NOVARTIS

Global Clinical Development - General Medicine

[RTH258/brolucizumab]

Clinical Trial Protocol [CRTH258B2301 / NCT03481634]

A Two-Year, Three-Arm, Randomized, Double-Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Diabetic Macular Edema (KESTREL)

Document type:	Amended Protocol Version
EUDRACT number:	2017-004742-23
Version number:	v04 (Clean)
Clinical trial phase:	III
Document status:	Final
Release date:	28-Sep-2021

Clinical Trial Protocol Template Version 3.4 (May 2017)

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List of abbreviations

ADA	Anti-drug antibody
AE	Adverse Event
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AR	Analysis restrictions
AST	Aspartate aminotransferase
BCVA	Best-corrected visual acuity
CFR	US Code of Federal Regulations
CI	Confidence interval
CNV	Choroidal neovascularization
CPO	Country Pharma Organization
COA	Clinical Outcome Assessment
CRC	Central Reading Center
eCRF	Case Report/Record Form (electronic)
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organization
CSFT	Central subfield thickness
CSFTns	Central Subfield Thickness-neurosensory retina
DDE	Direct Data Entry
DM	Diabetes mellitus
DMC	Data monitoring committee
DME	Diabetic macular edema
[redacted]	[redacted]
DR	Diabetic retinopathy
DRSS	Diabetic retinopathy severity scale
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAS	Full analysis set
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
IB	Investigator Brochure
ICH	International Conference on Harmonization
i.e.	Id est

[redacted]

IEC	Independent Ethics Committee
IOI	Intraocular inflammation
IOP	Intraocular pressure
IN	Investigator notification
IP	Investigational product
IRB	Institutional Review Board
IRF	Intraretinal fluid
IRT	Interactive Response Technology
ITT	Intention-to-treat
IUD	Intrauterine device
IUS	Intrauterine system
IVT	Intravitreal Treatment
kDa	kilo Daltons
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LFT	Liver function test
LOCF	Last observation carried forward
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model for repeated measures
nAMD	Neovascular age-related macular degeneration
n.a.	Not applicable
NEI	National Eye Institute
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
PPS	Per Protocol Set/Protocol analysis set
PRO	Patient reported outcome
PT	Preferred Term
QoL	Quality of Life
RBC	Red blood cells
RAO	Retinal artery occlusion
RO	Retinal vascular occlusion
RV	Retinal vasculitis
SAE	Serious Adverse Event
SAP	Statistical analysis plan
scFv	single-chain fragment variable
SD-OCT	Spectral domain optical coherence tomography
SGOT	Serum glutamic oxaloacetic transaminase

[redacted]

SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
SRF	Subretinal fluid
SUN	Standardization uveitis nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reactions
USM	Urgent safety measures
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VFQ-25	Visual Functioning Questionnaire-25
vs.	Versus
WBC	White blood cells
WHO	World Health Organization
WoC	Withdrawal of Consent
YAG laser	Yttrium aluminum garnet laser

[redacted]

Glossary of terms

Cohort	A specific group of patients fulfilling certain criteria
Control drug	Drugs(s) 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 patient in a time unit
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.
eSource DDE	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
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 active/sham injections)
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
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
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
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 drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Unmasked/treating investigator	For the entire study duration and all study patients, the treating investigator only performs the treatment (injection active/sham) and assesses patient safety following the active/sham injections
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
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
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.
Withdrawal of study 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

[redacted]

Amendment 4

Amendment rationale

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

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

Changes to the protocol

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

Section 1.1 Background:

- Information added to describe Urgent Safety Measures

Section 3.6 Risk and benefits:

- Information added to describe Urgent Safety Measures and additional information on gender imbalance on IOI following brolucizumab treatment

Section 5.5.4 Instruction for prescribing and taking study treatment

- Requirement of treatment discontinuation was added if subject developed RV and/or RO

Section 5.6.2 Discontinuation of study treatment:

- Changes were made as follows:
  - Use of prohibited treatment (see Section 5)
  - Any situation in which study participation might result in a safety risk to the subject
  - Subject developing retinal vasculitis and/or retinal vascular occlusion event

Section 6.5.4 Ophthalmic examination:

- Requirement of treatment discontinuation was added if subject developed RV and/or RO.

Other changes incorporated in this amendment

Section 5.5.7 Permitted concomitant therapy requiring caution and/or action:

- Added recommendations on the time window for a study subject to receive the COVID-19 vaccine.
- Other minor clarifications and corrections were made where applicable.

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

[redacted]

IRBs/IECs

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

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

Summary of previous amendments

Amendment 3

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 a new safety signal from post-marketing case reports and its impact on the benefit-risk balance.
- Section 5.5.4 Instructions for prescribing and taking study treatment: Additional guidance is 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 6-1 Assessment schedule
  - Section 6.4.3 Color fundus photography and fluorescein angiography:
  - Section 6.5.4 Ophthalmic Examination
  - Section 6.5.8 Appropriateness of safety measurements

Modifications were made to include importance of Estimands per ICH E9 (R1) guidance in the following Sections:

- Section 9.1 Analysis sets
- Section 9.4.1.2 Handling of missing values/censoring/discontinuations
- Section 9.4.3 Sensitivity and supportive analyses

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

- Section 6 Visit Schedule and Assessments

[redacted]

- Section 6.5 Safety
- Section 6.5.5 Laboratory evaluation
- Section 9 Data Analysis
- Section 10.2 Informed Consent Procedures

Other changes incorporated in this amendment:

- Section 5.1.1 Investigational and control drugs
- Section 5.4 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 5.5.4 Instructions for prescribing and taking study treatment: Language regarding the injection procedure was added replacing reference to an applicable manual.
- Section 6.5.4 Ophthalmic examination: Clarification on the use of same method for IOP measurement and timing for post-injection IOP measurement
- Section 6.6.4 Anti-drug antibodies (immunogenicity)
- Section 7.2.2 SAE Reporting: Clarification of the SAE reporting period
- Section 8.4 Data monitoring committee: Data monitoring committee was updated to program level data monitoring committee.
- [redacted]
- Section 12 References
- List of Abbreviations
- Other minor clarifications were made where applicable.

Amendment 2

Amendment rationale

This protocol amendment aims at maintaining the planned assessment of the primary objective whilst allowing enough time to enroll the planned number of Japanese patients.

The protocol is being amended to allow for the primary analysis to be conducted when the initially targeted total number of 534 randomized patients reach their Week 52 visit or terminate the study prior to Week 52. This total number of randomized patients will increase due to the continued enrollment in Japan. A second interim database lock will be performed after all randomized patients have completed their Week 52 visit or terminated the study prior to Week 52. An additional analysis will be conducted in order to allow for a consistency assessment of data between the Japanese and non-Japanese patients.

Changes to the protocol

Major changes are made to the protocol in the following sections:

- Section 3.5 Purpose and timing of interim analyses/design adaptations: This section was updated for the primary analysis to be conducted when the first 534 randomized patients

[redacted]

have completed their Week 52 visit or terminated the study prior to Week 52, and to clarify that data for the additional patients randomized in Japan beyond the study target of 534 patients is to be analyzed once these patients have completed their Week 52 visit or terminated the study prior to Week 52.

- Section 9 Data analysis and Section 9.7 Interim Analyses: Details were added regarding the primary Week 52 analysis and additional analyses to allow for consistency assessment of data between Japanese and non-Japanese patients.

[redacted]

- Other minor clarifications were made where applicable.

Amendment 1

Amendment rationale

The main purpose of this amendment is to:

- Compile the required changes in Informed Consent Forms with regards to the definition of "personal data" and "withdrawal of informed consent" in order to incorporate and reflect the European Economic Area (EEA) General Data Protection Regulation (GDPR) requirements.

In addition, the purpose of this amendment is to incorporate changes to the protocol language to improve clarity, accuracy and ensure better adherence.

- **Assessment schedule:** The anti-drug antibody schedule in assessment Table 6-1 was corrected in line with Section 6.6.4. The appearance of Table 6-1 was adjusted to improve clarity.
- **Inclusion criteria on cut-off value of central subfield retinal thickness:** Inclusion criteria no. 5 was revised to allow enrollment of patients with central subfield retinal thickness (measured from RPE to ILM inclusively) of ≥320 µm on SD-OCT at screening, in lieu of 340 µm in the original protocol. The revised cut-off of 320 µm corresponds to the highest cut-off for DME on the most common SD-OCT devices.
- **Contraception requirement:** The contraception requirement is extended from 40 days to 3 months after last dose, for consistency with the approved label of comparator in EU and US.

Changes to the protocol

Major changes are made to the protocol in the following sections:

[redacted]

- Glossary of terms and Section 5.6.3: Definition of "personal data" was added and "withdrawal of study consent (WOC)" was updated. The framework of analysis on study information collected from withdrawn patients is clarified. The definition of "Dosage" was updated to provide more clarity.
- Section 4.1 Inclusion Criteria and Protocol summary: In inclusion criterion no. 5, central subfield retinal thickness cutoff value on SD-OCT was updated from ≥ 340 µm to ≥ 320 µm.
- Section 4.2 Exclusion Criteria: In exclusion criterion no. 26 and Section 6.5.7:, The duration required for contraception after stopping investigational medication was updated from 40 days to 3 months, and this requirement was moved from the protocol section of exclusion criteria to the section of assessment of fertility.
- Table 6-1 Assessment schedule: The assessment schedule of anti-drug antibodies was corrected according to protocol body text Section 6.6.4. Assessment schedule of optional assessments [redacted] are clarified. An optional FSH (Follicle Stimulating Hormone) assessment was added for women needing to confirm reproductive status. The footnote list was also updated accordingly.
- [redacted]
- References: References were updated for 2 cited literature references in Section 1.1, and remove the other 2 references which were not required.
- List of abbreviations was updated.
- Unit of Creatinine was corrected in Appendix 1

[redacted]

Protocol summary

Protocol number	RTH258B2301
Full Title	A two-year, three-arm, randomized, double-masked, multicenter, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema (KESTREL)
Brief title	Study of efficacy and safety of brolucizumab vs. aflibercept in patients with visual impairment due to diabetic macular edema
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to evaluate the efficacy and safety of brolucizumab in treatment of patients with visual impairment due to diabetic macular edema (DME)
Primary Objective(s)	To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the visual outcome after the first year of treatment
Secondary Objectives	To assess the efficacy and the ocular and systemic safety of brolucizumab: • To demonstrate that brolucizumab is non-inferior to aflibercept with respect to visual outcome during the last 3 months of the first year of treatment • To estimate the proportion of patients treated at q12w frequency with brolucizumab • To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab • To evaluate the functional and anatomical outcome with brolucizumab relative to aflibercept • To evaluate the effect of brolucizumab relative to aflibercept on the Diabetic Retinopathy status • To assess the safety of brolucizumab relative to aflibercept • To evaluate the effect of brolucizumab relative to aflibercept on patient-reported outcomes (VFQ-25)
[redacted]	
Study design	In this 2-year, randomized, double-masked, multicenter, active controlled study consenting patients will participate in a screening period, lasting up to 14 days. Eligible patients will be randomized in a 1:1:1 ratio to one of the three treatment arms: • Brolucizumab 3 mg: 5 x q6w loading then q12w/q8w maintenance • Brolucizumab 6 mg: 5 x q6w loading then q12w/q8w maintenance • Aflibercept 2 mg: 5 x q4w loading then q8w maintenance
Population	Approximately 534 randomized patients ≥18 years of age with either type 1 or 2 controlled diabetes mellitus and visual impairment due to diabetic macular edema

[redacted]

Key Inclusion criteria	*General* 1. Patients must give written informed consent before any study related assessments are performed 2. Patients ≥18 years of age at baseline 3. Patients with type 1 or type 2 diabetes mellitus and HbA1c of ≤10% at screening 4. Medication for the management of diabetes must have been stable within 3 months prior to randomization and is expected to remain stable during the course of the study *Study Eye* 5. Visual impairment due to DME with: • BCVA score between 78 and 23 letters, inclusive, using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/320), at screening and baseline • DME involving the center of the macula, with central subfield retinal thickness (measured from RPE to ILM inclusively) of ≥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.
Key Exclusion criteria	1. Previous treatment with any anti-VEGF drugs or investigational drugs in the study eye 2. Active proliferative diabetic retinopathy in the study eye as per the investigator 3. Concomitant conditions or ocular disorders in the study eye at screening or baseline which could, in the opinion of the investigator, prevent response to study treatment or may confound interpretation of study results, compromise visual acuity or require medical or surgical intervention during the first 12-month study period (e.g., cataract, vitreous hemorrhage, retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization of any cause) 4. Any active intraocular or periocular infection or active intraocular inflammation (e.g., infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis, uveitis) in study eye at screening or baseline 5. Structural damage of the fovea in the study eye at screening likely to preclude improvement in visual acuity following the resolution of macular edema, including atrophy of the retinal pigment epithelium, subretinal fibrosis, laser scar(s), epiretinal membrane involving fovea or organized hard exudate plaques 6. 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 7. Neovascularization of the iris in the study eye at screening or baseline 8. Evidence of vitreomacular traction in the study eye at screening or baseline which, in the opinion of the investigator, affect visual acuity
Study treatment	• Brolucizumab 3 mg/0.05 mL • Brolucizumab 6 mg/0.05 mL • Aflibercept 2 mg/0.05 mL

[redacted]

Key Efficacy assessments	• BCVA testing using ETDRS chart • Anatomical markers on Spectral Domain Optical Coherence Tomography (SD-OCT) and Color Fundus photography • ETDRS DRSS score based on Color Fundus photography
Key safety assessments	• Adverse events • Standard ophthalmic examination • Intraocular pressure measurement • Vital signs • Blood chemistry/hematology/urinalysis
Other assessments	• Visual Function Questionnaire-25 (VFQ-25) • Anti-drug antibody (ADA)
Data analysis	**Primary analysis data set:** The primary data set for efficacy evaluation is the full analysis set (FAS) with missing values imputed by last observation carried forward (LOCF). The FAS includes all randomized patients who receive at least one intravitreal (IVT) injection. Sensitivity analyses will be performed using the per protocol analysis set (PPS) and alternative methods of handling missing and descriptive analyses based on observed data only. **Primary and key secondary endpoints:** The primary endpoint is the change from baseline in BCVA at Week 52. The key secondary efficacy endpoint involved in confirmatory testing is the change from baseline in BCVA averaged over the period Week 40 to Week 52. Additional key secondary endpoints are proportion of patients maintained at q12w up to Week 52 and proportion of patients maintained at q12w up to Week 52 within those patients that qualified for q12w at Week 36 (for brolucizumab treatment arms only) **Statistical Hypotheses and testing strategy:** The following non-inferiority hypotheses are related to a non-inferiority margin of 4 letters: B3 = Brolucizumab 3 mg - 5 x q6w loading then q12w/q8w maintenance B6 = Brolucizumab 6 mg - 5 x q6w loading then q12w/q8w maintenance A = Aflibercept 2 mg - 5 x q4w loading then q8w maintenance **$H0_1$**: $\mu_{B6} - \mu_A \leq -4$ letters vs. **HA_1**: $\mu_{B6} - \mu_A > -4$ letters **$H0_2$**: $\varphi_{B6} - \varphi_A \leq -4$ letters vs. **HA_2**: $\varphi_{B6} - \varphi_A > -4$ letters **$H0_3$**: $\mu_{B3} - \mu_A \leq -4$ letters vs. **HA_3**: $\mu_{B3} - \mu_A > -4$ letters **$H0_4$**: $\varphi_{B3} - \varphi_A \leq -4$ letters vs. **HA_4**: $\varphi_{B3} - \varphi_A > -4$ letters Where μ_{B6} μ_{B3} and μ_A are the corresponding unknown true mean changes from baseline in BCVA at Week 52; φ_{B6}, φ_{B3} and φ_A are the corresponding unknown true mean changes from baseline in BCVA averaged over the period Week 40 to Week 52; These 4 hypotheses will be tested sequentially in the order of their numbering (H_{An}, n=1, 2, 3, 4), i.e, confirmatory testing of the second, third and fourth hypotheses requires rejection of each preceding null hypothesis. In this setting, each hypothesis will be assessed at a one-sided significance level of 0.025, while keeping the global type I error rate at 0.025. **Primary statistical method:**

	Analysis of variance (ANOVA) models will be used to test the treatment differences regarding the endpoints 'change from baseline in BCVA at Week 52' and 'change from baseline in BCVA averaged over the period Week 40 to Week 52'. The models will include baseline BCVA category (≤65, >65 letters) and age category (<65, ≥65) as factors. Two-sided 95% confidence intervals (CI) for the least square means difference (brolucizumab - aflibercept) will be presented. Within the specified testing procedure, non-inferiority will be established if the lower limit of the corresponding 95% CI is greater than -4 letters. **Sample size justification:** A sample size of 160 patients per arm will allow demonstration of non-inferiority (NIM of 4 ETDRS letters) of brolucizumab 6 mg or 3 mg (either treatment regimen) vs. aflibercept 2 mg with respect to the BCVA change from baseline at Week 52, with 90% power (disregarding the dependence within the sequential testing procedure, i.e. local power for 3 mg) at a one-sided alpha level of 0.025, assuming equal means and a common standard deviation of 11 letters. Based on its nature it can be assumed that the endpoint 'change from baseline in BCVA averaged over the period Week 40 to Week 52' will not present a higher standard deviation, so that a (local) power of at least 90% can also be expected for its non-inferiority claim. To account for a drop-out rate of 10%, a total of 534 (178 per arm) patients will need to be randomized.
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 visual loss in patients with DR.

For anti-VEGF agents like ranibizumab or aflibercept a favorable benefit risk ratio was demonstrated with superior efficacy versus the previous standard of care (laser photocoagulation) in large Phase 3 programs that consequently led to their approval for the treatment of DME. Anti-VEGF treatment led to clinically relevant improvements of BCVA, reduction of fluid accumulation and decreased severity of diabetic retinopathy.

Current standard therapy

The current treatment options for patients with DME are: laser photocoagulation, IVT corticosteroids, IVT corticosteroid implants, or IVT anti-VEGF. Due to the efficacy and safety profile of anti-VEGF therapy, it has become the first-line treatment. Corticosteroids are 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 therapy (Ziemssen F 2017; Korobelnik JF 2014).

Despite the treatment success of existing anti-VEGFs, there remains a need for further treatment options to improve response rate and/or reduce resource use and injection frequency in patients with DME (Mitchell et al., 2011; Smiddy, 2011; Lang et al., 2013; Virgili et al., 2014; Agarwal et al., 2015).

Brolucizumab

Brolucizumab, formerly known as RTH258 and ESBA1008, is a humanized single-chain fragment variable (scFv), binding to VEGF-A (i.e. interfering with activation of VEGF-R1 and R2 on endothelial cells) with a molecular weight of ~26 kDa (kilo Daltons) that is also being developed for the treatment of choroidal neovascularization (CNV) associated with neovascular age-related macular degeneration (nAMD).

The characteristics of brolucizumab allow delivery of a high molar dose via intravitreal injection. A 6 mg dose of brolucizumab delivers a molar dose which is approximately 11 and 22 times higher than aflibercept 2 mg and ranibizumab 0.5 mg, respectively. Higher molar doses are expected to lead to longer presence of relevant drug levels in the eye. In addition, a low molecular weight and high concentration gradient between the vitreous and the retina may increase drug distribution to the target site of action, supporting effective control of anatomical disease activity.

In a single ascending dose Phase I study (C-10-083), the median time until patients fulfilled protocol defined criteria for receipt of standard of care treatment was 30 days longer for brolucizumab 3 mg (p=0.037) and 6 mg (p=0.036) versus ranibizumab. In a separate repeat

[redacted]

dosing study (C-12-006) comparing brolucizumab 6 mg (bimonthly [q8w], then quarterly [q12w] administration) against aflibercept (bimonthly administration [q8w]), brolucizumab achieved comparable visual outcome during the loading and q8w phase, with a lower number of patients requiring additional rescue treatments (5 vs. 10, respectively). Brolucizumab demonstrated a trend for greater improvements and more stability in retinal anatomy during the 4 cycles of q8w dosing (up to Week 40), e.g. simultaneous resolution of intraretinal and subretinal fluid which was achieved in 61% of brolucizumab patients versus 35% of aflibercept patients at Week 40.

In the Phase III studies (HAWK, HARRIER), brolucizumab demonstrated non-inferiority to aflibercept in mean change in best-corrected visual acuity from baseline to Week 48 in both trials. These results were achieved while a majority of patients on brolucizumab 6 mg – 56% in HAWK and 51% in HARRIER – were maintained on a q12w dosing interval following the loading phase through Week 48. Brolucizumab safety was comparable to aflibercept, with the overall incidence of adverse events balanced across all treatment groups in both studies.

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

Summary

Ranibizumab, aflibercept and brolucizumab all inhibit the activity of VEGF-A and all have demonstrated efficacy in the treatment of patients with nAMD. Both ranibizumab and aflibercept have also consistently demonstrated efficacy in the treatment of patients with visual impairment due to DME. These findings support the evaluation of brolucizumab in DME patients. Furthermore, the profile of brolucizumab in nAMD trials indicates a potential of brolucizumab to differentiate versus existing anti-VEGFs on duration of action and anatomical efficacy in DME patients:

- The higher dose administered with brolucizumab is intended to provide a prolonged duration of action compared with ranibizumab and aflibercept
- The positive nAMD study results regarding the q12w/q8w regimen support the administration of q6w loading regimen for brolucizumab and q12w/q8w during the maintenance phase, extending the total duration of the loading phase whilst also reducing the injection burden

The above supports the initiation of a Phase III program to evaluate the efficacy and safety of brolucizumab in treatment of patients with visual impairment due to DME with the intention of evaluating the potential to reducing the treatment burden for patients.

[redacted]

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of brolucizumab in treatment of patients with visual impairment due to DME.

[redacted]

2 Study objectives and endpoints

For the detailed description of endpoints and their statistical analysis, please refer to Section 9.4 for primary and key secondary endpoints, Section 9.5 for other secondary [redacted] 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 visual outcome after the first year of treatment	• Change from baseline in BCVA at Week 52
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To demonstrate that brolucizumab is non-inferior to aflibercept with respect to visual outcome during the last 3 months of the first year of treatment	• Change from baseline in BCVA averaged over a period Week 40 to Week 52
• To estimate the proportion of patients treated at q12w frequency with brolucizumab	• Proportion of patients maintained at q12w up to Weeks 52 & 100
• To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab	• Proportion of patients maintained at q12w up to Weeks 52 & 100, within those patients that qualified for q12w at Week 36
• To evaluate the functional and anatomical outcome with brolucizumab relative to aflibercept	• Change from baseline by visit up to Week 100 in BCVA and in parameters derived from SD-OCT, Color fundus photography and Fluorescein angiography
• To evaluate the effect of brolucizumab relative to aflibercept on the Diabetic Retinopathy status	• Change in ETDRS Diabetic Retinopathy Severity Scale (DRSS) score up to Week 100
• To assess the safety and tolerability of brolucizumab relative to aflibercept	• Incidence of Ocular and Non-ocular AEs, vital signs and laboratory values up to Week 100
• To evaluate the effect of brolucizumab relative to aflibercept on patient-reported outcomes (VFQ-25)	• Change in patient reported outcomes (VFQ-25) total and subscale scores from baseline up to Week 100

[redacted]

3 Investigational plan

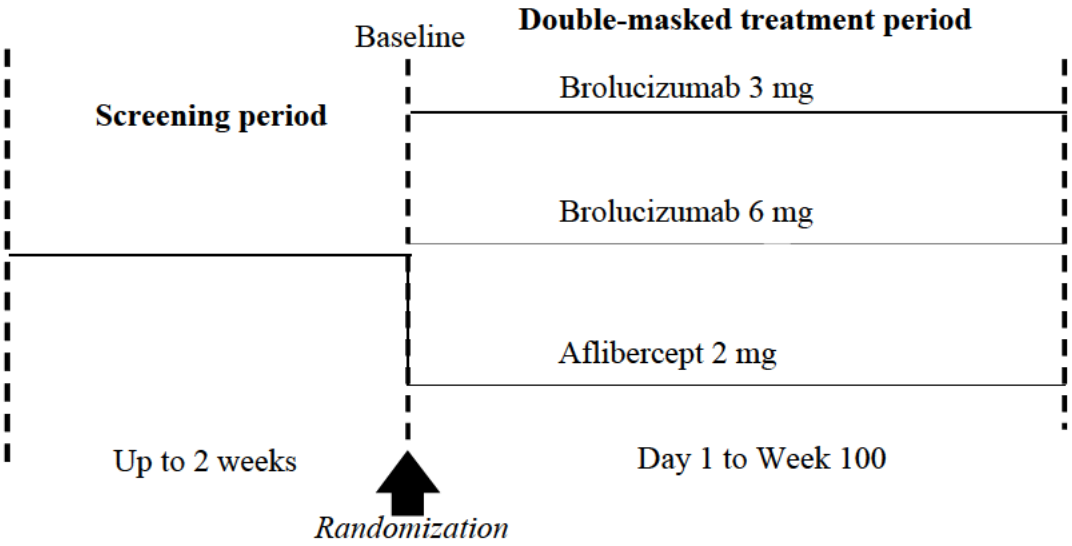
3.1 Study design

The study is a randomized, double-masked, multi-center, active-controlled, 3 armed study in patients with DME.

Patients who consent and meet all the inclusion and none of the exclusion criteria will be screened to evaluate eligibility. After confirmation of eligibility, patients will be randomized in a 1:1:1 ratio to one of three treatment arms:

- Brolucizumab 3 mg: 5 x q6w loading then q12w/q8w maintenance
- Brolucizumab 6 mg: 5 x q6w loading then q12w/q8w maintenance
- Aflibercept 2 mg: 5 x q4w loading then q8w maintenance

Figure 3-1 Study design



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

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

One time rescreening of patients is allowed, except for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the patient. As long as testing can be repeated within 14 days of the first screening, the other screening assessments do not need to be repeated. If rescreening is to occur beyond 14 days from the original screening visit date, then all screening procedures must be repeated. Medical judgment should be exercised to ensure that treatment of DME is not withheld in order for a patient to participate in the study.

2. Double masked treatment period: Day 1 to Week 96

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

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

The baseline visit is defined as Day 1/Visit 1, and end of treatment visit as Visit 27 (Week 96).

A study visit schedule will be established at the time of randomization for all patients. All efforts should be made to adhere to this study visit schedule ±7-day window. Treatment is intended to be administered on the day of study visit, or if this is not possible, within 3 days after the study visit when the per-protocol assessments took place. In addition, for a given protocol visit, assessments can be performed on two consecutive days.

Patients must have confirmed type 1 or type 2 diabetes at screening. Adequate glycemic control must be confirmed by an HbA1c level ≤10% at Screening.

3. Post-treatment follow-up period: Week 96 to Week 100

For all patients, the last study assessment will be performed at Week 100, at least four weeks after the last active study treatment in this study.

[redacted]

Patients withdrawn from the study prior to study completion will be asked to return for an early discontinuation visit (Visit 28), four weeks (±7 days) following their last study visit (see Section 5.6.2).

3.2 Rationale for study design

This study is designed as a multi-center, double-masked, 3 arm active controlled prospective study to demonstrate the safety and efficacy of brolucizumab 3 mg and 6 mg against the active control, aflibercept 2 mg, used per authorized label. Since the treatment schedule is different between arms, to ensure masking, the following will apply:

- in addition to every 4-week visits for all patients for 2 years, extra visits are scheduled at Weeks 6 and 18 for all treatment arms
- the patients will receive active/sham injection at each protocol visit except Weeks 20, 28 and 100 visits (No scheduled treatment for any arm)
- Disease activity assessment will be performed for all arms
- to fulfil the double-masking requirement, the investigational site will have masked and unmasked staff

Non-inferiority testing related to the primary efficacy parameter BCVA will be based on a margin of 4 letters. This non-inferiority margin provides assurance that any proof of non-inferiority only occurs if the observed treatment differences are of no clinical relevance.

The patient population will be described in more detail in the Section 4.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

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

- Based on the Phase III brolucizumab studies in nAMD, brolucizumab 6 and 3 mg doses showed comparable efficacy and safety profiles to existing anti-VEGFs with numerical advantages related to efficacy for the higher dose. Both doses are included in order to evaluate the dose-response following multiple dosing with brolucizumab in patients with DME.
- Current evidence from large anti-VEGF pivotal studies in DME indicates that in comparison to nAMD an extended period of intense treatment (loading regimen) is required to achieve maximal BCVA gain. Hence the loading regimen was extended to Week 24 for brolucizumab.
- The high dose of brolucizumab administered is intended to provide a prolonged duration of action. The positive nAMD study results regarding the q12w/q8w regimen in HAWK and HARRIER (Phase III clinical trials in nAMD) support q12w/q8w dosing during the maintenance phase also for DME in which treatment frequencies in the maintenance phase are similar. At the same time, these results support stretching the interval between injections in the loading regimen to 6 weeks. Both, extended intervals in the loading regimen and q12w/q8w dosing aim at reducing the injection burden.
- Aflibercept is applied as per the current labels in the EU and US.

[redacted]

- Based on the Phase III trials HAWK and HARRIER, 12 weekly disease activity assessments (DAA) were sufficient to verify whether patients were appropriately treated. Introduction of disease activity assessments 8 weeks following treatment (in HARRIER) did not result in earlier detection of disease activity attributable to the q12w status. Hence, disease activity assessments are scheduled every 12 weeks in this study.

Route of administration is intravitreal injection as for all anti-VEGF treatments currently approved for the treatment of DME. Study duration of 2 years (with treatment over 23 months) is warranted to assess longer-term efficacy and safety and to assess the q12w option for brolucizumab over time.

3.4 Rationale for choice of comparator

Aflibercept 2 mg q8w is an established standard of care option and has been chosen as comparator for this study due to the consistency of the approved dose and posology of aflibercept (Eylea®) across many countries especially EU and US for the targeted indication as compared to other approved anti-VEGF treatments.

3.5 Purpose and timing of interim analyses/design adaptations

The primary analysis will be conducted when the first 534 randomized patients have completed their Week 52 visit or terminated the study prior to Week 52 (first interim database lock). Data for additional patients randomized in Japan beyond the study target of 534 patients will be analyzed within the total population once these patients have completed their Week 52 visit or terminated the study prior to Week 52 (second interim database lock). However, if any special circumstance compromises the feasibility of the approach described above (first and second interim database locks), then the primary analysis will be conducted when all randomized patients have completed their Week 52 visit or terminated the study prior to Week 52.

Another analysis may be performed by locking the Week 76 data in case of regulatory request for supplemental data to be submitted during the review period.

Patients will remain in the study and will continue to receive masked treatment through the planned duration (100 weeks) to allow for further masked evaluation of efficacy and safety. Treatment masking of individual patients will remain intact for all patients, investigators and selected staff from the Sponsor who have contact with patients or investigators or those who are involved in the direct conduct of the study until the final database lock has occurred.

3.6 Risks and benefits

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 mechanism of action as ranibizumab and aflibercept) will likewise be efficacious and have a similar safety profile in the DME indication.

In both Phase III studies (HAWK, HARRIER) in nAMD, brolucizumab demonstrated non-inferiority to aflibercept in mean change in BCVA from Baseline to Week 48. These results were achieved while a majority of patients on brolucizumab 6 mg – 56% in HAWK and 51%

in HARRIER – were maintained on a q12w dosing interval following the loading phase through Week 48, i.e. with a reduced treatment frequency compared to aflibercept.

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

Based on clinical studies, IOI related adverse events, including retinal vasculitis and retinal vascular occlusion, were reported more frequently in female patients treated with brolucizumab than male patients (e.g. 5.3% females vs. 3.2% males in HAWK and HARRIER, Novartis data on file)

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

The higher intravitreal dose of brolucizumab (5.5- and 11-times molar excess for 3 and 6 mg, respectively vs. 2 mg aflibercept) is expected to similarly (to nAMD) confer a longer duration of effect in DME that will translate into a reduced frequency of injections with non-inferior efficacy. A reduced treatment frequency will provide benefit to patients and caregivers/physicians.

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

4 Population

The study population will be male and female patients ≥18 years old with visual impairment due to DME. Approximately 700 patients will be screened (20% screening failure rate expected) and 534 (178 per arm) patients will be randomized in approximately 130 centers worldwide. Approximately 60 patients will be from Japan.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Patients ≥18 years of age at baseline
3. Patients with type 1 or type 2 diabetes mellitus and HbA1c of ≤10% at screening.
4. Medication for the management of diabetes must have been stable within 3 months prior to randomization and is expected to remain stable during the course of the study

Study Eye

1. Visual impairment due to DME with:
    - BCVA score between 78 and 23 letters, inclusive, using ETDRS visual acuity testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/320) at screening and baseline

[redacted]

- DME involving the center of the macula, with central subfield retinal thickness (measured from RPE to ILM inclusively) of ≥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.

4.2 Exclusion criteria

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

1. Active Proliferative diabetic retinopathy in the study eye as per investigator
2. Concomitant conditions or ocular disorders in the study eye at screening or baseline which could, in the opinion of the investigator, prevent response to study treatment or may confound interpretation of study results, compromise visual acuity or require medical or surgical intervention during the first 12-month study period (e.g., cataract, vitreous hemorrhage, retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization of any cause)
3. Any active intraocular or periocular infection or active intraocular inflammation (e.g., infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis, uveitis) in study eye at screening or baseline
4. Structural damage of the fovea in the study eye at screening likely to preclude improvement in visual acuity following the resolution of macular edema, including atrophy of the retinal pigment epithelium, subretinal fibrosis, laser scar(s), epiretinal membrane involving fovea or organized hard exudate plaques
5. 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
6. Neovascularization of the iris in the study eye at screening or baseline
7. Evidence of vitreomacular traction in the study eye at screening or baseline which in the opinion of the investigator, affects visual acuity
8. Presence of amblyopia, amaurosis or ocular disorders with vision <20/200 (35 letters) in the fellow eye at screening or baseline
9. History of idiopathic or autoimmune uveitis in the study eye

Ocular treatments

10. Previous treatment with any anti-VEGF drugs or investigational drugs in the study eye
11. Use of dexamethasone intravitreal implant (Ozurdex) or fluocinolone acetonide intravitreal implant (Iluvien) in study eye at any time. Prior use of other intraocular or periocular corticosteroids in the study eye is not an exclusion provided at least 6-month wash-out prior to baseline
12. Laser photocoagulation (focal/grid or panretinal) in the study eye during the 3-month period prior to baseline
13. Intraocular surgery including yttrium aluminum garnet (YAG) laser in the study eye during the 3-month period prior to baseline

[redacted]

14. History of vitreoretinal surgery in study eye
15. Aphakia with the absence of posterior capsule in the study eye

Systemic conditions or treatments

16. Stroke or myocardial infarction during the 6-month period prior to baseline
17. Renal failure requiring dialysis or renal transplant
18. Uncontrolled blood pressure defined as a systolic value ≥160 mmHg or diastolic value ≥100 mmHg at screening or baseline
19. Systemic anti-VEGF therapy during the 3-month period prior to baseline
20. Systemic medications known to be toxic to the lens, retina or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol) used during the 6-month period prior to baseline
21. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes, or clinically relevant sensitivity to fluorescein dye as assessed by the investigator
22. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
23. History of a medical condition (disease, metabolic dysfunction 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
24. 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 (observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary)

Other

25. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG pregnancy test
26. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the study. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before baseline. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to baseline). For female patients in the study, the vasectomized male partner should be the sole partner for that patient

[redacted]

- 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 woman should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the ICF.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The investigational treatments used in this study are:

- Brolucizumab 3 mg/0.05 mL
- Brolucizumab 6 mg/0.05 mL

The control treatment is:

- Aflibercept 2 mg/0.05 mL

Brolucizumab is formulated as a sterile solution aseptically filled in a sterile glass vial for single use or may be provided in a prefilled syringe (PFS) in selected countries and the content of the vial must **not** be split.

Brolucizumab study kits will consist of a carton that contains 1 single use, sterile glass vial or may be provided in a prefilled syringe (in selected countries) containing sufficient brolucizumab to deliver to brolucizumab 3 mg/0.05 mL or brolucizumab 6 mg/0.05 mL.

Aflibercept will be provided in a single use, sterile glass vial, or may be provided in a prefilled syringe in selected countries containing sufficient Aflibercept to deliver a 2 mg dose when administering a volume of 0.05 mL. Sham injections refer to an imitation of an intravitreal injection procedure using an empty sterile syringe without a needle. There will be no empty sham vial.

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

[redacted]

5.1.2 Additional treatment

No additional treatment beyond investigational drug and control drug are included in this trial.

5.2 Treatment arms

- Brolucizumab 3 mg/0.05 mL 5 x q 6w loading then q12w/q8w maintenance
- Brolucizumab 6 mg/0.05 mL 5 x q6w loading then q12w/q8w maintenance
- Aflibercept 2 mg/0.05 mL 5 x q4w loading then q8w maintenance

5.3 Treatment assignment and randomization

At baseline visit, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms, in a ratio of 1:1:1, stratification for Japanese ethnicity (Japanese vs. non-Japanese) will be considered.

The investigator or her/his delegate will contact the IRT, after it was confirmed that the patient fulfills all the inclusion and none of the exclusion criteria. The IRT will assign a randomization number to the patient, which will link the patient to a treatment arm.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers.

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

5.4 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 have passed.

This study will be double-masked, with subjects randomized to be treated with brolucizumab 3 mg, brolucizumab 6 mg or aflibercept 2 mg. All members of the Sponsor study team will be masked to treatment assignments until all randomized patients complete Week 52 visit or terminate the study prior to Week 52 (sequentially if first and second interim database locks occur). Sponsor personnel who have access to treatment codes will not divulge the codes to subjects, investigators, site staff.

Unmasking of investigators and site personnel directly involved in the conduct of the study will only occur in the case of patient emergencies (see Section 5.6), and then at the time of the final analysis (see Section 3.5), at the conclusion of the study.

[redacted]

In the event of a medical emergency or an adverse event (AE) during the study where the knowledge of subject treatment is required (e.g. in case of 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 IP. The unmasked site personnel and unmasked injecting investigator must not perform BCVA, complete ophthalmic examination, disease activity assessments or administer the VFQ-25. Also, the unmasked site personnel and unmasked injecting physician must not perform assessment of any ocular or non-ocular safety parameters, or assess causality AEs for subjects during the course of the study except an event reported immediately following IVT injection.

The unmasked investigator/site personnel should, however, assess subject safety immediately following injection. Once the designated roles are determined, the unmasked investigator/site personnel roles must not be switched at any time after randomization to masked role. Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this masked study.

Treatment masking of individual subjects will remain intact until the final 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/treating investigator. During and after database lock at Week 52 and Week 100, the masked personnel and patients will remain masked to the treatment assignment until the conclusion of the study.

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

An independent, masked review of fundus photography, fluorescein angiography and optical coherence tomography (OCT) images for patients enrolled in the study will be performed at a CRC.

5.5 Treating the patient

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

5.5.1 Patient numbering

Upon signing the informed consent form, the patient is assigned the next sequential number available in electronic data capture (EDC) system. The investigator or her/his staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not

[redacted]

randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography Case Report/Record Form (electronic) (eCRF) should be completed.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug.

For brolucizumab, the study drug packaging has a 2-part label. A unique medication number is printed on each part of this label, which corresponds to one of the treatment arms. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before treating the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the unmasked investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

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

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

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

There will be two treatment phases for IVT injections with different timing for brolucizumab and aflibercept treatment arms:

Loading Phase

[redacted]

Brolucizumab (3 and 6 mg): In the loading phase, treatment with brolucizumab will occur every 6 weeks for five (5) consecutive injections (BL, Weeks 6, 12, 18 and 24). To preserve the masking, the patients assigned to this regimen will receive sham injection on Weeks 4, 8 and 16.

Aflibercept: In the loading phase, treatment with aflibercept will occur every 4 weeks for five (5) consecutive injections (BL, Weeks 4, 8, 12 and 16). To preserve the masking, the patients assigned to aflibercept Arm will receive sham injection on Weeks 6 and 18.

Maintenance Phase

The treatment interval during the maintenance phase will be as follows:

Brolucizumab 3/6 mg:

- From Week 24 onwards, patients will be scheduled to receive one injection of brolucizumab 6 mg / 3 mg every 12 weeks. If, however, disease activity is identified by the evaluating/masked investigator at Weeks 32, 36, 48, 60, 72, or 84, the patient will be assigned to receive treatment every 8 weeks (see Evaluation of Disease Activity below). A disease activity assessment will also be performed at Week 96 but will not be entered into IRT and will have no effect on the subject's treatment schedule.

Aflibercept 2 mg:

- From Week 16 onwards, patients will receive one injection of aflibercept 2 mg every 8 weeks (first injection after Week 16 to be given at Week 24) until Week 96 visit. Disease Activity assessments will be conducted by the evaluating/masked investigator for masking purposes and will not influence the treatment interval.

Evaluation of Disease Activity:

The concept of the brolucizumab q12w/q8w regimen is to allocate patients according to their individual treatment needs to either a q12w or a q8w treatment schedule. The initial schedule is q12w and a patient will remain on q12w as long as the masked investigator does not identify DME disease activity which in his opinion requires more frequent anti-VEGF treatment. Disease activity assessments (DAA) and a potential resulting adjustment of the treatment frequency are limited to pre-specified DAA-visits:

- A more closely monitoring of the patients individual treatment need will take place during the first q12w treatment interval with DAAs at Week 32 and 36 (i.e. for brolucizumab patients 8 and 12 weeks after the last loading injection) to make sure that patients with a high treatment need are identified early on
- After this first q12w treatment interval DAA will take place together with the scheduled q12w treatment visits, i.e. at Week 48, Week 60, Week 72 and Week 84. An additional DAA will be performed at Week 96 to document the adequacy of the q12w treatment schedule at the end of the 2 year follow-up (without having impact on the subject's treatment schedule)

The assessment of the disease activity is at the discretion of the masked investigator. He/she will assess DME disease activity in the study eye with reference to the patient's disease status

[redacted]

at Week 28 (outcome of the brolucizumab loading treatment). The outcome of this assessment will be captured as:

- 'q8w-need': identified disease activity which according to the masked investigator requires more frequent anti-VEGF treatment, e.g.: ≥5 letters loss in BCVA (compared to Week 28) which - based on anatomical parameters – is attributable to DME disease activity.
- 'no q8w-need' : otherwise

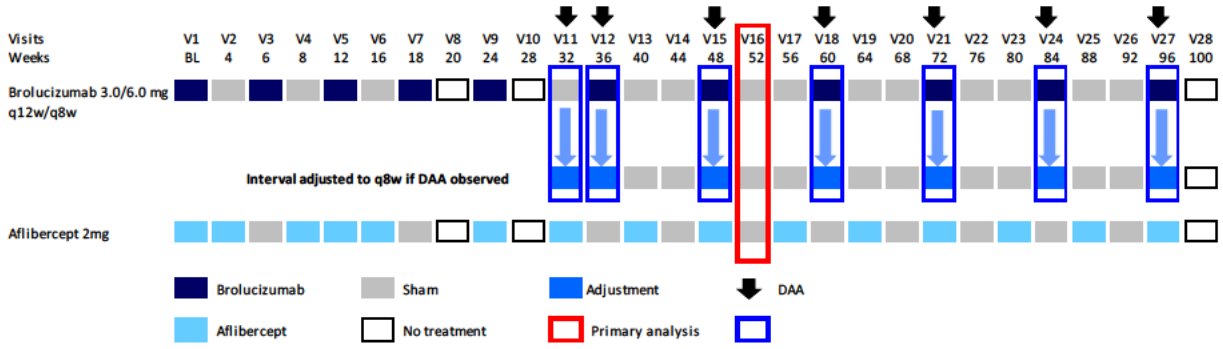
If DAA reveals a need for more q8w treatment the subject will be assigned to receive injections q8w thereafter, up to the end of the study.

The IRT system will make the necessary changes to the dosing schedule as per the masked investigator's assessment of disease activity.

A patient who misses Visit 11/Week 32 will undergo the disease activity assessment at Visit 12/Week 36 as he/she would have done if the visit had not been missed. If, however, a patient misses any of the following disease activity assessment visits (Visit 12/Week 36, Visit 15/Week 48, Visit 18/Week 60, Visit 21/Week 72, and Visit 24/Week 84) then the patient (brolucizumab patients only) will be assumed to have had a 'q8w-need' at this missed visit and will be assigned to a q8w schedule at the next visit (i.e. at the next visit the patient will receive an active injection) up to study exit. The IRT system will make the necessary changes once the missed visit is registered.

If a patient misses Visit 10/Week 28, then the Visit 9/Week 24 values should be applied as the reference for disease activity assessments.

Figure 5-1 Dosing schedule



In order to maintain masking, the evaluation of disease activity is conducted on all patients. The assessment of the masked/evaluating investigator will be passed to the unmasked/treating investigator or delegate in order to be entered in the IRT and obtain the applicable treatment, active or sham, as assigned by IRT depending on the treatment arm and the actual treatment frequency.

Brolucizumab patients who have disease activity identified will be reassigned to receive injections every 8 weeks thereafter until study exit.

[redacted]

Aflibercept patients will receive maintenance treatment every 8 weeks, regardless of the outcome of the Disease Activity Assessment as per approved regimen.

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

The sham injection should mimic an IVT injection including the aseptic and antimicrobial requirements. The tip of the sham injection syringe (the hub without a needle) will be placed on the eye for the approximate amount of time it would take to perform an IVT injection.

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

If any signs of intraocular inflammation are present, then an IVT injection **must not** be performed. Additional ophthalmic examination and imaging should be performed to evaluate IOI (see Section 6.5.4.).

If IOI is confirmed, subjects should be treated for IOI according to clinical practice and closely monitored since they may be at risk of developing retinal vasculitis and/or retinal vascular occlusion. If a subject develops retinal vasculitis and/or retinal vascular occlusion based on the investigator's evaluation, the study treatment must be discontinued.

At all applicable visits from Week 4 to Week 96, inclusive (with exception of Weeks 20 and 28 where no treatment is scheduled), a sham treatment will be performed to maintain patient masking. For the sham treatment the tip of an injection syringe (the hub without a needle) will be used.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Treatment dose adjustments and/or interruptions are not permitted unless interruptions are warranted by an AE.

5.5.6 Rescue medication/procedure

The study eye, in all treatment groups, identified as needing q8w at a previous visit could receive rescue treatments with laser photocoagulation from week 36 onward if DME worsened causing a ≥10-letter loss at 2 consecutive visits or ≥15-letter at 1 visit best previous measurement, with BCVA not better than baseline. When applicable, patients could receive both laser photocoagulation and active study treatment as scheduled at the same visit. Patients can continue with the study treatment.

Pan retinal photocoagulation is permitted at any time during the study as deemed necessary by the investigator, and the patient can continue the study.

In case the investigator deems it in the best interest of the patient to receive treatment in the study eye, which is prohibited by this protocol (aside from laser), instructions provided in Table 5-1 should be followed.

[redacted]

5.5.7 Concomitant medications and treatments

The investigator must instruct the patient to notify the study site about any new medications he/she takes after signing the study informed consent. All medications, procedures and significant non-drug therapies (e.g. blood transfusions) administered after the patient was enrolled into the study must be recorded in the appropriate eCRF page.

Each concomitant drug/procedure must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Sponsor medical monitor before randomizing a patient or allowing a new medication to be started.

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

5.5.8 Prohibited medication

Table 5-1 becomes effective with screening.

Table 5-1 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 medication	Any time	Discontinue study treatment
Laser photocoagulation (focal/grid)	Prior or at the time of first identification of DAA	Continuation of study treatment at the investigators discretion
Systemic		
Anti-VEGF therapy	Any time	Discontinue study treatment
Any investigational drug, biologic or device	Any time	Discontinue study treatment

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

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient 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 patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will

automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

If the treatment code needs to be broken in the interest of patient safety, the investigator is encouraged to contact an appropriate Sponsor representative prior to unmasking if there is sufficient time.

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

- protocol number
- study drug name (if available)
- patient number

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

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

5.6 Study completion and discontinuation

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

5.6.1 Study completion and post-study treatment

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

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

5.6.2 Discontinuation of study treatment

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

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.7 and Section 7.6)
- Use of prohibited treatment as per recommendations in Table 5-1
- Any situation in which study participation might result in a safety risk to the patient
- Subject develops a retinal vasculitis and/or a retinal vascular occlusion
- Unsatisfactory therapeutic effect

[redacted]

- Patient's condition no longer requiring study treatment

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the appropriate eCRF page.

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

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9

5.6.3 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 must make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient'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 patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in assessment Table 6-1 below.

Discontinued patients will not be replaced.

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

For US and Japan: 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 EU and 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.

5.6.4 Loss to follow-up

For patients 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 patient, e.g. dates of telephone calls, registered letters, etc.

5.6.5 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, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely discontinued patient. 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 patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all scheduled study visits and indicates with an "x" when a specific assessment is to be performed.

Patients must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed.

If the COVID-19 pandemic limits or prevents on-site study visits, study treatment could not be performed, and other study assessments may not be performed alternative methods of providing continuing care 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 6-1 Assessment schedule

Visit	Screening	1 Baseline	2	3	4	5	6	7	8	9	10	11	12	13
Week	**Up to 2 weeks**	**Day 1**	**4**	**6**	**8**	**12**	**16**	**18**	**20**	**24**	**28**	**32**	**36**	**40**
Informed Consent[a]	X													
Demographics	X													
Medical History	X													
Physical Examination[b]	X													
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X[d]												
Visual Function Questionnaire-25		X									X			
FSH (Follicle Stimulating Hormone)[m]	X[m]													
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[j]		X[j]												
Serum β-hCG Pregnancy test[e]	X													
Urine Pregnancy Test[e]		X	X		X	X	X		X	X	X	X	X	X
Chemistry/Hematology/Urinalysis	X					X				X[f]			X[f]	
[redacted]														
Blood Sample: Anti-Drug Antibodies	X		X			X				X			X	
Best-Corrected Visual Acuity	X[g]	X	X	X	X	X	X	X	X	X	X[g]	X	X	X
Intraocular pressure	X[g]	X	X	X	X	X	X	X	X	X	X[g]	X	X	X
Ophthalmic Exam[h, n]	X[g]	X	X	X	X	X	X	X	X	X	X[g]	X	X	X
Spectral Domain Optical Coherence Tomography[n]	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
Color Fundus Photography Fluorescein Angiography[n]	X[g]										X			
[redacted]														
Disease Activity Assessment												X	X	
Contact IRT	X	X[i]	X	X	X	X	X	X		X		X	X	X
Treatment		X	X	X	X	X	X	X		X		X	X	X

[redacted]

Visit	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28[c] Exit
Week	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**
Physical Examination															X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Function Questionnaire-25			X						X						X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[j]			X[j]												X[j]
Serum β-hCG Pregnancy test[e]			X												X
Urine Pregnancy Test[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	
Chemistry/Hematology/Urinalysis			X			X[f]			X[f]			X[f]			X
Blood Sample: Anti-Drug Antibodies			X						X						X
Best-Corrected Visual Acuity	X	X	X[g]	X	X	X	X	X	X[g]	X	X	X	X	X	X[g]
Intraocular pressure	X	X	X[g]	X	X	X	X	X	X[g]	X	X	X	X	X	X[g]
Ophthalmic Exam[h, n]	X	X	X[g]	X	X	X	X	X	X[g]	X	X	X	X	X	X[g]
Spectral Domain Optical Coherence Tomography[n]	X	X	X[g]	X	X	X	X	X	X	X	X	X	X	X	X[g]
[redacted]															
Color Fundus Photography / Fluorescein Angiography[n]			X[g]						X						X[g]
[redacted]															
Disease Activity Assessment		X			X			X			X			X	
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

a Must be signed/dated prior to performing any study procedures, including screening procedures
b At Visit 1, significant findings present prior to the study start (or known to being started before) must be recorded in the relevant Medical History; and any changes during the study which meet the definition of an Adverse Event must be recorded as an Adverse Event
c All exit procedures should be followed, regardless of when the patient exits the study (VFQ-25 will not be collected at early exit visit)
d Verify that inclusion/exclusion criteria are met as per section 4.1 and 4.2 prior to assignment of study treatment
e Women of childbearing potential only
f HbA1c only
g Both eyes
h Includes fundus and slit lamp examination. Pupil dilation optional according to local practice
i Patients will be randomized to one of the following treatments: brolucizumab 3 mg/50 µL or brolucizumab 6 mg/50 µL or aflibercept 2 mg/50 µL
j In Japanese sites only
[redacted]
l When equipment available at study site
m woman with the need to confirm child bearing potential
n Additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation

[redacted]

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next period will have the study completion eCRF pages for the screening period, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

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

- Date of birth, age
- Gender
- Race/Ethnicity
- Type of diabetes
- Vital signs
- Study eye
- Visual acuity
- Macular edema characteristics
- Intraocular pressure
- HbA1c and other laboratory test results
- Concomitant medications
- Past medical history and current medical conditions

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

6.3 Treatment exposure and compliance

Every time the study treatment is to be administered, IRT needs to be accessed 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 investigator staff or by unmasked field monitor on the appropriate study treatment dispensing form.

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

6.4 Efficacy

The following tests will be performed to assess activity of brolucizumab and aflibercept on visual function, retinal structure and leakage:

- Best-corrected visual acuity with ETDRS-like chart at initial testing distance of 4 meters

[redacted]

- Anatomical markers on Optical Coherence Tomography
- ETDRS DRSS score based on 7-field stereo Color Fundus Photography
- Vascular leakage evaluation by Fluorescein Angiography

6.4.1 Visual acuity

Visual acuity will be assessed at every study visit using best correction determined from protocol refraction (BCVA). BCVA measurements will be taken in a sitting position using ETDRS–like visual acuity testing charts. The details of the procedure and training materials are provided in the applicable manual. Certification of the assessment procedures and assessors will occur prior to any evaluation of study patients.

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

6.4.2 Optical coherence tomography

Optical Coherence Tomography (OCT) will be assessed in the study eye at every study visit and in both eyes at Screening, Week 52 and exit/premature discontinuation visit.

These assessments will be performed by trained technician or investigator at the sites and should be performed prior to any study drug administration. Evaluating investigators will evaluate the OCT to assess the status of disease activity. The OCT machine used for an individual patient should not change for the duration of the study.

In addition to the standard OCT assessment, as optional assessment at sites that have the applicable equipment, OCT angiography should be done at baseline, Week 28, Week 52, Week 76 and exit/premature discontinuation visit in the study eye. If OCT angiography will be performed, it must be done for a given patient from baseline. If OCT angiography was not performed at baseline, then it should not be introduced at later visits.

The images will be reviewed by a central reading center to ensure a standardized evaluation. For further procedural details, the investigator should refer to applicable manual provided by the Central Reading Center.

6.4.3 Color fundus photography and fluorescein angiography

Color fundus photography and fluorescein angiography will be performed in the study eye at Screening, Weeks 28, 52, 76 and exit/premature discontinuation visit, and in both eyes at Screening, Week 52 and exit/premature discontinuation visit. In case of premature termination there is no need to repeat the color fundus photography and fluorescein angiography if there was color fundus photography and fluorescein angiography within the previous 12 weeks, except if there is significant worsening of DME disease, in the opinion of the investigator.

[redacted]

[redacted]

[redacted]

The assessments will be performed by a trained technician at the sites. The images will be reviewed by a Central Reading Center to ensure a standardized evaluation. Grading for DRSS will be performed at the CRC. For further procedural details the investigator should refer to the Study Operations Manual provided by the Central Reading Center.

Additional images will be taken in case of any signs of intraocular inflammation. OCT, color fundus photography and fluorescein angiography [redacted] peripheral sweeps) should be performed for safety evaluation as described in Section 6.5.4.

6.4.4 Appropriateness of efficacy assessments

BCVA as a measure of retinal function and OCT images to analyze anatomical changes are standard assessments to monitor DME and potential treatment effects in routine practice and clinical trials. Likewise established is FA that helps classifying the type of macular edema and is used to assess vascular leakage. ETDRS DRSS is a recent addition to the tests conducted in clinical trials. This grading informs about the severity of the diabetic retinopathy underlying the macular edema. It was shown that anti-VEGF can improve the severity of the retinopathy the implications for the course of the edema and its treatment are currently being investigated.

6.5 Safety

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

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

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. The examination will be performed at screening and at the end of the study, exit/premature discontinuation.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the eCRF capturing Medical History. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the appropriate AE eCRF page.

6.5.2 Vital signs

Sitting blood pressure and heart rate will be collected at all visits before treatment 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

[redacted]

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.

On days when study drug is administered, vital signs will be measured before administration of study medication. The results will be recorded in the eCRF.

6.5.3 Height and Weight

Height and weight will be measured at the screening visit only.

Height in centimeters (cm) and body weight (to the nearest kilogram (kg), in indoor clothing but without shoes) will be measured at screening only. The results will be recorded in the eCRF.

6.5.4 Ophthalmic examination

The ophthalmic exam will consist of the following:

- **Anterior biomicroscopy (slit lamp examination)** will be completed at every (scheduled and unscheduled) visit to examine the anterior segment structures (e.g., eyelids/lashes, conjunctiva, cornea, anterior chamber, iris, lens and anterior part of the vitreous) of the study eye (fellow eye will be examined at screening and on discretion of the investigator). The outcome of the examination will be recorded in the source documents.

Slit lamp examination **must** be carefully performed before each study treatment. If there is 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 should be recorded on the adverse event page of the eCRF (events identified pre-Baseline should be recorded on the medical history page)

- **Intraocular pressure** will be assessed in the study eye, pre-dose and post-dose at every scheduled visit. In the fellow eye IOP will be assessed at Screening, Weeks 28, 52, 76 and exit/premature discontinuation. The values recorded in mmHg will be entered into the eCRF.

  Treatment and close monitoring of IOP should be performed by the investigator for any non-transient elevation in intraocular pressure (≥25 mmHg). Intravitreal procedure is not recommended unless normalization of the IOP has been achieved. Post dose IOP should be assessed after every IVT injection, within 60 minutes after injection and if ≥25 mmHg, assessment should be repeated until back to normal.

  Any clinically significant abnormalities should be recorded on the adverse event page of the eCRF (events identified pre-Baseline should be recorded on the medical history page).

- **Posterior segment (indirect fundus) examination** will be conducted by the investigator at the screening visit for both eyes. An examination of the peripheral retina must also be conducted to ensure that the intravitreal injection can safely be performed.

Posterior segment examination must be performed carefully before each study treatment. The results of the examination including any abnormalities (e.g. vitreous cells/haze, retinal

[redacted]

tear/detachment, hemorrhage and vascular occlusion, vasculitis, etc.) should be recorded in the source documents. If there is 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 will be recorded on the medical/ocular history page before Baseline and on the adverse event page of the eCRF for any findings identified after Baseline.

Instruct the patient to contact the site for any changes in vision or any symptoms of inflammation between scheduled visits. Every effort should be made to bring the subject for immediate examination. When IOI, retinal vasculitis, and/or Retinal Artery Occlusion (RAO) is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and conduct OCT, fluorescein angiography and color fundus photography ([redacted] with peripheral sweeps). These additional assessments will be documented in the source and appropriate eCRF pages as applicable. The images are requested to be uploaded onto the CRC portal. If subject develops retinal vasculitis and/or retinal vascular occlusion based on the investigator's evaluation, the study treatment must be discontinued. In addition, as some of the subjects who experience IOI may be at risk of developing retinal vasculitis and/or retinal vascular occlusion, the subject should be closely monitored and managed according to clinical practice.

6.5.5 Laboratory evaluations

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

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

6.5.5.1 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.

6.5.5.2 Clinical chemistry

- Glycosylated hemoglobin (HbA1c)
- Serum biochemistry tests

  Serum electrolytes (sodium, potassium, chloride, phosphorus, calcium), uric acid, urea nitrogen, creatinine, albumin, glucose, total protein, total bilirubin and direct bilirubin, SGOT (AST), SGPT (ALT), GGT, alkaline phosphatase and LDH
- Additional chemistry tests: Lipids panel triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and Total Cholesterol (TC)

[redacted]

6.5.5.3 Urinalysis

Dipstick measurements for specific gravity, pH, protein, glucose, ketones, urobilinogen, bilirubin, nitrite, leucocyte, esterase and urine occult blood.

6.5.6 Electrocardiogram (ECG)

At sites in Japan, electrocardiograms will be recorded at baseline visit, Weeks 52 and 100/ premature termination visits. The heart rate, PR interval, QRS interval, QT interval and QTc (QT interval corrected) will be collected as source data. Clinically significant abnormalities must be recorded on the relevant adverse event section of the eCRFs.

6.5.7 Pregnancy and assessments of fertility

High effective contraception is required for woman of childbearing potential during the study and for 3 months after stopping the investigational medication.

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

If no sufficient profile to support the reproductive status of female patients, a FSH (Follicle Stimulating Hormone) test can be conducted for female patients at Screening visit only to confirm the child bearing potential.

A serum pregnancy test will be conducted for all women of childbearing potential to assess pregnancy before inclusion into the study at screening visit and then at Week 52 and exit visits. During study, monthly pregnancy testing will be performed and results captured in the source documents.

6.5.8 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population. If there is any signs of IOI, additional assessment will be performed as described in Section 6.5.4.

6.6 Other assessments

Additional assessments that will be performed:

- Patient Reported Outcome: NEI VFQ-25
- Anti-drug antibodies

6.6.1 Clinical Outcome Assessments (COAs)

6.6.1.1 Clinician Reported Outcomes (ClinRO)

Not applicable.

6.6.1.2 Patient Reported Outcomes (PRO)

The impact of brolucizumab on patient visual function will also be assessed by a visual function questionnaire using the National Eye Institute VFQ-25 which is a validated instrument that has

[redacted]

been used in many studies of patients with DME. The VFQ-25 was developed to address the need to measure a patient's subjective assessment of vision-related QoL (Mangione, et al., 2001). This is part of the 51-item NEI-VFQ which was developed based on feedback from patients to measure vision-targeted functioning and the impact of vision problems on Health-Related Quality of Life (HRQL) across a number of common eye conditions. This allowed the developers to identify the content areas and aspects of visual disability that were most important and relevant to AMD patients. In addition to its use in measuring the treatment effect on vision-related function in AMD patients, the VFQ-25 has been used to measure treatment benefits in patients with DME (Klein et al., 2001).

At baseline and Weeks 28, 52, 76 and 100, the VFQ-25 will be completed and captured by masked site staff on behalf of the patients, at sites where local language versions are available, validated, and approved by the IEC/IRB. All these questionnaires should be completed before patients see the study physician where applicable.

A detailed training manual relating to the administrative procedures of the questionnaires will be provided to the sites.

Completed questionnaires will be reviewed and examined by the masked/evaluating investigator, before the clinical examination, for responses that may indicate potential AE or SAE. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

6.6.2 Resource utilization

Data for Healthcare Resource Allocation will not be collected for this study.

6.6.3 Pharmacokinetics

Not Applicable

6.6.4 Anti-drug antibodies (immunogenicity)

Collection of blood for ADA assessment will be done at Screening, Weeks 4, 12, 24, 36, 52, 76 and exit/premature discontinuation. Systemic exposure of brolucizumab will be measured concomitantly with ADA levels for interpretation purposes, no pharmacokinetic parameters will be determined from brolucizumab systemic exposure.

Blood draws should take place prior to the injection/sham. 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.

Additional pharmacodynamic assessment (e.g. systemic VEGF) may be conducted on the samples.

[redacted]

[redacted]

6.6.6 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

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

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

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

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, or
- they require therapy.

[redacted]

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 patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. As a general guidance, alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the appropriate eCRF capturing AEs under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity AE grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to:
  - the study drug
  - the ocular injection procedure
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding [investigational] treatment

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

- no action taken (e.g. further observation only)
- [investigational] treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

Information about common side effects already known about the investigational drug can be found in the investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

[redacted]

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

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:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - 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
  - 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
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the patient 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 Annex IV, ICH-E2D Guideline).

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 patient or might require intervention to prevent one of the other outcomes listed above. 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 Annex IV, ICH-E2D Guideline).

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

[redacted]

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period following the last study visit should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

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.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

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 Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

7.3 Liver safety monitoring

To ensure patient safety and to ensure that a full data package is collected to best understand events of liver dysfunction that emerge during the course of this study, a standardized process for evaluation of liver events has to be followed. This may involve referral of the patient to a suitable internal medicine physician.

This additional investigation is triggered by liver function test abnormalities and/or adverse events (irrespective of whether classified/reported as (S)AE and irrespective of investigator suspected causality).

[redacted]

Please refer to Table 14-1 in Appendix 2 as guidance for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory test abnormality trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site or a suitable internal medicine MD as summarized below.

For the liver laboratory test abnormality trigger, please use the guidance below:

- If the elevation is confirmed as clinically significant, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate. This observation may be conducted by the investigator or through referral of the patient to a suitable internal medicine MD.

For the liver adverse events, consider referral of the patient to a suitable internal medicine MD and the guidance below:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.
- If meeting SAE criteria, the event must be reported as per Section 7.2.2

All follow-up information, additional procedures performed and test results must be collected and documented at the study site.

7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered as guidance during the course of the study:

- Serum event:
  - confirmed (after ≥24h) increase in serum creatinine of ≥25% compared to baseline during normal hydration status
- Urine event
  - new onset (≥1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Table 15-1 in Appendix 3 as guidance and to be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 3.

For the renal adverse events, consider referral of the patient to a suitable internal medicine physician. All follow-up information, additional procedures performed and test results must be collected and documented at the study site.

[redacted]

7.5 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, patient or consumer (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 collected in the Dosing eCRF (date and time of the injection) and in the Dispensing Log at the Study site, irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

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

7.6 Pregnancy reporting

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

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be

performed by a centralized Novartis 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 patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. [Data not requiring a separate written record will be defined before study start and will be recorded directly on the eCRFs.] The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

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 useed 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 patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs) using fully validated secure web-enabled software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

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

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies 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 (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO).

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

The occurrence of relevant protocol deviations will be determined. After these 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.

[redacted]

8.4 Data Monitoring Committee

An independent program level Data Monitoring Committee (DMC) is established to monitor the safety of the trial participants, to ensure that the trial is being conducted with the highest scientific and ethical standards, and make appropriate recommendations based on the data seen.

The DMC charter will include the DMC membership and responsibilities, the timing of DMC meetings, the content of the analysis report for the DMC meetings, and the communications with the Sponsor. The DMC will only make recommendations for changes in study conduct.

8.5 Adjudication Committee

Not required.

9 Data analysis

The primary safety and efficacy analysis will be based on the Week 52 data, i.e. all data up to and including Week 52. This analysis will be performed when the first 534 randomized patients completed their Week 52 visits or terminate the study before Week 52, while patients continue to receive masked treatment through the planned study duration of 100 Weeks.

An additional analysis will be conducted when all of the patients randomized into the study have completed their Week 52 visit (or terminated the study before Week 52) to allow for a consistency assessment of data between the Japanese and non-Japanese patients. This analysis will include the Week 52 data from all randomized patients, and will be purely descriptive (no hypothesis testing for the primary and first key secondary endpoints), as further specified in the

[redacted]

SAP. However, if any special circumstance compromises the feasibility of the approach described above, then the additional analysis will not be conducted and the primary analysis will be performed when all randomized patients have completed their Week 52 visit or terminate the study prior to Week 52.

The analysis of the data collected after the Week 52 visit will be performed once all patients completed or discontinued from the study.

Summary statistics will be presented by treatment group unless otherwise specified. For continuous variables, summary statistics will generally include: n, mean, standard deviation, 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 SAP.

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

9.1 Analysis sets

The **Randomized Set** will consist of all randomized patients. Patients are considered randomized when they had been deemed eligible for randomization by the investigator and given a randomization number. Patients will be analyzed according to the treatment assigned to at randomization.

The **Full Analysis Set** (FAS) includes all randomized patients who receive at least one IVT injection of the study treatment. The full analysis set will serve as the primary analysis set for all efficacy analyses. Following the intent-to-treat principle, patients will be analyzed according to the treatment assigned to at randomization.

Supportive analyses of the primary and secondary endpoints will include analysis using the **Per Protocol Set** (PPS). PPS is a subset of the FAS and will exclude patients 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 e.g. lack of compliance (including missed treatments and treatment misallocation), missing data, prohibited concomitant medication and deviation from inclusion/exclusion criteria. Confounded data or discontinuation from treatment due to lack of efficacy and/or safety do not constitute a reason for exclusion from the PPS.

Before the Week 52 database lock the relevant protocol deviations will be identified at the patient level in the database. After the Week 52 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.

The FAS will be the analysis set for the primary estimand as defined in Table 9-1. However, when assessing the robustness of the overall efficacy conclusions, considerations will be given to the analysis based on the primary estimand using FAS and the supplementary estimand (see Table 9-1) using PPS, i.e., similar conclusions on non-inferiority based on both estimands are expected. Inconsistencies in key efficacy study results between the FAS and PPS will be examined and discussed in the clinical study report (CSR). The **Safety Analysis Set** (SAF) will

[redacted]

include all patients who receive at least one IVT injection. Patients in the safety analysis set will be analyzed according to the treatment arm from which they received majority of treatments up to and including Week 48.

9.2 Patient demographics and other baseline characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics for all analysis sets by treatment group and overall.

Relevant medical history and current medical conditions will be tabulated by system organ class (SOC) and preferred term of the MedDRA dictionary for the FAS.

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

9.3 Treatments

Study treatment

Descriptive statistics for exposure to study treatment will be provided for the safety set, FAS and PPS. For the efficacy analysis sets (FAS and PPS), the number of active and sham IVT injections will be presented by visit and cumulatively for the period baseline to Week 48 (Week 96), including separate analysis for the loading phases, i.e. up to Week 16 (last treatment of the 5*q4w loading of aflibercept) and up to Week 24 (last treatment of 5*q6w loading of brolucizumab), and maintenance phase. For the safety analysis set, summary will include exposure data up to Week 52 (Week 100).

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 treatment including those already started prior to the start of study treatment.

9.4 Analysis of the primary and first key secondary endpoints

9.4.1 Primary and first key secondary endpoints

The primary endpoint is the change from baseline in BCVA at Week 52.

The first key secondary endpoint is average change in BCVA from Baseline over the period Week 40 through Week 52. For each patient, this endpoint is defined as the average of the changes from baseline to Weeks 40, 44, 48 and 52. The motivation for the choice of this endpoint is that, averaging the BCVA values over Week 40 to Week 52 will account for both random fluctuations and potential trough and peak values during the different treatment cycles. During the period Week 40 to Week 52, aflibercept and brolucizumab patients on q8w will have two assessments 4 weeks after the last dose, and two assessments 8 weeks after the last dose. Brolucizumab patients on a q12w regimen will have two assessments 4 weeks after the last dose, one assessment 8 weeks after the last dose, and one assessment 12 weeks after the last dose.

[redacted]

The primary analysis of the primary and first key secondary endpoints will be based on the FAS.

9.4.1.1 Statistical model, hypotheses, and method of analysis

The objective related to the primary and first key secondary endpoints is to demonstrate non-inferiority of brolucizumab to aflibercept with respect to change from baseline in BCVA, considering a margin of 4 ETDRS letters.

Let:

B3 = Brolucizumab 3 mg - 5 x q6w loading then q12w/q8w maintenance

B6 = Brolucizumab 6 mg - 5 x q6w loading then q12w/q8w maintenance

A = Aflibercept 2 mg - 5 x q4w loading then q8w maintenance

The following non-inferiority hypotheses are related to a non-inferiority margin of 4 letters:

$\mathbf{H0_1}$: $\mu_{B6} - \mu_A \leq$ -4 letters vs. $\mathbf{HA_1}$: $\mu_{B6} - \mu_A >$ -4 letters

$\mathbf{H0_2}$: $\varphi_{B6} - \varphi_A \leq$ -4 letters vs. $\mathbf{HA_2}$: $\varphi_{B6} - \varphi_A >$ -4 letters

$\mathbf{H0_3}$: $\mu_{B3} - \mu_A \leq$ -4 letters vs. $\mathbf{HA_3}$: $\mu_{B3} - \mu_A >$ -4 letters

$\mathbf{H0_4}$: $\varphi_{B3} - \varphi_A \leq$ -4 letters vs. $\mathbf{HA_4}$: $\varphi_{B3} - \varphi_A >$ -4 letters

where μ_{B6} μ_{B3} and μ_A are the corresponding unknown true mean changes from baseline in BCVA at Week 52; φ_{B6}, φ_{B3} and φ_A are the corresponding unknown true mean changes from baseline in BCVA averaged over the period Week 40 to Week 52;

Based on the FAS, the above hypotheses will be tested via an analysis of variance (ANOVA) model. The model will include treatment, baseline BCVA (≤65, >65 letters) and age category (<65, ≥65) as factors. Two-sided 95% confidence interval (CI) for the least square means difference (brolucizumab - aflibercept) will be presented. Non-inferiority will be considered established if the lower limit of the corresponding 95% CI is greater than -4 letters.

These 4 hypotheses will be tested sequentially in the order of their numbering (H_{An}, n=1, 2, 3, 4), i.e., confirmatory testing of the second, third and fourth hypotheses requires rejection of each preceding null hypothesis.

In this setting, each hypothesis will be assessed at a one-sided significance level of 0.025, while keeping the global type I error rate at 0.025.

9.4.1.2 Handling of missing values/censoring/discontinuations

Missing BCVA values will be imputed by LOCF (Last Observation Carried Forward) as a primary approach. For patients with no post-baseline BCVA value, the baseline value will be carried forward. Data collected after start of alternative DME treatment in the study eye (e.g. other anti-VEGF treatment, laser or intraocular corticosteroids, as further detailed in the SAP) will be censored for the primary analysis.

From an estimand perspective, the main focus is to adequately reflect in the analysis unfavorable study outcome related to the treatment (e.g. lack of efficacy, safety problems).

[redacted]

The LOCF approach is expected to be sensitive to an early study termination 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 (DME), data collected after the start of such a treatment would be censored. LOCF will then be based on the last value prior to the start of this treatment, again expecting that this value would reflect the negative BCVA outcome under study treatment. In case of missing data due to lack of safety/tolerability with impairment of the 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 based on historical data both for the maintenance treatment phase (i.e. 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 termination during the loading phase, the LOCF method will result in a conservative estimate 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 aflibercept Ph III studies VIVID and VISTA was the BCVA change from Baseline to 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.

Table 9-1 Primary and supplementary estimands

Estimand	Estimand definition	Analysis set	Statistical methods (Including strategy for imputation/replacement of missing/censored data)
Primary estimand	Difference in change from baseline in BCVA at Week 52 excluding the effect of switching to alternative DME medication in the study eye	FAS	Analysis of variance (ANOVA) model including terms for treatment, baseline BCVA (≤65, >65 letters) and age category (<65, ≥65 years), and using LOCF imputation/replacement for missing/censored data.
Supplementary estimand	Difference in change from baseline in BCVA at Week 52 for patients adhering to the protocol as per the PPS definition	PPS	ANOVA model as per the primary estimand. LOCF imputation/replacement for missing/censored data

9.4.2 Additional key secondary endpoints

Additional key secondary endpoints are:

- Proportion of patients maintained at q12w up to Week 52 (for brolucizumab treatment arms only)

[redacted]

- Proportion of patients maintained at q12w up to Week 52, within those patients that qualified for q12w at Week 36 (for brolucizumab treatment arms only)

9.4.2.1 Statistical model, hypotheses, and method of analysis

The estimate for the proportion of patients with a positive q12w treatment status at Week 52 will be derived from Kaplan Meier time-to-event analyses for the event 'first q8w-need' applying a 'q8w-need' allocation in case of missing or confounded data attributable to lack of efficacy and/or lack of safety.

The proportion of patients with a positive q12w treatment status at Week 52 will be derived as follows requiring duration of effect (as assessed by q8w need) together with 'sufficient efficacy and safety':

- For the 'duration of effect' requirement patients will need to have the status of 'q8w need = no' at Weeks 32, 36 and 48 unless the 'q8w need = yes' is confounded by reasons other than lack of efficacy and/or safety (see censoring details below)
- The requirement regarding 'sufficient efficacy and safety' will be addressed by considering patients – even without an explicit 'q8w need = yes' – as having a negative q12w status in case any of the following confounding factors is attributable to lack of efficacy and/or lack of safety of the study treatment (assessed based on a masked medical review): early treatment/study discontinuation, use of forbidden concomitant medications/procedures and/or other deviation from treatment schedule (e.g. due to a missed visit/treatment). The corresponding q8w need will be allocated to the next disease activity assessment visit following the occurrence of such a confounding factor

In case missing or confounded data regarding the q12w treatment status are attributable to reasons other than lack of efficacy and/or safety, the patient is censored within the q12w treatment status analysis according to the following specifications:

- Early treatment/study discontinuation: censoring at the last valid disease activity assessment
- Single missed visit with a relevant disease activity assessment: censoring at the last valid disease activity assessment prior to the missed visit
- Prohibited concomitant medications/procedures: censoring at the last valid disease activity assessment prior to the corresponding application
- Discrepancy between disease activity assessment by investigator and the actual treatment received: censoring at the corresponding visit
- Other treatment allocations/applications deviating from the concept of 'treatment allocation according to disease activity': censoring at the last valid disease activity assessment

9.4.2.2 Handling of missing values/censoring/discontinuations

The details regarding handling of missing values and discontinuations including the timing of censoring within the time-to-event analyses for the event 'first q8w-need' are specified above.

[redacted]

From an estimand perspective, the assessment of failing study completion according to protocol due to lack of efficacy/safety is considered adequately represented by a negative q12w-status.

Alternative methods of handling missing or confounded data within sensitivity analyses will include an approach with 'q8w-need' allocation only in case of missing or confounded data attributable to lack of efficacy and an 'as observed' approach, i.e. an analysis without 'q8w-need' allocation.

9.4.3 Sensitivity and supportive analyses

Sensitivity analyses will be performed for primary and all key secondary endpoints using the per protocol analysis set (PPS), alternative methods of handling missing values (Section 9.4.1.2 and Section 9.4.2.2) and descriptive analyses based on observed data only (with and without censoring of data collected after use of alternative treatment for DME in the study eye, e.g. other anti-VEGF treatment, laser, intraocular corticosteroids, as further detailed in the SAP).

The following subgroup analyses will be conducted in FAS applying the primary analysis approach as specified above:

- Age category (<65, ≥65 years)
- Gender (male, female)
- Diabetes type (Type 1, Type 2)
- Baseline HbA1c (<7.5, ≥7.5%)
- Baseline BCVA categories (≤65, >65 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 IRF (presence, absence)
- Baseline status of SRF (presence, absence)
- Ethnicity (Japan, non-Japan)

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

9.5 Analysis of secondary endpoints

9.5.1 Efficacy endpoints

Secondary efficacy endpoints based on BCVA:

- Change from baseline in BCVA at each visit up to Week 100
- Average change from baseline in BCVA over the period Week 88 to Week 100.
- Average change from baseline in BCVA over the period Week 4 to Week 52/100.
- Average change from baseline in BCVA over the period Week 20 to Week 52/100 and Week 28 to Week 52/100.
- Gain in BCVA of ≥5,≥10 and ≥15 ETDRS letters from baseline to each post-baseline visit

  Note: Patients with BCVA value of 84 letters or more at a post-baseline visit will be considered as responders for the corresponding endpoint. This is to account for a ceiling

[redacted]

effect, e.g. for the' ≥15-letter gain' endpoint, for those patients with BCVA values at baseline ≥ 70 letters.

- Time to achieve gain of ≥5, ≥10 and ≥15 ETDRS letters from baseline (or reaching a score of 84 or more)
- Loss in BCVA of ≥5, ≥10 and ≥15 ETDRS letters from baseline to each post-baseline visit
- Absolute BCVA ≥73 ETDRS letters at each post-baseline visit

Secondary efficacy endpoints related to dosing regimen:

- Proportion of patients maintained at q12w up to Week 64 (after three q12w- treatment intervals) and 100 (for brolucizumab treatment arms only)
- Proportion of patients maintained at q12w up to Week 64 (after three q12w- treatment intervals) and 100, within those patients that qualified for q12w at Week 36 (for brolucizumab treatment arms only)
- q8w treatment need status assessed at Week 32

Secondary efficacy endpoints related to anatomy:

- Change from baseline in central subfield thickness (CSFT, as determined by SD-OCT from the central reading center) at each assessment visit
- Average change in CSFT from baseline over the period Week 40 through Week 52 / Week 88 through Week 100
- Average change in CSFT from baseline over the period Week 4 to Week 52 / 96
- Patient status regarding normal CSFT thickness (<280 microns) at each assessment visit
- Proportion of patients with presence of SRF, IRF and simultaneous absence of SRF and IRF at each assessment visit
- Proportion of patients with presence of leakage on FA at Weeks 52 and 100

Secondary efficacy endpoints related to the status of Diabetic Retinopathy:

- Patient status regarding a ≥2- and ≥3-step improvement or worsening from baseline in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score at each assessment visit
- Incidence of progression to PDR as assessed by ETDRS-DRSS score of at least 61 by Week 52 and Week 100

[redacted]

[redacted]

[redacted]

9.5.2 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 Set.

Adverse events

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

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

[redacted]

Patient listings of all adverse events will be provided. Deaths and other serious or clinically significant non-fatal adverse events will be listed separately.

Ophthalmic examinations

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

Laboratory tests, vital signs, and special tests

Laboratory data and vital signs will be summarized by presenting shift tables using extended normal ranges (as provided by the central laboratory) with thresholds representing clinical relevant abnormality and by presenting descriptive statistics of raw data and change from baseline. Values outside the extended normal range will be listed by patient and treatment arm and flagged in data listings.

9.5.3 Resource utilization

Not applicable

9.5.4 Pharmacokinetics

Not applicable

9.5.5 Biomarkers

Not applicable

9.5.6 PK/PD

Not applicable

9.5.7 PRO (Patient Reported Outcome)

The VFQ-25 questionnaires will be scored (total and subscale scores) at Baseline and Weeks 28, 52, 76, and 100 visits. Absolute scores and the absolute changes from baseline will be calculated and summarized descriptively.

Further details on the scoring algorithm and analysis will be provided in the SAP.

9.5.8 Anti-drug antibodies

Collection of blood for ADA assessment will be done at Screening, Weeks 4, 12, 24, 36, 52, 76 prior to the injection/sham, and exit/premature discontinuation.

[redacted] n addition, ADA titer pattern and shift table showing ADA titer at baseline relative to each post-baseline assessment visit, relative to the last assessment visit, and to any visit with most extreme increase in ADA titer will be presented by brolucizumab arm. Change from baseline in ADA will be summarized by brolucizumab arm as well. Patient listings of all ADA titer values will be presented for all patients in the brolucizumab arms.

[redacted]

[redacted]

9.7 Interim analyses

The analysis based on the Week 52 data will be the primary efficacy analysis for this study. The database including all Week 52 data will be locked when the first 534 randomized patients have completed the Week 52 visit or terminated the study prior to Week 52.

An additional analysis will be conducted once all enrolled patients have completed the Week 52 visit or terminate the study prior to Week 52. This will include the original study target of 534 patients plus additional patients enrolled in Japan to assess consistency of data between Japanese and non-Japanese patients.

Another analysis may be performed by locking the Week 76 data in case of regulatory request of supplemental data to be submitted during the review period.

9.8 Sample size calculation

A sample size of 160 patients per arm will allow to demonstrate a non-inferiority (NIM of 4 ETDRS letters) of brolucizumab 6 mg or 3 mg (either treatment regimen) vs. aflibercept 2 mg with respect to the BCVA change from baseline at Week 52, with 90% power (disregarding the dependence within the sequential testing procedure, i.e. local power for 3 mg) at a one-sided alpha level of 0.025, assuming equal means and a common standard deviation of 11 letters. Assuming that averaging over the 4 time points will not lead to an increase in the standard deviation a power of at least 90% can also be expected for its corresponding non-inferiority claim.

To account for a drop-out rate of 10%, a total of 534 (178 per arm) patients will need to be randomized.

[redacted]

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

For trials using an Electronic Informed Consent system where a date/timestamp is automatically generated, the system-generated date/timestamp is sufficient; additional input of the date at the time of consent is not required by the patient.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

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 requirement for the duration of the study and for 3 months after stopping the investigational medication. If there is any question that the patient will not reliably comply, they must not be entered in the study.

[redacted]

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

[redacted]

documented and confirmed by way of standard informed consent procedures at the earliest opportunity when the subject will be back at the trial sites.

10.3 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, informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. 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.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

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

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

11 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 patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction, 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.

11.1 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 intended to eliminate an apparent immediate hazard to patients 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 patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

12 References

References are available upon request.

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[redacted]

13 Appendix 1: Clinically notable laboratory values and vital signs

Table 13-1 Clinically notable laboratory values

Panel/Test	Type	Gender /Age	Conventional Unit	Conventional Low	Conventional High	SI Unit	SI Low	SI High	Non-numeric
Chemistry/ Calcium	alert	All	mg/dL	6.1	12.9	mmol/L	1.52	3.22	
Chemistry/ Creatinine	reference	All	mg/dL	0.7	1.4	µmol/L	62	124	
Chemistry/ Glucose (non fasting)	alert	All	mg/dL	40	450	mmol/L	2.22	24.98	
Chemistry/ Potassium	alert	All	mEq/L	2.8	6.3	mmol/L	2.8	6.3	
Chemistry/ Sodium	alert	All	mEq/L	117	160	mmol/L	117	160	
HCG	alert	All							Negative, inconclusive
Hematology/ Hematocrit	alert	All	%	18	60	%	18	60	
Hematology/ Hemoglobin	alert	All	g/dL	8	22	g/L	80	220	
Hematology/ Platelet	alert	All	K/cumm	30	900	x10^9/L	30	900	
Hematology/ WBC	alert	All	K/cumm	2	25	x10^9/L	2	25	

[redacted]

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT/AST ≤5 x ULN • 1.5 x ULN <TBL ≤2 x ULN
LIVER EVENTS	• ALT or AST >5 × ULN • ALP >2 × ULN (in the absence of known bone pathology) • TBL >2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST >3 × ULN and INR >1.5 • Potential Hy's Law cases (defined as ALT or AST >3 × ULN and TBL >2 × ULN [mainly conjugated fraction] without notable increase in ALP to >2× ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST >3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

* These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

[redacted]

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR)≥150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the eCRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	