NOVARTIS

Clinical Development

RFB002 (Ranibizumab, Lucentis®)

Clinical Trial Protocol CRFB002DDE26 / NCT02366468

A 12-months, randomized, VA-assessor blinded, multicenter, controlled phase IV trial to investigate non-inferiority of two treatment algorithms (discretion of the investigator vs. pro re nata) of 0.5 mg ranibizumab in patients with visual impairment due to diabetic macula edema

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List of abbreviations

AAO	American Academy of Ophthalmology
AE	Adverse event
AMD	Age related macular degeneration
ANCOVA	Analyses of covariance
BCVA	Best Corrected Visual Acuity
BPM	Beats per minute
BSL	Baseline
CRF	Case Report/Record Form (electronic)
CPO	Country Pharma Organization
CRC	Central Reading Center
CRO	Contract Research Organization
[redacted]	[redacted]
cSLO	Confocal scanning laser ophthalmoscope
CSRT	Central subfield retinal thickness
DHP	Data Handling Plan
DI	Discretion of the investigator
DME	Diabetic Macular Edema
DNA	Deoxyribonucleic acid
DR	Diabetic Retinopathy
DRS	Diabetic Retinopathy Study
DS&E	Drug Safety & Epidemiology
EDC	Electronic Data Capture
EPO	Erythropoietin
EOS	End of study
EOT	End of treatment
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
[redacted]	[redacted]
FAS	Full analysis set
FDA	Food And Drug Administration
FP	Fundus Photography
GFR	Glomerular filtration rate
HbA1c	Glycosylated hemoglobin
hCG	Human chorionic gonadotropin
IB	Investigators Brochure

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IRB	Institutional Review Board
[redacted]	[redacted]
IRT	Interactive Randomization Technology
IVT	Intravitreal
LOCF	Last observation carried forward
mCNV	Myopic choroidal neovascularization
MedDRA	Medical dictionary for regulatory activities
NEI	National Eye Institute
OCT	Optical coherence tomography
PDR	Proliferative Diabetic Retinopathy
PFS	Pre-filled syringe
PPS	Per Protocol Set
PRN	Pro re nata (as needed)
PRP	Panretinal Photocoagulation
RS	Randomized Set
RVO	Retinal vein occlusion
SAE	Serious adverse event
SCN	Screening
SD-OCT	Spectral domain OCT
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
T&E	Treat & Extend
TIA	Transient ischemic attack
VA	Visual acuity
VEGF	Vascular Endothelial Growth Factor
[redacted]	[redacted]
VI	Visual impairment

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	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)
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."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Subject Number	A number assigned to each patient who enrolls into the study
Part	A subdivision of a single protocol into major design components. These parts often are independent of each other and have different populations or objectives. For example, a single dose design, a multiple dose design that are combined into one protocol, or the same design with different patient populations in each part.
Period	A subdivision of a study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
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/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational 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

Summary of protocol amendments

Amendment 01

This amendment was issued to stop further recruitment to the study. The reason to stop recruitment is new and relevant scientific evidence regarding treatment patterns with ranibizumab which does not justify continuing the trial with newly included patients.

New clinical trials and analyses showed that other ranibizumab treatment approaches than PRN for DME are successful (PRN: pro re nata – as needed injections with monthly monitoring).

Already in 2010 first evidence was published in the DRCR.net Protocol I trial (Elman et al. 2010): The study protocol allowed the extension of monitoring intervals up to 16 weeks after the first year of treatment. But also in first year, where monthly visits took place and investigators treated the patients as needed, several patients required only very few injections (about 25% of patients only needed 4-6 injections) and from week 24 to week 48 the median of injections was only 3 (Diabetic Retinopathy Clinical Research et al. 2011).

In recent published data of RELIGHT study (Pearce et al. 2015) patients were initially treated with 3 injections, then monitored monthly for signs of disease activity and treated if needed. Beginning with month 6, patients were monitored bimonthly until month 18 and treated with ranibizumab as needed showing BCVA gains comparable to other trials like RESTORE with monthly monitoring intervals and RETAIN with a Treat and Extend approach. A recent post-hoc analysis (Framme 2015, Novartis data on file) indicates that in the PRN arms of RESTORE and RETAIN studies, there is a broad variance of injection frequency from month 5 to month 12 leading to the assumption that monitoring intervals for at least some patients can be extended quite early: 19.5% of patients did not need any treatment from month 5 to 12, 9.2% needed only 1, 8.5% of patients only 2 injections.

In summary these trials and analyses indicate that there is already a strong evidence for treating and monitoring DME patients at the discretion of the investigator.

Because of this evidence no further patients should be randomized to the trial after this amendment is effective (after approval of Independent Ethics Committee and Health Authorities).

Although recruitment stops early the data of already randomized patients will be evaluated descriptively and compared to the existing evidence. With the results of this (although down-sized version) clinical trial we aim to further support evidence for a patient-tailored, investigator-based approach regarding monitoring and treating patients with visual impairment secondary to Diabetic Macular Edema (DME).

As the current SmPC allows use of ranibizumab as outlined in the DI and PRN arm, already randomized patients can remain in the study and be treated according to protocol. The interventions are non-invasive or invasive but according to recommendations in the current guidelines on DME/Diabetes mellitus treatment, posing no additional risk for patients when further observed and treated in this trial (Stellungnahme der Deutschen Ophthalmologischen Gesellschaft, der Retinologischen Gesellschaft und des Berufsverbandes der Augenärzte Deutschlands, 2013; Matthaei et al. 2011, Landgraf et al. 2015).

This amendment will also clarify some aspects of the protocol. Primarily, clarifications have been provided around assessing and treating the patient. Also typos and format errors were corrected.

The trial is ongoing (approx. 130 patients enrolled). No impact on the study population or the patients' safety is expected.

Evaluation of movement patterns, pedometry and genetics were canceled before start of study due to technical reasons and therefore sections are deleted in the whole document. No blood samples for genetic evaluations were and will, respectively, be obtained in this trial.

Changes to Section 4.Population:

- Update of exclusion criterion 20: unfortunately in first protocol version there was no difference in pretreatment condition for anti-angiogenic drugs between study eye and fellow eye. To reduce unnecessary protocol deviations, that are present at the moment, section was updated to change conditions for the fellow eye (prior treatment less than 1 month)

Changes to Section 5 Treatment:

- 5.1.2 and 5.5.3.2.2: indication for panretinal laser photocoagulation was clarified
- [redacted]
- Chapter 5.5.3.2 was structured and additional information regarding combined treatment of laser and ranibizumab was added
- In chapter 5.5.3.3.1 further recommendations and clarifications for treatment were added
- Clarification on diabetes treatment was moved from chapter 5.5.8 to 5.5.7
- In chapter 5.5.8 section on concomitant medication was deleted (wrong chapter allocation), investigational drugs suspected to influence outcome were added and vitrectomy was limited to study eye
- Chapter 5.5.9 was updated to give further guidance on treatment discontinuation

Changes to Section 6 Visit schedule and assessments:

- Chapter 6: a clarification of documentation in DI-arm was added and a reference was added that visits can be split to several days
- Table 6-1 was revised for more convenient reading and updated to reflect the changes in protocol (e.g. genetic blood sampling deleted)
- Chapter 6.3: Information to be collected on previous DME treatments was added and recording of concomitant medication was aligned with chapter 5.5.7.
- Chapter 6.4: clarification was added that imaging at study start needs to be repeated if images not eligible
- [redacted]
- [redacted]

Changes to Section 7 Safety monitoring:

- Chapter 7.1.: reporting of events after end of study period was aligned with chapter 7.2 (30 days)
- Chapter 7.2: Period of SAE reporting was clarified

Changes to Section 9 Data analysis:

- Chapter 9.7. update to take reduced patient number into consideration

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Protocol synopsis

Protocol number	CRFB002DDE26
Title	A 12-months, randomized, VA-assessor blinded, multicenter, controlled phase IV trial to investigate non-inferiority of two treatment algorithms (discretion of the investigator vs. pro re nata) of 0.5 mg ranibizumab in patients with visual impairment due to diabetic macula edema
Brief title	Study of efficacy of ranibizumab in different regimens in patients with diabetic macula edema (DME) - DIVERSE
Sponsor and Clinical Phase	Novartis Phase 4 study
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to demonstrate non-inferiority of 0.5 mg ranibizumab in discretion of the investigator (DI) treatment regimen compared to 0.5 mg ranibizumab pro re nata (PRN) treatment regimen in patients with visual impairment due to DME. DI regimen may provide similar visual function benefit as PRN regimen.
Primary Objective(s) and Key Secondary Objective	The primary objective is to demonstrate that the mean average change of BCVA in patients with DME treated with ranibizumab injections at the discretion of the investigator (DI) and in accordance with disease activity criteria is non-inferior to current standard of care (PRN).
Secondary Objectives	To evaluate: • Mean change of visual acuity by comparing change of BCVA in ETDRS letters between baseline and month 12 • Frequency of visits and injections, treatment free intervals and visit • mean change of central subfield retinal thickness (CSRT) and foveal center point thickness from baseline will be evaluated by central reading center assessing OCT images • change in DRS retinopathy scale evaluated by central reading center scoring fundus photography • Influence of relevant HbA1c-, blood pressure and blood lipid levels changes on primary objective (ANCOVA Analysis)
Study design	This is a 12-months, phase IV, randomized, parallel-group, visual acuity assessor-masked, multi-center, interventional study assessing

	the efficacy and safety of DI vs. PRN regimens of 0.5 mg ranibizumab intravitreal (IVT) injections. Approximately 130 eligible patients with VI due to DME will be randomized. At the baseline visit on day 1, a patient whose eligibility is confirmed will be randomized 1:1 into one of the treatment arms.
Population	The study will include adult patients with Type 1 or Type 2 diabetes mellitus and visual impairment due to diabetic macular edema. A total of approximately 130 patients (65 in each treatment arm) will be randomized at approximately 30 centers across Germany. Patients will be treated in an outpatient setting.
Inclusion criteria	• Male or female patients > 18 years of age giving written Informed Consent and who are willing and capable to comply with all study procedures. • Patients with Type 1 or Type 2 diabetes mellitus with glycosylated hemoglobin (HbA1c) ≤ 12.0%. Inclusion criteria for the study eye at screening: • Patients with visual impairment due to DME in at least one eye. If both eyes are eligible, the one with the worse visual acuity, as assessed at Visit 1, will be selected by the investigator as the study eye. • BCVA ≥ 24 and ≤ 78 letters in the study eye, using ETDRS-like visual acuity testing charts. • Concomitant conditions in the study eye are only permitted if, they do not prevent improvement of visual acuity on study treatment
Main Exclusion criteria	Ocular medical history • Active intraocular inflammation • Any active infection • History of uveitis • Structural damage within 0.5 disc diameter of the center of the macular • Patients with both, a BCVA score of > 73 letters and a central subfield thickness (CSFT) of < 300 µm in the study eye. • Uncontrolled glaucoma • Neovascularization of the iris • Proliferative vitreoretinopathy in study eye • History of retinal detachment, retinal tear or macular hole Prior and planned Ocular treatments • Any intraocular surgery in the study eye within 4 months prior to randomization. • Vitrectomy/vitreoretinal surgery

	• Planned medical or surgical intervention • Treatment with anti-angiogenetic drugs within 3 months prior randomization for study eye and 1 month for fellow eye • Intravitreal steroids in phakic eye or without sufficient time since last treatment (at least 3 months, for dexamethasone implant 6 months or 3 years for fluocinolone implant Systemic conditions or treatments • History of stroke within 4 months prior to enrollment. • Untreated diabetes mellitus. • Blood pressure systolic > 160 mmHg or diastolic > 100 mmHg • Pregnant and nursing women and women physiologically capable of becoming pregnant, unless they are using effective methods of contraception
Investigational and reference therapy	The investigational treatment in this study is 0.5 mg ranibizumab 10 mg/ml solution for injection, supplied in prefilled syringes (PFS). If PFS are not available vials will be used.
Efficacy assessments	• Best Corrected Visual Acuity (ETDRS) • Spectral Domain Optical Coherence Tomography • [redacted]Color Fundus Photography
Safety assessments	• Adverse events • Vital signs • Standard ophthalmic examinations (including ophthalmoscopy, slit lamp, intraocular pressure, gonioscopy)
Key other assessments	• [redacted] [redacted] [redacted]
Data analysis	The primary objective of this trial is to demonstrate, that the ranibizumab treatment at the discretion of the investigator (DI) is non-inferior to ranibizumab PRN treatment with respect to the mean average BCVA change from baseline to month 12. However as the assumed patient number for primary outcome will not be reached the data analysis will be purely exploratory. The following hypothesis will be tested at a one-sided 0.025 level. Non-inferiority with respect to BCVA: H0: $\mu DI - \mu PRN \leq -\Delta$ versus HA: $\mu DI - \mu PRN > -\Delta$ where μDI and μPRN are the unknown mean average changes from baseline in BCVA to month 12 in the DI regimen and the PRN regimen, respectively. Δ is the non-inferiority margin and is pre-

	defined to be 4 letters. The hypothesis testing with respect to non-inferiority of BCVA will be carried out using an analysis of covariance model including treatment group and center as factor and baseline BCVA as continuous covariat. For the treatment contrast, the point-estimate will be given with its (two-sided, 95%-) confidence interval and the p-value for the (unshifted) null hypothesis $\mu DI - \mu PRN = 0$. The one-sided non-inferiority-p-value for the shifted hypothesis $\mu DI - \mu PRN \leq -\Delta$ will be calculated additionally. Non-inferiority will be claimed, if the lower limit of the confidence interval does not exceed $-\Delta$.
Key words	Ranibizumab, diabetic macular edema, discretion of the investigator regimen

1 Introduction

1.1 Background

Diabetes mellitus (DM) is the most common endocrine disease with prevalence estimates ranging between 2 to 5% of the world's population. Diabetic retinopathy (DR) and diabetic macular edema (DME) secondary to DR are common microvascular complications in patients with DM and may have a sudden and debilitating impact on visual acuity (VA) (Riordan-Eva, 2004).

Vision-threatening DME is characterized by swelling of the central part of the retina and arises from breakdown of the blood-retinal barrier (BRB) with subsequent 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) (Aiello 1997) (Vinores 1997). When VEGF was measured in eyes of patients with different pathologies involving macular edema, patients with DME showed the highest intraocular VEGF concentrations (Campochiaro 2009).

Intravitreal injection of a VEGF inhibitor is currently the gold standard treatment for visual impairment due to DME followed by laser photocoagulation (Stellungnahme der Deutschen Ophthalmologischen Gesellschaft, der Retinologischen Gesellschaft und des Berufsverbandes der Augenärzte Deutschlands, 2013, Bandello 2012).

Different treatment regimens have been tested to reduce visual impairment (VI) due to DME. Starting with monthly treatment in clinical studies (Massin et al. 2010; Do et al. 2012; Do et al. 2011; Brown et al. 2013; Nguyen et al. 2012), at the moment PRN (pro re nata, as needed) treatment with monthly monitoring visits is state of the art which was successfully tested in the RESTORE and DRCR.net study (Mitchell et al. 2011; Lang et al. 2013; Schmidt-Erfurth et al. 2014; Elman et al 2010, 2011, 2012 and 2015). But more and more data for "treat and extend treatment" (T&E) regimen (Prunte et al. 2015 or other schemes have been published and are currently under discussion (Korobelnik et al. 2014). RETAIN study has shown that monthly monitoring can be extended for certain patients, but mandatory injections in RETAIN at every visit lead to more injections than needed compared to PRN treatment schemes (RESTORE, RETAIN study). So there is a need for different treatment regimens that should also reflect the differences in clinical/office setting, improve patient adherence and takes into account disease subtypes and previous therapy.

As a consequence in this study we want to test an alternative treatment scheme, where the investigator decides when to monitor and/or treat the DME patient.

In addition this study might provide data on predictors by evaluating which patient needs more frequent monitoring and which patients need less monitoring. To further broaden the knowledge on DME and DR and to better reflect the daily routine in the clinics, patients with additional proliferative diabetic retinopathy (PDR) and retinal ischemia will not be excluded.

This study will also investigate new functional parameters (e.g. microperimetry) optionally at equipped centers.

Meanwhile the label of ranibizumab has been updated with corresponding data and is now supporting individualized treatment and monitoring intervals for patients with DME (see chapter "Summary of Amendment 01").

1.2 Purpose

The purpose of this trial is to demonstrate that the change of best corrected visual acuity (BCVA) is comparable in patients treated with ranibizumab at the discretion of the investigator vs. treatment according to PRN scheme with monthly monitoring. Furthermore the number of injections and visits will be compared between treatment groups as well as morphologic parameters. Subgroups and new methods will enlarge our knowledge on the efficacy of ranibizumab. With the results of this study we aim to present a patient-tailored, investigator-based approach to monitor and treat patients with visual impairment secondary to Diabetic Macular Edema (DME).

2 Study objectives

2.1 Primary and key secondary objectives

2.1.1 Primary objective

The primary objective is to demonstrate that the mean average change of BCVA in patients with DME treated with ranibizumab injections at the discretion of the investigator (DI) and in accordance with disease activity criteria is non-inferior to current standard of care (PRN).

2.1.2 Secondary objectives

To evaluate:

- Mean change of visual acuity by comparing change of BCVA in ETDRS letters between baseline and month 12
- Frequency of visits and injections, treatment free intervals and visit
- mean change of central subfield retinal thickness (CSRT) and foveal center point thickness from baseline will be evaluated by central reading center assessing OCT images
- change in DRS retinopathy scale evaluated by central reading center scoring fundus photography
- Influence of relevant HbA1c-, blood pressure and blood lipid levels changes on primary objective (ANCOVA Analysis)

[redacted]

3 Investigational plan

3.1 Study design

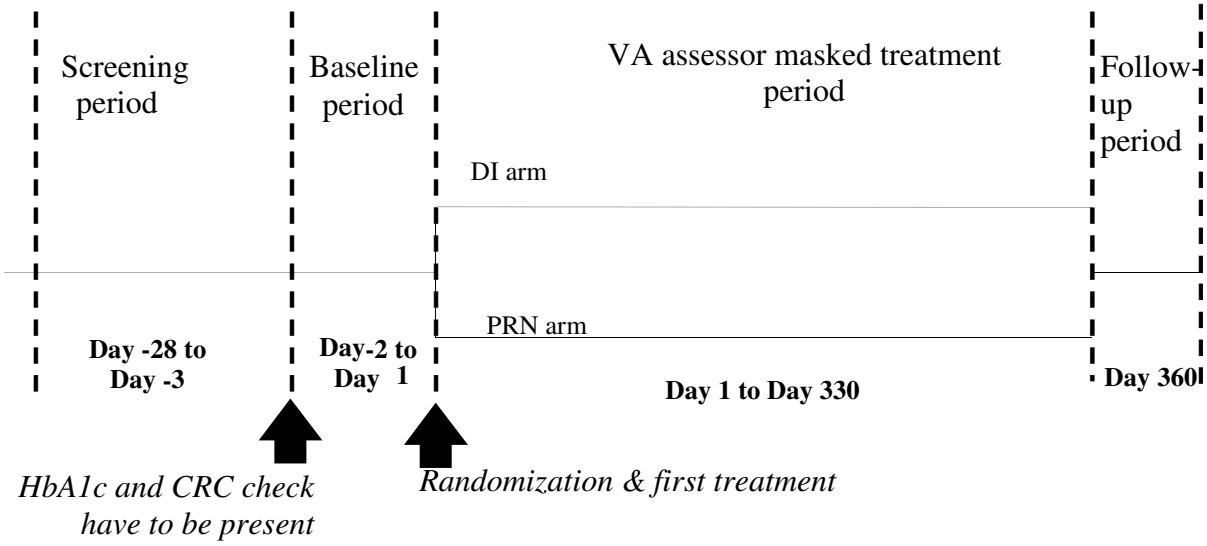
This is a 12-months, phase IV, randomized, parallel-group, visual acuity assessor-masked, multi-center, interventional study assessing the efficacy and safety of DI vs. PRN regimens of 0.5 mg ranibizumab intravitreal (IVT) injections. Approximately 130 eligible patients with VI due to DME will be randomized. The study duration will be up to 13 months:

- Screening period: to occur between day -28 and day -3,
- Baseline period: to occur between day -2 and day 1 (HbA1c and CRC check have to be present)
- Treatment period: from baseline (visit 2) to month 11
- Follow-Up period: from month 11 to month 12 (visit 14)

At the baseline visit on day 1, a patient whose eligibility is confirmed will be randomized 1:1 into one of the treatment arms:

- Arm 1 (discretion of the investigator, DI): Investigational, RFB002, 10 mg/ml
- Arm 2 (pro re nata, PRN): Standard of Care; RFB002, 10 mg/ml

Figure 3-1 Study design



3.2 Rationale of study design

Ranibizumab 0.5mg has been approved in the EU since 2011 for VI due to DME. The current standard of care treatment is PRN treatment with monthly monitoring (Stellungnahme der Deutschen Ophthalmologischen Gesellschaft, der Retinologischen Gesellschaft und des Berufsverbandes der Augenärzte Deutschlands, 2013, Bandello 2012). Ophthalmologists gained experience in treating modalities of DME patient with anti-VEGF therapies based on VA-changes and disease activity in the past years.

In RESTORE study with monthly monitoring and PRN treatment median of injections after 12 months were 7.0 in both ranibizumab groups (Mitchell et al. 2011). But already in the second half of the first year the injection rate decreased to 2.4 and 2.7 in the respective ranibizumab arms (Schmidt-Erfurth et al. 2014). After 24 months 11.0 to 11.3 injections were needed in both ranibizumab arms (Lang et al. 2013) that corresponds to 2.5 and 3.9 injections in the second year. Starting with the second half of the first year, rapidly declining injection frequencies over time did not correspond to lesser monitoring visits. Patients were still seen on a monthly basis. Therefore we suppose that monitoring intervals can be extended at least for some patients.

To address these disparity between injection frequency and monitoring visits, in the RETAIN study a treat and extend (T&E) treatment regimen was evaluated. Primary objective was the visual acuity change 12 and 24 months with two T&E treatment arms (ranibizumab with and without additional laser photocoagulation) tested against a PRN treatment (ranibizumab mono therapy). In this study the T&E arms treatment intervals could be extended by 1 month if patient was stable regarding vision to a maximum interval of 3 months between injections. T&E regimen were non-inferior to PRN treatment after 12 and 24 months (mean average

change of best corrected visual acuity of 5.9 and 6.1 in T&E arms vs 6.2 in PRN arm; Prunte et al.). After 24 months number of visits could be reduced by 40% in T&E arms vs. PRN arms (12.8 and 12.5 vs. 20.5 visits) but there were more injections in the T&E arm than in the PRN arm (median of 12 in T&E and 10 in PRN arm). Higher injection rate were due to protocol requirements, because T&E patients had to be treated at every visit independent of disease activity and patients had to visit the center at least every 3 months. Given the low rate of retreatment in RESTORE study we suppose that retreatment at every visit when a T&E approach is done, probably is not necessary for every patient.

As a conclusion of both RESTORE and RETAIN study we propose that monitoring visits can be reduced by extending monitoring intervals and injections do not have to take place at every visit. We suggest that the investigator should decide when to see the patient for the next visit and when to treat the patient based on disease activity criteria.

With this study we want to test the hypothesis that treatment and visit algorithm done at the discretion of the investigator (DI) will lead to equal visual gain, when compared with a treatment based on the current standard of care (i.e. PRN treatment with monthly monitoring). After initial monthly treatment until maximal VA and no disease activity or no further change in disease activity in both treatment arms, in the DI arm the following approach for monitoring and treatment will be conducted: monitoring intervals will be determined by the physician and will be based on disease activity, as assessed by visual acuity and/or morphological parameters. Intervals between study visits can be extended up to 3 months. Whenever disease activity is present, patients have to be treated. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography (OCT) or [redacted]). This approach may lead to a reduction of visit frequencies in the DI study arm, where physicians will consider when to see the patient for the next visit based on the individual response of the patient.

A non-inferiority margin of 4 letters was chosen, as it was indicated by the U.S. Food and Drug Administration (FDA) in regulatory discussions of Visudyne studies in 2008. In clinical practice 5 letters are usually expected to be clinical relevant. Five letters comprise one line on the ETDRS eye chart. So choosing the smaller FDA margin of 4 letters will serve both regulatory requirements and clinical practice.

To minimize bias on primary outcome, VA-assessors will be masked to the treatment assignment. Therefore at least 2 VA-assessors will alternate on a monthly basis so that it is unknown to them if treatment intervals have been expanded. As one scope of the trial is to make prolongation of treatment intervals possible, a blinding of patients and physicians would lead to a higher frequency of visits for all patients. To avoid the burden of additional visits to mask patients and physicians it was decided to omit further masking procedures.

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

The ranibizumab dose used in this study as intravitreal injection (0.5 mg) was shown to be safe and effective in previous approval trials investigating VI due to DME (e.g. RESTORE study) and is approved in the EU for treatment of age related macular degeneration (AMD), visual impairment due to DME, retinal vein occlusion (RVO) and myopic choroidal

neovascularization (mCNV). The comparator arm is the standard of care and treatment is according to the current lable of ranibizumab.

Initial treatment of both arms on a monthly basis until maximum BCVA and disease inactivity or no further change in disease activity is reflecting the current guidelines on how to treat DME using both functional and morphologic criteria (Stellungnahme der Deutschen Ophthalmologischen Gesellschaft, der Retinologischen Gesellschaft und des Berufsverbandes der Augenärzte Deutschlands, 2013, Bandello 2012)

The investigational arm, arm 1 (DI) is offering a treatment arm, where the investigator decides when to monitor and to treat the patient according to current visual acuity and disease activity. The rationale for this investigational arm is to find the optimal and individual treatment regimen based on the DME disease activity of each patient, reducing visits but gaining comparable VA outcome. As physicians do have experience with treatment of DME with anti-VEGF since at least 3 years we assume that this treatment arm is more realistic than complex (re-)treatments like the one investigated in the RETAIN study.

The maximum treatment duration might be 12 months in this study in both treatment arms.

As primary efficacy endpoint is BCVA local assessors are masked to the treatment assignment in order to ensure unbiased evaluation of the primary objective. To further reduce bias on secondary and exploratory objectives reading centers are blinded to treatment assignment.

3.4 Rationale for choice of comparator

PRN regimen with monthly monitoring with anti-VEGF medication based on VA and disease activity is the current standard of care for patients with VI due to DME (Stellungnahme der Deutschen Ophthalmologischen Gesellschaft, der Retinologischen Gesellschaft und des Berufsverbandes der Augenärzte Deutschlands, 2013, Bandello 2012). Also initial monthly therapy to reach maximum VA and disease inactivity or no further change in disease activity can be found in these guidelines. After this initial phase, patients will be monitored monthly and retreated if disease activity appears (e.g. impairment of VA or worsening of morphologic parameters).

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

Clinical experience with ranibizumab in DME has been well documented by several pivotal approval studies: the Phase II RESOLVE (CRFB002D2201), and the Phase III RESTORE (CRFB002D2301), RESTORE Extension (CRFB002D2301-E1), RETAIN (CRFB002D2304), REVEAL (CRFB002D2303), and RISE (FVF4170g), and RIDE (FVF4168g) (Massin et al 2010, Mitchell et al 2011, Nguyen et al 2012, Lang et al 2013, Schmidt-Erfurth et al 2014; Brown et al. 2013; Novartis data on file) in Caucasian, Asian and Black patients. In these studies 2023 patients were randomized, of which 1051 were successfully treated up to 3 years with 10 mg/ml Ranibizumab for VI due to DME. Another major clinical trial conducted by the DRCR.net study group provided further evidence for the

efficacy and tolerability of ranibizumab for the treatment of visual impairment due to DME (DRCR.net 2010, DRCR.net 2011a, DRCR.net 2012). In this trial 375 of 691 patients were randomized to 0.5 mg Ranibizumab treatment. All mentioned trials did not show any new safety findings compared to trials in AMD.

Also several non-interventional studies include patients with visual impairment due to DME (about 3700 in studies Luminous, CRFB002A2406 and Ocean, CRFB002ADE18, effective June 2014) which are currently still recruiting.

Weighing the substantial clinical benefit achieved with ranibizumab across multiple clinical trials, such as the RESOLVE, RESTORE, RESTORE Extension, REVEAL, RIDE, RISE, DRCR.net studies, and the safety profile as observed for up to 36 months, the results of these studies support the use of ranibizumab for the treatment of patients with visual impairment due to diabetic macular edema (Ranibizumab Investigators Brochure edition 14, December 2015).

Intravitreous injections have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Therefore proper aseptic injection techniques will be used and patients will be monitored to permit early treatment if an infection occurs.

Transient increases in intraocular pressure (IOP) have been seen within first hour after injection of ranibizumab. Sustained IOP increases have also been reported. Therefore, in this study pre- and post-injection IOP will be measured, reported and managed appropriately. Additionally, perfusion of the optic nerve head will be monitored as needed.

There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. Therefore, patients with known risk factors for stroke, including history of prior stroke or transient ischemic attack will be carefully evaluated by their physicians as to whether ranibizumab 0.5 mg treatment is appropriate and the benefit outweighs the potential risk. This risk to patients in this trial will be also minimized by compliance with the inclusion/exclusion criteria and close clinical monitoring.

There are no known clinically relevant disadvantages to participate in the study.

4 Population

The study will include adult patients with Type 1 or Type 2 diabetes mellitus and visual impairment due to diabetic macular edema. A total of 130 patients (60 in each treatment arm) will be randomized at approximately 30 centers across Germany. Patients will be treated in an outpatient setting.

The calculation of the sample size is provided in Section 9.7.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

Patient

1. Male or female patients > 18 years of age giving written Informed Consent and who are willing and capable to comply with all study procedures.
2. Patients with Type 1 or Type 2 diabetes mellitus with glycosylated hemoglobin (HbA1c) ≤ 12.0% (107 mmol/mol) at screening (Visit 1).

Inclusion criteria for the study eye at screening:

3. Patients with visual impairment due to DME in at least one eye. If both eyes are eligible, the one with the worse visual acuity, as assessed at Visit 1, will be selected by the investigator as the study eye.
4. BCVA ≥ 24 and ≤ 78 letters in the study eye, using ETDRS-like visual acuity testing charts at a testing distance of 4 resp. 1 meters (approximate Snellen equivalent of 20/32 to 20/320) at screening.
5. Concomitant conditions in the study eye are only permitted if, they do not prevent improvement of visual acuity on study treatment

4.2 Exclusion criteria

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

Patient Compliance/ Administrative

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG test.
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 of study treatment. Effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
   - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
   - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or 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%), for example 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.

Ocular medical history

3. Active intraocular inflammation (grade trace or above) in either eye at enrollment.
4. Any active infection (e.g., conjunctivitis, keratitis, scleritis, endophthalmitis) in either eye at the time of enrollment.
5. History of uveitis (any cause) in either eye at any time.
6. Structural damage within 0.5 disc diameter of the center of the macular in the study eye likely to preclude improvement in visual acuity following the resolution of macular edema, including atrophy of the retinal pigment epithelium, subretinal fibrosis, laser scar(s).
7. Patients with both, a BCVA score of > 73 letters and a central subfield thickness (CSFT) of < 300 μm in the study eye.
8. Uncontrolled glaucoma in either eye at screening (IOP > 24 mmHg on medication or according to investigator's judgment).
9. Neovascularization of the iris in either eye.
10. Vitreous hemorrhage impairing the adequate diagnosis of DME in the study eye
11. Evidence of clinically relevant vitreofoveal adhesion in the opinion of the investigator, vitreofoveal traction with foveal involvement or epiretinal membrane with foveal involvement in the study eye that is likely to prevent improvement of BCVA loss due to DME.
12. Proliferative vitreoretinopathy in study eye
13. History of retinal detachment, retinal tear or macular hole in the study eye.
14. Neovascularization covering an area of ≥ 2 disc areas within the macula (defined as area with 6mm diameter centered on the fovea), originating either from neovascularization of the disc or multiple neovascularization's elsewhere in study eye
15. Patients who are monocular or have a BCVA score in the non-study eye (fellow eye) < 24 letters (approximate Snellen equivalent of 20/320) at Visit 1.

Prior and planned Ocular treatments

16. Any intraocular surgery in the study eye within 4 months prior to randomization.
17. Vitrectomy/vitreoretinal surgery
    a. In the medical history or planned for study eye
    b. planned vitrectomy or vitrectomy in last 3 months in fellow eye
18. Planned medical or surgical intervention during the 12-months study period likely to interfere with study schedule or outcomes.

19. Panretinal laser or focal/grid laser photocoagulation in the study eye within 3 months prior to randomization unless sufficient documentation of laser photocoagulation in that period of time is available.
20. Treatment with anti-angiogenic drugs (pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, VEGF-Trap, etc.)
    - within 3 months prior to randomization for study eye
    - within 1 month prior randomization for fellow eye.
21. Use of other investigational drugs at the time of enrollment, or within 3 months or 5 half-lives from enrollment, whichever is longer.
22. History of intravitreal corticosteroid treatment in phakic study eye.
23. Intravitreal corticosteroids in post-cataract surgery study eye (aphakic or pseudophakic, without damaged posterior capsule) within 3 months or 6 months for dexamethasone implant (Ozurdex®) or 3 years for fluocinolone implant (Iluvien®) prior to randomization.
24. Ocular conditions in the study eye that require chronic concomitant therapy with topical ocular corticosteroids.

Systemic conditions or treatments

25. History of stroke within 4 months prior to enrollment.
26. Renal failure requiring dialysis or renal transplant.
27. Untreated diabetes mellitus.
28. Blood pressure systolic > 160 mmHg or diastolic > 100 mmHg at screening and randomization.
29. Conditions that require chronic concomitant therapy with systemically administered corticosteroids.
30. Current use of or likely need for systemic medications known to be toxic to the lens, retina or optic nerve, including Deferoxamine, Chloroquine/ hydroxychloroquine (Plaquenil), Tamoxifen, Phenothiazines and Ethambutol.
31. Use of any systemic anti-VEGF drugs within 3 months prior to Screening (e.g. bevacizumab [Avastin®], ziv-aflibercept [Zaltrap®]).
32. Known hypersensitivity to fluorescein or ranibizumab or any component thereof or drugs of similar chemical classes.
33. Any type of advanced, severe or unstable disease or its treatment, that may interfere with primary and/or secondary variable evaluations including any medical condition 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 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

- Ranibizumab/RFB002: 10 mg/ml solution for injection

Study medication will be supplied in commercially available packaging labeled with "Zur klinischen Prüfung bestimmt". Each vial or pre-filled syringe (PFS) will be labeled with the appropriate information. Medication labels will comply with the legal requirements and be printed in German. The storage conditions will be described on the label. Study medication should not be stored together with commercial Lucentis® to avoid mix up.

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile glass vial or PFS. Each vial or PFS contains ranibizumab in an aqueous solution (pH 5.5) with histidine, trehalose, and polysorbate 20. The vial and PFS do not contain preservatives and are suitable for single use only. Ranibizumab must be stored according to the label instructions and it must be kept in a secure locked facility.

Novartis will provide sufficient supplies of ranibizumab for treatment of the study eye to allow for completion of the treatment period.

5.1.2 Additional study treatment

Focal/grid laser can be applied additionally in both arms but earliest at month 3.

Patients with indication for PRP (e.g. PDR, large non-perfusion areas, severe non-proliferative diabetic retinopathy) will be treated with additional panretinal photocoagulation (PRP) at baseline or at least within 3 months after randomization in both arms.

Macular ischemia should not be treated with PRP according to already mentioned guidelines.

For more details please refer to chapter 5.5.3.2 Handling of other study treatment.

5.2 Treatment arms

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

- Arm 1 (DI): Investigational, RFB002, 10 mg/ml
- Arm 2 (PRN): Standard of Care; RFB002, 10 mg/ml

5.3 Treatment assignment, randomization

Randomization will be done within the eCRF. Only after confirmation of the diagnosis by CRC the randomization will be possible. At visit 2 an eligible patient will be given the lowest available randomization number. This number assigns the patient to one of the treatment arms.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Biometry using

a validated system ensuring assignment of treatment arms to randomization numbers in the specified ratio.

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

5.4 Treatment masking

In this study, the visual acuity assessor, who is assessing parameters constituting the primary endpoint (BCVA), will be masked to the treatment regimen and will not be allowed to perform any additional study tasks which would unmask him/her to study treatment. From Visit 2 on the BCVA assessment must be performed before any other assessments, and the timing of the BCVA assessment will be recorded in the visual outcome form and archived in the source document. At least two different BCVA assessors should be certified for this study, who will alternate monthly for BCVA assessment to support masking of treatment regimen.

[redacted]

Once the designated roles (masked / unmasked) are determined, the roles cannot be switched at any time during the conduct of the study. Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this partly masked study.

Novartis and Contract Research Organization (CRO) personnel involved with the statistical analysis and interpretation of the data and results will be masked until the Database Lock.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Patient-ID Number which is composed by the site number assigned by Novartis and a sequential subject number assigned by the investigator (per allocation card or equivalently). Once assigned to a patient, the Patient-ID Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number as given by the database upon data entry.

Patients who have signed the informed consent form, but fail to meet eligibility criteria for enrollment during the Screening Phase will be deemed screen failures and a reason will be documented in the Screening Log CRF.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance.

Via eCRF each patient will be randomized to one of the two treatment arms. Investigational treatment is identical for both arms.

Ranibizumab medication will be supplied as commercially available packaging of Lucentis® with the additional label “Zur klinischen Prüfung bestimmt”. The vial or prefilled syringe will

be taken from the labeled commercial package and treatment will be performed. After that the empty vial or prefilled syringe will be disposed. The commercial package has to be marked with patient number and visit date by the investigator to make drug accountability possible. It will be stored at a different place than unused packages and commercial (non-study) packages to avoid mix-up.
All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

The storage conditions for study drug will be described on the medication label.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol.

As commercial package is used medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the patient.

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

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

5.5.3.2 Handling of other study treatment

Active laser treatment has to be administered before intravitreal injections if treated at the same day. The minimum interval between the two treatments is 30 minutes.

Laser treatments will be monitored. Details are described in the monitoring plan.

Subthreshold laser can also be used for laser photocoagulation treatment.

All laser applications to the patient during the study and if applicable 3 months prior screening must be recorded on the Dosage Administration Record CRF.

5.5.3.2.1 Focal/grid laser photocoagulation

Focal/grid laser photocoagulation can be applied additionally in both arms but earliest at month 3 if investigator is of the opinion that patient will benefit from additional focal/grid laser photocoagulation. Focal/grid laser should be applied according common ETDRS laser recommendations. Sufficient distance to fovea has to be kept:

- Laser spots have to be at least 500µm from center of fovea

- Juxtafoveal lesions should not be treated at initial sessions

5.5.3.2.2 Panretinal photocoagulation (PRP)

Patients with indication for panretinal photocoagulation (PRP) (e.g. PDR, large non-perfusion areas, severe non-proliferative diabetic retinopathy) will be treated additional with PRP at baseline or at least within 3 months after randomization in both arms.

PRP should be applied according common laser recommendations listed in Appendix 2: PRP (panretinal laser photocoagulation) procedures.

5.5.3.3 Instructions for use of investigational treatment

5.5.3.3.1 Treatment of study eye

Arm 1 (DI): after initial monthly treatment until maximum BCVA and no signs or no further change of disease activity, investigator will treat patients at own discretion. There will be no strict recommendations for retreatment or scheduling of upcoming visits except:

- patients need to be monitored at least every 3 months
- patients have to be retreated if any signs of disease activity occur.
- If relevant* loss of visual acuity is the reason for retreatment, next monitoring visit should be scheduled in 4 weeks.

*Relevant loss is defined as loss of visual acuity with a range outside the daily fluctuation of VA in DME patients. E.g. if 3-4 letters loss since last visit is accompanied by fluid in OCT it is highly likely that no daily fluctuation is present, but a true loss of BCVA. Investigator will decide whether VA-loss is relevant or a daily fluctuation and will document the decision and the reasoning in the source data

Due to flexibility of DI-arm, also treatment schemes like PRN, Treat & Extend or fixed dosing are allowed.

Arm 2 (PRN): investigator will treat patients in a PRN scheme, i.e. after initial monthly therapy until maximum BCVA and no signs or no further improvement of disease activity, patients will be monitored every month and retreated if any signs of disease activity occur.

For both treatment arms the following procedures apply:

Initial monthly therapy for both treatment arms: Beginning at baseline, injections are administered monthly until maximum visual acuity is achieved and no signs or no further improvement of disease activity are present.

Disease activity: both functional and morphologic parameters will be taken into consideration when defining disease activity. That could for example be:

- BCVA: change of BCVA
- OCT: increase of retinal thickness
- [redacted]/FP/ophthalmoscopy: new signs of DME

If retreatment due to new disease activity is necessary, treatment should be continued until:

- maximum BCVA is achieved again or there is no improvement of BCVA compared to previous visit
- there is no further decrease of retinal thickness compared with previous visit
- there is no further regression and no further perspective of regression of other DME characteristics

The interval between 2 ranibizumab injections should not be shorter than 28 days.

If ranibizumab injection and other visit procedures as per assessment schedule cannot be performed on same day, the procedures and injection should be done within three days.

Administration for ranibizumab injections will follow the procedures described in the Lucentis® patient information.

All dosages dispensed to the patient during the study must be recorded on the Dosage Administration Record CRF.

5.5.3.3.2 Treatment of fellow eye

Patients, who develop a condition at the fellow eye that, in the investigator's opinion, qualifies for and requires treatment may be treated at the investigator's discretion according to the investigators standard of care. The fellow eye will not be treated with study medication. Administration of treatment to the fellow eye must be recorded on the Concomitant medication/Significant non-drug therapies page of the CRF (dose, timing and type of treatment).

5.5.4 Instructions for prescribing and taking study treatment

Not applicable (ranibizumab is not handed to patients).

5.5.5 Permitted dose adjustments and interruptions of study treatment

No adjustments of the ranibizumab dosing regimen described in Section 5.5.3.3.1 will be allowed.

Study drug treatment must be interrupted in case of an acute ocular or periocular infection in the study eye. Treatment may be resumed on the next visit, as far as the patient's condition allows.

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

5.5.6 Rescue medication

Rescue medication is not foreseen in this study.

If after detailed evaluation the therapeutic effect is considered insufficient by either the patient or the treating physician, the patient may be withdrawn from the study treatment and is able to receive whatever treatment is considered to be necessary (see section 5.5.9).

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded including start and stop dates and reason for use.

The treatment in this study will not replace the standard of care treatment of the underlying diabetes mellitus type 1 and type 2. The treatment of diabetes mellitus itself has to be continued over the duration of the trial as recommended by the responsible physician.

5.5.8 Prohibited Treatment

Use of the treatments displayed in Table 5-1 is NOT allowed after the start of study (V1).

Table 5-1 Prohibited treatment

Medication/Procedure	Action to be taken
Concurrent use of any anti-VEGF agents either systemic or in the study eye (only permitted in the fellow eye)	To be recorded as a major protocol deviation
Other (investigational) drugs and interventions of any type suspected to influence outcome, i.e. which might influence the course of the underlying ocular disease or the study treatment results, respectively	To be recorded as major or minor protocol deviation and depending on intervention study drug discontinuation to be considered
Concurrent use of peribulbar or intraocular corticosteroids in study eye	To be recorded as major protocol deviation
Concurrent use of intraocular corticosteroids inserts in study eye	Discontinuation from further study treatment
Vitrectomy of study eye	Discontinuation from further study treatment
Systemic medications known to be toxic to the lens, retina or optic nerve, including Deferoxamine, Chloroquine/ hydroxylchloro-quine (Plaquenil), Tamoxifen, Phenothiazines and Ethambutol	To be recorded in the eCRF
Treatment with glitazones or fingolimod when newly started during the study period.	To be recorded in the eCRF

5.5.9 Discontinuation of study treatment and premature patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information. Investigational treatment must be discontinued.

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

Investigational treatment must be discontinued under the following circumstances:

- Emergence of the following adverse events:
  - Rhegmatogenous retinal detachment or Stage 3 or 4 macular hole in the study eye
  - Transient ischemic attack (TIA) or a stroke during the study
- Pregnancy
- Use of prohibited treatment as per Table 5-1 that should lead to treatment discontinuation
- Any other protocol deviation that results in a significant risk to the patient's safety

Patients who prematurely withdraw from the study for any reason, should be scheduled for an early exit visit (EOS) as soon as possible, at which time all of the assessments listed in Table 6-1 will be performed (unless they are pregnant, withdraw informed consent or there is any other serious condition that would make visit 14 (EOS) assessments impossible).

Patients who discontinue investigational treatment should NOT be considered withdrawn from the study and the investigator should encourage the patient to continue in the study and to return to at least quarterly visits for assessments up until month 12. If a patient withdraws from treatment or is withdrawn from treatment by the investigator but remains in the trial, the patients should be scheduled for an End of Treatment (EOT) visit as soon as possible, at which time all of the assessments listed in Table 6-1 will be performed. If they fail to return for these assessments for unknown reasons, every effort should be made to contact them as specified in Section 5.5.11.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

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

5.5.10 Emergency breaking of treatment assignment

Not applicable due to open label treatment (partly masked trial).

5.5.11 Study completion and post-study treatment

Patients will be discharged from the study after visit 14 (month 12).

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. This care might include treatments as recommended in current guidelines (Stellungnahme der Deutschen

Ophthalmologischen Gesellschaft, der Retinologischen Gesellschaft und des Berufsverbandes der Augenärzte Deutschlands, 2013, Bandello 2012).

5.5.12 Early study termination

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

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

An "(X)" denotes optional assessments/procedures. All data obtained from the assessments listed in Table 6-1 must be supported in the patient's source documentation.

Patients should be seen for all visits on the designated day with an allowed "visit window" of ± 7 days beginning with month 1 (V3) but when intravitreal ranibizumab treatment is done at least 28 days have to pass between two ranibizumab injections.

If ranibizumab injection and other visit procedures as per assessment schedule cannot be performed on same day the procedures and injection should be done within three days.

In the DI-arm the next visit available in the eCRF will be used for documentation, independent of the date of visit. Only for EOS/EOT always visit 14/month 12 will be documented.

Patients will be instructed to contact their investigator at any time should they have health-related concerns and might return for an unscheduled visit.

If patients refuse to return for assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the reason. At a minimum, patients will be contacted for safety evaluations during the 30 days following the last study visit or following the last administration of investigational treatment if there are post-treatment follow-up visits (whichever is later), including a final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documentation.

Table 6-1 Assessment schedule

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Period	**SCN**	**BSL and treatment**												**EOS**	**EOT**
Treatment month		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study day	**-28 to – 3[#]**	**-2 to1[#]**	**30 (±7)**	**60 (±7)**	**90 (±7)**	**120 (±7)**	**150 (±7)**	**180 (±7)**	**210 (±7)**	**240 (±7)**	**270 (±7)**	**300 (±7)**	**330 (±7)**	**360[#] (±7)**	
Procedure															
Informed consent	X														
Randomization		X													
Medical History and Prior Medication	X	X													
Demographics	X														
Inclusion/Exclusion	X	X													
Vital signs	X	X[1]												X	X
Height and Weight	X													X[2]	X[2]
Serum Lipid Levels	X													X	X
Urine pregnancy Test****	X													X	X
[redacted]															
Gonioscopy*	X													X	X
Intraocular Pressure (independent of treatment)	X	X												X	X
Optional assessments (both arms)**															
[redacted]															

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Period	**SCN**	**BSL and treatment**												**EOS**	**EOT**
Treatment month		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study day	**-28 to – 3[#]**	**-2 to1[#]**	**30 (±7)**	**60 (±7)**	**90 (±7)**	**120 (±7)**	**150 (±7)**	**180 (±7)**	**210 (±7)**	**240 (±7)**	**270 (±7)**	**300 (±7)**	**330 (±7)**	**360[#] (±7)**	
[redacted]															
For patients in arm 2 (PRN)															
Best-Corrected Visual Acuity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Optical Coherence Tomography	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photography [redacted]	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	X
Ranibizumab therapy*** and Intraocular Pressure[§]		X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		
HbA1c	X				X					X				X	X
For patients in arm 1 (DI)															
Best-Corrected Visual Acuity	X	X	X (mandatory at every visit)											X	X
Ophthalmic Exam	X	X	X (mandatory at every visit)											X	X
Optical Coherence Tomography	X	X	X (mandatory at every visit)											X	X
Color Fundus Photography [redacted]	X	(X)	(X)											X	X

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Period	**SCN**	**BSL and treatment**												**EOS**	**EOT**
Treatment month		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study day	**-28 to – 3[#]**	**-2 to1[#]**	**30 (±7)**	**60 (±7)**	**90 (±7)**	**120 (±7)**	**150 (±7)**	**180 (±7)**	**210 (±7)**	**240 (±7)**	**270 (±7)**	**300 (±7)**	**330 (±7)**	**360[#] (±7)**	
Ranibizumab therapy*** and Intraocular Pressure[§]		X	X	Monthly treatment until stable BCVA and no signs or no further change of disease activity will be present, thereafter treatment at discretion of the investigator but mandatory when disease activity is present											
HbA1c	X	should be done about every 3-4 months												X	X
For all patients															
Focal/grid laser		Focal/grid laser can be applied additionally in both arms but earliest at month 3 (see 5.5.3.2.1)													
[redacted]															
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		[X]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Discharge														X	

SCN: Screening, BSL: Baseline; EOS: end of study; EOT: end of treatment;(X): at the discretion of the investigator; [X]: only after first treatment application

*unless done 1 month prior V1: then record in eCRF is sufficient

**at participating centers where equipment is available

***in both treatment arms: initial monthly therapy until maximum BCVA and/or no signs or no further change of disease activity; If ranibizumab injection and other visit procedures as per assessment schedule cannot be performed on same day the procedures and injection should be done within three days.

**** For women of childbearing potential urine pregnancy test at screening and EOS/early exit;

§Intraocular pressure should be monitored before and within 15 to 60 minutes after treatment

[1] have to be done prior any treatment

[2] at visit 14 only weight will be measured

[#] can be split to 2-3 days

6.1 Information to be collected on screening failures

All patients who have signed informed consent but are not randomized will have the, demographics, reason for failing and SAE data 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 adverse events **occurring after first study drug application** recorded on the Adverse Event CRF.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to first study drug application.

If patient was not eligible for randomization at visit 2 he/she can be rescreened at any time, if all in- and exclusion criteria are met. A new informed consent has to be signed, a new patient number will be used and all assessments of visit 1 have to be retaken.

6.2 Patient demographics/other baseline characteristics

The following information will be collected/documented at screening (V1) and/or baseline (V2) for each patient:

- Year of birth
- Sex
- Race
- Study eye
- Past medical history and current medical conditions
- Vital signs
- HbA1c
- Serum Lipid Levels
- Pregnancy testing for women of child-bearing potential
- Concomitant medications
- DME characteristics (e.g. thickness at the center subfield, evaluated by OCT, [redacted] FP [redacted]
- [redacted]
- BCVA
- Intraocular pressure
- Infection status by using slit lamp examination
- Exclusion of rubeosis iridis (Gonioscopy)
- Smoking history
- [redacted]

- [redacted]

6.3 Treatment exposure and compliance

Any deviations from the protocol in the administration of the ranibizumab injections must be described on the Dosage Administration Record of the eCRF.

With regard to concomitant medications (and, where applicable, the information for which eye), the type, reason for use, start date, stop date (or 'ongoing') of medications used after enrollment or during the study will be collected on the Concomitant medications/Significant non-drug therapies page of the eCRF. Furthermore history of treatment for DME (e.g. anti-VEGF, laser photocoagulation, intravitreal steroids) in the last 5 years will also be collected in Concomitant medications/Significant non-drug therapies page of the eCRF.

6.4 Efficacy

All efficacy assessments are to be done on the study eye and recorded in the eCRF. Efficacy assessments will include both functional and anatomical evaluations. The methods of evaluation and the primary, secondary and exploratory parameter to be assessed are listed below:

- Best Corrected Visual Acuity (ETDRS)
- Spectral Domain Optical Coherence Tomography
- [redacted]Color Fundus Photography (FP)

General notes:

If SD-OCT [redacted] or FP images are not eligible on V1, the image has to be retaken during Screening Phase (unscheduled visit) and the new pictures have to be uploaded for assessment. This procedure must be repeated until images are eligible. If eligible pictures cannot be obtained within 28 days during screening period, rescreening of the patient has to be done with all procedures of visit 1.

6.4.1 Best corrected visual acuity

BCVA assessment has to be performed at every visit **before** any procedure takes place requiring pupil dilation (i.e. SD-OCT, color fundus photography and [redacted].

BCVA will be tested using the ETDRS visual acuity testing protocol. VA measurements will be taken in a sitting position at an initial test distance of 4 meters using ETDRS charts. The overall BCVA score will be calculated using the BCVA worksheet which will be kept in the source data and recorded in the eCRF.

- BCVA will be assessed on the study eye at every visit as per Table 6-1.
- BCVA will be assessed on the fellow eye at screening (Visit 1), EOT and at the end of study visit (V14).

The site's staff performing the VA assessments will be certified prior study start by VA certifiers. A Study Operations manual for performing VA examinations and a BCVA worksheet to calculate overall BCVA score will be provided to each investigative site.

6.4.2 Optical Coherence Tomography

SD-OCT will be assessed in the study eye at every scheduled visit (Table 6-1). Fellow eye will be assessed at screening visit and at EOS (month 12)/EOT. The images will be filed in the source data. These assessments will be performed by trained technician or investigator at the sites and should be performed prior to any investigational drug administration. Image of screening visit will be evaluated by CRC (central reading center) for patient eligibility. Investigators will evaluate the OCT to assess the status of disease activity. The OCT device used for an individual patient must not change during the study.

Novartis requires certification for OCT evaluation. An operations manual and training materials for the certification will be provided by the central reading center. Certification will occur prior to any evaluation of study patients.

The images will be independently reviewed by a CRC, to ensure a standardized evaluation and will transfer the data to be used for the statistical analysis to Novartis or CRO. For further procedural details, the investigator should refer to the Study Manual provided by the CRC.

6.4.3 Color Fundus Photography [redacted]

An operations manual and training materials will be provided by the central reading center.

Patients must be assessed using the same camera throughout the course of the study.

[redacted]

These assessments will be performed by a trained technician at the sites at least at screening, EOT and at the end of study for all patients in study eye and the images will be sent to a CRC. At all other scheduled visits if the investigator is of the opinion to take [redacted]/FP images they should be done as described in the manual. These images will also be provided to the Reading center.

The images independently will be reviewed by the CRC to ensure a standardized evaluation and the data for the statistical analysis will be transferred to Novartis or CRO. For further procedural details the investigator should refer to the Study Operations Manual provided by the CRC.

6.4.4 Appropriateness of efficacy assessments

The selected efficacy assessments are those used in the clinical practice to assess the functional and anatomical changes of the affected macular area due to DME.

6.5 Safety

Safety assessments will consist of monitoring and recording of all AEs and SAEs, ophthalmic examinations, IOP by tonometry, vital signs and laboratory values.

The standard ophthalmic examinations are listed in paragraph 6.5.6.

Significant findings that are present prior signature of the informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's CRF. Significant findings made after first study treatment which meet the definition of an AE must be recorded on the AE page of the patient's CRF.

6.5.1 Physical Examination

Not applicable.

6.5.2 Vital signs

Vital signs will be measured at Screening, Baseline, EOT and visit 14 (EOS): patient's sitting blood pressure (systolic/diastolic measurement in mmHg) and pulse (beats per minute-bpm). If the investigator is of the opinion that blood pressure is too high because due to the agitation of the patient, measurements may be repeated up to three times. The results will be entered into eCRF. Clinically notable vital signs are defined in Appendix 1.

6.5.3 Height and Weight

Height in centimeters (cm) will be measured at visit 1.

Body weight (in indoor clothing, but without shoes) will be measured at visits 1, EOT and at visit 14.

6.5.4 Laboratory evaluations

Blood sampling will be performed at the visits indicated in Table 6-1. The results (HbA1c and lipid levels) from the central lab will be recorded. Clinically notable values are defined in Appendix 1, Table A1-2.

6.5.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a urine pregnancy test at screening (visit 1), EOT and at the end of study (visit 14 or early exit). Results will be recorded in the respective CRF. Urine testing sticks will be provided by Novartis for analysis of the urine.

6.5.6 Eye-specific safety monitoring

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

tonometry. They will be performed at every visit as indicated in Table 6-1. Slit lamp and fundus examinations will be performed prior to treatment with ranibizumab.

The test results will be recorded in the source documents and clinically significant abnormalities will be recorded on the medical/ocular history page (if occurring before BSL) and if occurring after the first injection with investigational drug, on adverse event page of the CRF.

6.5.6.1 Anterior segment biomicroscopy (slit lamp examination)

At every scheduled visit, the anterior segment's structures of the study eye will be carefully examined. If needed, an additional examination will be performed after application of any study medication. Fellow eye will be examined only at screening, EOS and EOT (if applicable) and during the study on discretion of the investigator.

6.5.6.2 Ophthalmoscopy

At visit 1 the posterior segment of both eyes will be examined by the investigator on dilated pupil using adequate ophthalmoscopy apparatus in order to confirm the clinical findings compatible visual impairment due to DME as inclusion criteria's assessments. Also a careful examination of the peripheral retina must be conducted to ensure that the intravitreal injection can safely be performed (i.e. iatrogenic retinal detachment, should not be receive intravitreal injections).

At the indicated visits from baseline (visit 2) on, assessment of the posterior of the study eye will be performed and recorded by the investigator and an additional examination if needed will be performed after the application of the study medication. If the patient experiences blurred vision and light flashes at any time, the investigator should perform the indirect ophthalmoscopy examination in order to detect any AEs and apply the appropriate treatment. In case of uncertainty regarding the clinical findings at the macular area with ophthalmoscopy, a complementary examination using a suitable lens through slit lamp apparatus can be done for the study eye by the investigator.

6.5.6.3 Intraocular pressure (IOP)

Both eyes IOP will be measured at Screening and End of Study/early exit visit. Pre-dose IOP in the study eye will be assessed by the investigator or trained technician at every scheduled visit as from Visit 2 (Day 1) as indicated in the assessment table and post-dose IOP will be assessed 15 – 60 min after injection in the study eye. The values will be recorded in mmHg and will be entered into the eCRF.

In case intraocular pressure is ≥25 mmHg in the study eye, and if not transient, for any reason and at any time during the study period, treatment and closer monitoring of IOP should be performed by the investigator in order to achieve similar values to the baseline measurement.

In this case, intravitreal procedure is not recommended unless normalization of the IOP has been achieved. The investigator should treat appropriately the increased IOP in order to allow the patient to continue in the study.

In addition, at the discretion of the investigator and/or according to the local requirements/practices, monitoring of optic nerve head perfusion may be appropriate within

30 minutes after injection. Results of these procedures will be recorded in the source documents. Only if the findings constitute an AE they have to be recorded in the AE eCRF.

6.5.7 Gonioscopy

Gonioscopy has to be performed on both eyes to exclude rubeosis iridis at screening visit, EOT and to check status at visit 14. If last gonioscopy was performed 1 month prior screening visit it need not be to be performed on visit 1. When done at visits it should be done after all other eye procedures were done, if necessary a visit outside the schedule can be performed within one week.

6.5.8 Hematology

Not applicable

6.5.9 Clinical chemistry

Not applicable

6.5.10 Urinalysis

Not applicable

6.5.11 Electrocardiogram (ECG)

Not applicable

6.5.12 Appropriateness of safety measurements

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

6.6 Other assessments

6.6.1 Resource utilization

Not applicable

[redacted]

6.6.3 Pharmacokinetics

Not applicable

6.6.4 Pharmacogenetics

Not applicable

6.6.5 Other biomarkers

Not applicable

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign including abnormal laboratory findings, symptom or disease) in a subject or clinical investigation subject after start of study treatment for participation in the study.

The occurrence of adverse events should 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, laboratory test, or other assessments.

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

- they induce clinical signs or symptoms,
- they are considered clinically significant that lead to discontinuation of study drug,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them accompanied by the following information.

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment (no/yes) or the injection procedure (no/yes) or the other study treatment (non-investigational) (no/yes),
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE)
- action taken regarding study treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for*:*

  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - 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, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

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

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study treatment dosage adjusted/temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event 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 treatment/ injection procedure/ non-investigational study treatment, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period up to 30 days) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should 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 event reporting

To ensure patient safety, every SAE, regardless of 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 the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (*either initial or follow up information)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to study treatment, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug 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 case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

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 investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational 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 Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

Not applicable

7.4 Pregnancy reporting

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

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

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs 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 CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that investigational treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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 CRFs 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 CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff or CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies, medical history and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples, FP-, [redacted] OCT-data and optional evaluations [redacted] will be processed centrally and the results will be sent electronically to Novartis (or designated CROs).

At the conclusion of the study, the occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Trial Statistician and Statistical Reporting and the Clinical Trial Leader.

8.4 Data Monitoring Committee

Not applicable

8.5 Adjudication Committee

Not required.

9 Data analysis

All analyses will be performed by Novartis personnel or a designated CRO.

Descriptive statistics include n, mean, standard deviation, median and ranges for continuous variables and frequencies and percentages for categorical variables and will be provided by treatment arm unless otherwise specified.

As baseline value the last assessment collected prior to start of treatment will be considered (i.e. data from screening or baseline).

Further technical details will appear in the Statistical Analysis Plan, which will be finalized prior to database lock.

9.1 Analysis sets

The **Randomized Set (RS)** will consist of all patients who were randomized to one of the treatment arms and who received at least one application of study treatment.

The **Full Analysis Set (FAS)** will consist of all patients as randomized who received at least one application of study treatment and have at least one post-baseline assessment for the primary endpoint, i.e. BCVA assessment was performed. Following the intent-to-treat principle, patients will be analyzed according to the treatment assigned. 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 study treatment as randomized and completed the treatment phase of the trial without major protocol deviations.

Criteria that are assumed to have such an impact will be defined in the data handling plan (DHP) and in the Data Review Meeting and documented on the protocol before unmasking.

The **Safety Set** will consist of all patients from the RS who had at least one post - baseline safety assessment. Patients will be analyzed according to treatment received. The statement that a patient had no adverse events also constitutes a safety assessment.

9.2 Patient demographics and other baseline characteristics

Descriptive statistics will be provided for patient demographics and all baseline characteristics (including the baseline values of the main efficacy endpoints).

Relevant medical history (ocular and non-ocular) and current medical conditions will be tabulated by system organ class 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 all randomized subjects.

9.3 Treatments

Investigational Treatment

Descriptive statistics will be provided for exposure to investigational treatment using the Safety Set. The number of ranibizumab injections will be presented by treatment arm in frequency tables and cumulatively. For the optional re-treatments, the number of re-treatments, the time to first re-treatment and the proportion of patients with a treatment-free interval of at least 3 months will be calculated.

Additional study treatment:

The number and percentage of other study treatment (including laser treatment) will be presented by treatment arm in frequency tables by visit and cumulatively.

Concomitant therapies

The number and percentage of patients taking concomitant therapies will be summarized by preferred term according to the WHO Drug Reference List dictionary using the Safety Set. Summaries will be presented separately for prior medications (received prior to the start of study) and for concomitant medications (received during the study).

9.4 Analysis of the primary and key secondary variable(s)

The primary objective is to demonstrate that the mean average change of BCVA, averaged over all post-baseline visits, in patients with DME treated with ranibizumab injections at the discretion of the investigator (DI) and in accordance with disease activity criteria is non-inferior to current standard of care (PRN).

9.4.1 Variable(s)

The primary variable of this study is the mean average change of BCVA in ETDRS letters from baseline to month 12, averaged over the individual changes in BCVA (differences in letters) from baseline to all post-baseline visits. The primary analysis will be performed on the FAS using the LOCF approach for imputing missing data. However, since this is a non-

inferiority-trial, the corresponding results obtained for the PPS are regarded as of almost equal importance for the interpretation.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary objective of this trial is to demonstrate, that the ranibizumab treatment at the discretion of the investigator (DI) is non-inferior to ranibizumab PRN treatment with respect to the mean average BCVA change from baseline to month 12.

The following hypothesis will be tested at a one-sided 0.025 level.

Non-inferiority with respect to BCVA:

H0: $\mu DI - \mu PRN \leq -\Delta$ versus HA: $\mu DI - \mu PRN > -\Delta$

where μDI and μPRN are the unknown mean average changes from baseline in BCVA to month 12 in the DI regimen and the PRN regimen, respectively. Δ is the non-inferiority margin and is pre-defined to be 4 letters (see section 3.2 for the justification of the margin).

The hypothesis testing with respect to non-inferiority of BCVA will be carried out using an analysis of covariance model including treatment group and center as factor and baseline BCVA as continuous covariat. For the treatment contrast, the point-estimate will be given with its (two-sided, 95%-) confidence interval and the p-value for the (unshifted) null hypothesis $\mu DI - \mu PRN = 0$. The one-sided non-inferiority-p-value for the shifted hypothesis $\mu DI - \mu PRN \leq -\Delta$ will be calculated additionally. Non-inferiority will be claimed, if the lower limit of the confidence interval does not exceed $-\Delta$. (Please notice that the lower limit of a 2-sided, 95% confidence interval is identical to the lower limit of a 1-sided, 90% confidence interval which is usually used to assess non-inferiority).

9.4.3 Handling of missing values/censoring/discontinuations

For the FAS, the analysis will follow a LOCF (Last Observation Carried Forward) approach with the specification that monotone missing values will be replaced by the last post-baseline observation prior to the missing time-point. Intermittent missing data will be replaced by the mean of the closest non-missing adjacent values.

9.4.4 Supportive analyses

The primary analysis will be repeated for the PPS using the same model as the one used for the primary analysis.

The change from baseline in BCVA will be compared between the two treatments based on the assumption of a “Missing at Random (MAR)” process, i.e. assuming that the statistical behavior of a patient who drops out post-withdrawal is the same as that for a patient remaining in the study and sharing the same covariates and the same measurement history.

Gender subgroup analysis will be done for primary objective and key secondary objectives.

[redacted] and

[redacted]

In case of significant outliers or deviations from normality assumptions, a nonparametic comparison (Wilcoxon Test) may be performed additionally to the primary analyses.

Further details about the models and analyses will be given in the statistical analysis plan. Any major discrepancies in the results across analyses will be investigated as needed.

9.5 Analysis of secondary and other variables

9.5.1 Efficacy variables

The analysis of the secondary efficacy objectives will focus on the study eye only and it will be based on the FAS.

At all the time points assessed, each efficacy variable will be presented graphically (where appropriate) and descriptive statistics provided based on absolute values and changes from baseline.

Of note is that for patients randomized to the DI, no monthly visit and consequently no monthly reporting schedule exists. Therefore efficacy data collected by visit will be described on a bi-weekly schedule for the DI arm. Furthermore and in order to allow for a visualization of data of both arms on a monthly basis, data collected in between two monthly visits (e.g. at Month 5.5) will be reported at the following monthly visit.

For continuous and ordered categorical variables, changes from baseline will be compared between treatment groups using ANCOVA models (with the baseline covariate)/ T-test. For treatment differences, 95% confidence intervals will be calculated for differences of means (based on ANCOVA models).

Secondary Efficacy variables

The variables related to the secondary objectives are described below:

1. Mean change from baseline in BCVA from baseline to month 12.
2. Number visits and injections, and treatment free intervals
3. Changes in central subfield retinal thickness (CSRT) and foveal center point thickness by SD-OCT.
4. Comparison of changes of 1,2 or more steps in DRS retinopathy scale between treatment arms compared to baseline
5. ANCOVA analysis of primary outcome with the additional covariates “relevant changes of HbA1c, blood pressure, lipid level”

9.5.2 Safety variables

Safety parameters will include adverse events, the results of ophthalmic examinations, IOP, vital signs, and laboratory results.

All safety analyses will be performed using the Safety Set.

Adverse Events

Adverse events will be deemed treatment emergent if the onset date is on or after the date of first treatment with investigational drug. Any adverse events recorded prior to the start of investigational drug will be listed together with all other adverse events. Only treatment emergent adverse events will be summarized.

Adverse events will be summarized by presenting for each treatment group the number and percentage of patients having any adverse event, having an eye-related adverse event, having an adverse event in each primary system organ class and having each individual adverse event based on the preferred term. Patients who experienced multiple adverse events for a preferred term will be counted once, similarly for patients with multiple adverse events per system organ class. Eye-related adverse events (as identified by the investigator) will be presented separate for the study eye and the fellow eye. Ocular AEs that were recorded in both eyes will be reported for each eye separately.

All other information collected (e.g., severity or relationship to study treatment) will be tabulated and listed as appropriate. Summary tables will also be presented for the subset of adverse events suspected to be treatment related.

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

Vital signs and IOP

Vital signs will be summarized by presenting shift tables using extended normal ranges with thresholds representing clinical relevant abnormality (Appendix 1) and by presenting descriptive statistics of raw data and change from baseline. Values outside the extended normal range will be listed by patient and treatment group and flagged in data listings. IOP measurements will be presented descriptively (absolute values and change from baseline).

9.5.3 Resource utilization

Not applicable.

[redacted]

9.5.5 Pharmacokinetics

Not applicable

9.5.6 Pharmacogenetics

Not applicable

9.5.7 Biomarkers

Not applicable

9.5.8 Pharmacokinetics

Not applicable

9.6 Interim analyses

No interim analyses will be performed.

9.7 Sample size calculation

A sample size of 133 patients per treatment arm will have 90% power to establish non-inferiority at a margin of 4 letters for the 0.5 mg ranibizumab "at investigators discretion" dosing regimens in comparison to 0.5 mg ranibizumab PRN in the mean average change in BCVA based on a one-sided 0.025 significance level, assuming a treatment difference of 0 letters, a standard deviation of 10 letters and an underlying normal distribution for an unstratified t-Test (nQuery Advisor 7.0).

The Phase III study (RESTORE) results in the FAS suggest a mean average change in BCVA of 6 letters with a standard deviation of about 7-8 letters for ranibizumab. To account for some more variability related to the retreatment concepts and subgroup treated with additional PRP laser in this study as compared to RESTORE, a standard deviation of 10 letters is assumed. To account for some drop outs 150 patients will be randomized per treatment arm.

Due to reasons mentioned in section "Summary of protocol amendments" recruitment will be terminated, resulting in a reduced sample size present for analysis.

As a consequence results are to be interpreted in a purely descriptive manner. With an estimate of about 120-150 patients to be enrolled by end of recruitment the expected power would be about 55-60% and will be evaluated accordingly.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented 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 Code of Federal Regulations Title 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 incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about

the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. 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 an informed consent form that complies with the ICH GCP guideline and regulatory requirements and is approved by the IRB/IEC.

Women of child bearing potential should be informed that application of study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study or longer, if applicable. 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

The protocol and the informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. 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 Clinical 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.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data

or conduct any additional procedures for any research related purpose involving any investigational drugs.

If the 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 it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

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. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

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13 Appendix 1: Clinically notable laboratory values and vital signs

Table A1-1 Critical values for vital signs

Variable	Type of abnormality	Critical values
Systolic blood pressure (mmHg)	High	Either >180 with an increase from baseline > 30 or > 200 absolute
	Low	Either < 90 with a decrease from baseline > 30 or < 75 absolute
Diastolic blood pressure (mmHg)	High	Either >105 with an increase from baseline > 20 or > 115 absolute
	Low	Either < 50 with a decrease from baseline > 20 or < 40 absolute
Pulse rate (bpm)	High	Either > 120 with an increase from baseline > 25 or > 130 absolute
	Low	Either < 50 with a decrease from baseline > 30 or < 40 absolute

Table A1-2 Critical values for laboratory values

Variable	Type of abnormality	Critical values
Cholesterol	Out of normal range (low): female	2.38 mmol/l; 92 mg/dl
	Out of normal range (low): male	2.12 mmol/l; 82 mg/dl
	Out of normal range (high): female	6.06 mmol/l; 234 mg/dl
	Out of normal range (high): male	4.97 mmol/l; 192 mg/dl
	Pathologic value: female and male	6.22 mmol/l; 240 mg/dl
	Extremely pathologic value: female and male	9.07 mmol/l; 350 mg/dl
HDL-Cholersterol	Out of normal range (low)	1.04 mmol/l; 40 mg/dl

	Pathologic value (low)	0.91 mmol/l; 35 mg/dl
	Extremely pathologic value (low)	0.65 mmol/l; 25 mg/dl
LDL-Cholesterol	Out of normal range (high)	3.38 mmol/l; 130 mg/dl
	Pathologic value (high)	4.94 mmol/l; 190 mg/dl
	Extremely pathologic value (high)	6.50 mmol/l; 250 mg/dl
Triglycerides	Out of normal range (high)	1.71 mmol/l; 150 mg/dl
	Pathologic value (high)	3.42 mmol/l; 300 mg/dl
	Extremely pathologic value (high)	5.13 mmol/l; 450 mg/dl
HbA1c	Out of normal range (high)	6.2%
	Pathologic value (high)	6.8%
	Extremely pathologic value (high)	14.6% (deviation alert above 12.1)

14 Appendix 2: PRP (panretinal laser photocoagulation) procedures

PRP should be applied in accordance with DRS recommendations that are as follows:

- PRP is applied in a scattered pattern to the retina with more than 2 disc diameters from the fovea out to the equator and where necessary out to the periphery.
- The laser spots size in the retina should be 500 microns and the spots 1 burn apart. 1200 to 1600 burns with mild to moderate intensity are recommended and the burn duration should be between 0.1 and 0.2 seconds. If more lasers spots are necessary for sufficient initial treatment, further spots can be applied.
- Usually the treatment is split into 2 to 5 or more sessions within 3 to 6 weeks maximum
- One session should not exceed 500-600 burns and max. 2 sessions should be made per week.
- If further PRP retreatment is necessary it should not be applied before 3 months have passed since last PRP treatment. If investigator is of the opinion that PRP treatment was insufficient, PRP treatment should start immediately independent of 3 months interval to last laser treatment.
- About 500 burns are recommended for re-treatment

To ensure adequate PRP treatment the following recommendations should be taken into consideration:

- sufficient treatment of non-perfused areas
- laser towards NVEs and eventually also centrally
- also consider treating NVEs with 100-200µm laser spots that are applied confluent