NOVARTIS

Medical Division

Ranibizumab/Lucentis®

Clinical Trial Protocol [CRFB002EJP09 / NCT02953938]

A 12-month, phase IV, open-label, randomiZed, actIve controlled, 2-arm, multiPle-center study Assessing the efficacy and safety of intravitreal raNibizumab combined with Grid&Direct short pulse laser photocoagulation versus a PRN Ranibizumab monotherapy in Japanese patients with macUlar edema secondary to branch retinal vein occlusion (BRVO): ZIPANGU study

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List of abbreviations

AE	Adverse event
AMD	Age-related macular degeneration
BCVA	Best-corrected visual acuity
BRB	Blood retinal barrier
BRVO	Branch retinal vein occlusion
BSL	Baseline
BQA	Biostatistics Quality Assurance
CF	Color fundus photography
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organization
CRVO	Central retinal vein occlusion
CSFT	Central subfield thickness
DAR	Drug administration record
DME	Diabetic macular edema
DS&E	Drug Safety and Epidemiology
eCRF	electronic Case Report Form
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
[redacted]	[redacted]
FAS	Full Analysis Set
IgG	Immunoglobulin G
IOP	Intraocular pressure
LOCF	Last observation carried forward
[redacted]	[redacted]
ME	Macular edema
MedDRA	Medical dictionary for regulatory activities
[redacted]	[redacted]
PFS	Prefilled syringes
PMDA	Pharmaceutical and Medical Devices Agency
PMS	Post marketing surveillance
PPS	Per Protocol Set
PRN	Pro re nata
[redacted]	[redacted]
RVO	Retinal vein occlusion
SAE	Serious adverse event
VA	Visual acuity
VEGF	Vascular endothelial growth factor
wAMD	wet age-related macular degeneration
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Decimal VA	Visual acuity expressed as a decimal. Best-corrected visual acuity will be assessed in a sitting position using Decimal VA testing charts at an initial testing distance of 5 meters at every visit.
Screening	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Enrollment	Point/time of patients to be randomized into the study; the point at which screening is completed and informed consent has been taken (prior to starting any of the procedures described in the protocol).
ETDRS (Early Treatment Diabetic Retinopathy Study)	A National Eye Institute-supported, multicenter, randomized clinical trial designed to evaluate photocoagulation and aspirin treatment in the management of patients with non-proliferative or early proliferative diabetic retinopathy.
Fellow treated eye	The fellow treated eye is the non-study eye treated with ranibizumab for visual impairment due to macular edema secondary to retinal vein occlusion.
Fellow untreated eye	The fellow eye that has not been treated with ranibizumab. The fellow untreated eye is the non-study eye until treated with ranibizumab for visual impairment due to macular edema secondary to retinal vein occlusion. After treatment, it becomes the fellow treated eye.
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
[redacted]	
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as Screening, Baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study before the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later.
Study drug	Any drug administered to the patient or therapeutic procedure as part of the required study procedures; includes investigational drug and any control drugs or therapeutic procedure.

Study eye	The study eye is the eye selected by the investigator at Baseline (according to the protocol) to receive the study treatment.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.

Amendment 2

Amendment rationale

The purpose of this amendment is to allow temporary use of phenothiazines for common cold and upper respiratory infection as mentioned in the below section.

Study CRFB002EJP09 was initiated on 15-Dec-2016 and enrollment is currently ongoing. As of 21-Jan-2018, 59 patients have been randomized in the study. This amendment will not impact the study population, drug administration, objectives, endpoints, or study results.

Changes to the protocol

Phenothiazine was included as prohibited medication in the final study protocol, as this medication is known to be toxic to the lens, retina or optic nerve. However, the symptoms are generally thought to occur with long-term use. Therefore, it is reasonable to allow the temporary use of phenothiazine with common cold and upper respiratory infection, which has been clarified in this amended version.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using red underlined for insertions. Appropriate changes are made in Section 4.2, Section 5.5.8, and Table 5-1.

A copy of this amended protocol will be used for Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) submissions.

The health Authority (HA) submission/notification will be assessed by Post-marketing Study Protocol Evaluation Committee (PSPEC) considering local HA requirements.

The changes herein do not affect the trial specific model ICF.

Amendment 1

Amendment rationale

The purpose of this amendment is to update and revise clinical chemistry parameters as mentioned in the below section.

This study is in the start-up phase and not enrolled/screened any patients at the time of this amendment. This amendment will not impact the study population, drug administration, objectives, endpoints, or study results.

Changes to the protocol

The clinical chemistry parameters VEGF-A, VEGF-B, and PlGF are replaced with VEGF in Table 6-1 footnote (# b) and Section 6.5.4.2.

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

A copy of this amended protocol will be used for Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) submissions.

The health Authority (HA) submission/notification will be assessed by Post-marketing Study Protocol Evaluation Committee (PSPEC) considering local HA requirements.

The changes herein do NOT affect the trial specific model ICF.

Protocol summary

Protocol number	CRFB002EJP09
Title	A 12-month, phase IV, open-label, randomized, active controlled, 2-arm, multicenter study assessing the efficacy and safety of intravitreal Ranibizumab combined with Grid&Direct short pulse laser photocoagulation versus a PRN Ranibizumab monotherapy in Japanese patients with macular edema secondary to branch retinal vein occlusion (BRVO).
Brief title	Study to show a superior benefit in terms of reduction of ranibizumab injections in patients receiving ranibizumab plus laser photocoagulation combination therapy without loss of efficacy and safety.
Sponsor and Clinical Phase	Novartis Pharma K.K (Phase IV)
Investigation type	Drug, Laser photocoagulation
Study type	Interventional
Purpose and rationale	This study is designed to evaluate comparative efficacy and safety data as well as injection frequency data for ranibizumab using a pro re nata (PRN) dosing, administered with Grid&Direct short pulse laser photocoagulation versus ranibizumab monotherapy using the same dosing up to Month 12 in Japanese patients with visual impairment due to macular edema (ME) secondary to BRVO.
Primary Objective	To demonstrate that PRN regimen (PRN, according to the Japanese label of ranibizumab) of ranibizumab combined with Grid&Direct short pulse laser photocoagulation reduces the burden of frequent ranibizumab injections as compared to ranibizumab monotherapy. The primary objective will be assessed by the difference in the mean number of ranibizumab injections applied up to Month 11 between the 2 treatment arms.
Secondary Objectives	The secondary objectives of this study are as follows: • To evaluate the efficacy of each arm as assessed by Best-corrected visual acuity (BCVA) • To evaluate the efficacy of each arm as assessed by center subfield thickness (CSFT) • To evaluate the safety of ranibizumab monotherapy and ranibizumab combined with Grid&Direct short pulse laser photocoagulation therapy in Japanese patients as assessed by the type, frequency, and severity of ocular and non-ocular adverse events (AEs) from Baseline (Day 1) to Month 12
Study design	This is a Phase IV, randomized, open-label, active-controlled, 2-arm, multicenter study. Patients will be randomized in a 1:1 ratio to 1 of the 2 treatment arms; i.e. Arm 1 ranibizumab monotherapy, Arm 2 ranibizumab with Grid&Direct short pulse laser photocoagulation combination therapy. In addition to screening and Baseline (Day 1), there will be monthly visits from Month 1 to Month 12. There will be 3 periods in this study: Screening Period, Treatment Period and Follow-up Period.
Population	This study will include male and female patients (≥20 years old) diagnosed

	with visual impairment due to ME secondary to BRVO. Assuming an approximate 20% drop out rate, approximately 70 patients will need to be screened to have at least 56 patients found eligible and commencing treatment in the trial.
Key Inclusion criteria	Key inclusion criteria: • Written informed consent must be obtained before any assessment is performed. • Male or female patients ≥ 20 years of age. • Diagnosis of visual impairment exclusively due to ME secondary to BRVO. • Best-corrected visual acuity score at Screening and Baseline (Day 1) between 0.5 and 0.05 decimal (i.e., between 73 and 19 letters in Early Treatment Diabetic Retinopathy Study (ETDRS) testing) with Landolt C charts inclusively (i.e., approximate logarithm of the minimum angle of resolution (logMAR) units of 0.3 to 1.30). • At Baseline (Day1), a maximum BCVA gain of 0.2 units logMAR conversion inclusively from screening is allowed as long as the BCVA score does not exceed the upper limit of 0.3 units logMAR. • Increased central subfoveal thickness (> 300 µm at Baseline (Day 1) when measured by SD-OCT). • Duration of vision deterioration ≤6 months (determined by self-report) at screening.
Key Exclusion criteria	Key exclusion criteria: • Pregnant or nursing (lactating) women. • Stroke or myocardial infarction less than 3 months before Screening. • Uncontrolled blood pressure defined as systolic value of >160 mm Hg or diastolic value of >100 mm Hg at Screening or Baseline (Day 1). Antihypertensive treatment can be initiated and must be taken for at least 30 days after which the patient can be assessed for study eligibility a second time. • Any active periocular or ocular infection or inflammation (e.g., blepharitis, conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) at the time of Screening or Baseline (Day 1) in either eye. • Uncontrolled glaucoma (intraocular pressure (IOP) ≥30 mm Hg on medication or according to investigator's judgment) at the time of Screening or Baseline (Day 1) or diagnosed within 6 months before Baseline (Day 1) in either eye. • Neovascularization of the iris or neovascular glaucoma in the study eye. • Use of any systemic anti-VEGF drugs within 6 months before Baseline (Day1) (e.g., sorafenib (Nexavar®), sunitinib (Sutent®), bevacizumab (Avastin®), ziv-aflibercept (ZALTRAP®)). • Treatment (or anticipated treatment in the fellow eye for non-RVO indications during the study) with any anti-angiogenic drugs (including any anti-VEGF agents) within 3 months before Baseline (Day1) in fellow eye or before Baseline (Day 1) in the study eye (e.g., pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®), and aflibercept (EYLEA®)). • Panretinal laser photocoagulation within 1 month before Baseline (Day1) or anticipated or scheduled within the next 12 months (Study periods) following Baseline (Day1) in the study eye. • Any giving of focal or grid laser photocoagulation before Baseline

	(Day1) in the study eye. • Use of intra- or periocular corticosteroids (including sub-Tenon) within 3 months before Screening in the study eye. • Any use of intraocular corticosteroid implants (e.g., dexamethasone (Ozurdex®), fluocinolone acetonide (Iluvien®)) in the study eye.
Study treatment	The investigational treatment used in this study is 0.5 mg ranibizumab applied PRN as intravitreal injection of 0.05 mL, with or without Grid&Direct short pulse laser photocoagulation treatment. **Arm 1:** Patients will start study treatment with ranibizumab on Baseline (Day 1) and having reached stable status (i.e., as per satisfied stabilization criteria as mentioned below) ranibizumab treatment may be temporarily discontinued. Patients should be monitored monthly for visual acuity (VA) and disease activity and ranibizumab injections will be given using PRN regimen. The minimum gap required between 2 injections of ranibizumab will be 30 ± 7 days. **Arm 2:** Patients will start study treatment with ranibizumab on Baseline (Day 1) and having reached stable status, ranibizumab treatment may be temporarily discontinued. Patients should be monitored monthly for VA and disease activity. Ranibizumab injections are given using PRN regimen. Grid&Direct short pulse laser photocoagulation treatment must be applied to the target within vascular arcades as soon as indicated. Following the complete application of the initial laser treatment, further laser treatment can be applied in the presence of ME due to BRVO at the investigator's discretion at minimal intervals of 30 ±7 days. **PRN (re-treatment/stabilization) criteria:** After Baseline (Day 1) visit, if any one or more criteria from the below list is met, the patient should be administrated ranibizumab treatment **(re-treatment criteria)** 1. Center subfield thickness ≥ 300 µm 2. An increase of CSFT ≥ 20% compare to minimum value during the treatment period. 3. The loss of VA due to disease activity secondary to BRVO (disease activity includes ME, intra-retinal cysts, sub-retinal fluid, macular hemorrhage etc.). This criteria is based on Investigator's judgement including the following scenarios: • The VA is expected to improve if the existing disease activity is removed, hence investigator decides to treat with ranibizumab • The VA is expected to be decreasing because of the existing disease activity, hence investigator decides to treat with ranibizumab • The VA has decreased as compared to the previous month because of the appearance of disease activity, hence investigator decides to treat with ranibizumab (This criterion is to restart ranibizumab after interruption) If all the above criteria are not satisfied, then the patient shouldn't be treated with ranibizumab **(stabilization criteria),** i.e., • Center subfield thickness < 300 µm • An increase of CSFT < 20% compare to minimum value during the treatment period • Visual acuity is stable and the disease activity is in the state

	of not affecting VA (based on investigator's judgement)
Efficacy assessments	Efficacy assessments will include: • Decimal and ETDRS Best-Corrected Visual Acuity (BCVA). • Color fundus photography (CF) [redacted]. [redacted]. [redacted].
Key safety assessments	Safety assessments will include the following evaluations: AEs, ophthalmic examinations, vital signs, laboratory evaluations, and pregnancy assessments.
Other assessments	No other assessments will be performed.
Data analysis	The primary variable is the mean number of ranibizumab injections applied up to Month 11 between the 2 treatment arms in patients with visual impairment due to ME secondary to BRVO. The statistical hypothesis testing of the number of ranibizumab treatments will be based on a stratified Cochran-Mantel-Haenszel (CMH) test. Stratification will be done based on categories of baseline decimal VA (<0.3, or $\geq$ 0.3). Difference of mean number of injections, 95% confidence interval (CI) of difference and one-sided p-value of the CMH test will be reported. No imputation is required for the primary endpoint which is number of ranibizumab injections, based on PRN regimen.
Key words	Macular edema, Branch retinal vein occlusion, best-corrected visual acuity, central subfield thickness, pro re nata, ranibizumab, laser photocoagulation.

1 Introduction

1.1 Background

Retinal vein occlusion (RVO) is the second most common retinal vascular permeability disorder after diabetic retinopathy and it is a significant cause of visual handicap (Wong and Scott 2010). According to the Hisayama study which is prospective large-scale cohort study in Japan, the prevalence of RVO was 2.1% (2.0% for branch RVO (BRVO) and 0.2% for central RVO (CRVO)) (Yasuda et al. 2010), and the 9-year incidence of RVO was 3.0% (2.7% for BRVO and 0.3% for CRVO) (Arakawa et al. 2011) in Japan. Macular edema (ME) is the major complication causing the central vision loss in patients with BRVO or CRVO. ME is characterized by swelling of the central part of the retina that mediates high-resolution vision. When the area of swelling is located within one disc diameter (approximately 1500 μm) from the center of the fovea, vision is likely to be impaired.

ME arises from breakdown of the blood retinal barrier (BRB), resulting in the pathologic accumulation of both fluid and macromolecules in the retina. The breakdown of the BRB may be mediated in part by vascular endothelial growth factor (VEGF). It has been demonstrated in an *in vivo* model that VEGF can increase vascular permeability (Aiello et al. 1994) and that intraocular levels of VEGF in the eyes with RVO have been elevated (Campochiaro et al. 2009).

Ranibizumab (Lucentis®) is a recombinant humanized Immunoglobulin G1 (IgG1) κ isotype monoclonal antibody fragment (Fab) that selectively binds VEGF-A. Ranibizumab (intravitreal injections of 0.5 mg) is approved for the treatment of ME due to RVO in more than 100 countries worldwide, including Japan. Based on the 6-month results of 2 phase III, randomized, double-masked, 12-month controlled studies – BRAVO study for BRVO and CRUISE study for CRVO (Brown et al. 2010, Campochiaro et al. 2010), ranibizumab (0.5 mg) was approved in June 2010 by the United States Food and Drug Administration, and in May 2011 in the European Union for the treatment of ME secondary to RVO. Furthermore, based on the 3-month results of study RFB002E2301, a phase III, open-label, single arm, multicenter study for Japanese patients, ranibizumab (0.5 mg) was approved in Aug 2013 by the Ministry of Health, Labour and Welfare in Japan for the treatment of ME due to RVO.

In BRAVO study, monthly treatment with both 0.3 mg and 0.5 mg ranibizumab induced rapid best-corrected visual acuity (BCVA) improvement within the first week followed by continued gradual improvement up to Month 6. The visual acuity (VA) gain was maintained on average until Month 12 by the pro re nata (PRN) treatment administered as from Month 6. The observed safety profile of ranibizumab was consistent with the previously established safety profile of ranibizumab in wet age-related macular degeneration (wAMD) patients and no new ranibizumab or intravitreal injection procedure related adverse events (AEs)/risks were identified in RVO patients (Campochiaro et al. 2010). In Japan, the phase III study (CRFB002E2301) confirmed these findings in Japanese patients (Kamei et al. 2016).

Recently BRIGHTER study (phase IIIb study for BRVO using ranibizumab) has confirmed the efficacy and safety for 24 months using VA stability-guided PRN dosing for 0.5 mg ranibizumab (as approved in the EU SmPC) and each subgroup analyses (e.g. macular ischemia, duration of vision deterioration by BRVO and baseline VA) also confirmed that

clinically relevant increase in VA was observed irrespective of the differences of these factors (Tadayoni et al. 2016). In addition to these studies, VIBRANT study (aflibercept phase III study for BRVO) and MARVEL study (ranibizumab versus bevacizumab using PRN dosing) confirmed the efficacy and safety of anti-VEGF treatment for BRVO (Clark et al. 2016, Narayanan R et al. 2015).

Based on the result of these studies, anti-VEGF treatment is recommended as standard of care in patient with BRVO in overseas guidelines (Pulido et al. 2016, The ROYAL COLLEGE of OPHTHLMOLOGIST. 2015), and it has established as the standard treatment in patients with BRVO in Japan.

However there are cases of repeated recurrences and poor responders to anti-VEGF therapy. In BRIGHTER study, more than 40% of patients needed more than twelve ranibizumab injections in ranibizumab monotherapy arm. In addition especially in Japan, due to high co-pay financial burden for patients (especially younger patients with RVO and diabetic macular edema (DME)), Japanese physicians and patients demand the way to reduce the number of anti-VEGF drug injections while maintaining efficacy. Hence it needs to be further examined how to deal with those patients that requires many anti-VEGF injections.

Before anti-VEGF drugs were approved with ME secondary to BRVO, grid laser photocoagulation was the gold standard, and this exceled in maintaining VA (The Branch Vein Occlusion Study Group 1984). Therefore, medical experts expect the effect of laser photocoagulation to reduce the number of anti-VEGF injections when used in combination with anti-VEGF therapy.

A few small scale single center past studies demonstrated that laser combination therapy potentially reduced the number of anti-VEGF drug injections in BRVO (Hayashi et al. 2011, Donati et al. 2012, Farese et al. 2014, Salinas-Alaman et al. 2011, Iesato et al. 2016). Moreover, navigated laser photocoagulation (NAVILAS®) combined with ranibizumab contributed to reduce the number of ranibizumab injections in DME because of accuracy of the navigated laser system towards the pathologic area (e.g. leaking points and fluid area) (Liegl et al. 2014, Kozak et al. 2011, Neubauer et al. 2013). These results indicate that macular laser photocoagulation combined with anti-VEGF drug has a potential to reduce the number of anti-VEGF drug injections if it is used properly.

In this study, we will apply a new laser photocoagulation method, which we call Grid&Direct short pulse laser photocoagulation. Basically, the method is based on a modified Early Treatment Diabetic Retinopathy Study (ETDRS) procedure in DME. Moreover, this study will adopt a short pulse laser method to reduce the risk for retinal tissue damage (e.g. expanding atrophic creep and retinal hemorrhage). [redacted]

We expect the photocoagulation method used in this study will allow for a significant reduction of recurrences and therefore ranibizumab injections in BRVO patients. This study aims to show a superior benefit with regards to the reduction of ranibizumab injections in the laser photocoagulation combination arm without loss of efficacy and safety.

We expect that this phase IV study will further help to reduce the treatment burden for Japanese BRVO patients and will contribute to the advancement of BRVO treatment in Japan.

1.2 Purpose

The present study will generate comparative efficacy and safety data as well as injection frequency data for 0.5 mg ranibizumab using a PRN dosing as defined in the protocol (i.e., according to the Japanese label of ranibizumab), administered with Grid&Direct short pulse laser photocoagulation versus 0.5 mg ranibizumab monotherapy using the same dosing (the current standard treatment) up to Month 12 in Japanese patients with visual impairment due to ME secondary to BRVO. [redacted] The results of this study will provide 1 year safety, efficacy and injection frequency data to further guide recommendations on the use of ranibizumab with or without laser photocoagulation in BRVO.

2 Study objectives and endpoints

2.1 Primary objective

To demonstrate that PRN regimen (PRN, according to the Japanese label of ranibizumab) with 0.5 mg ranibizumab combined with Grid&Direct short pulse laser photocoagulation reduces the burden of frequent ranibizumab injections as compared to ranibizumab monotherapy. The primary objective will be assessed by the difference in the mean number of ranibizumab injections applied up to Month 11 between the 2 treatment arms.

2.2 Secondary objectives

The secondary objectives of this study are as follows:

- To evaluate the efficacy of each arms as assessed by BCVA.
- To evaluate the efficacy of each arms as assessed by center subfield thickness (CSFT).
- To evaluate the safety of ranibizumab monotherapy and ranibizumab combined with Grid&Direct short pulse laser photocoagulation therapy in Japanese patients as assessed by the type, frequency, and severity of ocular and non-ocular AEs from Baseline (Day 1) to Month 12.

3 Investigational plan

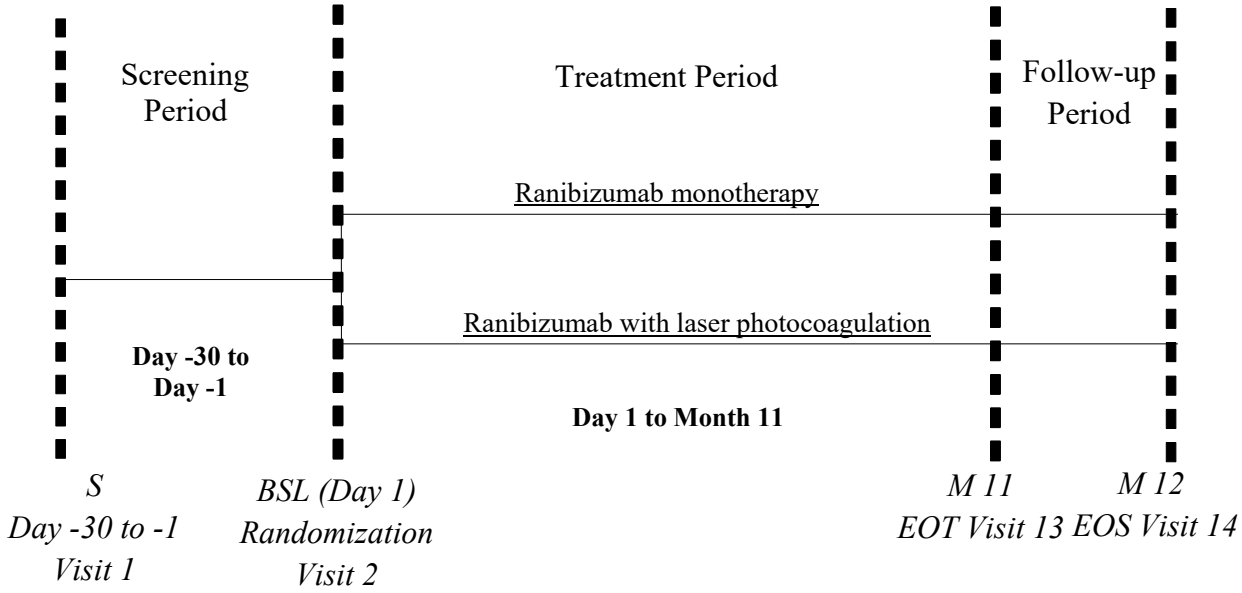
3.1 Study design

This is a phase IV, randomized, open-label, active-controlled, 2-arm, multicenter study. Patients will be randomized in a 1:1 ratio to 1 of the 2 treatment arms; i.e. Arm 1 ranibizumab monotherapy, Arm 2 ranibizumab with Grid&Direct short pulse laser photocoagulation combination therapy.

In addition to screening and Baseline (Day 1), there will be monthly visits from Month 1 to Month 12.

There will be 3 periods in this study: the Screening Period, Treatment Period and Follow-up Period (Figure 3-1).

Figure 3-1 Study design



Abbreviations: BSL= Baseline, EOT = End of Treatment Period, EOS = End of Study, S= Screening.

Screening Period: Day -30 to Day -1

Screening (Visit 1) to occur between Day -30 and Day -1 where screening assessments will be done between Day -30 and Day -4 after signing the informed consent form to check the eligibility for the study and administration of pre-ranibizumab treatment antimicrobials will occur between Day -3 to Day -1.

Treatment Period: Baseline (Day 1) to Month 11, PRN treatment with monthly monitoring

After eligibility confirmation and randomization at Baseline (Day 1), patients will receive one of the below treatment.

Arm 1 (ranibizumab monotherapy)

Patients will start study treatment on Baseline (Day 1) and receive further ranibizumab treatment using PRN regimen i.e., according to the Japanese label of ranibizumab.

Arm 2: (ranibizumab + Grid&Direct short pulse laser photocoagulation combination therapy)

Patients will start study treatment on Baseline (Day 1) and receive further ranibizumab treatment using PRN regimen i.e., according to the Japanese label of ranibizumab. The laser treatment must be given to the target within vascular arcades as soon as indicated.

The criteria for PRN of injections of ranibizumab are described in Section 5.5.4.2. Refer to Section 5.5.4 and Section 5.5.4.1 for more details on treatment administration.

Post-treatment Follow-up Period: Month 11 to Month 12

The last study assessment will be performed at Month 12, i.e., 1 month after the last possible ranibizumab injection/laser treatment in this study.

3.2 Rationale for study design

A 2-arm design is required to compare ranibizumab administered with the laser treatment to ranibizumab monotherapy. To focus on collection of additional data for ranibizumab in a PRN dosing regimen as real world treatment using mainly [redacted] guided methods in Japan and given its known efficacy profile, a 1:1 randomization scheme is considered appropriate.

An open-label study design has been chosen because masking of the laser treatment is not feasible. Laser burns are visible by fundus examination to the investigator and patients with a history of laser treatment would be able to differentiate between the past and present burns.

However, masking the treatment to the Vision Examiner who will be assessing the key secondary endpoint parameters (BCVA) has been chosen to provide as much unbiased assessment as possible. Efficacy and safety of ranibizumab applied as per the Japanese treatment recommendations will be assessed in both arms.

Ranibizumab treatment and laser photocoagulation have different modes of action that, on average, are both beneficial for VA in patients with BRVO. Laser treatment has a stabilizing effect with low average BCVA gain but infrequent treatments, while ranibizumab confers a relatively higher BCVA gain at the expense of frequent (every month) monitoring (and possibly, treatment). Thus, the combination of the 2 treatments may result in synergistic effects. For example, the lasting effect of the laser treatment may result in better maintenance of the VA gains obtained with ranibizumab treatment such that the need for retreatment with ranibizumab or even follow-up visits is reduced. Therefore we choose the primary endpoint as the number of ranibizumab injections.

The possibility of a synergistic effect is explored by treating patients with ranibizumab and the Grid&Direct short pulse laser photocoagulation in Arm 2 and comparing the results with those obtained with ranibizumab monotherapy (Arm 1).

Gold standard of care for the treatment of ME due to BRVO was grid laser photocoagulation before. However, several recent large clinical trials, e.g. BRAVO, BRIGHTER and VIVLANT, show the efficacy of significant visual gain and long term safety profile of anti-VEGF treatment. Therefore, the current standard treatment for BRVO in Japan is anti-VEGF therapy, which will be used as active-control in Arm 1.

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

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

The evidence from 2 studies in BRVO patients (BRAVO and BRIGHTER), starting with 6 and 3 consecutive monthly injections respectively, then PRN treatment or VA stabilization guided PRN injections demonstrated that the gains in VA seen with ranibizumab treatment have a rapid onset (as early as day 8 after the first treatment), with on average maintenance of the improvement in BCVA over a 12-month period.

In Japan, the 3-month phase III confirmatory study (CRFB002E2301) confirmed these findings in Japanese patients.

In MARVEL study (Narayanan et al. 2015), as 1 + PRN treatment, the mean gains of BCVA were +18.1 letters in ranibizumab monotherapy and the mean number of ranibizumab injections were 3.2 at 6 months. Authors suggested that the result was consistently good like BRAVO study.

Therefore, a treatment regimen according to the approved Japanese label, as assessed in this study (Arm 1), is likely to result in significant gains in BCVA comparable to those seen in these studies. The efficacy assessments conducted at Months 1, 2 and 3 are appropriate to assess the fast onset of treatment effect. By assessing monthly BCVA from Month 1 onwards, the magnitude and profile of efficacy achieved with the individualized treatment regimen can be evaluated though Month 12.

3.4 Rationale for choice of comparator

Anti-VEGF monotherapy (in this study, ranibizumab) is the standard treatment of ME due to BRVO and is approved in Japan since 20-Aug-2013.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

The administration of ranibizumab in this study is according to the approved label in Japan in both treatment arms. The risks and benefits for treating Japanese patients with BRVO with ranibizumab have been assessed in the Japanese phase III “CRFB002E2301”study. Further safety assessments are currently conducted in the ongoing BRVO post marketing surveillance (PMS) study. The latest Pharmaceutical and Medical Devices Agency (PMDA) report from the BRVO PMS study has not shown any further safety concerns for ranibizumab in Japanese patients (5th Periodic safety report for patients with macular edema secondary to retinal vein occlusion. 2015).

The main risks of laser photocoagulation are scotoma, visual field defect, atrophy, and retinal hemorrhage. In this study, we will adopt short pulse laser photocoagulation method that it will contribute to reduce these risks.

The overall risks to subjects in this trial will further be minimized by compliance with the inclusion/exclusion criteria and close clinical monitoring.

The benefits for patients participating in this trial are the potential chance to obtain a similar efficacy to the standard treatment but with less numbers of injections, if randomized in the laser combination arm.

Overall the results of this trial will provide evidence that help to further optimize the treatment strategies for Japanese BRVO patients.

4 Population

This study will include male and female patients (≥20 years old) who are diagnosed with visual impairment due to ME secondary to BRVO. Assuming an approximate 20% drop out rate, approximately 70 patients will need to be screened to have at least 56 patients found eligible and commencing treatment in the trial.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria (at Screening and confirmed at Baseline (Day 1)

Inclusion criteria for patient

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female patients ≥20 years of age.

Inclusion criteria for study eye

3. Diagnosis of visual impairment exclusively due to ME secondary to BRVO.
4. BCVA score at Screening and Baseline (Day 1) between 0.5 and 0.05 decimal (i.e., between 73 and 19 letters in ETDRS testing) with Landolt C charts inclusively (i.e., approximate logarithm of the minimum angle of resolution (logMAR) units of 0.3 to 1.30).
5. At Baseline (Day1), a maximum BCVA gain of 0.2 units logMAR conversion inclusively from screening is allowed as long as the BCVA score does not exceed the upper limit of 0.3 units logMAR.
6. Increased central subfoveal thickness (> 300 μm at Baseline (Day 1) when measured by SD-OCT)
7. Duration of vision deterioration ≤6 months (determined by self-report) at screening.

If both eyes are eligible, the one with the worse VA at screening will be selected as study eye, unless, based on medical reasons, the investigator deems the other eye to be more appropriate for treatment and study.

If the fellow eye presents with visual impairment due to ME secondary to RVO, it may also be treated with ranibizumab medication, laser photocoagulation or others and in line with the Japanese label and at the discretion of the investigator, however, any anti-VEGF treatments other than ranibizumab is not allowed. The fellow eye treated with ranibizumab is then labeled the fellow treated eye. Bilateral treatment with ranibizumab cannot be performed on the same day. Bilateral treatment indicates the number of patients who received 3 or more injections of ranibizumab (study and fellow treated eye) within a 30 ± 7 days period.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

Exclusion criteria for patient

1. Inability to comply with study or follow-up procedures
2. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing study treatment. Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before 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 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository.
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), e.g., hormone vaginal ring or transdermal hormone contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).

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

Reliable contraception should be maintained throughout the study and for 3 months after study treatment discontinuation.

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or bilateral tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

3. 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 laboratory test.

Exclusion criteria for systemic medical history and conditions

4. Any type of systemic disease or its treatment, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk.
5. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
6. Stroke or myocardial infarction less than 3 months before Screening.
7. Uncontrolled blood pressure defined as systolic value of >160 mm Hg or diastolic value of >100 mm Hg at Screening or Baseline (Day 1). Values will be measured 3 times using an automated validated device with an appropriately sized cuff. The repeat sitting measurements will be made at 1- to 2-minute intervals and the mean of the 3 measurements will be used. Antihypertensive treatment can be initiated and must be taken

for at least 30 days after which the patient can be assessed for study eligibility a second time.

8. Known hypersensitivity to ranibizumab or any component of the ranibizumab formulation, or fluorescein.

Exclusion criteria for ocular medical history and conditions

Any ocular medical conditions that may confound interpretation of study results, compromise VA, affect ME or require medical or surgical intervention in the study eye during the 12-month study period. These conditions include:

For both eyes

9. Any active periocular or ocular infection or inflammation (e.g., blepharitis, conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) at the time of Screening or Baseline (Day 1).
10. Uncontrolled glaucoma (intraocular pressure (IOP) ≥30 mm Hg on medication or according to investigator's judgment) at the time of Screening or Baseline (Day 1) or diagnosed within 6 months before Baseline (Day 1).
11. Inability of obtaining fundus photographs or fluorescein angiograms of sufficient quality to be analyzed.

For study eye

12. Cataract, aphakia, pseudoexfoliation, hemorrhage reducing VA, rhegmatogenous retinal detachment, macular hole, diabetic retinopathy and diabetic maculopathy requiring treatment, or choroidal neovascularization of any cause (e.g., age-related macular degeneration (AMD), ocular histoplasmosis, diabetic ME, pathologic myopia).
13. Substantial cataract that, in the opinion of the investigator, is likely to be decreasing VA by 3 lines or more (i.e. Cataract would be reducing acuity to 20/40 or worse if eye was otherwise normal).
14. Brisk afferent pupillary defect.
15. Neovascularization of the iris or neovascular glaucoma.
16. Vitreomacular traction at the time of Screening or Baseline (Day 1).
17. Structural damage within 0.5 disc diameter of the center of the macula (e.g., epiretinal membrane, scar, laser burn, foveal atrophy, dense pigmentary changes, dense subfoveal hard exudates).
18. History of herpetic ocular infection or ocular toxoplasmosis.
19. History of idiopathic central serous chorioretinopathy.

Exclusion criteria for prior or current systemic medication

20. Use of other investigational drugs within 30 days or 5 half-lives of Baseline (Day 1), whichever is longer.
21. Use of any systemic anti-VEGF drugs within 6 months before Baseline (Day1) (e.g., sorafenib (Nexavar®), sunitinib (Sutent®), bevacizumab (Avastin®), ziv-aflibercept (ZALTRAP®)).
22. Current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine (Plaquenil®),

tamoxifen, phenothiazines other than temporary use with common cold and upper respiratory infection (i.e. exclude PL granules), and ethambutol.

Exclusion criteria for prior or current ocular treatment

For both eyes

23. Treatment (or anticipated treatment in the fellow eye for non-RVO indications during the study) with any anti-angiogenic drugs (including any anti-VEGF agents) within 3 months before Baseline (Day1) in fellow eye or before Baseline (Day 1) in the study eye (e.g., pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®), and aflibercept (EYLEA®)).

For study eye

24. Panretinal laser photocoagulation within 1 month before Baseline (Day1) or anticipated or scheduled within the next 12 months (Study periods) following Baseline (Day1).
25. Any giving of focal or grid laser photocoagulation before Baseline (Day1).
26. Any intraocular procedure (including Yttrium-Aluminum-Garnet capsulotomy) within 2 months before Baseline (Day1) or anticipated within the next 12 months following Baseline (Day1).
27. Topical ocular or systemic corticosteroids administered for at least 30 consecutive days within 6 months before Screening.
28. Use of intra- or periocular corticosteroids (including sub-Tenon) within 3 months before Screening.
29. Any use of intraocular corticosteroid implants (e.g., dexamethasone (Ozurdex®), fluocinolone acetonide (Iluvien®)).
30. History of optic neurotomy, sheathotomy, or filtration surgery at any time.
31. Macular BRVO (Battaglia Parodi et al. 1999).

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The investigational treatment used in this study is 0.5 mg ranibizumab applied PRN as intravitreal injection of 0.05 mL, with or without the laser treatment. Commercially available ranibizumab prefilled syringes (PFS) for injection will be supplied (open label) to each study center by Novartis Pharma K.K. for the treatment of study eye. Novartis Pharma K.K. will not be providing/supporting ranibizumab for the treatment of fellow eye however investigator can treat visual impairment of fellow eye due to ME secondary to RVO using ranibizumab purchased by patient. Each PFS contains ranibizumab in the concentration of 10 mg/mL. PFSs of ranibizumab are for single use only and the content of the PFS must not be split.

Arm 1: Patients with visual impairment due to ME secondary to BRVO are treated with ranibizumab monotherapy with an individualized stabilization-criteria-driven PRN dosing regimen as described in Section 5.5.4.1 and Section 5.5.4.2.

Arm 2: Patients with visual impairment due to ME secondary to BRVO are treated with ranibizumab with an individualized stabilization-criteria-driven PRN dosing regimen. The laser photocoagulation is applied as described in Section 5.5.4.1 and Section 5.5.4.2.

5.1.2 Additional treatment

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

5.2 Treatment arms

Patients will be assigned to one of the following 2 treatment arms in a ratio of 1:1.

Arm 1: ranibizumab monotherapy

Arm 2: ranibizumab with Grid&Direct short pulse laser photocoagulation combination therapy

5.3 Treatment assignment and randomization

At Baseline (Day1) all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients/subjects and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

The randomization will be balanced by VA (0.3<, or ≥0.3 assessed by decimal VA which is translated into 58 letters in EDTRS).

The randomization scheme for patients will be reviewed and approved by a member of the Biostatistics Quality Assurance (BQA) Group.

5.4 Treatment blinding

This is an open-label study; therefore treatment blinding (masking) is not applicable. However, masking of the Vision Examiner, assessing parameters constituting the secondary endpoint (BCVA), will be chosen at each site before the study start. Therefore, the Vision Examiner will not be allowed to access unmasked medical records and to perform any other tasks involving direct patient care which may unmask him/her to the patient's treatment.

5.5 Treating the patient

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

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. For studies using electronic Case Report Forms (eCRFs), only the assigned patient number must be entered in the field labeled "Patient ID" on the electronic data capture (EDC) data entry screen (e.g. enter '1', '2', etc.). Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography eCRF should also be completed.

5.5.2 Dispensing the study drug

Each study site will be supplied with investigational drug in packaging.

Immediately before dispensing and administering the investigational drug, Investigator staff will write the drug name, strength, Packaging lot number and expiry date from the label onto the source document (and/or Drug Accountability Log) containing that patient's unique patient number. Site may apply an additional label/sticker on the drug kit containing the following information for accountability purpose: Study number, Study name.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

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

Medication labels will be in the local language and comply with the legal requirements of Japan.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by 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, unused packaging and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

For the entire trial, regardless of randomization, the following rules apply:

- Ranibizumab should be administered in the study eye on the day of the study visit. In any case, study treatment has to occur within the visit window as described in Section 6.
- Treatments of the fellow eye with ranibizumab must not be performed on the same day as treatments with ranibizumab of the study eye.
- When ranibizumab and laser photocoagulation are to be applied on the same day to the same eye, the laser treatment has to be applied at least 30 minutes before the ranibizumab injection. When ranibizumab and laser photocoagulation are not to be applied on the same day to the same eye, laser treatment can be deferred for up to 14 days relative to the ranibizumab treatment.
- Initially, Grid&Direct short pulse laser photocoagulation may be performed in a staged manner as macular hemorrhage and severe edema (thicker than 400 µm as a guide) resolve, i.e. initial laser treatment can be split into 2 or more sessions.
- On days when ranibizumab and/or laser treatment is to be administered, efficacy assessments and pre-injection safety measures (tonometry, slit lamp and fundus examinations) must be conducted before administration of ranibizumab and/or laser photocoagulation.

If study visit assessments and a corresponding treatment occur on separate days, a repeat ophthalmoscopy should be performed as safety check-up before treatment of the eye. Results will be documented in the source documents but not in the eCRF. If any concern arises, treatment needs to be cancelled and a re-evaluation needs to take place. Efficacy assessments (BCVA, [redacted]) already performed at the scheduled study visit should not be repeated on the day of treatment unless the patient indicates a sudden change in vision.

Instructions on how to prepare ranibizumab PFSs for intravitreal injection and its administration under aseptic conditions are provided in the package insert of the provided PFS. Information on pre- and post-injection procedures including administration of antibiotic eye drops is provided in Appendix 2 and Appendix 3, respectively. Laser photocoagulation should be applied as approved for the indication and further outlined below. Instructions on post-laser treatment procedures are outlined in Appendix 4. Study treatment (ranibizumab, laser photocoagulation) prescribed and dispensed to the patient during the study must be recorded on the dosage administration record eCRF.

5.5.4.1 Treatment Period (Day 1 to Month 11)

Arm 1: Ranibizumab monotherapy

Patients will start study treatment with ranibizumab on Baseline (Day 1) and having reached stable status (i.e., satisfied stabilization criteria as per Section 5.5.4.2) ranibizumab treatment may be temporarily discontinued. Patients should be monitored monthly for VA and disease activity. Ranibizumab injections are given using PRN regimen i.e., according to the Japanese label of ranibizumab. The minimum gap required between 2 injections of ranibizumab will be 30 ± 7 days.

If there is no improvement in VA [redacted] imaging over the course of the first 3 injections, continued treatment is not recommended and the patient may receive alternative treatment at the investigator's discretion (for consequences refer to Section 5.6.2).

Arm 2: Ranibizumab + Grid&Direct short pulse laser photocoagulation

Patients will start study treatment with ranibizumab on Baseline (Day 1) and having reached stable status (i.e., satisfied stabilization criteria as per Section 5.5.4.2), ranibizumab treatment may be temporarily discontinued. Patients should be monitored monthly for VA and disease activity. Ranibizumab injections are given using PRN regimen i.e., according to the Japanese label of ranibizumab. The minimum gap required between 2 injections of ranibizumab will be 30 ±7 days.

Grid&Direct short pulse laser photocoagulation treatment must be applied to the target within vascular arcades as soon as indicated. If in the investigator's opinion dense macular hemorrhage and/or severe retinal edema preclude laser treatment, laser photocoagulation should be postponed until resolution of the hemorrhage permits laser treatment. The criteria for PRN of Grid&Direct short pulse laser photocoagulation is defined in laser operation manual in detail.

Following the complete application of the initial laser treatment, further laser treatment can be applied in the presence of ME due to BRVO at the investigator's discretion at minimal intervals of 30 ±7 days.

Laser photocoagulation will be optional if BCVA is greater than or equal to 0.8 in decimal VA which is equivalent to 0.12 units in logMAR (or 79 letters in ETDRS) or in the absence of ME.

5.5.4.2 PRN (re-treatment/stabilization) criteria

The PRN criteria for ranibizumab treatment is as detailed below:

After Baseline (Day 1) visit, if any one or more criteria from the below list is met, the patient should be considered for ranibizumab treatment **(re-treatment criteria)**

1. Center subfield thickness ≥ 300 µm
2. An increase of CSFT ≥ 20% compare to minimum value during the treatment period
3. The loss of VA due to disease activity secondary to BRVO (disease activity includes macular edema (ME), intra-retinal cysts, sub-retinal fluid, macular hemorrhage etc.). This criteria is based on Investigator's judgement including the following scenarios:
   a. The VA is expected to improve if the existing disease activity is removed, hence investigator decides to treat with ranibizumab
   b. The VA is expected to be decreasing because of the existing disease activity, hence investigator decides to treat with ranibizumab
   c. The VA has decreased as compared to the previous month because of the appearance of disease activity, hence investigator decides to treat with ranibizumab (This criterion is to restart ranibizumab after interruption)

- If all the above criteria are not satisfied, then the patient should not be treated with ranibizumab **(stabilization criteria),** i.e.,
  1. Center subfield thickness < 300 µm

2. An increase of CSFT < 20% compare to minimum value during the treatment period
3. VA is stable and the disease activity is in the state of not affecting VA (based on investigator's judgement).

5.5.4.3 Treatment of the fellow eye

Patients who develop visual impairment due to ME secondary to RVO in the fellow eye (non-study eye) during the study that, in the investigator's opinion, qualifies for and requires treatment, may be treated at the investigator's discretion according to the standard treatment, including administration of ranibizumab. Ranibizumab will be injected in accordance with the rule of usual care and should be applied as per Japanese label.

Treatments of the fellow eye with ranibizumab should not be performed on the same day as treatments with ranibizumab of the study eye. Treatment of the fellow eye must be scheduled in a way not to disturb the schedule for visits and treatments of the study eye. Treatment will be captured on the eCRF. The fellow treated eye must be monitored according to routine practice and AE(s) and serious adverse events (SAEs) are captured on eCRFs. If fellow eye is treated with ranibizumab, examinations will be same as study eye.

Treatment with other anti-VEGF medication (e.g., pegaptanib (Macugen®), bevacizumab (Avastin®), aflibercept (EYLEA®)) and intra- or periocular corticosteroids (including sub-Tenon) are prohibited.

Treatment with ranibizumab for non-RVO indications in the fellow eye will be permitted in the same rule with RVO in the fellow eye within the limits of Japanese package insert, but the other anti-VEGF medication is prohibited.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Dose adjustments, i.e., adjustments of the injection volume of ranibizumab dose solution, are not permitted.

Adjustments of the PRN dosing regimen of ranibizumab that is described as part of the study treatment administration in Section 3.1 and Section 5.5.4 are not permitted.

Ranibizumab treatment should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of:

- A decrease in BCVA of ≥0.6 units in logMAR compared with the last assessment of VA,
- An IOP of ≥30 mm Hg,
- A retinal break,
- Performed or planned intraocular surgery within the previous or next 28 days.

Laser photocoagulation should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of:

- A significant increase in macular ischemia as judged by the investigator,
- Absence of macular edema,
- Dense macular hemorrhage.

These changes must be recorded on the Dosage Administration Record eCRF.

5.5.6 Rescue medication

Rescue medication will not be permitted in this study.

5.5.7 Concomitant medication

The investigator should instruct the patient to notify the study site about any relevant prior medications (especially those related to ocular treatment) and any medications he or she takes preceding Baseline (Day 1) (once the informed consent is signed) until the conclusion of the study participation. Any relevant medications and significant non-drug therapies administered preceding Baseline (Day 1) before start of study treatment will be listed on Prior medication therapy page of eCRF and all medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment must be listed on the concomitant medications/significant non-drug therapies eCRF.

Protocol specific medications (e.g., dilating drops, fluorescein dyes) and pre- and post-injection medications (e.g., topical anesthetics, topical antimicrobials) used by a patient during the study are not considered concomitant medications although these are listed in eCRF if used.

5.5.8 Prohibited medication

The following treatments are not allowed in the study eye throughout the entire study:

- Pan retinal and sector laser photocoagulation on the outside of vascular arcade or any other type of intervention for RVO (e.g. vitrectomy, optic neurotomy, sheathotomy, filtration surgery).
- Any type of intraocular surgery including cataract surgery.
- Intra-/peri-ocular corticosteroids (including sub-Tenon, but excluding topical formulations of any drug) and intra-ocular corticosteroid implants (e.g. dexamethasone (Ozurdex®), fluocinolone acetonide (Iluvien®)).

The use of the following medications is not allowed in both eyes throughout the entire study:

- Non-study anti-angiogenic drugs (including any anti-VEGF drugs) (e.g. pegaptanib (Macugen®), bevacizumab (Avastin®), and aflibercept (EYLEA®)).

The following systemic medications are not allowed throughout the entire study:

- Corticosteroids,
- Anti-VEGF drugs (e.g. sorafenib (Nexavar®), sunitinib (Sutent®), bevacizumab (Avastin®) and ziv-aflibercept (ZALTRAP®)),
- Medications known to be toxic to the lens, retina or optic nerve including deferoxamine, chloroquine/hydroxychloroquine (Plaquenil), tamoxifen, phenothiazines other than temporary use with common cold and upper respiratory infection (i.e., exclude PL granules), and ethambutol.

Furthermore, any type of investigational drug or investigational intervention (e.g. isovolumic hemodilution, intravitreal tissue plasminogen activator (TPA)) is prohibited throughout the study.

Prohibited treatments are summarized in Table 5-1.

Table 5-1 Prohibited treatment

Medication	Action to be taken
Other anti-VEGF drugs (ocular or systemic)	Discontinue study treatment and study
Pan-retinal laser photocoagulation – study eye	Discontinue study treatment and study
Intra-/peri-ocular corticosteroids (including sub-Tenon) – study eye	Discontinue study treatment and study
Intra-ocular corticosteroid implants – study eye	Discontinue study treatment and study
Systemic corticosteroids	Discontinue study treatment
Intraocular surgery – study eye	Discontinue study treatment and study
Deferoxamine	Discontinue study treatment
Chloroquine/hydroxychloroquine	Discontinue study treatment
Tamoxifen	Discontinue study treatment
Phenothiazines other than temporary use with a common cold and an upper respiratory infection	Discontinue study treatment
Ethambutol	Discontinue study treatment
Investigational drugs and interventions	Discontinue study treatment

5.5.9 Emergency breaking of assigned treatment code

Not applicable.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

Patients who successfully complete the study through Month 12 will be considered to have completed the study.

No extension to this study has been planned.

5.6.2 Discontinuation of study treatment

Patients can discontinue treatment because of the appearance of a new health condition suspected to require appropriate care or require medications prohibited by the protocol (Section 5.5.8), unacceptable AEs, refusal to continue treatment, or at the investigator's discretion based on his/her clinical judgment.

Study treatment *must* be discontinued under the following circumstances:

- Emergence of the following AEs:
  - Rhegmatogenous retinal detachment
  - Stage 3 or 4 macular hole
  - Stroke or transient ischemic attack (TIA)
- Pregnancy
- Use of prohibited treatment as per Table 5-1.
- Any other protocol deviation that results in a significant risk to the patient's safety.

The reason for study treatment discontinuation will be recorded on the Treatment Period Completion eCRF.

Patients who permanently discontinue study treatment and start certain prohibited treatments (see Table 5-1) should be withdrawn from the study and undergo all assessments for the Visit 14 (End of study (EOS)) as described in Table 6-1.

Patients who discontinue study treatment and do not start a prohibited medication per Table 5-1 should NOT be considered withdrawn from the study and continue their scheduled follow-up assessments until Visit 14 (EOS). A Study Treatment Period Completion eCRF should be completed, giving the date and primary reason for stopping study treatment.

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

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

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

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

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 5.6.2 for a prematurely withdrawn patients. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or IECs of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and procedures to be performed by study visits.

All data obtained from these assessments must be supported in the patient's source documentation. Assessments are indicated with an "X" when they need to be performed.

A planned study visit schedule will be established at the time of Baseline (Day 1) for all patients. Study assessments will be performed at Screening, Baseline (Day1), and at monthly visits (defined as every 30 days calculated from Baseline (Day1)) from Month 1 through Month 12, ± 7 days to allow for flexibility in scheduling. Ranibizumab should be administered in the study eye on the day of the study visit. Only when ranibizumab and laser photocoagulation are not to be applied on the same day to the same eye, laser treatment can be deferred for up to 14 days relative to the ranibizumab treatment. In the other case, study treatment has to occur within the visit window as specified in Table 6-1.

Should a deviation from the study visit schedule occur, all efforts should be made to return to the planned visit schedule.

Table 6-1 Assessment schedule

Period	**Screening**	**Treatment Period**												**FUP**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Month (relative to BSL)			**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11 EOT**	**M12 EOS [p]**
Day (relative to BSL)	**-30 to -1 [a]**	**1 BSL**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**
Visit window			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Informed consent	X													
Review of inclusion/exclusion	X	X												
Diagnosis	X													
Demography	X													
Height and weight	X													
Medical history	X	X												
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests [b] - hematology (incl. coagulation panel) - clinical chemistry	X													X
Serum pregnancy test [c]	X													X
Urine Pregnancy Test [c]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Vital signs [d, e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Decimal BCVA [d, f]	X [g]	X [g]	X	X	X	X	X	X [g]	X	X	X	X	X	X [g]

Period	**Screening**	**Treatment Period**												**FUP**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Month (relative to BSL)			**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11 EOT**	**M12 EOS [p]**
Day (relative to BSL)	**-30 to -1 [a]**	**1 BSL**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**
ETDRS BCVA [d, f]		X						X						X
Ophthalmic examination [h]	X [g]	X [g]	X	X	X	X	X	X [g]	X	X	X	X	X	X [g]
Tonometry [d, i]	X [g]	X [g]	X	X	X	X	X	X [g]	X	X	X	X	X	X [g]
[redacted]														
Color fundus photography	X [g]	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]	X [g]	X [k]	X [k]	X [k]	X [k]	X [k]	X [g]
[redacted]														
Dispense antibiotic medication [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization		X												
Ranibizumab injection		X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Grid&Direct short pulse laser treatment [m]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Post injection safety [n]		X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Follow-up contact [o]		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

Period	Screening	Treatment Period												FUP
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Month (relative to BSL)			M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11 EOT	M12 EOS [p]
Day (relative to BSL)	-30 to -1 [a]	1 BSL	30	60	90	120	150	180	210	240	270	300	330	360
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BCVA = best-corrected visual acuity, BSL = Baseline, EOS = End of Study, EOT = End of Treatment Period, ETDRS = Early Treatment Diabetic Retinopathy Study, FUP = Follow-Up Period, IOP = intraocular pressure, M = month, [redacted], PRN = Pro re nata, VA = Visual acuity, VEGF = Vascular endothelial growth factor.

(X) Indicates that ranibizumab injection or laser treatment should be given PRN as per protocol. If the fellow eye presents with visual impairment due to ME secondary to RVO, it may also be treated with ranibizumab medication, laser photocoagulation in line with the Japanese label and at the discretion of the investigator, however, any anti-VEGF treatments other than ranibizumab is not allowed. The fellow eye treated with ranibizumab is then labeled the fellow treated eye. Bilateral treatment with ranibizumab cannot be performed on the same day.

a. Screening (Visit 1) to occur between Day -30 and Day -1 where screening assessments will be done between Day -30 and Day -4 after signing the informed consent form to check the eligibility for the study and administration of pre-ranibizumab treatment antimicrobials will occur between Day -3 to Day -1.

b. Hematology includes: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential count (neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils and other cells), and platelet count. In addition, the coagulation panel (activated partial thromboplastin and prothrombin time), D-dimer, and thrombin-antithrombin complex: TAT will be assessed. Clinical chemistry includes: sodium, potassium, chloride, bicarbonate, creatinine, glucose, total protein, albumin, total bilirubin, direct bilirubin, uric acid, urea, phosphorus, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total cholesterol, low-density lipoprotein cholesterol and calcium. In addition, Leptin, highly sensitive C-reactive protein and VEGF will be assessed.

c. Serum pregnancy test will be performed on women of childbearing potential at Screening and EOS visits. Urine pregnancy tests will be optionally performed to confirm pregnancy status during the course of the study.

d. BCVA, vital signs, tonometry: Perform pre-treatment with ranibizumab and/or laser photocoagulation and before dilation.

e. Vital signs will be taken after the patient has been sitting for 5 minutes, with back supported and both feet placed on the floor. Systolic and diastolic blood pressure will be measured 3 times. The repeat sitting measurements will be made at 1- to 2-minute intervals and the mean of the 3 measurements will be used. Vital signs will include sitting pulse.

f. BCVA: The VA examiner must be masked to the treatment arm. The VA examiner is not allowed to access unmasked medical records and to perform any other tasks involving direct patient care which may unmask him/her to the patient's treatment.

g. Assessments will be performed in both eyes.

h. Ophthalmic examinations will include slit lamp examination, anterior chamber examination, and direct and indirect ophthalmoscopy of the macular and peripheral retina. Must be performed pre-treatment with ranibizumab and/or laser photocoagulation.

i. Tonometry: In the study eye, tonometry is conducted at every study visit in all treatment arms to assess IOP, regardless of treatment administration afterwards. On visits when ranibizumab and/or laser treatment is administered, also post-injection tonometry should be performed between 15 and 60 minutes after treatment in the study eye. In the fellow untreated eye, tonometry will be conducted at Screening, Baseline (Day 1), Month 6, and the EOS visit.

[redacted]

k. These assessments are optional if the investigator requires the respective information to assess the need for retreatment.

l. Before the study treatment with ranibizumab, ensure that patients have self-administered their antimicrobials 4 times daily for 3 days before each scheduled study treatment and instruct patients to self-administer their antimicrobials again 4 times daily for 3 days post-treatment with ranibizumab.

m. In Arm 2, the first laser treatment must be given to the target within vascular arcades as soon as indicated, but can be deferred by a maximum of 14 days relative to the ranibizumab injection.

n. Post injection safety after ranibizumab and/or laser treatment, comprising: central artery perfusion, vision check, IOP. (Perform finger count, hand motion, and light perception (when indicated) within 15 minutes post-treatment for the study eye only).

o. Follow-up Contact: Contact the patient by telephone for safety evaluations 2 (± 1) days following each study visit when study treatment (ranibizumab and/or laser photocoagulation) is administered.

p. EOS: For patients, who complete, withdraw or are discontinued early (refer to Section 5.6.2) from the study, perform 30 days (+ 7 days) following the last study treatment or the last study visit.

[redacted]

6.1 Information to be collected on screening failures

Patients who are screened but determined not eligible for treatment are considered screening failures. The reason for this will be documented on the Screening Log. In addition, for all screening failures, the Screening Visit date, demography eCRF, Informed Consent eCRF, inclusion/exclusion, reason of screen failure on Screening Disposition, Demography and SAE data will be collected.

Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. For all patients who have signed informed consent and are entered into the next period of the study will have all AEs occurring after informed consent is signed recorded on the AE eCRF.

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

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients as shown in Table 6-1 include:

Demography: date of birth, gender, race, ethnicity

Study eye selection

RVO specific baseline characteristics including date of BRVO diagnosis. Other assessments performed at screening to determine eligibility are listed in Table 6-1.

6.3 Treatment exposure and compliance

Information regarding drug administration will be collected on the “Drug administration record” (DAR) eCRFs. The reason for dosing of ranibizumab or the reason for change of dosing must be described on the DAR page of the eCRF.

The reason for dosing of ranibizumab/laser photocoagulation or the reason for dose/no dose will be described on the DAR eCRF for the study eye.

In addition, confirmation of disease activity as assessed by the investigator through decreasing VA due to ME secondary to BRVO and abnormalities detected by [redacted] CF will be captured for the study eye.

6.4 Efficacy

Efficacy assessments will include both functional and anatomical evaluations. The methods of evaluation and the parameters to be assessed are described below.

These assessments are performed according to the schedule in Table 6-1.

On days when ranibizumab and/or laser treatment is administered, efficacy assessments must be conducted before administration of ranibizumab and/or laser photocoagulation.

If study visit assessments and a corresponding treatment occur on separate days, efficacy assessments (BCVA, [redacted]) already performed at the scheduled study visit would not be repeated on the day of treatment unless the patient indicates a sudden change in vision.

6.4.1 Decimal Best-Corrected Visual Acuity

BCVA will be assessed in a sitting position using Decimal VA testing charts at an initial testing distance of 5 meters at every visit. VA examiners will examine it according to their standards' practice. For the study eye, the BCVA will be assessed at every visit, and at Screening, Baseline (Day 1), Month 6, and EOS in the fellow untreated eye as per Table 6-1.

6.4.2 ETDRS Best-Corrected Visual Acuity

BCVA will be also assessed in a sitting position using ETDRS VA testing charts at an initial testing distance of 4 meters.

If it is not possible to perform a subjective refraction or VA testing at 4 meters because VA is too poor for the patient to read at least 4 letters on the refraction/VA chart at this distance, the refraction/VA testing should be attempted at 1 meter. Further details on refraction technique and VA testing will be described in the VA testing manual provided by Novartis. For the study eye, the BCVA will be assessed at Baseline (Day1), Month 6, and EOS as per Table 6-1.

[redacted]

6.4.4 Color fundus photography [redacted]

The ocular fundus is assessed by Color Fundus photography (CF) [redacted]

For both eyes, CF [redacted] images will be taken at Screening, at Month 6, and at study completion (EOS) as per Table 6-1. [redacted]

Investigators will evaluate the images according to their standards' practice.

[redacted] Additional [redacted] CF images may be taken at other monthly visits at the investigator's discretion. The investigator will evaluate the images according to their standards' practices, will capture the presence or absence of macular edema, capillary leakage and non-perfusion within the 3 mm perifoveal subfield in the eCRF and may use the images to inform his or her decision for retreatment. The decision for retreatment needs based on his or her evaluation of the [redacted]/CF images will be documented in the eCRF.

[redacted]

6.4.8 Appropriateness of efficacy assessments

The efficacy assessments selected for this study are standard for this indication and patient population.

6.5 Safety

Safety will be assessed by the type, frequency and severity of AEs. Methods applied for the evaluation of safety include ophthalmic examinations, vital signs and laboratory tests. Safety assessments are performed according to the schedule in Table 6-1.

Post injection safety after ranibizumab and/or laser treatment, will be evaluated as mentioned in Table 6-1. Post-injection safety comprising the following: central artery perfusion, vision check, IOP. (Perform finger count, hand motion, and light perception (when indicated) within 15 minutes post-treatment for the study eye only).

All ocular assessments enabling identification of possible AEs will be performed on both eyes.

6.5.1 Ophthalmic examinations

The standard ophthalmic examinations include slit lamp examination, anterior chamber examination, direct and indirect ophthalmoscopy of the macular and peripheral retina, and tonometry.

Slit lamp and fundus examinations will be performed prior to treatment with ranibizumab for study eyes at all visits and at Screening, Baseline (day1), Month 6, and EOS in the fellow untreated eye as per Table 6-1. Results will be assessed whether they are normal, clinically insignificantly abnormal or clinically significantly abnormal and will be recorded as such in the eCRF. Any clinically significant abnormalities of either eye will be recorded either in the Medical/ocular history eCRF or in the AE eCRF depending on when the test abnormality occurred (see Section 6.1).

For both eyes, tonometry should be conducted at Screening, at Baseline (Day1), at Month 6 and at EOS visit as per Table 6-1. Intraocular pressure in the study eye will be assessed before, as well as between 15 and 60 minutes after treatment with ranibizumab at every visit. The IOP values recorded in mmHg will be entered into the eCRF.

6.5.2 Vital signs

These include assessment of the sitting blood pressure (systolic, diastolic measurement in mmHg) and pulse rate (in bpm) at each visit.

On days when ranibizumab treatment is administered, vital signs will be measured prior to administration of ranibizumab.

The results will be recorded in the eCRF.

Clinically notable vital signs are defined in Appendix 1.

6.5.3 Height and weight

Height (in cm) and weight (in kg, in indoor clothing but without shoes) will be assessed at screening (Visit 1) only. The results will be recorded in the eCRF.

6.5.4 Laboratory evaluations

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

Whether a sample was collected at Screening and EOS or not will be recorded in the eCRF. Laboratory results will not be recorded in the eCRF but transferred directly from the central laboratory to data management upon completion of the study.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential count (neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils and other cells), and

platelet count will be measured. In addition, the coagulation panel (activated partial thromboplastin and prothrombin time), D-dimer, and thrombin-antithrombin complex: TAT will be assessed.

6.5.4.2 Clinical chemistry

Sodium, potassium, chloride, bicarbonate, creatinine, glucose, total protein, albumin, total bilirubin, direct bilirubin, uric acid, urea, phosphorus, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total cholesterol, low-density lipoprotein cholesterol and calcium will be measured. In addition, Leptin, highly sensitive C-reactive protein and VEGF will be assessed.

6.5.4.3 Urinalysis

Not applicable.

6.5.5 Electrocardiogram (ECG)

Not applicable.

6.5.6 Pregnancy assessments

All pre-menopausal women who are not surgically sterile will have pregnancy testing at screening (Visit 1) and study completion visits (Visit 14). Additional pregnancy testing might be performed if needed.

Serum pregnancy test will be performed on women of childbearing potential at Screening and EOS visits. Urine pregnancy tests will be optionally performed as per Table 6-1 to confirm pregnancy status during the course of the study.

Patients who are determined to be post-menopausal as defined in Section 4.2 before or during the study are not required to undergo subsequent pregnancy testing.

6.5.7 Appropriateness of safety measurements

The safety assessments selected for this study are standard for this indication and patient population.

6.6 Other assessments

No additional tests will be performed in this study.

6.6.1 Clinical Outcome Assessments (COAs)

Not applicable.

6.6.2 Resource utilization

Not applicable.

6.6.3 Pharmacokinetics

Not applicable.

6.6.4 DNA sampling

Not applicable.

6.6.5 Pharmacogenetics

Not applicable.

6.6.6 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 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 until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

Abnormal laboratory values or test results constitute AEs 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 (Day1) or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying AEs.

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

1. the severity grade. If CTCAE grading does not exist for an AE, use 1=mild, 2=moderate, 3=severe, 4=life threatening. CTCAE Grade 5 (death) is not used, but is collected in other eCRFs (Study Completion).
2. site (non-ocular, left eye, right eye, both eyes).

3. its relationship to the ocular injection/study drug(s) (Yes/No).
4. its duration (start and end dates or if continuing at final exam).
5. whether it constitutes an SAE (see Section 7.2.1 for definition of SAE).

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the AE should be recorded on the Adverse Event eCRF.

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

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

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.2.

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

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

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

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

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

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.

Paper SAE form will be used in this study. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to study drug, complete the SAE Report Form in Japanese and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department (DS&E). The telephone and telecopy number of the contact persons in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report

Form and the fax confirmation sheet must be kept with the eCRF documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (where applicable), and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a DS&E 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.

7.3 Liver safety monitoring

Not applicable.

7.4 Renal safety monitoring

Not applicable.

7.5 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, patient or consumer.

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE. Guidance for capturing study treatment errors including misuse/abuse is given in Table 7-1.

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

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.6 Pregnancy reporting

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

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis DS&E Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.7 Prospective suicidality assessment

Not applicable.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator

must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

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

8.2 Data collection

Field monitors will review the eCRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

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

8.3 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs 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 the Novartis/designated CRO. The Novartis/CRO data management staff will perform a reconciliation of the data entered into the eCRF versus what is received from the central laboratory. At a minimum, this reconciliation will include header reconciliation, visit window checks, duplicate record checks, out of range checks as defined by the Clinical Trial Team and checks to address missing laboratory data.

Randomization codes and data about all study treatments dispensed to the patient will be tracked in the drug dispensing log eCRF. The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be

complete and accurate, the database will be declared locked and made available for data analysis.

Authorization is required prior to making any database changes to locked data, by the Medical Advisor or Equivalent; prior authorizing the database un-lock, a CTT meeting will be hosted, to discuss the issues leading to database unlock and update. For EDC studies, after database lock, the investigator will receive paper copies of the patient data for archiving at the investigational site.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

The statistical analysis will be performed by Product Lifecycle Services (PLS) of Novartis.

The primary objective is to demonstrate that PRN regimen of 0.5 mg ranibizumab with Grid&Direct short pulse laser photocoagulation reduces the burden of frequent ranibizumab injections as compared to ranibizumab monotherapy.

The primary objective will be assessed by the mean number of ranibizumab injections applied up to Month 11.

Summary statistics for continuous variables will generally include the number of patients (N), minimum, lower quartile, mean, median, upper quartile, and maximum. For categorical or binary variables, the number and percent of patients in each category will be presented. P-values presented will be 2-sided unless otherwise specified.

Data analyses will be presented at all time points assessed, by treatment group including graphical presentations, where appropriate. For statistical analysis purpose, baseline values will be considered to be the last available values collected before Day 1. Day 1 will be defined for statistical analysis purpose as the time point of first treatment (associated to baseline visit).

For patients who receive a prohibited medication for the study indication in the study eye, the efficacy data will be excluded from the per-protocol efficacy analysis.

Further details will be provided in the statistical analysis plan (SAP).

9.1 Analysis sets

The **Randomized Set** will consist of all randomized patients.

The Full Analysis Set (FAS) will consist of all randomized patients who received at least one administration of ranibizumab injection. In case there are safety concerns after administration of laser photocoagulation at Baseline (Day 1) and ranibizumab injection is not given during the entire study, the patient will still be included in the FAS, as there was an intention to treat

the patient with ranibizumab. Following the intent-to-treat principle, patients will be evaluated according to the treatment assigned to at randomization.

No data will be excluded from the FAS analyses because of protocol deviations.

The Per Protocol Set (PPS) will consist of all patients in the FAS who received at-least the first mandatory administration of ranibizumab injection and have at least one post-baseline assessment for BCVA and have no clinically significant protocol deviations.

Clinically significant protocol deviations will be defined in the Statistical Analysis Plan. The criteria and determination of clinically relevant protocol deviations and patient specific identification of data to be excluded from the PPS will be databased and finalized prior to database lock.

The **Safety Set** will consist of all patients who received at least one administration of ranibizumab injection and had at least one post-baseline safety assessment. The statement that a patient had no AEs also constitutes a safety assessment. Patients will be evaluated according to treatment received.

9.2 Patient demographics and other baseline characteristics

9.2.1 Demographics and baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristic variables (including the baseline values of the secondary efficacy variables) for each treatment group and for all patients in the randomized set. The number and percentage of patients in each category will be presented for categorical variables for each treatment group and all patients.

Demographic and baseline disease characteristics will be summarized for the variables listed in Section 6.2.

9.2.2 Medical history

Relevant medical history (ocular and non-ocular) and current medical conditions will be tabulated by site (non-ocular, ocular (study/fellow eye)), system organ class (SOC) and preferred term of the MedDRA dictionary. Other relevant baseline information will be listed and summarized as appropriate with descriptive statistics. Analyses will be based on the Randomized Set.

9.3 Treatments

9.3.1 Study treatment

Descriptive statistics will be provided to characterize study treatment using the Safety Set.

The number of patients receiving ranibizumab injections and laser treatments will be presented in frequency tables and cumulatively by treatment group. Summaries will be presented for the study eye only and for all ranibizumab injections/laser treatments in both the study eye and the fellow treated eye as appropriate. Other data related to the treatment or application procedure will be summarized as appropriate.

9.3.2 Bilateral treatment

The number of patients who received 3 or more injections of ranibizumab (study and fellow treated eye) within a 30 ± 7 days period will also be summarized by treatment group within the Safety Set.

9.3.3 Prior and concomitant medication

Prior and concomitant medications will be summarized in separate tables by treatment group.

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered.

Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Significant prior and concomitant non-drug therapies and procedures will be summarized by primary system organ class and MedDRA preferred term using the Safety Set.

9.4 Analysis of the primary variable

9.4.1 Variable

The primary variable is the mean number of ranibizumab injections applied up to Month 11 between the 2 treatment arms in patients with visual impairment due to ME secondary to BRVO.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will be conducted at Month 12 within the FAS using observed data.

The following 1-sided hypothesis will be tested at the alpha level of 0.025:

H_0: $\mu_{\text{Ranibizumab-Laser}} - \mu_{\text{Ranibizumab-Mono}} = 0$ versus

H_1: $\mu_{\text{Ranibizumab-Laser}} - \mu_{\text{Ranibizumab-Mono}} \leq 0$

where $\mu_{\text{Ranibizumab-Laser}}$ and $\mu_{\text{Ranibizumab-Mono}}$ are the unknown mean values of the number of ranibizumab injections for the related treatment arms up to Month 11.

The statistical hypothesis testing of the number of ranibizumab treatments will be based on a stratified Cochran-Mantel-Haenszel (CMH) test. Stratification will be done based on categories of baseline decimal VA (<0.3, or ≥ 0.3). Difference of mean number of injections, 95% confidence interval (CI) of difference and one-sided p-value of the CMH test will be reported.

9.4.3 Handling of missing values/censoring/discontinuations

No imputation is required for the primary endpoint which is number of ranibizumab injections, based on PRN regimen that is the number of injections during the study period will be used for the primary endpoint.

9.4.4 Sensitivity analyses

For sensitivity purposes, the primary analysis will be repeated for the PPS population. Any major discrepancies in the results across analyses will be investigated as necessary.

The primary analysis may also be supported by using a stratified non-parametric Wilcoxon-Mann-Whitney test. Further analyses performed if any, will be provided in SAP.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The following secondary efficacy endpoints will be evaluated for the study eye:

- The mean change in BCVA from Month 1 through Month 12 compared to Baseline (Day1) using decimal chart converted to be logMAR units, and ETDRS (Month 6, and Month 12) by both the treatment arms.
- The mean average change in BCVA from Month 1 through Month 12 compared to Baseline (Day1) using decimal chart converted to be logMAR units by both the treatment arms.
- The proportion of patients achieving BCVA improvement of ≥5, ≥10, ≥15, and ≥30 letters and proportion of patients experiencing a loss of <15 letters from Baseline (Day1) to Month 12 by treatment arms.
- The proportion of patients reaching BCVA values ≥73, ≥80, and ≥85 letters (approximate 0.5, 0.8, and 1.0 Decimal equivalent) at Month 12 by treatment arms.
- The mean change in CSFT from Month 1 through Month12 compared to Baseline (Day1) by the treatment arms.
- The mean average change in CSFT from Month 1 through Month12 compared to Baseline (Day1) by the treatment arms.

The analyses for the secondary endpoints are described below.

All endpoints relating to secondary objectives will also be summarized descriptively. Summary statistics will include relative and absolute frequencies for the categorical variables and the number of patients (N), minimum, mean, median and maximum for continuous variables. Further analyses, if required, will be described in SAP.

9.5.1.1 BCVA from Month 1 through Month 12

The mean change in BCVA from Month 1 through Month 12 will be compared to Baseline (Day1) using decimal chart and ETDRS (only at Baseline (Day1), Month 6, and Month 12) between the 2 treatment arms. The analyses at each visit will be based on an analysis of variance (ANOVA) model with treatment group, and stratification factors. Stratification will be done based on categories of baseline decimal VA (<0.3, or ≥ 0.3). The Least Squares

Means (LS Means) estimates of BCVA compared to Baseline (Day1), difference of LS Means, their 95% confidence interval (CI) and the p-value (related to the null hypothesis that difference in mean change is zero) will be reported.

The mean average change in BCVA from Month 1 through Month 12 will also be compared to baseline characteristic to the above model using decimal chart converted to be logMAR units by both the treatment arms.

To obtain the mean average BCVA change from Month 1 through Month 12, the sum of single patient's average BCVA changes will be divided by the number of patients.

The average change in BCVA will be calculated for each single patient as follows:

$$\text{Average } \Delta \text{ BCVA} = \frac{\Delta \text{ BCVA}_{M1} + \Delta \text{ BCVA}_{M2} + \ldots + \Delta \text{ BCVA}_{M12}}{12}$$

Where Δ BCVA_{Mx} = change in BCVA from Baseline (Day1) at Month x

The analyses will be conducted within the FAS using the LOCF approach.

Endpoints related to the number and proportion of patients with BCVA letter gain or loss from Baseline (Day1) will be analyzed via stratified CMH test with stratification factors as described above.

9.5.1.2 Central subfield thickness from Month 1 through Month 12

The mean change in investigator-assessed CSFT from Month 1 through Month 12 will be compared to Baseline (Day1) by the treatment arms. The analyses at each visit will be based on an analysis of variance (ANOVA) model as analogous to BCVA.

The mean average change in investigator-assessed CSFT from Month 1 through Month 12 will also be compared to Baseline (Day1) analogous to the above model by both the treatment arms.

The analyses will be conducted within the FAS using the LOCF approach.

9.5.1.3 Handling of missing values/censoring/discontinuations

For the secondary efficacy variables (BCVA, CSFT etc.), the analysis will follow a LOCF approach with the specification that missing values will be replaced by the last post baseline observation before the missing time point.

9.5.1.4 Sensitivity analyses

For sensitivity purposes, the secondary efficacy analysis may be repeated for the PPS population using as observed and LOCF approach. Any major discrepancies in the results across analyses will be investigated as necessary.

9.5.2 Safety variables

Safety parameters will be AEs, ophthalmic examinations, IOP, vital signs, and laboratory results.

9.5.2.1 Adverse events

Adverse events will be deemed treatment emergent if the onset date is on or after the date of first study treatment (Day 1). All treatment-emergent AEs will be summarized. Any AEs recorded prior to the start of study treatment will be listed separately and together with all other AEs.

Adverse events will be presented separately by site (non-ocular, study eye, fellow eye). Adverse events will be summarized by treatment group, presenting the number and percentage of patients having an AE in each primary system organ class and having each individual AE based on the preferred term. Patients who experienced multiple AEs for a preferred term will be counted once, similarly for patients with multiple AEs per system organ class.

All information pertaining to AEs noted during the study will be listed by patient, detailing AE (e.g., verbatim given by the investigator as well as the system organ class and preferred term according to MedDRA), date of starting and ending, causality, severity, relationship to the study drug or procedure, and eye (for ocular events). The AE onset will also be shown relative (in number of days) to the day of (first) initial study treatment (ranibizumab injection or laser photocoagulation as applicable) and relative (in number of days) to the Day 1.

Summary tables will also be presented and described for subsets of AEs, e.g. events potentially related to VEGF-inhibition. Adverse events which are part of the Risk Management plan (RMP) will be listed based on the latest RMP version available at the time of DBL.

The following AE listings will be provided:

- Any AE recorded before Day 1.
- Any treatment-emergent AEs with the exception of ocular AEs of the fellow untreated eye starting on or after first treatment with ranibizumab within this eye.
- Any treatment-emergent AEs of the fellow treated eye starting on or after the first treatment with ranibizumab within this eye.
- Any AEs for patients who (bilateral patients) received 3 or more injections of study drug within a 30 ± 7 days period starting on or after the third injection within the 30 ± 7 days period.

Deaths, SAEs, and AEs leading to discontinuation of study treatment will be listed separately and, if appropriate, summarized by primary system organ class and preferred term.

9.5.2.2 Laboratory data

Laboratory data for two groups of tests (hematology and chemical chemistry) will be summarized by presenting shift tables using extended normal ranges with thresholds representing clinical relevant abnormality and by presenting descriptive statistics of raw data and change from Baseline (Day1). Values outside the extended normal range will be listed by patient and treatment arm and flagged in data listings.

9.5.2.3 Vital signs

Vital signs will be summarized by presenting shift tables using thresholds representing clinical relevant abnormality (Appendix 1) and by presenting descriptive statistics of raw data and change from Baseline (Day1). Values outside the extended normal range will be listed by patient and treatment arm and flagged in data listings.

9.5.2.4 Ocular assessments

Ocular assessments (including IOP) will be summarized descriptively by time point and treatment group based on the safety set. Intraocular pressure changes (pre-injection) from Baseline (Day1) by visit and changes from before dosing to after dosing within a visit will be descriptively summarized.

Summaries will be presented separately for the study eye only and for the fellow treated eye.

9.5.3 Resource utilization

Not applicable.

9.5.4 Pharmacokinetics

Not applicable.

9.5.5 DNA

Not applicable.

9.5.6 Biomarkers

Not applicable.

9.5.7 PK/PD

Not applicable.

9.7 Interim analyses

Not applicable.

9.8 Sample size calculation

In order to detect a clinically meaningful difference in the number of injections (at least 2 injections) at Month 11, as suggested by the principal investigators, this study will randomize at least 56 patients (28 per arm).

For the sample size calculation, we will assume a difference between arms of 2 injections and a standard deviation (SD) of 2.32 (based on CAVNAV study (Liegl et al. 2014)). Based on the non-parametric Wilcoxon-Mann Whitney test for the difference in means this would require 25 patients per arm with 80% power and a 0.025 significance level (1sided), however assuming approximate 10% drops out rate, a total of at least 56 patients (28 per arm) are required to be randomized.

Approximately 70 patients will need to be screened in order to have at least 56 patients eligible and commencing treatment in the trial.

All sample size calculations performed using EAST 6.0.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent or if applicable, after such consent has been provided by a legally acceptable representative of the patient.

In cases where the patient's legally acceptable representative (LAR) gives consent, the patient should be informed about the study to the extent possible given his/her understanding. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol).

The process of obtaining informed consent should be documented in the patient source documents.

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

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/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.

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

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

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

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

11 Protocol adherence

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

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

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

12 References

References are available upon request.

Aiello LP, Avery RL, Arrigg PG, et al (1994) Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med; 331(22):1480-7.

Arakawa S, Arakawa S, Yasuda M, Nagata M, et al (2011) Nine-year incidence and risk factors for retinal vein occlusion in a general Japanese population: the Hisayama Study. Invest Ophthalmol Vis Sci;52(8):5905-9.

Battaglia Parodi M, Saviano S, Ravalico G, (1999) Grid laser treatment in macular branch retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol; 237(12):1024-7.

Brown DM, Campochiaro PA, Singh RP, et al (2010) Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology; 117(6):1124-33.

Campochiaro PA, Choy DF, Do DV, et al (2009) Monitoring ocular drug therapy by analysis of aqueous samples. Ophthalmology; 116(11):2158-64.

Campochiaro PA, Heier JS, Feiner L, et al (2010) Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Opthalmology; 117(6):1102-12.

Clark WL, Boyer DS, Heier JS, et al (2016) Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion: 52-Week Results of the VIBRANT Study. Ophthalmology;123(2):330-6.

Donati S, Barosi P, Bianchi M, et al (2012) Combined intravitreal bevacizumab and grid laser photocoagulation for macular edema secondary to branch retinal vein occlusion. Eur J Ophthalmol.; 22: 607–14.

Farese E, Cennamo G, Velotti N, et al (2014) Intravitreal bevacizumab combined with grid photocoagulation in recurrent macular edema secondary to retinal vein occlusion. Eur J Ophthalmol.; 24: 761–70.

Finkelstein D (1986) Argon laser photocoagulation for macular edema in branch vein occlusion. Ophthalmology; 93(7):975-7.

Hayashi A, Yunoki T, Miyakoshi A, et al (2011) Intravitreal injection of bevacizumab combined with macular grid laser photocoagulation for macular edema in branch retinal vein occlusion. Jpn J Ophthalmol; 55: 625–31.

Iesato Y, Imai A, Murata T, et al (2016) Effect of leaking capillaries and microaneurysms in the perifoveal capillary network on resolution of macular edema by anti-vascular endothelial growth factor treatment. Jpn J Ophthalmol ; 60(2):86-94.

Ishibashi T, Li X, Koh A, et al (2015) The REVEAL Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy in Asian Patients with Diabetic Macular Edema. Ophthalmology;122(7):1402-15.

Kamei M, Terasaki H, Yoshimura N, et al (2016) Short-term efficacy and safety of ranibizumab for macular oedema secondary to retinal vein occlusion in Japanese patients. Acta Ophthalmologica; in press.

Kozak I, Oster SF, Cortes MA, et al (2011) Clinical evaluation and treatment accuracy in diabetic macular edema using navigated laser photocoagulator NAVILAS. Ophthalmology; 118(6):1119-24.

Liegl R, Langer J, Seidensticker F, et al (2014) Comparative evaluation of combined navigated laser photocoagulation and intravitreal ranibizumab in the treatment of diabetic macular edema. PLoS One;9(12):e113981.

Mitchell P, Bandello F, Schmidt-Erfurth U, et al (2011) The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology; 118(4):615-25.

Narayanan R, Panchal B, Das T, et al (2015) A randomised, double-masked, controlled study of the efficacy and safety of intravitreal bevacizumab versus ranibizumab in the treatment of macular oedema due to branch retinal vein occlusion: MARVEL Report No. 1. Br J Ophthalmol; 99(7):954-9.

Neubauer AS, Langer J, Liegl R, et al (2013) Navigated macular laser decreases retreatment rate for diabetic macular edema: a comparison with conventional macular laser. Clin Ophthalmol; 7: 121-8.

Operational manual for Grid&Direct short pulse laser photocoagulation, 04 Aug 2016.

Pulido JS, Flaxel CJ, Adelman RA, et al (2016) Retinal Vein Occlusions Preferred Practice Pattern(®) Guidelines. Ophthalmology; 123(1):182-208.

Salinas-Alaman A, Zarranz-Ventura J, Caire González-Jauregui JM, et al (2011) Intravitreal bevacizumab associated with grid laser photocoagulation in macular edema secondary to branch retinal vein occlusion. Eur J Ophthalmol; 21: 434–9.

Tadayoni R, Waldstein SM, Boscia F, et al (2016) Individualized Stabilization Criteria-Driven Ranibizumab versus Laser in Branch Retinal Vein Occlusion: Six-Month Results of BRIGHTER. Ophthalmol; 123: 1332-44.

The Branch Vein Occlusion Study Group (1984) Argon laser photocoagulation for macular edema in branch vein occlusion, The Branch Vein Occlusion Study Group. Am J Ophthalmol;98(3):271-82.

The ROYAL COLLEGE of OPHTHALMOLOGISTS (2015) Retinal Vein Occlusion (RVO) Guidelines July 2015 (Internet) Available from: <https://www.rcophth.ac.uk/standards-publications-research/clinical-guidelines/> (Accessed 06 Jul 2016).

Wong TY, Scott IU (2010) Clinical practice. Retinal-vein occlusion. N Engl J Med;363(22):2135-44.

Yasuda M, Kiyohara Y, Arakawa S et al (2010) Prevalence and systemic risk factors for retinal vein occlusion in a general Japanese population: the Hisayama study. Invest Ophthalmol Vis Sci;51(6):3205-9.

13 Appendix 1: Clinically notable vital signs

The criteria for clinically notable abnormal vital signs are shown below. In order to be identified as being potentially clinically notable abnormal, an on-treatment vital signs value would need to meet the criterion value, and represent a change of at least the magnitude noted in the change column.

Clinically notable abnormal vital signs values for adults

Variable	Criterion Value	Change Relative to Baseline
Heart Rate	≥ 120 b.p.m. ≤ 50 b.p.m.	increase of ≥ 15 b.p.m. decrease of ≥ 15 b.p.m.
Systolic blood pressure	≥ 180 mm Hg ≤ 90 mm Hg	increase of ≥ 20 mm Hg decrease of ≥ 20 mm Hg
Diastolic blood pressure	≥ 105 mm Hg ≤ 50 mm Hg	increase of ≥ 15 mm Hg decrease of ≥ 15 mm Hg

14 Appendix 2: Pre-Injection procedures for ranibizumab

The following procedures (except where noted) will be conducted by the injecting physician to assure aseptic conditions:

1. Before treatment, the patients should be instructed to self-administer antimicrobial drops four times daily for three days prior to treatment.
2. Patients should be sufficiently anesthetized and administered with broad-spectrum antimicrobial eye drops before ranibizumab administration.
3. Intravitreal injection of ranibizumab should be conducted under aseptic conditions:
    - The technician assembles the supplies and prepares a sterile field. Supplies include swabs, sterile surgical gloves, sterile pads, pack of sterile cotton-tipped applicators, eyelid speculum, sterile ophthalmic drape, topical anesthetic, disinfectant ophthalmic solution, subconjunctival anesthetic, ophthalmic broad spectrum antimicrobial solution, and injection supplies.
    - The physician is to perform surgical hand and finger disinfection and use sterile gloves.
    - Disinfect the periocular skin and eyelid of the study eye in preparation for injection. Scrub the eyelid, lashes, and periorbital skin with disinfectant ophthalmic solution swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Make certain that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.
    - Place a sterile ophthalmic drape to isolate the field, and place the sterile speculum underneath the eyelid of the study eye.
    - Sterilize the conjunctiva sac of the study eye according to local practice, making sure the planned injection site on the conjunctiva has been disinfected.
    - Use a sterile pad in a single wipe to absorb excess liquid and to dry the periocular skin.
4. Instruct patient to direct gaze away from syringe prior to ranibizumab injection.

15 Appendix 3: Post-Injection procedures for ranibizumab Instructions

1. Immediately following the ranibizumab injection, instill a broad spectrum antimicrobial in the study eye.
2. Discard all syringes and needles in the sharps container.
3. Seal the study drug kit (including the used vial).
4. Finger counting will be tested on each patient's study eye within 15 minutes after each injection; hand motion and light perception will be tested when necessary.
5. Measure the intraocular pressure in the study eye between 15 and 60 minutes following the ranibizumab injection.
6. Intravitreal injection may cause a transient increase in intraocular pressure. After ranibizumab administration, the perfusion of the optic nerve head should therefore be confirmed and the increase in intraocular pressure should be appropriately managed.
7. Instruct the patient to self-administer a broad spectrum antimicrobial four times daily for three days following each ranibizumab injection.
8. In addition, any other safety assessments according to local practice will be performed.
9. If there are no safety concerns following the injection the patient will leave the clinic. If any concern or immediate toxicity is noted, the patient will remain at the clinic and will be treated according to the Investigator's clinical judgment.
10. Contact the patient by telephone for safety evaluations 2 (± 1) days following each study visit when study drug is administered. Alternatively, any safety assessments according to local practice may be performed. Document the attempts to contact the patient or the visits to sites in the patient's source documents.

16 Appendix 4: Post-treatment procedures for laser photocoagulation

1. Finger counting will be tested on each patient's study eye within 15 minutes after each laser application; hand motion and light perception will be tested when necessary.
2. Measure the IOP in the study eye following the laser application.
3. After laser application, the perfusion of the optic nerve head should be confirmed.
4. In addition, any other safety assessments according to local practice will be performed.
5. If there are no safety concerns following the laser treatment, the patient will leave the clinic. If any concern is noted, the patient will remain at the clinic and will be treated according to the investigator's clinical judgment.
6. Contact the patient by telephone for safety evaluations 2 (± 1) days following each study visit when study treatment is administered. Alternatively, any safety assessments according to local practice may be performed. Document the attempts to contact the patient or the visits to study sites in the patient's source documents.