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RTH258

Clinical Trial Protocol CRTH258D2301 / NCT04278417

A 96-week, two-arm, randomized, single-masked, multi-center, phase III study assessing the efficacy and safety of brolucizumab 6 mg compared to panretinal photocoagulation laser in patients with proliferative diabetic retinopathy (CONDOR)

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List of abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
AR	Analysis restriction
ATC	Anatomical therapeutic chemical
BCVA	Best corrected visual acuity
CFP	Color fundus photography
CFR	Code of federal regulation
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
COA	Clinical outcome assessment
COVID-19	Coronavirus disease-2019
CRC	Central reading center
CRO	Contract Research Organization
CSFT	Central sub-field thickness
DM	Diabetes mellitus
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRSS	Diabetic retinopathy severity scale
eCRF	Electronic case report/record form
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAS	Full analysis set
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin A1c
IB	Investigator's brochure
ICF	Informed consent
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent ethics committee
IOI	Intraocular inflammation
IOP	Intraocular pressure
IRB	Institutional review board
IRT	Interactive response technology
IVT	Intravitreal
LOCF	Last observation carried forward
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)

nAMD	neovascular age-related macular degeneration
[redacted]	[redacted]
NIH	National Institutes of Health
OCT	Optical coherent tomography
[redacted]	[redacted]
PD	Protocol deviation
PDR	Proliferative diabetic retinopathy
PFS	Prefilled syringe
[redacted]	[redacted]
PPS	Per protocol set
[redacted]	[redacted]
PRP	Panretinal photocoagulation
q12w	Every 12 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QoL	Quality of life
RBC	Red blood cell(s)
[redacted]	[redacted]
RO	Retinal vascular occlusion
RV	Retinal vasculitis
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
scFv	Single-chain antibody fragment
SD	Standard deviation
SD-OCT	Spectral domain optical coherence tomography
SGOT	Serum glutamic oxaloacetic transaminase
GPT	Serum glutamic pyruvic transaminase
SUN	Standardization of uveitis nomenclature
SUSAR	Suspected unexpected serious adverse reaction
USM	Urgent Safety Measures
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
VF	Visual function
[redacted]	[redacted]
WBC	White blood cell(s)
WFCFP	Wide field color fundus photography
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic data capture	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Patient	An individual with the condition of interest for the study
[redacted]	[redacted]
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.

Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A subject who is screened but is not treated or randomized
Source Data/Documentation	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.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)/ Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 2 28-Sep-2021

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 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 or vitrectomy. Some other administrative changes have also been incorporated.

Changes to the protocol

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

- Section 1.1 Background: Information added to describe Urgent Safety Measures
- Section 4.5 Risk and benefits: Information added to describe Urgent Safety Measures and additional information on gender imbalance on IOI following brolucizumab treatment
- Section 6.7.2 Instruction for administering study treatment: Requirement of treatment discontinuation was added if subject developed RV and/or RO, in both arms.
- Section 8.4.5 Ophthalmic examination: Requirement of treatment discontinuation was added if subject developed RV and/or RO.
- Section 9.1.1 Discontinuation of study treatment: Requirement of treatment discontinuation was added if subject developed RV and/or RO.

Other changes incorporated in this amendment

- The glossary of terms has been updated to the latest template wording
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action: added recommendations on the time window for a study subject to receive the COVID-19 vaccine or vitrectomy.
- Use of prohibited treatment (see Section 6.2.2)
- Section 8.4.3 Pregnancy: Correction for inconsistency. Requirement to apply the same pregnancy testing in both arms, throughout the study (see also Table 8-1).
- Section 9.1.2 Clarified the definition of Withdrawal of Consent (WoC).
- 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 strikethrough red font for deletions and red underlined for insertions.

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

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

Amendment 1 05-Jun-2020

Amendment rationale

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

Changes to the protocol

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

- Section 1.1 Background: Information was added to describe new safety signal from post-marketing case reports and its impact on the benefit-risk balance.
- Section 6.7.2 Instructions for prescribing and taking study treatment: Additional guidance was added to this section emphasizing that if any sign of intraocular inflammation is present, an IVT injection **must not** be performed and patients should be treated for IOI according to clinical practice.
- Additional examination and assessments included to fully characterize cases of intraocular inflammation were made in the following sections:
  - Table 8-1 Assessment schedule
  - Section 8.3.2 Color fundus photography and fluorescein angiography
  - Section 8.4 Safety
  - Section 8.4.5 Ophthalmic examination
  - Section 8.4.6 Appropriateness of safety measurements

Changes incorporated in this amendment regarding the COVID-19 pandemic:

- Section 5.2 Exclusion criteria
- Section 6.2.2 Prohibited medication
- Section 7 Informed Consent Procedures
- Section 8 Visit Schedule and Assessments
- Section 8.4 Safety
- Section 8.4.2 Laboratory evaluation
- Section 12 Data Analysis and statistical methods

Other changes incorporated in this amendment:

- Title Page: Added approved study bird nickname.
- Section 3 Study Design: Protocol clarification regarding the window definition of the Baseline/Day 1 visit window and timing of EOS visit for early study discontinuation.
- Section 5.2 Exclusion Criteria: Protocol clarification regarding exclusion criteria Number 8, 13 and Number 20.

- Section 6.3.1 Subject numbering: To ensure protocol consistency with Section 8.1.
- Section 6.4 Treatment masking: Clarification of masking language to accurately describe the masked study personnel for this protocol.
- Section 7 Informed Consent procedures: Clarification the timeframe of acceptable FA images can be used prior to the Screening Visit.
- Section 8.1 Screening: Clarification the timeframe of acceptable FA images can be used prior to the Screening Visit and clarification regarding a one-time reassessment of a subject.
- [redacted]
- Section 8.4.4 Ophthalmic examination: Post-injection IOP measurement timing was updated from approximately 30-60 minutes to read within 60 minutes.
- Section 8.5.1 Clinical Outcome Assessments (COAs): [redacted]
- Section 10.1.3 SAE reporting: The reporting period is clarified.
- Section 12 Data analysis and statistical methods: Clarification per ICH E9 (R1) guidelines.
- Table 12-1 Primary, key secondary and supportive estimands: clarified terms
- Section 15 References
- List of Abbreviations
- Other minor clarifications were made where applicable.

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Protocol summary

Protocol number	CRTH258D2301
Full Title	A 96-week, two-arm, randomized, single-masked, multi-center, phase III study assessing the efficacy and safety of brolucizumab 6 mg compared to panretinal photocoagulation laser in patients with proliferative diabetic retinopathy (CONDOR)
Brief title	Study of efficacy and safety of brolucizumab versus panretinal photocoagulation laser in patients with proliferative diabetic retinopathy
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate the efficacy and safety of brolucizumab compared to panretinal photocoagulation laser (PRP) in patients with proliferative diabetic retinopathy (PDR).
Primary Objective(s)	To demonstrate that brolucizumab is non-inferior to PRP with respect to the change from Baseline in visual acuity at Week 54 by assessing the change from Baseline in best corrected visual acuity (BCVA) at Week 54
Secondary Objectives	To demonstrate that brolucizumab is superior to PRP in reducing diabetic retinopathy (DR) severity after 54 weeks of treatment by assessing the proportion of subjects with no PDR at Week 54 To demonstrate that brolucizumab is superior to PRP in preventing the development of center-involved diabetic macular edema (DME) up to Week 54 by assessing the proportion of subjects with center-involved DME up to Week 54 To compare the effect of brolucizumab relative to PRP with respect to visual acuity by assessing the area under the curve in change from Baseline in BCVA up to Week 54 and Week 96 To compare the effect of brolucizumab relative to PRP on DR status by assessing the change from Baseline in ETDRS diabetic retinopathy severity scale (DRSS) score at Week 54 and Week 96 and the proportion of subjects with no PDR at Week 96 To compare the effect of brolucizumab relative to PRP on ocular complications by assessing the proportion of subjects developing vision-threatening complications associated with DR up to Week 54 and Week 96 and the proportion of subjects with center-involved DME up to Week 96 To assess the safety and tolerability of brolucizumab relative to PRP
Study design	The study is a 96-week, two-arm, randomized, single-masked, multi-center, active-controlled, non-inferiority study in patients with proliferative diabetic retinopathy (PDR). Subjects who meet all the inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio to one of the two treatment arms: • Brolucizumab 6 mg: 3 x q6w loading then q12w maintenance through Week 90, with the option from Week 48 onwards to extend the treatment interval by 6 weeks at a time up to 24 weeks. • PRP: initial treatment in 1-4 sessions up to Week 12, followed with additional PRP treatment (may split into 2-4 sessions) as needed up to Week 90.

Population	Approximately 941 adult patients will be screened (25% screen failure rate expected) and approximately 706 patients (353 per arm, 15% dropout rate expected) will be randomized in a 1:1 ratio in approximately 180 centers worldwide. The maximum study duration for one subject is 99 weeks, including Screening and post-treatment follow-up.
Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study. • Patients ≥ 18 years of age at Screening. • Participant cooperation sufficient for adequate fundus photographs and retinal images. • Patients diagnosed with diabetes mellitus (DM) type 1 or 2, and HbA1c ≤ 12% at Screening. • Any medication administered for the management of diabetes should be stable within 3 months prior to randomization and is expected to remain stable during the course of the study, as medically acceptable. • PDR in the study eye as assessed by the investigator using standard or wide-field color fundus photography (CFP) and fluorescein angiography (FA), with no evidence of previous PRP, and that requires treatment with either anti-Vascular Endothelial Growth Factor (VEGF) agent or PRP in the opinion of the investigator. • BCVA ≥ 34 ETDRS letters (Snellen equivalent 20/200) in the study eye at Screening and Baseline.

Key Exclusion criteria	• Concomitant conditions or ocular disorders in the study eye at Screening or Baseline as well as planned medical/surgical intervention during the first 54-week study period that could compromise functional or structural response to study treatment, in the opinion of the investigator
	• Presence of center-involved DME in the study eye at Screening or Baseline, as assessed by the investigator.
	• Other ocular conditions in the study eye:
	  • Any active intraocular or periocular infection or active intraocular inflammation (IOI) at Screening or Baseline.
	  • Uncontrolled glaucoma in defined as intraocular pressure (IOP) > 25 mmHg despite treatment with IOP lowering medication, or according to investigator's judgment, at Screening or Baseline.
	  • Iris or anterior chamber angle neovascularization, or neovascular glaucoma.
	  • Moderate or dense pre-retinal or vitreous hemorrhage that prevents clear visualization of the macular and / or optic disc or prevents PRP treatment at Baseline.
	  • Significant fibrovascular vitreoretinal proliferation or tractional retinal detachment.
	• Presence of amblyopia, amaurosis or ocular disorders in the fellow eye with BCVA < 20/200 at screening (except when due to conditions for which treatment or surgery may improve VA).
	• Ocular treatments in the study eye:
	  • PRP any time prior to Baseline.
	  • Intravitreal anti-VEGF treatment within six months prior to Baseline.
	  • Vitreoretinal surgery at any time prior to Baseline or anticipated need for vitreoretinal surgery within the next 12 months.
	  • Laser treatment of the macula within 3 months prior to Baseline.

	• Treatment with fluocinolone acetonide intravitreal implant at any time prior to Baseline. Other intraocular or periocular corticosteroid injection within 6 months prior to Baseline. • Intraocular surgery within 3 months prior to Baseline or anticipated need for cataract extraction within the next 12 months. • Systemic conditions or treatments: stroke or myocardial infarction during the 6-month period prior to baseline, end stage renal disease requiring dialysis or renal transplant, systemic anti-VEGF therapy at any time.
Study treatment	Brolucizumab 6 mg Panretinal photocoagulation
Efficacy assessments	BCVA using ETDRS-like chart ETDRS DRSS score based on 7-field CFP Anatomical markers based on spectral domain optical coherence tomography (SD-OCT)
Key safety assessments	Adverse event monitoring Ocular examinations Vital signs Monitoring of laboratory biomarkers (hematology, clinical chemistry, urinalysis) and pregnancy
Other assessments	[redacted] Wide field CFP FA [redacted]
Data analysis	The objective related to the primary endpoint is to demonstrate non-inferiority of brolucizumab versus PRP with respect to the change from Baseline in BCVA at Week 54, assuming a non-inferiority margin of 4 ETDRS letters. The primary estimand is defined as the between-treatment difference in change from Baseline in BCVA at Week 54, excluding the confounding effect of alternative DR/DME treatment(s) applied to the study eye. The hypothesis will be tested via an analysis of covariance (ANCOVA) model. The model will include treatment, baseline DR Severity category, age category, and region as factors, with baseline BCVA as a covariate. The two-sided 95% confidence interval (CI) for the least square mean difference (brolucizumab - PRP) at Week 54 will be presented. Non-inferiority will be considered established if the lower limit of the corresponding 95% CI is greater than -4 letters. Superiority hypothesis for the primary endpoint may be further evaluated after non-inferiority for the primary endpoint and superiority for the first key secondary endpoint are established. The objective related to first key secondary endpoint is to demonstrate superiority of brolucizumab versus PRP with respect to increasing the proportion of subjects with no PDR at Week 54. It will be tested via Cochran-Mantel-Haenszel (CMH) test at a one-sided significance level of 0.025, after non-inferiority for the primary endpoint is established.

	The objective related to the other key secondary endpoint is to demonstrate superiority of brolucizumab versus PRP with respect to reducing the proportion of subjects with center-involved DME up to Week 54. It will be tested via CMH test at a one-sided significance level of 0.025, after superiority is established for both primary endpoint and first key secondary endpoint. Summary statistics will be presented by treatment arm unless otherwise specified.
Key words	Proliferative diabetic retinopathy, retinal neovascularization, anti-VEGF, brolucizumab, intravitreal injection, panretinal photocoagulation

1 Introduction

1.1 Background

Diabetes mellitus (DM) is a global epidemic disease with significant morbidity and mortality in both developing and developed countries that was estimated to affect 451 million adults worldwide in 2017, with the numbers expected to rise to more than 690 million in 2045 (Cho et al 2018). diabetic retinopathy (DR) is a common and microvascular complication of DM and remains the leading cause of preventable blindness in working-age people (Cheung et al 2010, Whitehead et al 2018). The two major sight-threatening complications of DR are diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR). In 2010, DR accounted for 2.6% of all blindness and 1.9% of all moderate and severe vision impairment worldwide (Leasher et al 2016). PDR is the end stage in the natural history of DR. The main pathological pathway involved is a severe hypoxia from retinal capillary closure, which leads to an increase in levels of the angiogenic vascular endothelial growth factor (VEGF) and retinal neovascularization (Wong et al 2016). The new retinal vessels are fragile and prone to bleeding. As they also tend to grow into the vitreous, they can be associated with retinal detachment and vitreous hemorrhage, which are vision-threatening complications.

Treatment options for PDR include panretinal photocoagulation (PRP), anti-VEGF agents, and vitrectomy (Wong et al 2018). Vitrectomy is essentially reserved for cases of non-clearing vitreous hemorrhage or traction retinal detachment threatening or involving the macula. PRP has been the standard of care for PDR for over 40 years; it reduces the risk of severe visual loss by 50% or more (Diabetic Retinopathy Study Research Group 1981). However, PRP is a destructive procedure that is associated with permanent sequelae on visual function; these include final visual acuity below driving standards, peripheral visual field loss that precludes driving, night vision difficulties, loss of color vision, and reduced contrast sensitivity, as well as exacerbated macular edema (ETDRS Research Group 1991, Brucker et al 2009, Preti et al 2013, Subash et al 2016). Therefore, there is an unmet need for novel treatments that reduce the risk of severe visual loss in PDR while causing fewer adverse events. Anti-VEGF therapies have recently demonstrated superior outcomes compared to PRP, both in terms of visual acuity (Sivaprasad et al 2017, Lang et al 2019) and peripheral visual field (Gross et al 2015, Sivaprasad et al 2017). Furthermore, anti-VEGF agents were associated with a reduction in emergent macular edema as well as vision-threatening complications of PDR, compared to PRP (Gross et al 2015, Sivaprasad et al 2017, Lang et al 2019).

Brolucizumab

Brolucizumab (RTH258, formerly known as ESBA1008), is a humanized single-chain antibody fragment (scFv) inhibitor of VEGF-A with a molecular weight of ~26 kDa. Brolucizumab binds to the receptor-binding site of the VEGF-A molecule, thereby preventing the interaction of VEGF-A with its receptors VEGFR1 and VEGFR2 on the surface of endothelial cells (Escher et al 2015). Brolucizumab is designed for ophthalmic use and is administered by intravitreal (IVT) injection. In this setting, the smaller molecular weight of the scFv is expected to have advantages over immunoglobulin G antibodies and larger antibody fragments due to the delivery of a higher molar dose (i.e. VEGF binding equivalents per mg protein), which may prolong the therapeutic effect, assuming comparable ocular half-lives and potency, and enable better tissue penetration at the retina.

In two large Phase III pivotal studies (RTH258-C001 [HAWK] and RTH258-C002 [HARRIER]), neovascular Age-related Macular Degeneration (nAMD) subjects received brolucizumab every 12 weeks (q12w), with the option of adjusting to an 8-week dosing interval (q8w) based on disease activity, or aflibercept q8w, after three monthly loading doses. Brolucizumab was non-inferior to aflibercept with regards to change from Baseline in best corrected visual acuity (BCVA) at Week 48, with over half of the subjects in the brolucizumab 6 mg arm maintained exclusively on the q12w dosing interval (56% in HAWK and 51% in HARRIER) (Dugel et al 2019). The visual acuity gains observed in the first year were maintained in the second year. Significantly fewer subjects in the brolucizumab 6 mg arm had disease activity at Week 16 in a head-to-head comparison based on matched dosing intervals, with a relative decrease of 30% versus aflibercept (P = 0.0022). Significantly fewer subjects on brolucizumab had intraretinal fluid (IRF) and/or subretinal fluid (SRF), with a 35% and 33% reduction relative to aflibercept at Week 16 in HAWK and HARRIER, respectively (P < 0.001 for both), and a 31% and 41% reduction relative to aflibercept at Week 48 in HAWK and HARRIER, respectively (P < 0.0001 for both). Brolucizumab 6 mg achieved superior reductions in central subfield thickness (CSFT) versus aflibercept in both the matched dosing and maintenance phases (P = 0.0016 and P = 0.0023 at Week 16 and Week 48, respectively, in HAWK; P < 0.0001 at both Week 16 and Week 48 in HARRIER). These advantages for brolucizumab were maintained in the second year. Safety was comparable between the treatment arms over two years.

Brolucizumab for PDR

Ranibizumab, aflibercept, and brolucizumab all inhibit VEGF-A, a key mediator of retinal neovascularization and PDR. Both ranibizumab and aflibercept have demonstrated efficacy and safety in the treatment of subjects with PDR. These findings support the evaluation of brolucizumab in patients with PDR.

The improved efficacy of anti-VEGF therapies in PDR subjects compared to the standard of care PRP and the efficacy profile of brolucizumab in nAMD subjects signal the potential for brolucizumab to differentiate from PRP in terms of reduction in DR severity as well as decrease in the rate of ocular complications, including emergent center-involved macular edema, with visual acuity outcomes at least comparable to PRP.

There remains a need for anti-VEGF medicines with extended therapeutic durability that could support longer intervals between visits and treatment administration compared to current pharmaceutical options. The durability profile of brolucizumab in nAMD subjects, whose majority was maintained on a 12-week treatment interval in the first year of treatment, points to a potential for brolucizumab to address treatment and visit burden and warrants the concept of visit frequency every 6 weeks and the evaluation of treatment intervals up to 24 weeks.

These considerations advocate the initiation of a Phase III clinical program to evaluate the efficacy and safety of brolucizumab in the treatment of patients with PDR, with the objective to evaluate the potential to improve therapeutic outcomes compared to the current standard of care, while minimizing treatment burden for subjects.

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.

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of brolucizumab compared to PRP in subjects with PDR.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that brolucizumab is non-inferior to PRP with respect to the change from Baseline in visual acuity at Week 54	• Change from Baseline in BCVA at Week 54
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To demonstrate that brolucizumab is superior to PRP in reducing diabetic retinopathy severity at Week 54	• Proportion of subjects with no PDR at Week 54
• To demonstrate that brolucizumab is superior to PRP in preventing the development of center-involved DME up to Week 54	• Proportion of subjects with center-involved DME up to Week 54
• To compare the effect of brolucizumab relative to PRP with respect to visual acuity	• Area under the curve in change from Baseline in BCVA up to Week 54 and Week 96
• To compare the effect of brolucizumab relative to PRP on diabetic retinopathy status	• Change from Baseline in ETDRS Diabetic Retinopathy Severity Scale (DRSS) score at Week 54 and Week 96 • Proportion of subjects with no PDR at Week 96
• To compare the effect of brolucizumab relative to PRP on ocular complications	• Proportion of study eyes developing vision-threatening complications associated with diabetic retinopathy up to Week 54 and Week 96 • Proportion of subjects with center-involved DME up to Week 96
• To assess the safety and tolerability of brolucizumab relative to PRP	• Incidence of ocular and non-ocular adverse events (AE) up to Week 54 and Week 96

Objective(s)	Endpoint(s)
[redacted]	

3 Study design

The study is a 96-week, two-arm, randomized, single-masked, multi-center, active-controlled, non-inferiority study in subjects with PDR.

Subjects who consent will undergo screening assessments to evaluate their eligibility based on the inclusion and exclusion criteria. Subjects who meet all the inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio to one of the following treatments (Figure 3-1):

- Brolucizumab 6 mg: 3 x q6w loading then q12w maintenance through Week 90, with the option from Week 48 onwards to extend the treatment interval by 6 weeks at a time up to 24 weeks.
- PRP: initial treatment in 1-4 sessions up to Week 12, followed with additional PRP treatment (may split into 2-4 sessions) as needed up to Week 90.

Visits will occur every 6 weeks throughout the study, regardless of treatment or not.

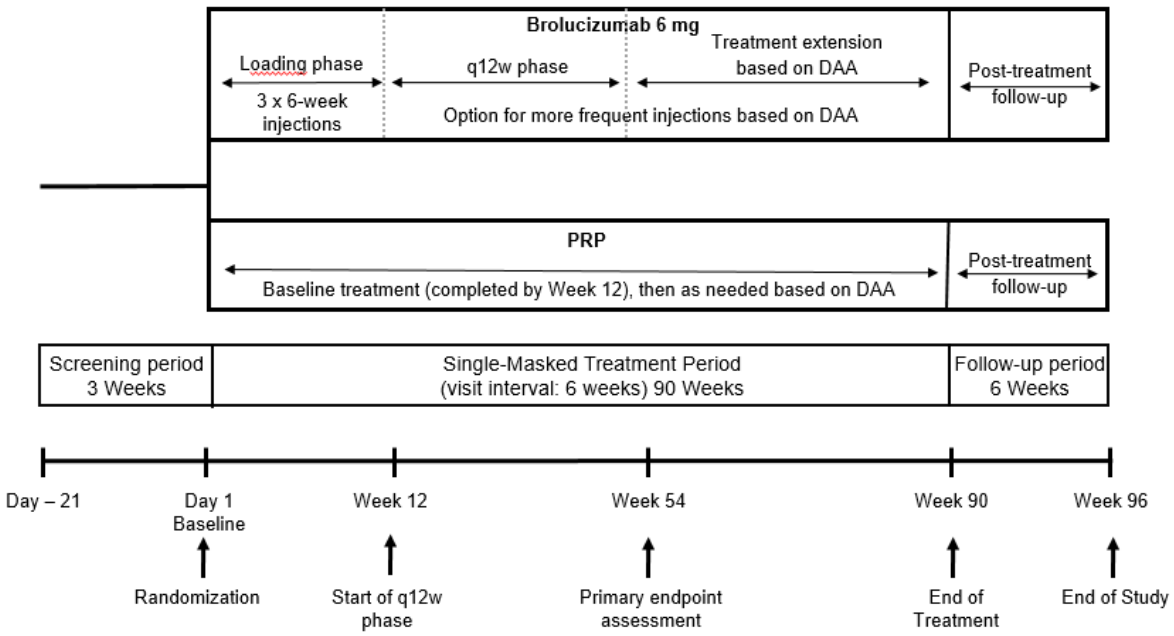
Approximately 941 adult subjects will be screened (25% screen failure rate expected) and approximately 706 subjects (353 per arm, 15% dropout rate expected) will be randomized in a

1:1 ratio in approximately 180 centers worldwide. The maximum study duration for one subject is 99 weeks, including Screening and post-treatment follow-up.

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

- Screening period: from Day -21 to Baseline (Day 1)
- Single-masked treatment period: from Baseline (Day 1) to Week 90 (End-of-Treatment)
- Post-treatment follow-up period: from Week 90 to Week 96 (End-of-Study).

Figure 3-1 Study design



DAA: Disease activity assessment

Screening period: Day -21 to Day -1

Subjects will be screened for enrollment into the study at the Screening visit. The screening period may last up to 3 weeks to assess eligibility. Further details are provided in Section 8.1. The assessment of the PDR status will be carried out by the investigator at the Screening visit. The Central Reading Center (CRC) will not be involved in the assessment of the PDR status and the subject's eligibility during the Screening period. Only one study eye can be selected per subject.

Single-masked treatment period: Day 1 to Week 90

After confirmation of eligibility at the Baseline visit, defined as Baseline / Day 1, subjects will be randomized in a 1:1 ratio to one of the treatment arms. A study visit schedule will be established at the time of randomization for all subjects. All efforts should be made to adhere to this study visit schedule within a ±7-day window (except Baseline / Day 1). For a given protocol visit, assessments can be performed on two consecutive days, provided both days are within the visit window. Treatment is intended to be administered on the day of study visit, or

if this is not possible, within 3 days after the study visit when the per-protocol assessments will have taken place.

For all subjects, the last potential study treatment will be at the Week 90 visit.

Brolucizumab arm:

Loading phase (Baseline / Day 1 to Week 12): Subjects will receive three consecutive injections every 6 weeks at Baseline, Week 6 and Week 12 during the loading phase.

Maintenance phase (Week 18 to Week 90): Subjects will then receive q12w injections in the maintenance phase. Additional assessment visits are planned for disease monitoring, not for treatment administration; however, injections may be administered at these visits if disease worsens, at the investigator's discretion. After Week 48, the treatment interval may be extended by 6 weeks at a time, up to 24 weeks, at the investigator's decision based on the assessment of diabetic retinopathy disease activity. The investigator may opt to revert to q12w injections if disease worsens. Further details are provided in Section 6.7.2.

PRP arm:

Subjects in the PRP arm will receive an initial treatment at Baseline / Day 1. The initial treatment may be split into 2-4 sessions up to Week 12, as per local clinical practice. Additional PRP may be performed in the study eye from Week 18 during the course of the study if disease worsens and may be split into 2-4 sessions, at the investigator's discretion, according to local clinical practice.

Post-treatment follow-up period: Week 90 to Week 96

For all subjects completing the study, the End-of-Study (EOS) assessment will be performed at Week 96, six weeks (±7 days) following their last possible study treatment administration (Week 90).

Subjects withdrawn from the study prior to study completion should be asked to return for an early discontinuation (EOS) visit. If study withdrawal occurred less than six weeks after the last study treatment, the EOS visit should take place at least six weeks following their last study treatment administration.

4 Rationale

4.1 Rationale for study design

The study is designed as a 96-week, two-arm, randomized, single-masked, multi-center, active-controlled, non-inferiority study to evaluate the efficacy and safety of brolucizumab compared to PRP in subjects with PDR.

Because of the difference in the mode of administration of brolucizumab (the investigational drug) and PRP (the comparator treatment), the duration of the two procedures, and the visible scars resulting from PRP on color fundus photography (CFP), subjects as well as the evaluating and treating investigators will not be masked to treatment. However, at each site, BCVA [redacted] assessments will be carried out by masked certified personnel. Retinal images, e.g. 7-Field CFP and spectral domain optical coherence tomography (SD-OCT), will also be evaluated by masked independent readers at the CRC.

The primary efficacy endpoint is based on BCVA assessed by masked certified personnel. The change from baseline in BCVA at a selected time point has been used as primary endpoint in prior studies comparing anti-VEGF agent and PRP in subjects with PDR (Gross et al 2015, Sivaprasad et al 2017) as well as in studies evaluating brolucizumab in subjects with DME (RTH258B2301; RTH258B2302). The BCVA assessment has its own variability and, generally in the clinical practice, a change of BCVA > 5 letters would be considered as clinically relevant regardless of the underlying disease. In this study, non-inferiority testing related to this primary efficacy parameter 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 first key secondary endpoint will be based on the ETDRS DRSS score assessed on 7-Field CFP by independent readers masked to the study treatment, the study visit, and the investigator's disease activity assessment. The proportion of subjects with no PDR as defined by a DRSS score < 61 after 54 weeks of treatment will allow the assessment of the relative effectiveness of the study treatments in reducing the severity of diabetic retinopathy to non-proliferative stage.

The primary analysis will be conducted after approximately one year of treatment (Week 54), in agreement with other non-inferiority studies in retinal vascular diseases, including diabetic macular edema and retinopathy, in which the primary endpoint is based on BCVA. The 54-week duration is deemed long enough to evaluate the efficacy and safety of both study treatments.

4.2 Rationale for dose/regimen and duration of treatment

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

- Based on the Phase III brolucizumab studies in nAMD (RTH258-C001 - HAWK and RTH258-C002 - HARRIER studies), both brolucizumab 3 mg and/or 6 mg doses showed comparable functional efficacy and safety profiles to aflibercept, with numerical advantages related to efficacy for the 6 mg dose, compared to the 3 mg dose.
- The dosing regimen comprises a loading phase of three injections followed by a maintenance phase of q12w injections in the first year of treatment, and the option of fewer treatments in the second year by extending the treatment interval up to 24 weeks. The estimated minimum of 6 injections in the first year and 2-3 injections in the second year are consistent with the treatment needs of subjects with PDR and no center-involved DME in prior studies with other anti-VEGF treatments (Gross et al 2015, Sivaprasad et al 2017, Lang et al 2019), in which visual acuity was at least preserved or even improved from Baseline, and a higher proportion of subjects were PDR-free after one or two years of treatment, when compared to PRP.
- The 6 mg dose of brolucizumab administered is intended to provide a prolonged duration of action. The increase of 30 days to 75 days in the median time to retreatment in nAMD subjects initially treated with brolucizumab 6 mg vs ranibizumab 0.5 mg in the SEE study (RTH258-C10-083) as well as the positive nAMD Phase III study results regarding the q12w/q8w regimen in HAWK and HARRIER support stretching the minimum interval between injections to 6 weeks.
- The route of administration is an intravitreal injection as for all anti-VEGF treatments currently approved for the treatment of retinal diseases, including DR.

Study duration of 96 weeks allows assessing the long-term efficacy and safety of brolucizumab and PRP in subjects with PDR.

4.3 Rationale for choice of comparator treatment

Brolucizumab 6 mg will be compared to PRP laser. PRP has been the standard of care for the treatment of PDR worldwide for more than 40 years (Diabetic Retinopathy Study Research Group 1981, Moutray et al 2018), including the USA where Lucentis® and Eylea® have been recently approved for the treatment of DR. No anti-VEGF agents have been approved for the treatment of PDR in other countries participating in the study.

4.4 Purpose and timing of interim analyses/design adaptations

The primary analysis will be conducted when all ongoing subjects have completed their Week 54 visit. Subjects will remain in the study and will continue to receive treatment through the planned duration of the treatment period up to Week 90, to allow for further evaluation of efficacy and safety. Treatment masking of individual subjects will remain in effect for the masked personnel at the sites and CRC until the final database lock has occurred.

4.5 Risks and benefits

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

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 must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continued in the study.

The approved VEGF-A inhibitors ranibizumab and aflibercept have consistently demonstrated efficacy in VEGF-driven retinal pathologies, including PDR, with benefits outweighing the risks. Assuming an anti-VEGF class-effect, one can expect that the novel anti-VEGF brolucizumab, which is approved in the USA for the treatment of nAMD, will likely demonstrate a favorable benefit / risk profile in PDR subjects.
Intravitreal injections, including those with brolucizumab, have been associated with endophthalmitis and retinal detachments. Acute intraocular pressure (IOP) increases have also been reported. 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.

PRP is still the standard of care and has a positive effect on the severity of DR. However, PRP is a destructive procedure and can reduce peripheral and night vision. In addition, it can transiently or permanently reduce central vision. Rarely, it can cause transient increase in IOP. In some cases, retrobulbar or peribulbar injection may be used to anesthetize the eye and to reduce eye movements during the administration of PRP, which may have potential rare complications.

In view of the outcomes of recent trials comparing anti-VEGF agents and PRP in PDR subjects, subjects entering this trial may benefit from treatment with brolucizumab via better preservation of peripheral and central vision compared to PRP. In addition, brolucizumab may be more efficient than PRP in reducing the severity of DR and decreasing the risk of vision-threatening complications due to the disease as well as the risk of developing DME.

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

5 Population

The study population will be adult male and female patients with type 1 or type 2 DM diagnosed with PDR, with no evidence of prior PRP in the study eye, and able to comply with study procedures.

Assuming a 25% screening failure rate, approximately 941 patients will be screened and approximately 706 (353 per arm, 15% dropout rate expected) patients will be randomized in a 1:1 ratio in approximately 180 centers worldwide.

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

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Patients ≥ 18 years of age at Screening.
3. Participant cooperation sufficient for adequate fundus photographs and retinal images.
4. Patients diagnosed with type 1 or 2 DM, and HbA1c ≤ 12% at Screening.
5. Any medication administered for the management of DM should be stable within 3 months prior to randomization and is expected to remain stable during the course of the study, as medically acceptable.

   Study eye

6. PDR as assessed by the investigator using standard or wide-field CFP and FA, with no evidence of previous PRP, and that requires treatment with either anti-VEGF or PRP in the opinion of the investigator.
7. BCVA ≥ 34 ETDRS letters (Snellen equivalent 20/200) at Screening and Baseline.

5.2 Exclusion criteria

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

Ocular conditions

1. Concomitant conditions or ocular disorders in the study eye at Screening or Baseline as well as planned medical/surgical intervention during the first 54-week study period that could compromise functional or structural response to study treatment, in the opinion of the investigator.
2. Presence of center-involved diabetic macular edema in the study eye at Screening or Baseline, as assessed by the investigator.
3. Any active intraocular or periocular infection or active intraocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, infectious blepharitis, uveitis) in the study eye at Screening or Baseline.
4. Uncontrolled glaucoma in the study eye defined as IOP > 25 mmHg despite treatment with IOP-lowering medication, or according to investigator's judgment, at Screening or Baseline.
5. Moderate or dense pre-retinal or vitreous hemorrhage that prevents clear visualization of the macular and /or optic disc or prevents PRP treatment in the study eye at Baseline.
6. Significant fibrovascular vitreoretinal proliferation or tractional retinal detachment of the study eye.
7. Iris or anterior chamber angle neovascularization, or neovascular glaucoma in the study eye.
8. Presence of amblyopia, amaurosis, or ocular disorders in the fellow eye with BCVA < 20/200 at Screening (except when due to conditions for which treatment or surgery may improve VA, e.g. cataract).

Ocular treatments in the study eye

9. PRP any time prior to Baseline.
10. Intravitreal anti-VEGF treatment within 6 months prior to Baseline.
11. Vitreoretinal surgery at any time prior to Baseline or anticipated need for vitreoretinal surgery within the next 12 months.
12. Laser treatment of the macula within 3 months prior to Baseline.
13. Treatment with fluocinolone acetonide intravitreal implant (e.g. ILUVIEN® or RETISERT®) at any time prior to Baseline. Other intraocular or periocular corticosteroid injection within 6 months prior to Baseline.
14. Aphakia with the absence of posterior capsule.
15. Intraocular surgery within 3 months prior to Baseline or anticipated need for cataract extraction within the next 12 months.

Non-ocular conditions and treatments

16. Stroke or myocardial infarction during the 6-month period prior to baseline.
17. End stage renal disease requiring dialysis or renal transplant.
18. Uncontrolled blood pressure defined as a systolic value ≥ 180 mmHg or diastolic value ≥ 100 mmHg at screening or baseline. (In case there is an elevated blood pressure measurement, it should be repeated after approximately 20 minutes. If the repeat measurement is elevated, then the patient is not eligible to be enrolled into the study).
19. Systemic anti-VEGF therapy at any time.
20. Systemic medications known to be toxic to the lens, retina or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol) used during the 6-month period prior to Baseline except temporary use for Coronavirus 19 (COVID-19) treatment.
21. History of hypersensitivity to any of the study drugs or their excipients or to drugs of similar classes, or clinically relevant sensitivity to fluorescein dye as assessed by the investigator.
22. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years prior to Screening, regardless of whether there is evidence of local recurrence or metastases.
23. History of a medical condition (e.g. metabolic dysfunction disease with exception of type 1 or 2 DM, 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; or longer if required by local regulations (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 human chorionic gonadotropin pregnancy test.
26. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during the study drug administration and for at least one month after stopping the investigational medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject

- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system, or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

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

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

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

6 Treatment

6.1 Study treatment

6.1.1 Investigational drug

Table 6-1 Investigational drug

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor
Brolucizumab 6 mg (RTH258 6 mg/ 0.05 mL)	Solution for injection	Intravitreal use	Open label patient specific (Glass vials or PFS)	Global

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

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

6.1.2 Comparator treatment

The PRP procedure may be performed using conventional lasers or automated pattern delivery systems, at the investigator's discretion according to local clinical practice. Instructions for administering PDR treatment are provided in Section 6.7.2.

6.1.3 Additional study treatments

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

6.1.4 Treatment arms/group

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

- Brolucizumab 6 mg: 3 x q6w loading then q12w maintenance through Week 90, with the option from Week 48 onwards to extend the treatment interval by 6 weeks at a time up to 24 weeks.
- PRP: initial treatment in 1-4 sessions up to Week 12, followed with additional PRP treatment (may split into 2-4 sessions) as needed up to Week 90.

6.1.5 Treatment duration

The planned duration of treatment is 90 weeks. Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the subject or the investigator.

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

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator must instruct the subject to notify the study site about any new medications he / she takes after signing the study informed consent. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate electronic case report form (eCRF) page.

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Fellow eyes

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

Study eyes

Administration of topical ocular medications, including corticosteroids, is allowed in the study eye during the study. Corticosteroids administered via intra-nasal, inhaled, intra-articular or

non-extensive dermal route (< 20% total body surface area) are also permitted during the study. For other routes of corticosteroid administration, refer to Table 6-2.

If cataract surgery is necessary in the study eye, it should be attempted to schedule the surgery ≥ 7 days after the most recent study treatment. Study treatment may be resumed ≥ 14 days after cataract surgery, assuming an absence of surgically-related complications.

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

If vitrectomy is necessary in the study eye, it should be attempted to schedule the surgery ≥ 14 days after the most recent study treatment. Study treatment may be given during vitrectomy surgery if deemed necessary according to investigator's discretion.

If the subject 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.

6.2.2 Prohibited medication

The treatments displayed in the table below are not allowed after Screening, unless otherwise indicated.

Table 6-2 Prohibited medications and surgical procedures

Medication/Procedure	Prohibition period	Action taken
Study eye		
Anti-VEGF therapy other than assigned study medication	Anytime	Discontinue study treatment
PRP other than assigned study treatment	Anytime	Discontinue study treatment
Any periocular injection or intraocular administration of corticosteroids (except if use of short-acting corticosteroids for the treatment of AE)	Anytime	Discontinue study treatment, except in the case of injections of short-acting corticosteroids (e.g. for the treatment of AE)
Grid/focal laser photocoagulation for macula edema treatment (except if performed for the treatment of AE)	Anytime	Continuation of study treatment if performed for the treatment of AE
Any other investigational drug, biologics or device	Anytime	Discontinue study treatment
Non-ocular		
Anti-VEGF treatment	Anytime	Discontinue study treatment
Any investigational drug, biologic or device	Anytime	Discontinue study treatment

Medication/Procedure	Prohibition period	Action taken
Medications known to be toxic to the lens, retina or optic nerve, including ethambutol, chloroquine, hydroxychloroquine, deferoxamine, phenothiazines and tamoxifen except temporary use for COVID-19 treatment	Anytime	Discontinue study treatment

Any medication used according to medical practice or PRP to treat the fellow eye is permitted and should be recorded in the appropriate eCRF page; however, treatment of the fellow eye with any other investigational product (drug, biologic or device) is prohibited.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.) that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (4 digit number for Center No. as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it (3 digit number for Subject No.), so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available in the electronic data capture (EDC) system.

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

6.3.2 Treatment assignment, randomization

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

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

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from masked staff. A subject randomization list will be produced using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms. A separate medication list will be produced by or under the responsibility of

Novartis Global Clinical Supply using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug. The randomization will be stratified by region.

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

6.4 Treatment masking

The intent of masking is to limit the occurrence of conscious and unconscious bias in the conduct of the clinical study and the interpretation of its results. Bias could arise from the influence that the knowledge of a specific treatment assignment may have on the recruitment and allocation of subjects, their subsequent care, the assessment of endpoints, the handling of withdrawals, and so on.

This study will be single-masked with subjects randomized using IRT to be treated with brolucizumab 6 mg or PRP. Because of the difference in the mode of administration of brolucizumab (the investigational drug) and PRP (the comparator treatment), the duration of the two procedures, and the visible scars resulting from PRP on CFP, subjects as well as evaluating and treating investigators cannot be masked to treatment.

To ensure single masking, the site personnel who will perform the BCVA [redacted] assessments will be masked to the identity of the treatment from the time of randomization until the final database lock. The masked site personnel will be independent from the unmasked site staff who will perform the clinical evaluation and administer the study treatment. Once the designated roles are determined, the unmasked investigator/site personnel must not be switched at any time after randomization to masked role. The source documentation specific to BCVA [redacted] assessments will be separately filled and provided to unmasked staff with no communication about treatment of the subject. The masked personnel will not have access to the other source documentation and the EDC system.

Subjects, field monitors, and unmasked site staff will be asked not to communicate any information related to the study treatment to the masked site personnel, as documented in the patient informed consent form and in any other study form describing staff responsibilities.

Masking to the original treatment assignment will be maintained for the masked personnel at the site level until the end of the study.

Additionally, an independent review of images collected at pre-defined time-points (see Section 8.3.2 and Section 8.3.3) for subjects enrolled in the study will be performed at a CRC. Independent readers of CFP images will be masked to the study treatment, the study visit number, and the investigator's disease activity assessment.

6.5 Dose escalation and dose modification

No dose modification, nor deviation to dose intervals during the loading phase, nor dose adjustment during the whole study is allowed for the investigational drug.

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

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Investigator will comply with IRT treatment assignment for the investigational drug and to their local practice for PRP.

IRT needs to be accessed by unmasked study personnel at every visit. Registration of all visits in the IRT system is necessary and when treatment is warranted, IRT will provide a medication (kit) number to administer the investigational drug to the subject. The date and time of all study treatments administered during the study and any deviations from the protocol treatment schedule will be captured by the unmasked study personnel or by field monitor on the appropriate study treatment dispensing form.

Exposure to brolucizumab will be based on the number of injections administered. The field monitor will assess compliance with the investigational drug by using counts of vials and PFS as applicable, and information provided by the pharmacist or by the unmasked study personnel.

6.7 Preparation and dispensation

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

6.7.1 Handling of study treatment

Investigational drug must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all investigational drug must be stored according to the instructions specified on the labels and in the Investigator’s Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization 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 investigational drug but no information about the subject except for the medication number.

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

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

6.7.2 Instruction for administering study treatment

Treatment schedules are illustrated in Figure 6-1. Visits will occur every 6 weeks. Every effort should be made to ensure that the subject adheres to the visit schedule.

During the study, disease activity should be assessed in both treatment arms using retinal imaging and visual functional outcomes, at the investigator's discretion (e.g. standard or wide-field CFP, fluorescein angiography (FA), BCVA). Disease activity will be assessed at each visit from Week 12 to Week 96 (EOS). The investigator's disease activity assessment will be entered in the IRT system and eCRF.

Arm 1: Brolucizumab 6 mg

All kits of investigational drug assigned by the IRT will be recorded in the IRT system.

Treatment schedule

Loading phase (Baseline to Week 12): Subjects will receive three consecutive injections every 6 weeks at Baseline, Week 6 and Week 12 during the loading phase.

Maintenance phase (Week 18 to Week 90):

- Subjects will receive q12w injections in the maintenance phase, i.e. at Week 24, Week 36, and Week 48 in the first year.
- During the maintenance phase, the additional visits (e.g. Week 30) are planned for disease monitoring, not for treatment administration. However, additional injections may be administered at these visits at the investigator's discretion only if disease worsens, e.g. new or expanding retinal neovascularization compared to the previous visit. No injection should be administered if retinal neovascularization has been stable. Any additional injection will not impact the q12w injection schedule, i.e. injections at Week 24, Week 36, and Week 48 will be nonetheless performed.
- From Week 48 onwards,
  - The treatment interval may be extended by 6 weeks at a time, up to 24 weeks, at the investigator's discretion if, based on the investigator's assessment of disease activity, there is disease stability or regression, e.g. regressed or stabilized retinal neovascularization from the previous injection visit.
  - Thus, at Week 48 the investigator may elect to extend the treatment interval from 12 weeks to 18 weeks and treat the study eye at Week 66, if the disease did not worsen, e.g. no new or expanding retinal neovascularization, between Week 36 and Week 48 and there was no injection at Week 42. At Week 66, the investigator may elect to further extend the treatment interval from 18 weeks to 24 weeks, and treat the study eye at Week 90, if the disease did not worsen between Week 48 and Week 66, and there were no injections at Week 54 and Week 60.
  - The investigator may opt to revert to q12w injections if, in the investigator's opinion based on disease activity assessment, the subject needs more frequent treatment.
- The last potential brolucizumab injection may be administered at the Week 90 visit.

Brolucizumab administration

The IVT injection will be carried out by the investigator under controlled, aseptic conditions and antimicrobial requirements according to local clinical practice. Every injection administered to the subject will be recorded in the eCRF.

If any safety concern arises related to the study eye that, in the opinion of the investigator, may be further impacted by the study treatment or injection procedure, treatment should not be administered. IVT injection is contraindicated in subjects with active ocular or periocular infections and in subjects with active intraocular inflammation (IOI); therefore, the investigators must verify that these conditions are not present in the study eye prior to every injection. Any adverse events must be recorded in the eCRF.

If any signs of intraocular inflammation are present, then an IVT injection **must not** be performed. Additional ophthalmic examination and imaging should be performed to evaluate IOI (see Section 8.4.5).

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 subject develops retinal vasculitis and/or retinal vascular occlusion based on the investigator's evaluation, the study treatment must be discontinued.

Arm 2: PRP

Subjects in the PRP arm will receive an initial treatment at Baseline. The treatment may be split into 2-4 sessions up to Week 12 as per local clinical practice. The additional sessions should coincide with the visit schedules (i.e. Week 6 and Week 12), whenever possible, at the discretion of the investigator, as long as treatment is adequately administered to the subject.

From Week 18, all subjects in the PRP arm will be assessed for treatment response every 6 weeks. Additional PRP may be performed in the study eye if disease worsens, e.g. new or expanding retinal neovascularization compared to the previous visit, at the investigator's discretion, according to local clinical practice. Additional PRP may be deferred until next visit if the ocular media are too hazy to perform the procedure.

PRP is typically administered using conventional lasers or automated delivery pattern systems delivered through either a slit lamp system or indirect ophthalmoscope (headlamp/BIO). Approximately 1500-5000 burns may be administered in 1 to 4 sessions, according local clinical practice and applicable guidance for PRP.

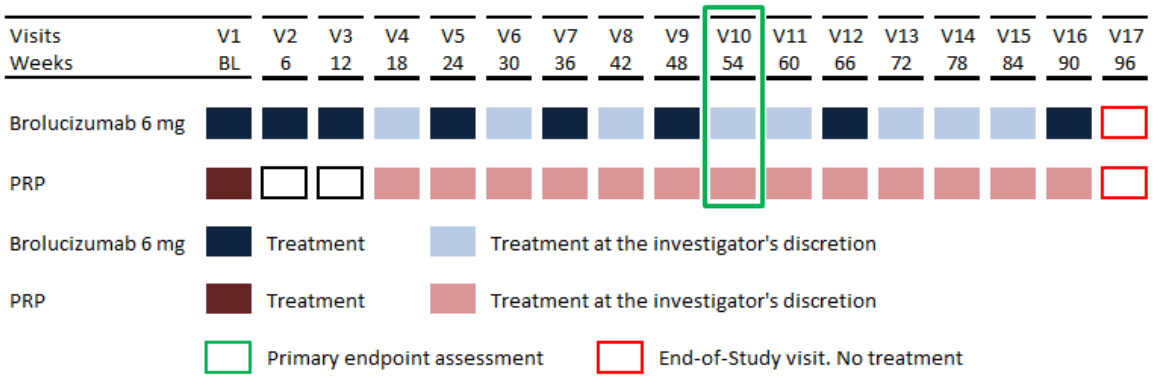
PRP performed as a day case hospitalization should not be recorded as a serious adverse event (SAE) despite hospitalization.

If any safety concern arises related to the study eye that, in the opinion of the investigator, may be further impacted by PRP, treatment needs to be deferred. Any adverse events must be recorded in the eCRF.

If subject develops retinal vasculitis and/or retinal vascular occlusion based on the investigator's evaluation, the study treatment must be discontinued.

The last potential PRP treatment may be administered at the Week 90 visit.

Figure 6-1 Treatment schedule (example)



BL: Baseline, V: visit

7 Informed consent procedures

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

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

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol), except for FA images that can be used from a previous routine evaluation that would have taken place no more than 14 days prior of the Screening visit (see Section 8.1). The process of obtaining informed consent must be documented in the subject source documents.

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

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. As new information becomes available, informed consent to be updated and then must be discussed with the subject.Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

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

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

8 Visit schedule and assessments

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

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

A ± 7-day visit window is allowed, except for Baseline / Day 1, should the subject be unable to return per scheduled visit. All efforts should be made to revert back to the planned visit schedule taking into consideration the restrictions on the minimum treatment interval for brolucizumab, i.e. two consecutive injections should be at least 21 days apart.

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

Treatment is intended to be administered on the day of study visit - if this is not possible, within 3 days after the study visit at which the per-protocol assessments took place - after completing all assessments required to be performed prior to the administration of study treatment. IOP will also be measured, and other ocular examinations may also be performed, after administration of study treatment for safety assessment.
Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the EOS final visit will be performed.

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

Table 8-1 Assessment Schedule

Period	Screening	Treatment																Post-Treatment Follow-Up
Visit Name	**Screening**	**Baseline**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/EOT**	**17/EOS**
Days	**-21 to -1**	**1**	**43**	**85**	**127**	**169**	**211**	**253**	**295**	**337**	**379**	**421**	**463**	**505**	**547**	**589**	**631**	**673**
Weeks	**-3 to -1**	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**	**84**	**90**	**96**
Informed consent	X																	
Demography	X																	
Inclusion / Exclusion criteria	X	X																
Medical history/current medical conditions	X																	
Prior / concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c	X			X		X		X			X				X			X
Hematology	X					X					X				X			X
Clinical chemistry	X					X					X				X			X
Urinalysis	X					X					X				X			X
Pregnancy test[1]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
[redacted]																		

Period	Screening	Treatment																Post-Treatment Follow-Up
Visit Name	**Screening**	**Baseline**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/EOT**	**17/EOS**
Days	**-21 to -1**	**1**	**43**	**85**	**127**	**169**	**211**	**253**	**295**	**337**	**379**	**421**	**463**	**505**	**547**	**589**	**631**	**673**
Weeks	**-3 to -1**	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**	**84**	**90**	**96**
[redacted]																		
Trial feedback questionnaire (optional)		X									X							X
Best corrected visual acuity[11]	OU[4]	X	X	X	X	X	X	X	X	X	OU	X	X	X	X	X	X	OU
Intraocular pressure	OU	X	X	X	X	X	X	X	X	X	OU	X	X	X	X	X	X	OU
Ophthalmic examination[10]	OU	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
7-Field color fundus photography[5, 10]	OU				X						OU			X				OU
Fluorescein angiography[5, 10]	OU										X							X

Period	Screening	Treatment																Post-Treatment Follow-Up
Visit Name	**Screening**	**Baseline**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/EOT**	**17/EOS**
Days	**-21 to -1**	**1**	**43**	**85**	**127**	**169**	**211**	**253**	**295**	**337**	**379**	**421**	**463**	**505**	**547**	**589**	**631**	**673**
Weeks	**-3 to -1**	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**	**84**	**90**	**96**
Spectral domain optical coherence tomography[10]	OU	X	X	X	X	X	X	X	X	X	OU	X	X	X	X	X	X	OU
[redacted]																		
Wide-field color fundus photography, if available[5]	OU				X						OU			X				OU
Disease activity assessment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study treatment - brolucizumab arm		X	X	X	Option[6]	X	Option[6]	X	Option[6]	X	Option[6]	Ext. period[7]	Ext. period[7]	Ext. period[7]	Ext. period[7]	Ext. period[7]	Ext. period[7]	

Period	Screening	Treatment																Post-Treatment Follow-Up
Visit Name	**Screening**	**Baseline**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/EOT**	**17/EOS**
Days	**-21 to -1**	**1**	**43**	**85**	**127**	**169**	**211**	**253**	**295**	**337**	**379**	**421**	**463**	**505**	**547**	**589**	**631**	**673**
Weeks	**-3 to -1**	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**	**84**	**90**	**96**
Study treatment - PRP arm		X[8]			PRN[9]	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] For all women of child-bearing potential. Serum pregnancy test to be conducted at the Screening and Week 96/EOS visits. Urine pregnancy test at the other visits.
[redacted]
[4] Oculus uterque, both eyes
[5] May be performed at other visits, at the investigator's discretion
[6] Based on disease activity, e.g. new or worsening retinal neovascularization from previous visit. Treatment should be held off if stabilized disease.
[7] Treatment interval can be extended by 6 weeks at a time, up to 24 weeks, based on disease stabilization or regression. Treatment interval can revert to q12w if subject needs more frequent treatments.
[8] PRP treatment at Baseline can be split into 2-4 sessions until Week 12
[9] Pro re nata, based on disease activity.
[redacted]
[11] BCVA will also be measured in the fellow eye if the BCVA in the study eye has dropped by 10 or more ETDRS letters from the previous visit

8.1 Screening

A screening period of up to 3 weeks will be used to assess subject eligibility.

For the purpose of screening, FA images from a previous **routine** evaluation may be used as long as FA was performed within 14 days of the Screening visit using CRC-certified equipment operated by CRC-certified personnel.

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

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and who are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF page. The demographic information, informed consent, inclusion/exclusion and disposition eCRF pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced an SAE during the screening phase (see Section 10.1.3 for reporting details). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. If the subject is not eligible to be randomized, the IRT should be notified within 2 days of the screen fail that the subject was not randomized.

8.2 Subject demographics/other baseline characteristics

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

The following information will be collected / documented at Screening and/or Baseline visit (see Table 8-1) for each randomized subject:

- Age
- Sex
- Race / Ethnicity
- History of primary diagnosis, including type of diabetes and PDR
- Medical history / current medical conditions
- Prior / concomitant medications and procedures, including anti-VEGF intravitreal injection or PRP for the treatment of PDR in the fellow eye that occurred within 20 weeks prior to the Baseline visit
- Vital signs
- BCVA
- IOP

- Study eye
- Retinal imaging
- HbA1c and other laboratory test results
- [redacted]
- [redacted]

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

8.3 Efficacy

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

- Best-corrected visual acuity with ETDRS-like charts at initial testing distance of 4 meters
- ETDRS DRSS score based on 7-Field stereo CFP
- Anatomical retinal evaluation by SD-OCT, FA, [redacted]), Wide-field CFP
- [redacted]

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

8.3.1 Visual acuity

Visual acuity will be assessed in the study eye at every study visit and in the fellow eye at the Screening, Week 54 and Week 96/EOS visits using best correction determined from protocol refraction (BCVA). BCVA will also be measured in the fellow eye if the BCVA in the study eye has dropped by 10 or more ETDRS letters from the previous visit.

BCVA measurements will be taken in a sitting position using ETDRS–like visual acuity testing charts at an initial testing distance of 4 meters. The details of the refraction technique and VA testing, as well as training material, are provided in the applicable manual. Certification of the assessment procedures and assessors will occur prior to any evaluation of study subjects.

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

8.3.2 Color fundus photography and fluorescein angiography

Seven-Field stereo CFP, or equivalent as per the CRC manual, will be performed in both eyes at Screening, Week 54, and Week 96 / EOS and in the study eye at Week 18 and Week 72.

At sites that have the applicable equipment, **optional** Wide-Field (at least 100 degrees) CFP (WFCFP) should be performed in both eyes at Screening, Week 54, and Week 96/EOS and in the study eye at Week 18 and Week 72. If WFCFP images were not taken at Screening, they should not be introduced at later visits. Additional CFP images may be captured at other visits, at the investigator's discretion.

7-Field standard (non-stereoscopic) or Wide-Field FA will be performed in the study eye at the Screening, Week 54, Week 96 / EOS visits and in the fellow eye at the Screening visit. FA may be performed at other visits, at the investigator's discretion. The FA camera model used for an individual subject should not change for the duration of the study.

For the purpose of screening, FA images from a previous routine evaluation may be used as long as FA was performed within 14 days of the Screening visit using CRC-certified equipment operated by CRC-certified personnel.

In case of premature discontinuation from the study, there is no need to repeat the 7-Field CFP and FA if there was a 7-Field CFP and FA performed within the previous 12 weeks, except if there is significant disease worsening in the opinion of the investigator.

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

The CRC will provide sites with a Study Manual and training materials for the specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software will be certified and validated by the CRC as specified in the Study Manual. All 7-Field CFP, WFCFP, and FA images will be obtained by trained and study-certified site personnel at the study sites and forwarded to the CRC for independent standardized analysis and for storage.

The CRC will create a database with the agreed variables as indicated in the CRC grading charter (a separate document) and will transfer the data from this database to Novartis for analysis. The CRC data will be used for the evaluation of the objectives having 7-Field CFP and FA parameters and their change over time as endpoints to ensure a standardized evaluation. Grading for DRSS score will be performed at the CRC.

For further procedural details, the investigator should refer to the applicable manual provided by the CRC.

Additional images will be taken in case of any signs of intraocular inflammation. OCT, Color fundus photography and fluorescein angiography (preferably wide-field or with peripheral sweeps) should be performed for safety evaluation as described in Section 8.4.5.

8.3.3 Optical coherence tomography

SD-OCT images will be obtained and assessed in both eyes at Screening, Week 54 and Week 96/EOS visits, and in the study eye at all other visits.

These assessments will be performed by a trained and CRC-certified technician or investigator at the sites and should be performed **after** BCVA assessment and **prior** to any study treatment. Investigators will evaluate the SD-OCT images to assess the status of macular edema. The SD-OCT model used for an individual subject should not change for the duration of the study.

[redacted]

In addition to the standard assessment, at sites that have the applicable equipment, wide-field or standard should be performed at each visit in the study eye.

The investigators will evaluate the OCT images according to their clinical practice. Their findings about both quantitative and qualitative OCT parameters will not be captured in the eCRF but should be included in the source documentation at the study site.

A CRC will be used in this study. The CRC will provide sites with a Study Manual and training materials for the specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software will be certified and validated by the CRC as specified in the Study Manual. All SD-OCT images will be obtained by trained and CRC-certified site personnel at the study sites. All SD-OCT images will be forwarded to the CRC for independent standardized analysis and for storage.

The CRC will create a database with the agreed variables as indicated in the CRC grading charter (a separate document) and will transfer the data from this database to Novartis for analysis. The CRC data will be used for the evaluation of the objectives having SD-OCT parameters to ensure a standardized evaluation. For further procedural details, the investigator should refer to the applicable manual provided by the CRC.

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8.3.5 Appropriateness of efficacy assessments

The use of BCVA as a measure of retinal function as well as 7-Field CFP to analyze structural changes of the peripheral retina are standard assessments to monitor PDR and treatment effects both in clinical practice and in clinical trials. ETDRS DRSS assessed on 7-Field CFP is a standardized evaluation of the severity of DR in clinical trials.

FA is also an established procedure used to identify retinal neovascularization and monitor its change.

SD-OCT images are routinely used in clinical trials and practice to assess [redacted] monitor the emergence and evolution of DME, a vision-threatening complication of diabetes, which may occur in PDR subjects.

8.4 Safety

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

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

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

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

8.4.1 Vital sign assessments

Vital signs include assessment of sitting blood pressure (systolic and diastolic pressure in mmHg) and pulse rate (beats per minute) and will be collected at all visits. In case there is an elevated blood pressure measurement as specified in the exclusion criteria, at the Screening and Baseline visits, the blood pressure measurement should be repeated after approximately 20 minutes. If the repeat measurement is elevated as specified in the exclusion criteria, then the subject is not eligible to be enrolled into the study.

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

8.4.2 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected at Screening, Week 24, Week 54, Week 78, and Week 96/EOS visits. Blood samples will also be collected for HbA1c assessment at Week 12 and Week 36. Details on the collections, shipment of the samples and reporting of the results by the central laboratory are provided to investigators in the central laboratory manual.

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.

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

Table 8-2 Laboratory assessments

Test Category	Test Name
HbA1c	Glycosylated Hemoglobin
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.

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

8.4.3 Pregnancy

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

Highly effective contraception is required for women of child-bearing potential during the study drug administration and for one month after stopping the investigational medication.

A **serum** pregnancy test will be conducted for all women of child-bearing potential to assess pregnancy before inclusion into the study at Screening visit, and then at Week 96/EOS visit. During the study, **urine** pregnancy testing will be performed before any study treatment at the other visits. If a urine test is positive after inclusion into the study, a serum pregnancy test must be performed for confirmation; if the serum test is positive, the subject must discontinue study treatment. Results of all pregnancy testing must be available as source documentation.

8.4.4 Intraocular Pressure

IOP will be assessed in the study eye at all scheduled visits. At visits when study treatment is administered, pre-treatment and post-treatment IOP will be assessed. The same method of tonometry has to be used through the whole study. In the fellow eye, IOP will be assessed at Screening, Week 54 and Week 96 / EOS visit. The values recorded in mmHg for either eye will be entered into the eCRF.

Treatment and close monitoring of IOP should be performed by the investigator for any non-transient elevation in IOP ($\geq$ 25 mmHg). Intravitreal injection is not recommended unless normalization of the IOP has been achieved. Post-dose IOP should be assessed in the within 60 minutes after study treatment and if $\geq$ 25 mmHg, it is recommended that assessment should be repeated until back to normal. Perfusion of the optic nerve head should also be monitored and managed appropriately, at the discretion of the investigator and/or according to local requirements / practice. Results of these procedures will be recorded as appropriate in the source documents, and if the findings constitute an AE, it should be recorded in the eCRF.

8.4.5 Ophthalmic examination

The ophthalmic examination will consist of the following:

- **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 according to local clinical practice. At visits when study treatment is administered, the examination will be performed pre-treatment; if needed, an additional examination may be performed post-treatment. The fellow eye will be examined at Screening for eligibility, and at other visits at the discretion of the investigator. The results of the examination of either eye should be recorded in the source documents as appropriate.

Slit lamp examination must be carefully performed before each study treatment. If there are any signs of IOI, severity of anterior chamber cells and flare should be assessed according to the standardization of uveitis nomenclature (SUN) working group grading system (Jabs et al 2005). The test results will be recorded in the source documents (e.g., ophthalmic examination tool) and captured in the appropriate eCRF as applicable.

Ophthalmoscopy 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 study treatment can be safely performed. As of Baseline visit, the fundus examination will be performed only in the study eye at every scheduled visit. Posterior segment examination must be performed carefully before each study treatment. The results of the examination including any abnormalities (e.g. vitreous cells/haze, retinal tear/detachment, hemorrhage and vascular occlusion, vasculitis, etc.) should be recorded in the source documents. If there are any signs of IOI, vitreous cells and haze should be assessed using National Institutes of Health (NIH) grading system (Nussenblatt et al 1985). The outcome of the examination will be documented in the source document (e.g., ophthalmic examination tool) and appropriate eCRF page as applicable. Pupil dilation for slit lamp examination and ophthalmoscopy is optional, at the discretion of the investigator or according to local clinical practice.

Instruct the patient to contact the site for any changes in vision or any symptoms of inflammation between scheduled visits. Every effort should be made to bring the subject for immediate examination. When IOI, retinal vasculitis, and/or Retinal Artery Occlusion (RAO) is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and will conduct OCT, fluorescein angiography and color fundus photography (preferably wide-field or with peripheral sweeps). These additional assessments will be documented in the source and appropriate eCRF pages as applicable. The images are requested to be uploaded onto the CRC portal. 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.

8.4.6 Appropriateness of safety measurements

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

If there is any signs of IOI, additional assessment will be performed as described in Section 8.4.5.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

[redacted]

Trial Feedback Questionnaire

During the treatment period, subjects will be asked to complete an optional anonymized questionnaire, the "Trial Feedback Questionnaire", to provide feedback on their clinical trial experience at Baseline, Week 54 and Week 96/EOS visits. Subjects may opt in or opt out of completing this questionnaire.

Responses will not be reviewed by investigators. Responses will be used to understand where improvements can be made in the clinical trial process. This questionnaire is not meant to collect data about the subject's disease, symptoms or adverse events, and therefore will not be considered trial data.

9 Study discontinuation and completion

9.1 Discontinuation

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

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

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

9.1.1 Discontinuation of study treatment

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

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

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy (see Section 8.4.3 and Section 10.1.4)
- Use of prohibited treatment (see Section 6.2.2)
- Any situation in which study participation might result in a safety risk to the subject
- Subject develops a retinal vasculitis and/or a retinal vascular occlusion Unsatisfactory therapeutic effect

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

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2). Where possible, they should return for the assessments indicated in the Assessment Schedule (Table 8-1). If they fail to return for these assessments

for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section (Section 9.1.3). This contact should preferably be done according to the study visit schedule.

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

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

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

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

9.1.1.1 Replacement policy

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

9.1.2 Withdrawal of informed consent

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

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

and

- No longer wishes to receive study treatment

and

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

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

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

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

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

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

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

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

9.1.3 Lost to follow-up

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

9.1.4 Early study termination by the sponsor

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

9.2 Study completion and post-study treatment

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

All randomized and / or treated subjects should have a safety follow-up call conducted approximately 30 days after last administration of study treatment, unless they have completed the EOS visit at least 6 weeks after the last treatment administration. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the subject should be recorded in the source documentation.

After study completion, the subject may receive standard of care or other treatments, at the discretion of the investigator and / or referring physician, if needed.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

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

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

1. The severity grade:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment (e.g. study drug, the intravitreal injection procedure, or laser procedure). If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the study treatment, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes an SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - No action taken (e.g. further observation only)
   - Study treatment interrupted/withdrawn
   - Concomitant medication or non-drug therapy given

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

6. its outcome
   - not recovered / not resolved;
   - recovered / resolved;
   - recovered / resolved with sequelae;
   - fatal;
   - unknown.

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

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

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

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

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

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

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

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity

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

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

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

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

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

10.1.3 SAE reporting

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

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

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office & Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for

health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

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

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

10.1.4 Pregnancy reporting

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

Pregnancy should be recorded and reported by the investigator to the Novartis CMO & PS Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to brolucizumab (investigational treatment) with any pregnancy outcome.

Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

Table 10-1 Guidance for capturing the study treatment errors

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

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

10.2 Additional Safety Monitoring

Not applicable.

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

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

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis. CFPs, FAs, and OCT images will be processed centrally by the CRC and the results will be sent electronically to Novartis. COA data will be processed centrally by designated vendors and the results will be sent electronically to Novartis. The Data management staff will review data received from the CRC, central lab, and COA (except Trial Feedback Questionnaire) vendors. Data Review will be done for data structure and data completeness/accuracy as defined in Vendor Data Transfer Specifications.

Randomization codes and data about all study treatments dispensed to the subject will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

The occurrence of relevant protocol deviations will be determined prior to the Week 54 Database Lock and again prior to the final Database Lock. Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be

locked and the treatment codes will be unmasked and made available for data analysis. However, masking to the original treatment assignment will be maintained at the site level i.e., BCVA [redacted]) after the Week 54 Database Lock until the end of the study (see Section 6.4). Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis (or designated CRO) representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality / integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis (or designated CRO) Clinical Research Associates organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

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

12 Data analysis and statistical methods

The database including all Week 54 data will be locked once all initially planned subjects have completed the Week 54 visit or terminated the study prior to Week 54. The primary analysis based on Week 54 data, will be derived from this database. All subjects still in the study beyond Week 54 will continue to receive study treatment as scheduled through the planned study duration. The analysis of the data collected after the Week 54 visit will be performed once all subjects complete the EOS visit or discontinue from the study.

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

median, quartiles, minimum, and maximum. For categorical variables, these will generally include: n, frequency and percentage in each category. Further technical details and discussions of the statistical considerations will be provided in the Statistical Analysis Plan (SAP).

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

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

12.1 Analysis sets

The **All-Enrolled Set** includes all subjects who have signed informed consent and are assigned subject numbers.

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

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

The **Safety Analysis Set** (SAF) includes all subjects who receive at least one study treatment. Subjects in the SAF will be analyzed according to the actual study treatment they received, where treatment received is defined as the randomized/assigned treatment if the subject took at least one dose of that treatment, or the first treatment received if the randomized/assigned treatment was never received.

The **Per Protocol Set** (PPS) is a subset of the FAS and will exclude or censor data from subjects with important protocol deviations (PDs) and analysis restrictions (ARs) that are expected to majorly affect the validity of the assessment of efficacy at Week 54 .

Before the Week 54 database lock the relevant protocol deviations will be identified at the subject level in the database. Censoring applied in relation to specific PDs and ARs will be specified as well.

12.2 Subject demographics and other baseline characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics for the FAS by treatment arm and overall. Relevant medical history and current medical conditions will be listed for ocular and non-ocular events. Other relevant baseline information will be listed and summarized with descriptive statistics as appropriate.

12.3 Treatments

Descriptive summary statistics for exposure to study treatment will be provided for the SAF.

Ocular and non-ocular prior and concomitant medications will be listed for each treatment arm. Ocular medications will be listed for the study eye and the fellow eye separately.

Anti-VEGF medications will be summarized by ATC class and preferred term for systemic route, the study eye, and the fellow eye separately.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The primary endpoint is the change from Baseline in BCVA at Week 54. BCVA is defined in Section 8.3.1.

The key secondary endpoints are the proportion of subjects with no PDR in the study eye at Week 54, and the proportion of subjects with center-involved DME in the study eye up to Week 54. The endpoints are defined as follows:

- The event "no PDR" is defined as a DRSS score < 61. The DRSS score will be assessed by the CRC using 7-field CFP images.
- Subjects that have at least one center-involved DME event in the study eye after Baseline will be classified as with center-involved DME. Center-involved DME will be defined according to CRC evaluation of predefined anatomical parameters.

All endpoints are defined with respect to the study eye. The different estimands of interest for this study are detailed in Table 12-1.

12.4.2 Statistical model, hypothesis, and method of analysis

12.4.2.1 Analysis of change from baseline in BCVA at Week 54

The objective related to the primary endpoint is to demonstrate non-inferiority of brolucizumab versus PRP with respect to the change from Baseline in BCVA at Week 54, assuming a non-inferiority margin of 4 ETDRS letters.

Let:

B = Brolucizumab 6 mg

P = PRP

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

H_{01}: $\mu_B - \mu_P \leq -4$ letters versus H_{A1}: $\mu_B - \mu_P > -4$ letters

where μ_B and μ_P are the corresponding unknown true mean changes from Baseline in BCVA at Week 54 in the brolucizumab and PRP arms, respectively.

The primary estimand associated with the above hypotheses is defined as the between-treatment difference in change from Baseline in BCVA at Week 54, excluding the confounding effect of alternative DR/DME treatment(s) applied to the study eye (e.g. alternative anti-VEGF treatments, as further detailed in Section 6.2.2 and in the SAP). The analysis set for the primary estimand will be the FAS as described in Table 12-1.

Based on the FAS, the above hypotheses will be tested via an analysis of covariance (ANCOVA) model. The model will include treatment, Baseline DR Severity category (Moderate PDR or better, High-risk PDR or worse), age category (< 55, ≥ 55) and region as factors, with Baseline BCVA as a covariate.

The two-sided 95% confidence interval (CI) for the least square mean difference (brolucizumab - PRP) at Week 54 will be presented. Non-inferiority will be considered established if the lower limit of the corresponding 95% CI is greater than -4 letters.

The following superiority hypotheses for the primary endpoint may be further evaluated after non-inferiority for the primary endpoint and superiority for the first key secondary endpoint are established:

H_{02}: $\mu_B - \mu_P \leq 0$ letters versus H_{A2}: $\mu_B - \mu_P > 0$ letters.

Superiority in BCVA will be considered established if the lower limit of the corresponding 95% CI from the same ANCOVA model used to assess for non-inferiority analysis is greater than 0 letters.

Multiplicity control of primary endpoint and key secondary endpoints is discussed in Section 12.4.2.4.

12.4.2.2 Analysis of PDR status at Week 54

The objective related to this key secondary endpoint is to demonstrate superiority of brolucizumab versus PRP with respect to increasing the proportion of subjects with no PDR at Week 54. The following hypotheses are defined:

H_{03}: $\pi_B - \pi_P \leq 0$ versus H_{A3}: $\pi_B - \pi_P > 0$

where π_B and π_P are the corresponding unknown true proportions of subjects with no PDR in the study eye at Week 54 in the brolucizumab and PRP arms, respectively.

The above hypotheses will be tested via Cochran-Mantel-Haenszel (CMH) test at a one-sided significance level of 0.025 using the FAS, after non-inferiority for the primary endpoint is established. The CMH test will include baseline DR Severity category (Moderate PDR or better, High-risk PDR or worse), age category (< 55, ≥ 55) and region as adjusting factors. Multiplicity control is discussed in Section 12.4.2.4.

The difference in proportion between treatment arms will be estimated using the weighted average of the proportion differences over adjusting factors using the Mantel-Haenszel weights. Adjusting factors will be the same as for the CMH test.

12.4.2.3 Analysis of emergent center-involved DME up to Week 54

The objective related to this key secondary endpoint is to demonstrate superiority of brolucizumab versus PRP with respect to reducing the proportion of subjects with center-involved DME up to Week 54. The following hypotheses are defined:

H_{04}: $\lambda_B - \lambda_P \geq 0$ versus H_{A4}: $\lambda_B - \lambda_P < 0$

where λ_B and λ_P are the corresponding unknown true proportions of subjects with at least one center-involved DME event in the study eye up to Week 54 in the brolucizumab and PRP arms, respectively.

The above hypotheses will be tested via CMH test at a one-sided significance level of 0.025 using the FAS. The CMH test will include the same adjusting factors as for the first key secondary endpoint described in Section 12.4.2.2. Multiplicity control is discussed later in Section 12.4.2.4.

The difference in proportions between treatment arms will be estimated using the weighted average of the proportion differences over adjusting factors using the Mantel-Haenszel weights. Adjusting factors will be the same as for the CMH test.

Kaplan-Meier estimates of the proportions of subjects with center-involved DME over time and at Week 54 will also be presented for each treatment arm.

12.4.2.4 Multiplicity control of primary and key secondary endpoints

To control the overall type I error rate at a one-sided 0.025 level, testing of non-inferiority for the primary endpoint, superiority for the primary endpoint and superiority for the key secondary endpoints will be conducted in a hierarchical sequence as described below:

1. Non-inferiority for primary endpoint (BCVA): H_{01} versus H_{A1}
2. Superiority for key secondary endpoint 1 (PDR): H_{03} versus H_{A3}
3. Superiority for primary endpoint (BCVA): H_{02} versus H_{A2}
4. Superiority for key secondary endpoint 2 (center-involved DME): H_{04} versus H_{A4}

12.4.3 Handling of missing values/censoring/discontinuations

The primary estimand and other supplementary estimands of interest are noted in Table 12-1 below together with their key attributes, including the handling of intercurrent events associated with the intake of alternative treatments for DR/DME in the study eye. The estimands outlined below will be discussed in further detail in the SAP, including the handling of additional intercurrent events of interest.

Table 12-1 Primary, key secondary and supplementary estimands

Endpoint	Estimand	Estimand definition	Analysis set	Data included in analysis[1]	Statistical methods (including missing data strategy)
BCVA	Primary estimand	Difference in change from Baseline in BCVA at Week 54 excluding the effect of alternative DR/DME treatment(s)	FAS	All data captured until the start of alternative DR/DME treatment(s) will be included	ANCOVA model as specified in Section 12. 4.2.1. Last observation carried forward (LOC F) imputation / replacement for missing data (e.g data unavailable due to lost to follow-up) /censored data (e.g. data unavailable due to use of alternative anti-VEGF).
BCVA	Sensitivity to primary estimand	Same as above	Same as above	Same as above	ANCOVA model as per the primary estimand and alternative methods of handling missing or confounded data.
BCVA	Supplementar y estimand A0	Difference in change from Baseline in BCVA at Week 54 regardless of alternative DR/DME treatment(s)	FAS	All data captured will be included	ANCOVA model as per the primary estimand. LOCF imputation for missing data.

Endpoint	Estimand	Estimand definition	Analysis set	Data included in analysis[1]	Statistical methods (including missing data strategy)
BCVA	Supplementary estimand B0	Difference in change from Baseline in BCVA at Week 54 excluding the effect of alternative DR/DME medication(s) and important protocol deviations/ARs as per the definition of the PPS	PPS	All data captured until the start of alternative DR/DME treatment(s) will be included	ANCOVA model as per the primary estimand. LOCF imputation / replacement for missing /censored data.
DRSS	Key secondary estimand 1	Difference in proportions of subjects with no PDR at Week 54 excluding the effect of alternative DR/DME treatment(s)	FAS	All data captured until the start of alternative DR/DME treatment(s) will be included	CMH test and weighted proportion difference as specified in Section 12.4.2.2 LOCF imputation/ replacement for missing / censored data
DRSS	Sensitivity to key secondary estimand 1	Same as above	Same as above	Same as above	CMH test and weighted proportion difference with alternative methods of handling missing or confounded data.
DRSS	Supplementary estimand A1	Difference in proportions of subjects with no PDR at Week 54 regardless of alternative DR/DME treatment(s)	FAS	All data captured will be included	CMH test and weighted proportion difference as specified in Section 12.4.2.2. LOCF imputation for missing data.

Endpoint	Estimand	Estimand definition	Analysis set	Data included in analysis[1]	Statistical methods (including missing data strategy)
Center-involved DME	Key secondary estimand 2	Difference in proportions of subjects with center-involved DME up to Week 54.	FAS	All data captured will be included Subjects who receive alternative DME treatment(s) will be classified as with center-involved DME.	CMH test and weighted proportion difference as specified in Section 12.4.2.3.

[1] Other intercurrent events of interest may be defined in the SAP.

12.4.4 Sensitivity and supplementary analyses

Sensitivity and supplementary analyses for the primary endpoint and key secondary endpoints are specified in Table 12-1.

The following subgroup analyses will be explored using the FAS for primary endpoint:

- Age category
- Sex
- Baseline BCVA categories
- Diabetes type
- Baseline HbA1c categories
- Baseline DR severity categories
- Region

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

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoints

All endpoints related to secondary objectives are defined with respect to the study eye.

Secondary efficacy endpoints related to diabetic retinopathy status:

- Proportion of subjects with at least 2 steps improvement from Baseline in ETDRS DRSS score at Week 54 and Week 96
- Proportion of subjects with at least 3 steps improvement from Baseline in ETDRS DRSS score at Week 54 and Week 96
- Proportion of subjects with no PDR at Week 96

Secondary efficacy endpoints related to visual acuity:

- Area under the curve in change from Baseline in BCVA up to Week 54 and Week 96

Secondary efficacy endpoints related to ocular complications:

- Proportion of subjects developing vision-threatening complications associated with DR up to Week 54 and Week 96
- Proportion of subjects with center-involved DME up to Week 96

Details and other additional analyses (e.g. efficacy presentation by visit) for the secondary endpoints will be described in SAP.

12.5.2 Safety endpoints

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

- Adverse events
- IOP
- Vital signs
- Laboratory results

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

Adverse events

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

- by treatment, primary system organ class and preferred term
- by treatment, primary system organ class, preferred term and maximum severity

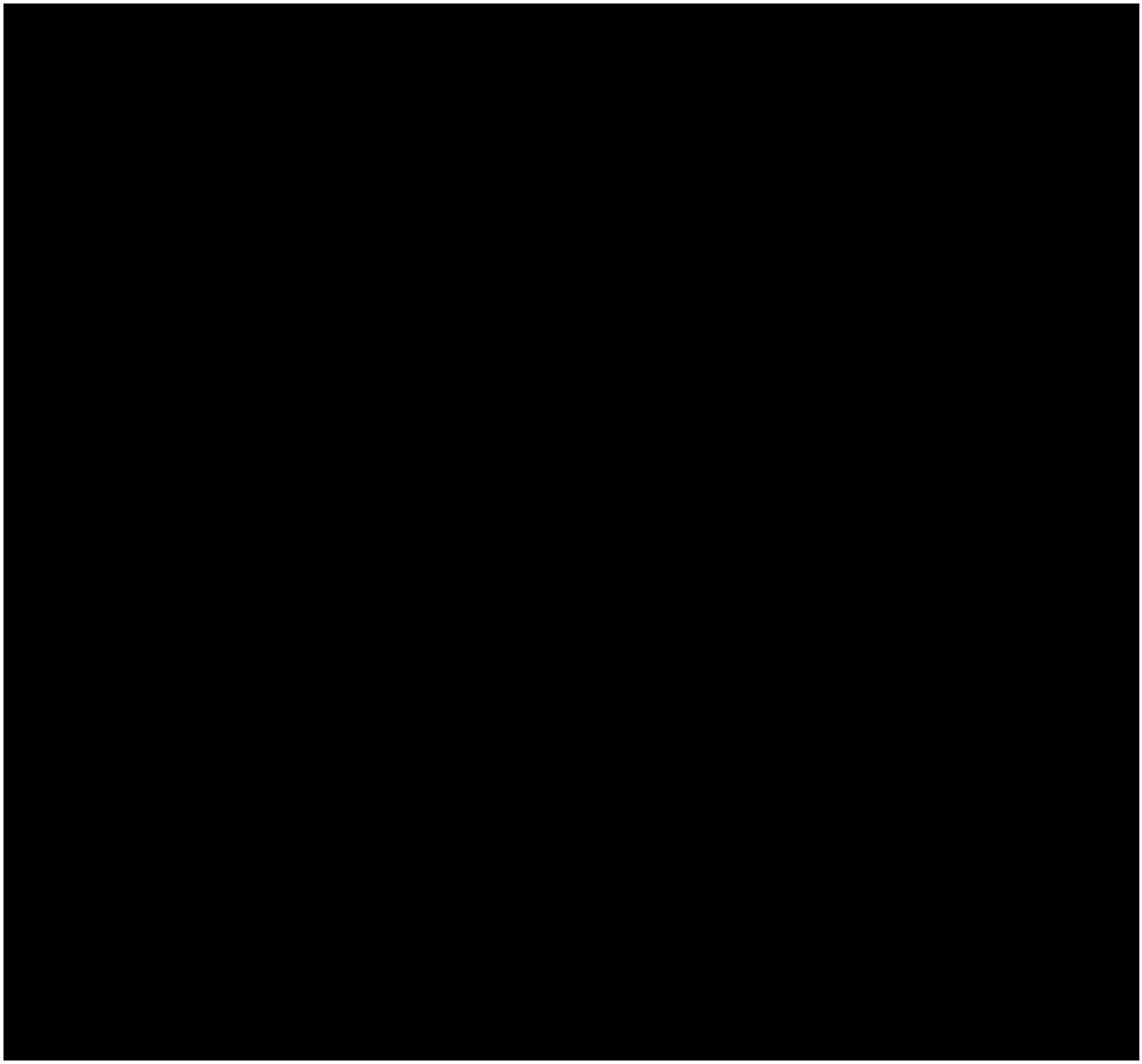
Separate summaries will be provided for study treatment related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation of study treatment or the study. In addition, a separate summary for death including on-treatment and post-treatment deaths will be provided. Separate presentations will be provided related to ocular events in the study eye and fellow eye and non-ocular events. Additional summaries will be provided by severity and causality (separately assessed for the treatment procedure and the drug).

Subject listings of all adverse events will be provided. Deaths and other serious or clinically significant non-fatal adverse events will be listed separately. A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

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

IOP, vital signs and clinical laboratory evaluations

Pre-treatment and post-treatment IOP measurements will be presented descriptively . Vital signs and laboratory results will be summarized descriptively.



12.7 Interim analyses

The database including all Week 54 data will be locked once all subjects have completed the Week 54 visit or terminated the study prior to Week 54. The primary analysis based on Week 54 data will be derived from this database. Formal testing of the primary endpoint and key secondary endpoints will be performed at the primary analysis time point.

12.8 Sample size calculation

A sample size of 300 subjects per arm will allow the assessment of brolucizumab 6 mg versus PRP for non-inferiority with respect to the primary endpoint and superiority with respect to the key secondary endpoints.

To account for a drop-out rate of 15%, a total of approximately 706 (353 per arm) subjects will need to be randomized.

12.8.1 Primary endpoint(s)

A sample size of 300 subjects per arm will allow assessment of non-inferiority (using a non-inferiority margin of 4 ETDRS letters) of brolucizumab 6 mg versus PRP with respect to the change from Baseline in BCVA at Week 54. Assuming that the BCVA changes follow a normal distribution with equal means between treatments, and a common standard deviation of 10 letters, for a one-sided alpha level of 0.025, there is >99% power to reject the null hypothesis that brolucizumab 6 mg is inferior to PRP. Sensitivity to the assumptions used to assess power for both non-inferiority and superiority testing is shown in Table 12-2.

Table 12-2 Power for primary endpoint

True treatment difference for brolucizumab vs PRP (letters)	SD (letters)	Power for non-inferiority test	Power for superiority test
0	10	> 99%	2.5%
0	13	96%	2.5%
3	10	> 99%	96%
3	13	> 99%	81%
5	10	> 99%	> 99%
5	13	> 99%	> 99%

12.8.2 Secondary endpoint(s)

A sample size of 300 subjects per arm will allow assessment of superiority of brolucizumab 6 mg versus PRP with respect to increasing the proportion of subjects with no PDR at Week 54. Assuming that the proportion of such events in the PRP arm is 15%, and the difference in proportion is 11% (i.e. the proportion in the brolucizumab arm is 26%), for a one-sided alpha level of 0.025, nominally there is 90% power to reject the null hypothesis that brolucizumab 6 mg is not superior to PRP.

A sample size of 300 subjects per arm will allow assessment of superiority of brolucizumab 6 mg versus PRP with respect to reducing the proportion of subjects with central-involved DME up to Week 54. Assuming that the proportion of such events in the PRP arm is 16%, and the difference in proportion is 9% (i.e. the proportion in the brolucizumab arm is 7%), for a one-sided alpha level of 0.025, nominally there is 92% power to reject the null hypothesis that brolucizumab 6 mg is not superior to PRP.

The above calculations use the normal approximation for the binomial distribution with a continuity correction.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

14.1 Protocol amendments

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

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

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

15 References

References are available upon request

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16 Appendices

Not applicable.