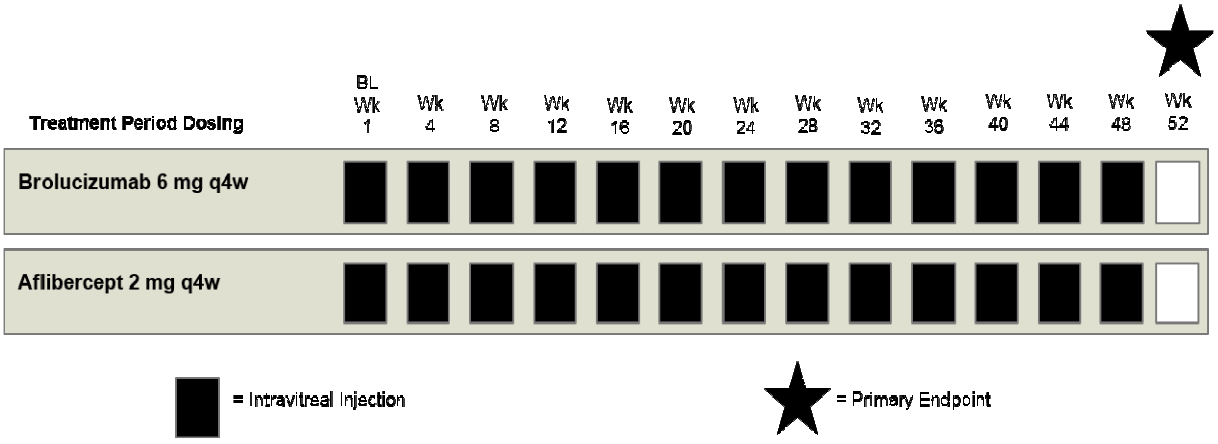
[redacted]

Brolucizumab 6 mg will be administered via intravitreal injection every 4 weeks up to and including Visit 13 (Week 48) to subjects randomized to the brolucizumab 6 mg q4 week treatment arm.

Arm 2: Aflibercept 2 mg q4 weeks

Aflibercept 2 mg will be administered via intravitreal injection every 4 weeks up to and including Visit 13 (Week 48) to subjects randomized to the aflibercept 2 mg q4 week treatment arm.

Figure 6-1 Dosing schedule



BL=Baseline

Intravitreal injection

The IVT injection will be carried out under controlled, aseptic conditions and antimicrobial requirements, per local clinical practice by the unmasked investigator according to the IRT randomization/kit assignment.

An IVT injection is contraindicated in subjects with active ocular or periocular infections and in subjects with active intraocular inflammation (IOI); therefore, the investigators must verify that these conditions are not present in the study eye prior to every injection.

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

If IOI is confirmed, subjects should be treated for IOI according to clinical practice.

Every injection administered to the subject will be recorded in the eCRF.

7 Informed consent procedures

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

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given

[redacted]

his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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

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

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

During the COVID-19 pandemic that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc). Remote informed consent should be appropriately documented and confirmed by way of standard informed consent procedures at the earliest opportunity when the subject will be back at the trial sites.

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

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

8 Visit schedule and assessments

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

A planned study visit schedule will be established at Baseline/Day 1, randomization (first day of treatment), for all subjects. All post-baseline scheduled visits will be calculated based on the Day 1 visit date. All efforts should be made to adhere to all scheduled visits and assessments as outlined in the assessment schedule (Table 8-1).

[redacted]

Patients must be seen for all visits on the designated day, or as close to it as possible, with a minimum of 21 days between treatments.

For a given protocol visit (except for Baseline/Day 1), assessments can be performed on 2 consecutive days.

Treatment is intended to be administered on the day of study visit or, if this is not possible, within 3 days after the study visit at which the per-protocol assessments took place.

A ± 7 days visit window is allowed (except for Baseline/Day 1), should the subject be unable to return per scheduled visit.

For all visits, efficacy assessments (Section 8.3) and safety assessments (Section 8.4) should be performed prior to any administration of study treatment. IOP should be measured pre-IVT and post-IVT injection.

Missed or rescheduled visits should not lead to automatic study treatment or study discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the End of Study (EOS) final visit will be performed.

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

[redacted]

Table 8-1 Assessment Schedule

Period	Screening	Treatment													Follow up
Visit Name	**Screening**	**Baseline**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EOT**	**14/ EOS**
Weeks	**-2 to -1**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Informed consent	X														
Inclusion / Exclusion criteria	X	X													
Demography	X														
Medical history/current medical conditions	X														
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood collection for anti-drug antibody (ADA)	X		X		X			X			X				X
Blood collection for study drug systemic exposure	X		X		X			X			X				X
Hematology	X							X							X
HbA1C	X				X			X			X				X
Clinical Chemistry	X							X							X
Pregnancy test (serum), if applicable (Section 8.4.2)	X														X
Pregnancy test (urine), if applicable (Section 8.4.2)		X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X							X							X

[redacted]

Period	Screening	Treatment													Follow up
Visit Name	Screening	Baseline	2	3	4	5	6	7	8	9	10	11	12	13/ EOT	14/ EOS
Weeks	-2 to -1	1	4	8	12	16	20	24	28	32	36	40	44	48	52
Best-corrected visual acuity (BCVA) (*both eyes where indicated)	X*	X	X	X	X	X	X	X*	X	X	X	X	X	X	X*
Intraocular pressure (IOP) (*both eyes where indicated)	X*	X	X	X	X	X	X	X*	X	X	X	X	X	X	X*
Ophthalmic Exam [a,b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spectral domain optical coherence tomography (SD-OCT) (*both eyes where indicated)[a]	X*	X	X	X	X	X	X	X*	X	X	X	X	X	X	X*
Color fundus photography (*both eyes where indicated)[a]	X*				X			X*							X*
Fluorescein angiography (FA) both eyes (** at the discretion of the investigator)[a]	X							X**							X
[redacted]															

[redacted]

Period	Screening	Treatment													Follow up
Visit Name	Screening	Baseline	2	3	4	5	6	7	8	9	10	11	12	13/ EOT	14/ EOS
Weeks	-2 to -1	1	4	8	12	16	20	24	28	32	36	40	44	48	52
[redacted]															
Trial feedback questionnaire (optional)		X						X							X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration		X	X	X	X	X	X	X	X	X	X	X	X	X	

[a] Additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation

[b] Ophthalmic exam includes fundus and slit lamp examination. Pupil dilation optional according to local practice

[redacted]

8.1 Screening

A screening period of up to 2 weeks will be used to assess subject eligibility. The completion of assessments for this visit may occur on different days. The screening period starts with the first screening procedure (other than signing of the informed consent).

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

One-time reevaluation of subjects is allowed during the 14 day screening period to confirm eligibility, except for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the subject. Medical judgment should be exercised to ensure that treatment of DME is not withheld in order for a subject to participate in the study.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and who are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF page. The informed consent, demographic information, inclusion/exclusion and disposition eCRF pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event (SAE) during the screening phase (see SAE Section 10.1.2 for reporting details). Adverse events that are not Serious Adverse Events (SAE)s will be monitored by the investigator and collected only in the source data. If the subject is not eligible to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

8.2 Subject demographics/other baseline characteristics

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

The following information will be collected/documented at screening and/or baseline visits as relevant (see Table 8-1) for each subject:

- Age
- Gender
- Race/Ethnicity
- Type of diabetes
- Vital signs
- Study eye
- Best-corrected visual acuity
- Anatomical parameters of the retina
- Intraocular pressure
- Pregnancy test, if applicable

[redacted]

- Prior and concomitant medications and procedures
- Medical history/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 prior to study drug administration to evaluate the effect of brolucizumab and aflibercept on visual function, retinal and vascular structure:

- Best corrected visual acuity using ETDRS-like charts starting at an initial distance of 4 meters
- ETDRS diabetic retinopathy severity scale (DRSS) score based on 7-field stereo CP
- Anatomical retinal evaluation by SD-OCT, FA, [redacted]

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 both eyes at Screening, Week 24 and Week 52/EOS visits using best correction determined from protocol refraction (BCVA). BCVA measurements will be taken in a sitting position using ETDRS–like visual acuity testing charts at an initial testing distance of 4 meters. The details of the procedure and training materials are provided in the applicable manual. Certification of the assessment facilities and assessors will occur prior to any evaluation of study subjects.

8.3.2 Optical coherence tomography

Spectral Domain Optical Coherence Tomography (SD-OCT) will be assessed in the study eye at every study visit and in both eyes at Screening, Week 24 and Week 52/EOS visits.

The SD-OCT model used for an individual subject should not change for the duration of the study.

[redacted]

A Central Reading Center (CRC) will be used in this study. The CRC will provide sites with a Study Manual and training materials for the specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software will be certified and validated by the CRC as specified in the Study Manual. All SD-OCT [redacted] images will be forwarded to the CRC for independent standardized analyses and storage.

The CRC will create a database with the agreed OCT 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 assessment of the objectives having SD-OCT [redacted]

[redacted]

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

8.3.3 Color fundus photography and fluorescein angiography

Color fundus photography (7-field) (CP), or equivalent as per CRC, will be performed in both eyes at Screening, Week 24 and Week 52/EOS visits and in the study eye at Week 12.

Fluorescein angiography (FA) will be performed in both eyes at Screening and Week 52/EOS visit. In addition, FA may be performed at Week 24, at the discretion of the investigator. In case of premature study drug discontinuation, the need to repeat the FA is at the discretion of the investigator.

[redacted]

The CRC will provide sites a manual and training materials for the specified study 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 CP and FA images, [redacted], will be obtained by trained and study-certified site personnel at the study sites and forwarded to the CRC for independent standardized analysis and storage.

The CRC will create a database with the agreed imaging variables as indicated in the CRC grading charter and will transfer the data from this database to Novartis for analysis. The CRC data will be used for the assessment of the objectives having CP, FA, [redacted] parameters as endpoints to ensure a standardized evaluation. Grading for DRSS score will be performed at the CRC. For further procedural details, the investigator should refer to the applicable manual provided by the CRC.

Additional images will be taken in case of any signs of intraocular inflammation. [redacted], Color fundus photography and fluorescein angiography [redacted] should be performed for safety evaluation as described in Section 8.4.3.

8.3.4 Appropriateness of efficacy assessments

BCVA as a measure of visual function of the retina, as well as SD-OCT images to analyze anatomical changes, are standard assessments to monitor DME and potential treatment effects both in routine practice and clinical trials. Likewise, FA is an established tool to classify the type of macular edema and is used to assess retinal vascular structure and leakage. ETDRS DRSS assessed via 7-field color fundus photography is a standardized evaluation of the severity of diabetic retinopathy. This grading informs about the severity of the diabetic retinopathy underlying the macular edema.

[redacted]

8.4 Safety

Safety assessments will include physical examination, vital signs, ophthalmic examinations, laboratory evaluation as well as the monitoring and recording of the 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 subject´s health status, until the subject can again visit the site.

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

For details on AE collection and reporting refer to Section 10.1.

Table 8-2 Vital signs assessment

Assessment	Specification
Physical examination	A complete physical examination will include general health check according to local clinical practice. The examination will be performed at Screening and at EOS visit. Clinically relevant findings that are present prior to signing informed consent must be included in the eCRF capturing Medical History. Significant findings identified after providing written informed consent which meet the definition of an Adverse Event must be recorded on the appropriate AE eCRF page.
Vital Signs	Vital signs include assessment of sitting blood pressure (systolic and diastolic pressure in mmHg) and pulse (beats per minute). In case there is an elevated blood pressure measurement as specified in the exclusion criteria, at the screening or baseline visits, the blood pressure measurement should be repeated after 20 minutes. If the repeat measurement is elevated, then the patient is not eligible to be enrolled into the study. Sitting blood pressure and pulse rate will be collected at all visits before administration of study medication. The results will be recorded in the eCRF.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected at applicable visits. Details on the collection, shipment of the samples and reporting of the results by the central laboratory are provided to investigators in the central laboratory manual.

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

Table 8-3 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute and percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and quantitative platelet count.

[redacted]

Test Category	Test Name
HbA1c	Glycosylated Hemoglobin
Chemistry	**Serum biochemistry tests:** Serum electrolytes (sodium, potassium, chloride, phosphorus, calcium), uric acid, blood urea nitrogen, creatinine, albumin, glucose, total protein, total bilirubin and direct bilirubin, serum glutamic oxaloacetic transaminase (SGOT)/ aspartate aminotransferase (AST), serum glutamic pyruvic transaminase (SGPT)/ alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) **Additional chemistry tests:** Lipids panel-triglycerides (TG), low-density lipoproteins (LDL), high-density lipoproteins (HDL), total cholesterol (TC)
Urinalysis	Dipstick measurements for specific gravity, pH, protein, glucose, ketones, urobilinogen, bilirubin, nitrite, leucocyte, esterase and urine occult blood

8.4.2 Pregnancy

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if necessary according to local requirements. Highly effective contraception is required for women of childbearing potential during the study drug administration and for 3 months after stopping the study treatment.

A serum pregnancy test will be conducted for all women of childbearing potential to assess pregnancy before inclusion into the study at the Screening visit and then at Week 52/EOS visit. During the study, monthly urine pregnancy testing will be performed at visits when serum pregnancy testing will not be conducted. Results of all pregnancy testing must be available as source documentation.

8.4.3 Ophthalmic examination

The ophthalmic examination will consist of the following:

- **Biomicroscopy (slit lamp examination)** will be completed at every (scheduled and unscheduled) visit by the masked investigator to examine the structures (e.g., eyelids/lashes, conjunctiva, cornea, anterior chamber, iris, lens and anterior part of the vitreous) of the study eye according to the clinical practice (fellow eye will be examined 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 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.

  Any clinically significant abnormalities deemed by the investigator as adverse event must be recorded on the adverse event page of the eCRF (events identified prior to signing informed consent should be recorded on the medical history page).
- **Intraocular pressure** (IOP) will be assessed in the study eye, pre- and post-IVT injection, at every scheduled visit. In the fellow eye, IOP will be assessed at Screening, Week 24, and Week 52/EOS visits. The values recorded in mmHg will be entered into the eCRF for either

[redacted]

eye. Post-IVT injection IOP should be assessed within 60 minutes after injection and if ≥25 mmHg, the assessment should be repeated until back to normal. Treatment and close monitoring of IOP should be performed by the investigator according to local clinical practice. The method used for measuring a subject's IOP must remain consistent throughout the study. Any clinically significant abnormalities deemed by the investigator as an adverse event must be recorded on the adverse event page of the eCRF.

- **Fundus (posterior segment) examination** will be conducted at every scheduled visit by the masked investigator according to the clinical practice (fellow eye will be examined at the discretion of the investigator). An examination of the peripheral retina must also be performed to ensure that the intravitreal injection can safely be performed. 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. Any clinically significant abnormalities of either eye identified prior to signing the informed consent will be recorded on the medical history eCRF page, and on the adverse event page of the eCRF for any findings identified after signing the informed consent.

Instruct the patient to contact the site for any changes in vision or any symptoms of inflammation between scheduled visits.

Every effort should be made to bring the subject for immediate examination. When IOI, retinal vasculitis, and/or retinal artery occlusion (RAO) is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and will conduct [redacted], fluorescein angiography and color fundus photography [redacted]. These additional assessments will be documented in the source and appropriate eCRF pages as applicable. The images are requested to be uploaded onto the CRC portal.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population. If there are any signs of IOI, additional assessment will be performed as described in Section 8.4.3.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Trial Feedback Questionnaire

During the treatment period, subjects will be asked to complete an optional anonymized questionnaire, the "Trial Feedback Questionnaire", to provide feedback on their clinical trial experience at Baseline, Week 24 and Week 52/EOS visits. Subjects may opt in or opt out of completing this questionnaire.

Responses will not be reviewed by investigators. Responses will be used to understand where improvements can be made in the clinical trial process. This questionnaire is not meant to collect

[redacted]

data about the patient's disease, symptoms or adverse events, and therefore will not be considered trial data.

8.5.2 Anti-drug antibodies (immunogenicity)

Anti-brolucizumab antibodies, anti-drug antibodies, (ADAs) assessment will be performed at Screening, Weeks 4, 12, 24, 36, and 52/EOS visits in subjects treated with brolucizumab only. However, in order to maintain masking, collection of blood samples for ADA assessment will be performed in both treatment arms. In case of intraocular inflammation (eg, uveitis) diagnosed and reported as an AE at a scheduled visit (without ADA sampling) or at an unscheduled visit, an additional ADA sample will be collected. Concentrations of free brolucizumab will be determined at the same timepoints as the determination of ADA status/titer. These data will be used for interpretation of the ADA data. No pharmacokinetic (PK) parameters will be determined from brolucizumab systemic exposure. Additional pharmacodynamic assessment (e.g. systemic VEGF) may be conducted on the samples. Samples collected from subjects assigned to aflibercept treatment will not be assayed for ADA nor for systemic drug concentration.

At all applicable visits, blood draws should take place prior to the IVT injection. A standardized procedure for the collection, processing, storage and shipment of these blood samples is provided by the central laboratory. Further details on sample collection, numbering, processing and shipment can be found in the central laboratory manual.

9 Study discontinuation and completion

9.1 Discontinuation

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

A subject will be considered to have completed the study when the subject has completed the last visit planned in the protocol (see Table 8-1).

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

9.1.1 Discontinuation of study treatment

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

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

Study treatment must be discontinued under the following circumstances

- Subject/guardian decision
- Pregnancy (see Section 8.4.2 and Section 10.1.4)
- Use of prohibited treatment (see Section 6.2.2)

[redacted]

- Any situation in which study participation might result in a safety risk to the subject
- Following emergency unmasking

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

Subjects 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). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (eg, telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section, Section 9.1.3. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule. In this scenario, after study treatment discontinuation, at a minimum the following data should be collected at clinic visits or via telephone/email contact:

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

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section (Section 6.6.2).

9.1.1.1 Replacement policy

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

9.1.2 Withdrawal of informed consent

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

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

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

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

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

[redacted]

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

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

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

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

9.1.3 Lost to follow-up

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

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

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

After study completion the subject may receive standard of care if needed.

[redacted]

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (eg, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

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

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

1. The severity grade

mild: usually transient in nature and generally not interfering with normal activities

moderate: sufficiently discomforting to interfere with normal activities

severe: prevents normal activities

2. its relationship to the study treatment or the ocular injection procedure. If the event is due to lack of efficacy or progression of underlying illness (ie, 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 subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

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

- No action taken (eg, further observation only)
- [Investigational] treatment interrupted/withdrawn

[redacted]

- Concomitant medication or non-drug therapy given
- Subject hospitalized/subject's hospitalization prolonged (see Section 10.1.2 for definition of SAE)

6. its outcome

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

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

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

Adverse event monitoring should be continued 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 (eg, continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

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

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any adverse event (appearance of [or worsening of any pre-existing]) undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity

[redacted]

- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, eg, defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis Safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator

[redacted]

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 (EC) in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

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

10.1.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the brolucizumab (investigational) and/or aflibercept with any pregnancy outcome . Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Novartis Safety only if associated with an SAE.

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

Treatment error type	Document in Dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE

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

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

[redacted]

The RTH258 program level Data Monitoring Committee (DMC) will monitor ocular safety. DMC will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

11 Data Collection and Database management

11.1 Data collection

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

Designated masked investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR (Code of Federal Regulation) 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 (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

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

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

11.2 Database management and quality control

Novartis personnel (or designated Contract Research Organization (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 masked investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

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

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis. Color fundus photographs, fluorescein angiograms, and OCT images processed centrally by the Central Reading Center and the results will be sent electronically to Novartis.

[redacted]

The data management staff will perform a reconciliation of the data entered on the eCRF versus what is received from the central reading center and central laboratories.

Randomization codes and data about all study treatment (s) dispensed to the subject will be tracked using an 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.

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

The occurrence of relevant protocol deviations (PDs) will be determined. Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unmasked** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis (or delegated CRO) representative will review the protocol and data capture requirements (ie, 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 masked field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice as well as the progress of enrollment. The unmasked field monitor will ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitors during these visits. Continuous remote monitoring of each site's data may be performed by the field monitors or a centralized Novartis (or delegated CRO) Clinical Research Associates (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 subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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

[redacted]

12 Data analysis and statistical methods

The primary safety and efficacy analysis will be based on the Week 52 data, ie, all data up to and including Week 52. This analysis will be performed once all subjects complete their Week 52/EOS visit or terminate the study before Week 52. Summary statistics will be presented by treatment group unless otherwise specified. For continuous variables, summary statistics will generally include: n, mean, standard deviation (SD), median, quartiles, minimum and maximum. For categorical variables, this will generally include: n, frequency and percentage in each category.

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

Further technical details and discussions of the statistical considerations will be provided in the Statistical Analysis Plan (SAP). Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Randomized Analysis Set (RAS) consists of all enrolled subjects who are randomized in IRT. Subjects are considered randomized when they have been deemed eligible for randomization by the investigator and given a randomization number. Subjects will be analyzed according to the treatment assigned to them at randomization.

The Full Analysis Set (FAS) comprises all randomized subjects who receive at least one IVT injection of the study treatment. Subjects in the FAS will be analyzed according to the treatment assigned to them at randomization.

The Safety Analysis Set (SAF) includes all subjects who receive at least one IVT injection of the study treatment. Subjects in the Safety Set will be analyzed according to the study treatment from which they received the majority of treatments up to and including Week 48.

The Per Protocol Set (PPS) is a subset of the FAS and will exclude or censor data from subjects with protocol deviations (PDs) and analysis restrictions (ARs) that are expected to majorly affect the validity of the assessment of efficacy at Week 52 including, for eg, lack of compliance (including missed treatments and treatment misallocation), missing data, prohibited concomitant medications, and deviations from inclusion/exclusion criteria. Confounded data or discontinuation from study treatment due to lack of efficacy and/or safety do not constitute, in itself, a reason for exclusion from the PPS.

Before the final database lock at Week 52 the relevant protocol deviations will be identified at the subject level in the database. After the database lock, analysis restrictions will be derived in the analysis database. Censoring applied in relation to the specific PDs/ARs will be specified as well.

12.2 Subject demographics and other baseline characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics for the FAS by treatment group and overall. Summary statistics for other analysis sets will only be generated if these are anticipated to be different given the subset of the subjects included in the particular analysis set. Relevant medical history and current medical conditions will be tabulated by system organ class (SOC) and preferred term of the MedDRA dictionary for the

[redacted]

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

12.3 Treatments

Study treatment

Descriptive summary statistics for exposure to study treatment will be provided for the SAF, FAS and PPS populations if these are different. The cumulative number of IVT injections will be presented for the period baseline to Week 48, by treatment arm. For the safety analysis set, summary statistics will include exposure data up to Week 52.

Prior medication and concomitant therapies

The number and percentage of patients taking prior medication or concomitant therapies will be summarized by preferred term according to the WHO Drug Reference List dictionary using the Safety Set and FAS (in case there are differences between those two). The concomitant therapies (medications and procedures) will include all therapies received after start of study including those already started prior to the start of the study treatment.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The primary endpoint is the change from baseline in BCVA at Week 52. BCVA will be assessed by the masked investigator using ETDRS-like charts at an initial testing distance of 4 meters as described in Section 8.3.1.

12.4.2 Statistical model, hypothesis, and method of analysis

The objective related to the primary endpoint is to demonstrate non-inferiority of brolucizumab versus aflibercept with respect to the change from baseline in BCVA at Week 52, assuming a non-inferiority margin of 4 ETDRS letters (see Section 12.8 for details on the rationale for the non-inferiority margin).

Let:

B = Brolucizumab 6 mg

A = Aflibercept 2 mg

Consider the following non-inferiority hypotheses related to a non-inferiority margin of 4 letters:

H_0: $\mu_B - \mu_A \leq$ -4 letters vs H_A: $\mu_B - \mu_A >$ -4 letters,

where μ_B and μ_A represent the unknown true mean change from baseline in BCVA at Week 52 in the brolucizumab and aflibercept arms, respectively.

The primary estimand associated with the above hypothesis is defined as the between-treatment difference in change from baseline in BCVA at Week 52,excluding the effect of relevant DME prohibited medication(s) applied to the study eye (eg, alternative anti-VEGF treatments for DME, as further detailed in Section 6.2.2 and in the SAP). The analysis set for the primary estimand will be the FAS.

[redacted]

Based on the FAS, the above hypotheses will be tested via an analysis of variance (ANOVA) model. The model will include treatment, baseline BCVA (≤ 34, > 34 letters) and age category (< 65, ≥ 65) as factors. Additional factors may also be included as appropriate, as well as interactions between treatment and factors of interest.

The two-sided 95% confidence interval (CI) for the least square mean difference (brolucizumab - aflibercept) at Week 52 will be presented. Non-inferiority will be considered established if the lower limit of the corresponding 95% CI is greater than -4 letters. The same approach for non-inferiority assessment in change from baseline in BCVA at Week 52 will be applied to any supplementary estimand.

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

Table 12-1 Primary and supplementary estimands

Estimand	Estimand definition	Analysis set	Use of data after discontinuation of study treatment due to[a]:		Statistical methods (Including missing data strategy)
			use of DME prohibited medication	any other reason	
Primary estimand	Difference in change from baseline in BCVA at Week 52 excluding the effect of DME prohibited medication(s)	All randomized subjects who receive at least 1 IVT injection of the randomized study treatment (FAS)	Not included; treated as missing	Included	Analysis of variance (ANOVA) model assessed at a two-sided significance level of 0.05, and including terms for treatment, baseline BCVA (≤ 34, > 34 letters) and age category (< 65, ≥ 65), and using last observation carried forward (LOCF) imputation/replacement for missing/censored data.
Supplementary estimand	Difference in change from baseline in BCVA at Week 52 excluding the effect of DME rescue medication(s) and protocol deviations as per the definition of the PPS	All randomized subjects who adhere to the protocol as per the definition of PPS	Not included; treated as missing	Not included; treated as missing	ANOVA model as per the primary estimand. LOCF imputation/replacement for missing/censored data

[redacted]

a) Note that, for all estimands as applicable, all data captured until the start of rescue medication will be included in the analysis.

12.4.3 Handling of missing values/censoring/discontinuations

As stated in the definition of the primary estimand, missing BCVA values will be imputed by Last Observation Carried Forward (LOCF) as the primary approach. For subjects with no post-baseline BCVA value, the baseline value will be carried forward. Data collected after the start of certain alternative DME treatments in the study eye (eg, other anti-VEGF treatment) will be censored (further details will be discussed in the SAP).

The LOCF approach is expected to be sensitive to an early study treatment discontinuation/study discontinuation due to lack of efficacy, assuming that such lack of efficacy is reflected in the last observed BCVA measurement. In case of the use of alternative treatment for the underlying disease as described above, data collected after the start of such a treatment would be censored. LOCF will then be based on the last BCVA value prior to the start of this treatment, again expecting that this value would reflect the negative BCVA outcome under study treatment that led to the use of alternative treatment for DME. In case of missing data due to lack of safety/tolerability with impairment of the visual function of the study eye, the LOCF method would also provide a sensitive approach to capture such an unfavorable outcome.

In case of missing data occurring independently of the response to study treatment, the LOCF approach assumes stability which seems to be adequate for this population based on historical data both for maintenance treatment phase (ie, stabilization of BCVA) and also in case of the absence of any treatment effect, with an average natural disease progression in terms of BCVA of only 1-2-letter loss over 1 year. In case of an early study discontinuation within the first 6 months of treatment, the LOCF method will likely result in a conservative estimate of the BCVA measure within each arm, potentially underestimating the true outcome.

LOCF is an established method within the assessment of efficacy of anti-VEGF treatments in terms of BCVA outcome. Non-inferiority studies should follow the main design features (primary variables, the dose of the active comparator, eligibility criteria, etc) as the previously conducted superiority trials in which the active comparator demonstrated clinically relevant efficacy. The primary endpoint in the aflibercept phase III studies VIVID and VISTA was the change from baseline in BCVA at Week 52, with missing data imputed based on LOCF. Based on those studies, the percentage of missing data regarding BCVA is not considered critical (<10%) which limits the impact of the missing data imputation method.

Other methods of handling missing or confounded data within sensitivity analyses will be performed, as detailed in the SAP.

12.4.4 Sensitivity and Supportive analyses

Sensitivity and supportive analyses for the primary endpoint, change from baseline in BCVA at Week 52, are specified in terms of sensitivity and supportive estimands as described in Table 12-1. This describes different approaches to deal with intercurrent events such as intake of prohibited DME medication in the study eye, or any event leading to exclusion from the PPS, and the resulting missing/censored data. The same approaches to deal with intercurrent events and/or missing data may be applied to some or all of the secondary endpoints as appropriate.

[redacted]

For the primary and relevant secondary endpoints, descriptive analyses based on observed data only (with and without censoring of data collected after use of relevant prohibited medication for DME as described in Section 6.2.2 and further details in the SAP) may also be produced.

The following subgroup analyses may be explored using the FAS and the statistical model described in the primary estimand in Table 12-1:

- Age category (< 65, ≥ 65 years)
- Gender (male, female)
- Diabetes type (Type 1, Type 2)
- Baseline HbA1c (< 7.5, ≥ 7.5%)
- Baseline BCVA categories (≤ 34, > 34 letters)
- Duration of DME (≤ 3, >3-<12, ≥ 12 months)
- DME type (focal, diffuse) as per CRC
- Baseline CSFT (< 450, ≥450 - <650, ≥ 650 µm)
- Baseline status of Intraretinal fluid (IRF) (presence, absence)
- Baseline status of Subretinal fluid (SRF) (presence, absence)
- Baseline status of DRSS score (<61, ≥ 61)

Further description of all the supportive and sensitivity analyses will be detailed in the SAP.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Secondary efficacy endpoints related to anatomy:

- Change from baseline in central subfield thickness (CSFT) at each post-baseline visit
- Proportion of study eyes with fluid-free macula at each post-baseline visit:
  - Proportion of study eyes with absence of SRF
  - Proportion of study eyes with absence of IRF
  - Proportion of study eyes with simultaneous absence of SRF and IRF at each post-baseline visit
- Proportion of study eyes with absence of DME (CSFT < 280 µm) at each post-baseline visit
- Time to first fluid-free macula:
  - Time to first absence of SRF
  - Time to first absence of IRF
  - Time to first simultaneous absence of SRF and IRF
- Time to first absence of DME (CSFT < 280 µm)

Secondary efficacy endpoints based on BCVA:

- Change from baseline in BCVA at each post-baseline visit
- Proportion of study eyes with gain in BCVA of 5/10/15 letters or more at each post-baseline visit compared to baseline

[redacted]

Note: subjects with BCVA value of 84 letters or more at a post-baseline visit will be considered as responders for this endpoint. This is to account for a ceiling effect, for example, for the "15 letters or more" endpoint, for those subjects with BCVA values at baseline ≥ 70 letters.

Secondary efficacy endpoints related to status of Diabetic Retinopathy:

- Change from baseline in ETDRS Diabetic Retinopathy Severity Scale (DRSS) score at Week 12, Week 24, and Week 52

Details regarding the analysis of secondary endpoints will be described in the SAP.

12.5.2 Safety endpoints

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

- Extent of exposure
- Adverse events
- Ophthalmic examinations
- Vital signs
- Laboratory results

There are no formal safety hypotheses in this study. All safety analyses will be performed using the safety analysis set, SAF.

Adverse events

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

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

Separate summaries will be provided for study treatment related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation of study treatment or the study. Separate presentations will be provided related to ocular events in the study eye and fellow eye and non-ocular events. Additional summaries will be provided by severity, causality (separately assessed for the injection procedure and the drug) and outcome. Subject listings of all adverse events will be provided. Deaths and other serious or clinically significant non-fatal adverse events will be listed separately. A subject with multiple adverse events of same preferred term or within a primary system organ class is only counted once towards the total of the preferred term or primary system organ class.

An adverse event of special interest (ESI) is one of scientific and medical interest to the Sponsor and includes, but is not limited to, the following:

- Endophthalmitis
- Uveitis: all cases of anterior, posterior, or panuveitis
- ≥ 30 letter decrease in BCVA compared with baseline visual acuity
- New retinal tear or detachment

[redacted]

Ophthalmic examinations

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

Vital signs

All vital signs data will be listed by treatment group, subject, and visit and, if ranges are available, abnormalities will be flagged with thresholds representing clinical relevant abnormality. Summary statistics of absolute and change from baseline data will be provided by treatment and visit. Shift tables using the low/normal/high classification will be used to compare baseline to the worst on-treatment value.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit, and abnormalities will be flagged (using extended normal ranges as provided by the central laboratory) with thresholds representing clinical relevant abnormality. Summary statistics of absolute and change from baseline data will be provided by treatment and visit. Shift tables using the low/normal/high classification will be used to compare baseline to the worst on-treatment value.

12.5.3 Anti-drug antibody

Assessment of ADAs (screening and confirmatory assay followed by titer and neutralizing antibody (nAb) for confirmed positive samples) will be performed at Screening, Weeks 4, 12, 24, 36, and 52/EOS visits in subjects randomized to treatment with brolucizumab. However, in order to maintain masking, collection of blood samples for ADA assessment will be performed in both treatment arms. In case of intraocular inflammation (eg, uveitis) diagnosed and reported as an AE at a scheduled visit (with no ADA sampling) or at an unscheduled visit, an additional ADA sample will be collected.

The number and percent of subjects according to their ADA status (including negative, positive without boost, treatment-induced, treatment-boosted, persistent and transient) will be presented. Subject listings of all ADA titer values and the corresponding free brolucizumab concentration will be presented for all subjects in the brolucizumab arm.

Further details of the ADA analyses will be described in the SAP.

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12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The primary objective is to demonstrate non-inferiority of brolucizumab versus aflibercept with respect to the change from baseline in BCVA at Week 52.

The fixed-margin method is used to derive an appropriate non-inferiority margin (NIM) for this study (FDA 2016). Results from a meta-analysis of the phase III studies VIVID and VISTA comparing monthly aflibercept 2 mg vs laser in patients with DME suggest a pooled mean treatment effect of 10.8 letters (95% CI, [8.0, 13.6]) favoring aflibercept in the change from baseline in BCVA at Week 52. The smallest effect of aflibercept vs laser is defined as the lower limit of the 95% CI for the pooled mean BCVA, ie, an effect of 8.0 letters. The NIM is then set as the value which preserves 50% of this effect, ie, the NIM is set to 4 letters. This non-inferiority margin provides assurance that any proof of non-inferiority only occurs if the effect of brolucizumab is superior to that of laser, and the observed treatment difference to aflibercept is of no clinical relevance.

Subjects will be randomized to the brolucizumab and aflibercept arms in a ratio of 2:1. A total sample size of 357 subjects (238 on the brolucizumab arm vs 119 on the aflibercept arm) will allow assessment of non-inferiority (using a NIM of 4 letters) of brolucizumab 6 mg versus aflibercept 2 mg with respect to the change from baseline in BCVA at Week 52. Assuming equal means and a common standard deviation of 11 letters, for a NIM of 4 letters and a two sided alpha level of 0.05, there is 90% power to reject the null hypothesis that brolucizumab is inferior to aflibercept. To ensure that at least 300 patients are treated with brolucizumab 6 mg on a fixed q4w regimen, the total sample size will be increased to 450 subjects total (300 on the brolucizumab arm vs 150 on the aflibercept arm). This results in a statistical power for assessing non-inferiority of 95%.

Given the planned unequal sample size of 300 vs 150, there is a higher probability that infrequent AEs will occur in the brolucizumab arm than in the aflibercept arm in this study. For example, for an AE with a probability of occurrence of 0.01, the probabilities of observing at least one event are 95% and 78% for the brolucizumab and aflibercept arms, respectively, using a Binomial distribution.

To account for a dropout rate of 9%, a total of approximately 495 subjects (330 on the brolucizumab arm vs 165 on the aflibercept arm) will need to be randomized.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive

2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol,

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other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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

14.1 Protocol amendments

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

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

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

15 References

References are available upon request

Agarwal A, Sarwar S, Sepah YJ, et al (2015) What have we learnt about the management of diabetic macular edema in the antivascular endothelial growth factor and corticosteroid era? Curr Opin Ophthalmol; 26(3):177-83.

Bansal AS, Khurana RN, Wieland MR, et al (2015) Influence of Glycosylated Hemoglobin on the Efficacy of Ranibizumab for Diabetic Macular Edema: A Post Hoc Analysis of the RIDE/RISE Trials. Ophthalmology; 122(8):1573-9.

Bressler SB, Ayala AR, Bressler NM, et al (2016) Persistent Macular Thickening After Ranibizumab Treatment for Diabetic Macular Edema With Vision Impairment. JAMA Ophthalmol; 123(6):278-85.

Bressler SB, Odia I, Maguire MG, et al (2019) Factors Associated With Visual Acuity and Central Subfield Thickness Changes When Treating Diabetic Macular Edema With Anti-Vascular Endothelial Growth Factor Therapy: An Exploratory Analysis of the Protocol T Randomized Clinical Trial. AMA Ophthalmol; 1:6786.

Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, US Food and Drug Administration (2005) Guidance for Industry: Premarketing risk assessment.

Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, US Food and Drug Administration (2016) Guidance for industry: Non-inferiority clinical trials to establish effectiveness.

Ciulla TA, Bracha P, Pollack J, et al (2018) Real-world outcomes of anti-vascular endothelial growth factor therapy in diabetic macular edema in the United States. Ophthalmol Retina; 1-9.

Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group (2005) Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005 Sep;140(3):509-16.

Korobelnik JF, Do DV, Schmidt-Erfurth U, et al (2014) Intravitreal aflibercept for diabetic macular edema. Ophthalmology; 121(11):2247-54.

Lee R, Wong TY, Sabanayagam C (2015) Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis (Lond); 215(17):1-25.

Nussenblatt RB, Palestine AG, Chan CC, et al (1985) Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology; 92(4):467-71

Pieramici D, Singh RP, Gibson A, et al (2018) Outcomes of diabetic macular edema eyes with limited early response in the VISTA and VIVID studies. Ophthalmol Retina; 2(6): 558-66.

Pieramici DJ, Wang PW, Ding B, et al (2016) Visual and Anatomic Outcomes in Patients with Diabetic Macular Edema with Limited Initial Anatomic Response to Ranibizumab in RIDE and RISE. Ophthalmology; 123(6):1345-50.

[redacted]

Sivaprasad S, Oyetunde S (2016) Impact of injection therapy on retinal patients with diabetic macular edema or retinal vein occlusion. Clin Ophthalmol; 10:939-46.

Staurenghi G, Feltgen N, Arnold JJ, et al (2018) Impact of baseline Diabetic Retinopathy Severity Scale scores on visual outcomes in the VIVID-DME and VISTA-DME studies. Br J Ophthalmol; 102:954-58.

Virgili G, Parravano M, Menchini F, et al (2014) Cost-effectiveness of treatments for diabetic macular oedema: should we pay more attention to the appraisal and reporting of economic evaluations? Br J Ophthalmol: 98(4):421-2.

Wells JA, Glassman AR, Ayala AR, et al (2016) Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology; 123(6):1351-9.

Wykoff CC, Elman MJ, Regillo CD, et al (2016) Predictors of Diabetic Macular Edema Treatment Frequency with Ranibizumab During the Open-Label Extension of the RIDE and RISE Trials. Ophthalmology; 123(8):716-21.

Ziemssen F, Cruess A, Dunger-Baldauf C, et al (2017) Ranibizumab in Diabetic Macular Oedema - A Benefit-risk Analysis of Ranibizumab 0.5 mg PRN Versus Laser Treatment. Eur Endocrinol; 13(2):91-98.

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16 Appendices

Not applicable.

[redacted]