NOVARTIS

Clinical Development

[RFB002/Ranibizumab]

Clinical Trial Protocol [CRFB002DTR01] / NCT02262260

A Randomized, Open-label Non-inferiority Study to Compare Safety and Efficacy of Labeled Versus Wait and Extend Regimen of Lucentis (ranibizumab) in Turkish Patients With Visual Impairment Due to Diabetic Macular Edema.

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List of abbreviations

ADA	American Diabetes Association
AE	Adverse Event
AMD	Age related macular degeneration
BCVA	Best corrected visual acuity
CRF	Case report form
CRO	Contract Research Organization
CRT	Central retinal thickness
DBP	Diastolic blood pressure
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
ECG	Electrocardiogram
ETDRS	The Early Treatment Diabetic Retinopathy Study
FFA	Fundus fluorescein angiography
FSH	Follicle-stimulating hormone
HA	Health Authority
IEC	Independent Ethics Committee
logMAR	Logarithm of the minimum angle of resolution
MedDRA	Medical dictionary for regulatory activities
OCT	Ocular coherence tomography
RPE	Retinal pigment epithelium
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SD	Standard deviation
SOP	Standard Operating Procedure
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VFQ-25	Visual Function Questionnaire
WOCBP	Women of childbearing potential

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
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Subject Number	A number assigned to each patient who enrolls into the 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

Protocol synopsis

Protocol number	CRFB002DTR01
Title	A randomized, open-label non-inferiority study to compare safety and efficacy of labeled versus wait and extend regimen of Lucentis (ranibizumab) in Turkish patients with visual impairment due to diabetic macular edema.
Brief title	Study of efficacy and safety of Ranibizumab in Turkish patients with visual impairment due to diabetic macular edema.
Sponsor and Clinical Phase	Novartis / Phase III
Investigation type	Drug Research
Study type	Interventional Study
Purpose and rationale	The purpose of this study is to demonstrate the non-inferiority of “wait and extend” regimen of ranibizumab to labeled posology in Turkish patients with visual impairment due to diabetic macular edema with respect to the mean change in BCVA at 12th month from baseline.. Data from RESOLVE and RESTORE trials supporting monthly assessments and PRN Lucentis injections assumed to be considered as “gold standard” for future treatment of patients with visual impairment due to diabetes macula edema as it is for wet AMD. However, there is a need to explore a more clinical feasible treatment regime to provide satisfactory treatment effect with a lower number of visits and injections. A “wait and extend” regimen has been demonstrated efficient for treatment of wAMD in SALUTE study as mentioned above and found to be safe and tolerable. The rationale of this pilot study is to show that similar approach is applicable in treatment of DME.
Primary Objective(s) and Key Secondary Objective	The primary objective of this study is to demonstrate the non-inferiority of “wait and extend” regimen of ranibizumab to labeled posology in Turkish patients with visual impairment due to diabetic macular edema with respect to the mean change in BCVA at 12th month from baseline..
Secondary Objectives	• to compare mean change in CRT at 12th month from baseline between two groups with OCT • to assess the number of injections needed over a 12-month treatment period with a “wait and extend” dosing regimen • to assess the number of visits needed over a 12-month treatment period with a “wait and extend” dosing regimen • to evaluate the number of patients with improvement in BCVA from baseline • to evaluate the number of patients with improvement of 5 or more letters from baseline

	• to evaluate the number of patients with improvement of 10 or more letters from baseline • to evaluate the number of patients with improvement of 15 or more letters from baseline • to evaluate the safety of intravitreal injections of Lucentis (ranibizumab) in patients with DME • to describe the change in Patient reported functional ability of Lucentis-treated patients.
Study design	This is a randomized controlled, multicenter, 12 month study of Lucentis (ranibizumab) that the consenting patients will participate in a screening period and will be evaluated for their eligibility to enroll the study. After the screening period and the eligibility assessment of the patient, only one eye will be selected / treated as the study eye. After eligibility confirmation at baseline, patients will be randomized into one of the treatment arms as below: • Arm 1 - Labeled regime arm: Treatment will be given monthly and will be continued until maximum visual acuity is achieved (the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment). Thereafter patients should be monitored monthly for visual acuity. Treatment will be resumed when monitoring indicates loss of visual acuity due to DME. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month. • Arm 2 - Wait and Extend regime arm: Lucentis (ranibizumab) 0.5 mg will be injected subsequently at baseline, month 1 and 2. After the three initial loading doses, patients will be called for the control visits 1 month later. If the visual acuity has reached a stable level and there is no sign of edema on OCT, patients will not receive intravitreal injection and will be called to come back 6 weeks later. The interval is increased by 2 weeks until a maximum of 8 weeks as long as the patient presents as stable regarding visual acuity, central retinal thickness and clinical findings. If there is a negative change, the interval is shortened back to 4 weeks.
Population	The study population will consist of male and female patients (over 18 years old) admitted to hospital with Type 1 or Type 2 diabetes mellitus (according to ADA or WHO guidelines) with HbA1c not more than 12.0% at screening (Visit 1). Patients should be on diet, exercise, and/or pharmacological treatment for diabetes and should have a visual impairment due to focal or diffuse macular edema with center involvement in at least one eye, as demonstrated with color fundus photography, fluorescein angiography and OCT within 28 days of the baseline treatment. It is aimed to randomize a total of 86 patients in approximately 12 centers in Turkey. Since a 20% screening failure rate is expected, 104

	patients have to be screened.
Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. 2. Male or female patients >18 years of age who have signed an informed consent 3. Patients with Type 1 or Type 2 diabetes mellitus (according to ADA or WHO guidelines) with HbA1c not more than 12.0% at screening (Visit 1). Patients should be on diet, exercise, and/or pharmacological treatment for diabetes. 4. Patients with visual impairment due to focal or diffuse macular edema with center involvement in at least one eye, as demonstrated with color fundus photography, fluorescein angiography and OCT within 28 days of the baseline treatment. If both eyes are eligible, the one with the worse visual acuity, as assessed at Visit 1, will be selected for study treatment unless, based on medical reasons, the investigator deems the other eye the more appropriate candidate for study treatment. The study eye must fulfill the following criteria at Visit 1: • BCVA score between 78 and 39 letters, inclusively, using ETDRS-like visual acuity testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/160) • Decrease in vision is due to DME and not due to other causes, in the opinion of the investigator
Exclusion criteria	Exclusion criteria 1. Concomitant conditions in the study eye according to defined criteria such as infection, inflammation, uncontrolled glaucoma 2. Active proliferative diabetic retinopathy or evidence of vitreomacular traction in the study eye 3. 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 4. The history of vitrectomy in the study eye. 5. Concomitant systemic condition according to defined criteria, eg. history of stroke, uncontrolled diabetes, renal failure, unsatisfactory controlled hypertension 6. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days until the expected PD effect has returned to baseline, whichever is longer. 7. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes. 8. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases. 9. 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 laboratory test. 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.

	Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
Investigational and reference therapy	The investigational drug in this study will be ranibizumab 0.5 mg. No additional treatment beyond investigational treatment is requested for this trial.
Efficacy assessments	• Mean change in Best-corrected visual acuity (BCVA) with ETDRS-like chart at a starting distance of 4 meters, at 12th month from baseline • Mean change in CRT (µm) by Optical coherence tomography at 12th month from baseline • Mean no. of injections over a 12-month treatment period • Mean no. of visits over a 12-month treatment period • Proportion of patients who gained ≥0, ≥5, ≥10 and ≥15 letters in BCVA at 12th month • Mean change in VFQ25 scores at 12th month from baseline
Safety assessments	• Incidence of adverse events (AEs) and serious AEs (SAEs), by ophthalmic examinations and IOP measurements, and by changes in vital signs and laboratory parameters over the 12-month assessment period.
Other assessments	There is no other planned analysis to be performed for this study.
Data analysis	A sample size of 86 (43 for each treatment arm) can achieve 90% power to detect non-inferiority limit of 5 letter between treatment arm when significance level of the test is 0.025 and the mean (standard deviation) letter change of labeled regime arm will be around 7 (7). To eliminate the effects of incomplete data which are expected in 1 year follow-up period, a priori 20% of drop-out rate is accepted; therefore at least 104 patients (52 for each treatment arm) will be included to the study.
Key words	Optic Coherence Tomography, Diabetic Macular Edema, Ranibizumab, Tolerability, Safety, Wait and Extend

1 Introduction

1.1 Background

Diabetes mellitus (DM) is the most common endocrine disease in developed countries, with prevalence estimates ranging between 2 to 5% of the world's population. Diabetic retinopathy (DR) and diabetic macular edema (DME) are common microvascular complications in patients with diabetes and may have a sudden and debilitating impact on visual acuity (VA), eventually leading to blindness. DME is a frequent manifestation of DR [Riordan-Eva, 2004] and is the major cause of visual loss in patients with DR.

If left untreated, >50% of patients lose >2 lines of visual acuity (VA) within 2 years. DME mostly affects the working-age population, imposing a significant burden both on society and on individual patients - a burden that is expected to increase with the rising prevalence of diabetes [Bandello, 2012]

Diabetic macular edema (DME) can occur at any stage of non-proliferative and proliferative diabetic retinopathy. It is characterized by a swelling of the macular area that normally accounts for high-resolution visual acuity (VA), and DME therefore leads to visual deterioration. Clinically significant DME (CSME) is defined as retinal thickening with or without hard exudates within one diameter of the macular center and results in visual impairment when the foveola is involved. This is referred to as CSME with center involvement (CSME-CI) [Lang, 2012].

One important aspect of the pathophysiology of DME is that cytokine signaling and expression are deregulated in patients with diabetic retinopathy. The permeability of retinal endothelial cells (REC) is controlled by VEGF and regulated by its binding to the VEGF receptor 2. DME results from a breakdown of the blood-retinal barrier and leads to retinal thickening caused by an accumulation of fluid and molecules in the retina. The leakage can arise from microaneurysms or capillaries. The primary endogenous mediator of DME is VEGF, a glycoprotein that is secreted by REC, pericytes and pigment epithelial cells. REC dysfunction seems to be an important step in the development of DME. Hyperglycemia and hypoxia-induced VEGF release are important confounding factors [Lang, 2012].

For the last decades, laser was the gold standard for the treatment of patients with CSME. This treatment, however, is destructive and it rather prevents further visual deterioration than improves vision. Therefore, new treatment modalities were developed to overcome the unmet medical need to restore vision [Lang, 2012].

Ranibizumab (Lucentis) is a recombinant humanized IgG1 κ isotype monoclonal antibody fragment (Fab) that selectively binds VEGF. Ranibizumab (intravitreal injections of 0.5 mg) is approved for the treatment of neovascular age-related macular degeneration (AMD), the treatment of visual impairment due to diabetic macular edema (DME) and the treatment of

visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO) in anumber of countries worldwide [Product information].

Five trials, ie, two DRCR.net trials, RESTORE, RISE, and RIDE, have provided level I evidence supporting use of ranibizumab for the treatment of DME, and two additional trials have provided level II evidence. These trials demonstrate that ranibizumab therapy for DME is safe and effective for two years [Stewart, 2013] The approval of ranibizumab for patients with visual impairment due to DME with center involvement has improved the visual prognosis and offers therapy for an up to now unmet medical need [Lang, 2012].

The recommended dose for Lucentis is 0.5 mg given monthly as a single intravitreal injection.

Treatment is continued until maximum visual acuity is achieved i.e the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed when monitoring indicates loss of visual acuity due to DME Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments. The interval between two doses should not be shorter than 1 month.However, there is a need to explore a more clinical feasible treatment regime to provide satisfactory treatment effect with a lower number of visits and injections [Product information}

A "wait and extend" regimen has been demonstrated efficient for treatment of wAMD in SALUTE study as mentioned above and found to be safe and tolerable [ASRS 2013]. The rationale of this pilot study is to show that similar approach is applicable in treatment of DME.

According to the SALUTE study performed in Turkey with 104 screened patients, Ranibizumab usage with Wait & Extend or Treat & Observe approach provided improvements in terms of best corrected visual acuity and central retinal thickness. and no significant differences between treatment approaches were found. In per protocol population; visit count in Wait & Extend group is significantly lower than Treat & Observe group. In conclusion, using ranibizumab in patients with choroidal neovascularisation due to AMD with Wait & Extend regimen seems to be as efficient, safe and tolerable as Treat & Observe regimen with less number of visits [ASRS 2013].

The rationale of this pilot study is to show that similar approach is applicable in treatment of DME.

1.2 Purpose

The purpose of this study is to demonstrate the non-inferiority of "wait and extend" regimen of ranibizumab to labeled posology in Turkish patients with visual impairment due to diabetic macular edema with respect to the mean change in BCVA at 12th month from baseline..

2 Study objectives

2.1 Primary and key secondary objectives

The primary objective of this study is to demonstrate the non-inferiority of "wait and extend" regimen of ranibizumab to labeled posology in Turkish patients with visual impairment due to diabetic macular edema with respect to the mean change in BCVA at 12th month from baseline.

2.2 Secondary objectives

- to compare mean change in CRT at 12th month from baseline between two groups with OCT
- to assess the number of injections needed over a 12-month treatment period with a "wait and extend" dosing regimen
- to assess the number of visits needed over a 12-month treatment period with a "wait and extend" dosing regimen
- to evaluate the number of patients with improvement in BCVA from baseline
- to evaluate the number of patients with improvement of 5 or more letters from baseline
- to evaluate the number of patients with improvement of 10 or more letters from baseline
- to evaluate the number of patients with improvement of 15 or more letters from baseline
- to evaluate the safety of intravitreal injections of Lucentis (ranibizumab) in patients with DME
- to describe the change in Patient reported functional ability of Lucentis-treated patients.

2.3 Exploratory objectives

Not Applicable

3 Investigational plan

3.1 Study design

This is a randomized controlled, multicenter, 12 month study of Lucentis (ranibizumab) that the consenting patients will participate in a screening period and will be evaluated for their eligibility to enroll the study. After the screening period and the eligibility assessment of the patient, only one eye will be selected / treated as the study eye. After eligibility confirmation at baseline, patients will be randomized into one of the treatment arms as below:

- Arm 1 - Labeled regime arm: Treatment will be given monthly and will be continued until maximum visual acuity is achieved (the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment). Thereafter patients should be monitored monthly for visual acuity.

- Retreatment criteria:

    - According to this protocol VA stability means BCVA ≥ 84 letters (approximate Snellen equivalent of 20/20) or OCT <300 microns in the last 2 consecutive visits or no improvement can be achieved according to the investigators evaluation regarding VA and OCT measures in the last 2 visits . Stable patients do not require reinjection and should be evaluated in the next visit for reinjection.

    - If VA decreases ≥ 5 letters compared to previous visit and OCT is >300 microns, patients will be retreated.

    - If VA decreases ≥5 letters compared to the previous visit or CRT increases >50 microns compared to the previous visit, patients will be retreated.

    - After 3 monthly injections of the investigational drug laser photocoagulation can be administered if VA worsens ≥10 letters and/or CRT increases >100 microns.

- The interval between two doses should not be shorter than 1 month.

- Arm 2 - Wait and Extend regime arm: Lucentis (ranibizumab) 0.5 mg will be injected subsequently at baseline, month 1 and 2. After the three initial loading doses, patients will be called for the control visits 1 month later. If the visual acuity has reached a stable level and there is no sign of edema on OCT, patients will not receive intravitreal injection and will be called to come back 6 weeks later. The interval is increased by 2 weeks until a maximum of 8 weeks as long as the patient presents as stable regarding visual acuity, central retinal thickness and clinical findings. If there is a negative change, the interval is shortened back to 4 weeks.

  Retreatment criteria:

    - According to this protocol VA stability means BCVA ≥ 84 letters (approximate Snellen equivalent of 20/20) or OCT <300 microns in the last 2 consecutive visits or no improvement can be achieved according to the investigators evaluation regarding VA and OCT measures in the last 2 visits . Stable patients do not require reinjection and should be evaluated in the next visit for reinjection.

    - If VA decreases ≥ 5 letters compared to previous visit and OCT is >300 microns, patients will be retreated.

    - If VA decreases ≥5 letters compared to the previous visit or CRT increases >50 microns compared to the previous visit, patients will be retreated.

    - After 3 monthly injections of the investigational drug laser photocoagulation can be administered if VA worsens ≥10 letters and/or CRT increases >100 microns.

Figure 3-1 Study design

Study Design For Labelled Regime Arm

Phase	Screening		Main Treatment			
Visit	1	2	3	4	5	6 -14
Month	0		1	2	3	4 – 12
Day	–7 to –1	B	30	60	90	120 – 360

Study Design For Wait and Extend Arm

Phase	Screening		Main Treatment			
Visit	1	2	3	4	5	Visit number may vary acoording to the response of the patient
Month	0		1	2	3	4 – 12
Day	–7 to –1	B	30	60	90	120 – 360

3.2 Rationale of study design

A “wait and extend” regimen has been demonstrated efficient for treatment of wAMD in SALUTE study as mentioned above and found to be safe and tolerable. The rationale of this pilot study is to show that similar approach is applicable in treatment of DME.

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

The dose, dose regimen, titration scheme and tapering-off scheme, etc. are in accordance with product labeling in Arm 1. Since a “wait and extend” regimen has been demonstrated efficient for treatment of wAMD in SALUTE study and found to be safe and tolerable, it was decided to show the similar approach for the treatment of DME.

3.4 Purpose and timing of interim analyses/design adaptations

There will be no interim analysis.

3.5 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with the inclusion/exclusion criteria, close clinical monitoring, since the study has been designed in a similar approach to a newly completed study which was completed with no major safety and tolerability concerns there are no unknown risks to *Ranibizumab* which may be serious and unforeseen.

4 Population

The study population will consist of male and female patients (over 18 years old) admitted to hospital with Type 1 or Type 2 diabetes mellitus (according to ADA or WHO guidelines) with HbA1c not more than 12.0% at screening (Visit 1). Patients should be on diet, exercise, and/or pharmacological treatment for diabetes and should have a visual impairment due to focal or diffuse macular edema with center involvement in at least one eye, as demonstrated with color fundus photography, fluorescein angiography and OCT within 28 days of the baseline treatment. It is aimed to randomize a total of 86 patients in approximately 12 centers in Turkey. Since a 20% screening failure rate is expected, 104 patients have to be screened.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female patients >18 years of age who have signed an informed consent
3. Patients with Type 1 or Type 2 diabetes mellitus (according to ADA or WHO guidelines) with HbA1c not more than 12.0% at screening (Visit 1). Patients should be on diet, exercise, and/or pharmacological treatment for diabetes.
4. Patients with visual impairment due to focal or diffuse macular edema with center involvement in at least one eye, as demonstrated with color fundus photography, fluorescein angiography and OCT within 28 days of the baseline treatment. If both eyes are eligible, the one with the worse visual acuity, as assessed at Visit 1, will be selected for study treatment unless, based on medical reasons, the investigator deems the other eye the more appropriate candidate for study treatment. The study eye must fulfill the following criteria at Visit 1:
    - BCVA score between 78 and 39 letters, inclusively, using ETDRS-like visual acuity testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/160)
    - Decrease in vision is due to DME and not due to other causes, in the opinion of the investigator

4.2 Exclusion criteria

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

1. Concomitant conditions in the study eye according to defined criteria such as infection, inflammation, uncontrolled glaucoma
2. Active proliferative diabetic retinopathy or evidence of vitreomacular traction. in the study eye
3. 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
4. The history of vitrectomy in the study eye.
5. Concomitant systemic condition according to defined criteria, eg. history of stroke, uncontrolled diabetes, renal failure, unsatisfactory controlled hypertension
6. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days until the expected PD effect has returned to baseline, whichever is longer.
7. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
8. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
9. 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 laboratory test.

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

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

The investigational drug in this study will be ranibizumab 0.5 mg.

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile glass vial. Each

vial contains ranibizumab in an aqueous solution (pH 5.5) with histidine, trehalose, and polysorbate 20. The vial contains no preservative and is suitable for single use only. Ranibizumab must be stored according to the label instructions and it must be kept in a secure locked facility. The vials must be kept away from direct sunshine and must be kept in a refrigerator between 2°C -8°C (36°F – 46°F) and must not be FREEZED.

No additional treatment beyond investigational treatment is requested for this trial.

5.2 Treatment arms

Patients will be assigned to one of the following "2" treatment arms randomly

A study-specific randomization scheme will be prepared by the CRO to follow up the randomization.

- Arm 1 - Labeled regime arm: Treatment will be given monthly and continued until maximum visual acuity is achieved (the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment). Thereafter patients should be monitored monthly for visual acuity.

  Treatment is resumed when monitoring indicates loss of visual acuity due to DME. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month.

- Arm 2 - Wait and Extend regime arm: Lucentis (ranibizumab) 0.5 mg will be injected subsequently at baseline, month 1 and 2. After the three initial loading doses, patients will be called for control 1 month later. If the visual acuity has reached a stable level and there is no sign of edema on OCT, patients will not receive intravitreal injection and will be called to come back 6 weeks later. The interval is increased by 2 weeks until a maximum of 8 weeks as long as the patient presents as stable regarding visual acuity, central retinal thickness and clinical findings. If there is a negative change, the interval is shortened back to 4 weeks.

5.3 Treatment assignment, randomization

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 investigator will enter the randomization arm on the CRF. Randomization will be performed in 1:1 ratio.

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 the CRO via a special randomization scheme prepared study specific for this study.

5.4 Treatment blinding

The study is an open label study so there are no blinding procedures applicable.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number as given by the investigator using the next blank CRF book. If an enrolled patient fails to be randomized or treated for any reason, the reason will be entered on the related page of the CRF.

5.5.2 Dispensing the investigational treatment

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

The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to the treatment arms, according to the confidential randomization list. Immediately before dispensing investigational treatment to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

5.5.3 Handling of study 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.

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 except for the randomization number.

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. Patients will be asked to return all unused investigational treatment and packaging at the end of the study or at the time of discontinuation of investigational treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator 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.

5.5.4 Instructions for prescribing and taking study treatment

All dosages prescribed and dispensed to the patient should be tracked in the related section of the CRF in each visit.

The investigator should promote compliance and the importance of the attendance to the study visits by instructing the patient to attend the study visits since the injections will be followed up during the study visits and by stating that compliance is necessary for the patient's safety and the validity of the study.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Dose interruptions are permitted to achieve patient compliance and study completion. There are some guidelines that shows the below interruptions are suitable or not.

The guidelines showing the interruptions are suitable or not

Event	Dose interruption criteria
Intraocular Inflammation	Discontinue the medication if intraocular inflammation is ≥2+ Study treatment will be allowed when intraocular inflammation returns to baseline or a better level.
Loss of Visual Acuity	Discontinue the medication if BCVA is decreased ≥30 letters compared to the baseline values as a result of the study treatment. Study treatment will be allowed when the change in BCVA returns back to ≤10 letters below the final BCVA assessment at the final injection before interruption of the medication.
Intraocular Pressure (IOP)	Discontinue the medication if IOP ≥30 mmHg in the study eye. Study treatment will be allowed when the IOP assessed by the investigator returns back to <30 mmHg level with treatment or spontaneously.
Vitreous Hemorrhage	Discontinue the medication if there is ≥2+ vitreous hemorrhage and ≥30 letters decrease in BCVA compared to Baseline.
Rhegmatogen Retinal Tears or Detachment	Discontinue the medication if there is retinal tear or detachment. The patient with grade 3 or 4 macular holes will not continue to the study treatment.
Intraretinal Hemorrhage	Discontinue the medication if there is intraretinal hemorrhage affecting the fovea and the size of the hemorrhage is equal to the 50% or more than the total lesion or ≥1 disc area.
Local or Systemic Infection	Discontinue the medication if one of the below occurs: If either of the two eye has infectious conjunctivitis, keratitis, scleritis or if the patient receives active treatment for a systemic infection.
Intraocular Surgery	Discontinue the medication if there is an intraocular surgical intervention during the last 30 days.
Grade 2 Target Adverse Events	Discontinue the medication until the event returns back to Grade 1 or a better level.

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

5.5.6 Rescue medication

After 3 monthly injections of the investigational drug laser photocoagulation can be administered if VA worsens >10 letters and/or CRT increases >100 microns.

5.5.7 Concomitant treatment

Moxifloxacin (Vigamox®) drop will be administered to the injection eye after injection. 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.

5.5.8 Prohibited Treatment

Any concomitant medications including prescription drugs or over-the-counter preparations used by a patient during the study and until the conclusion of the study participation (except for routine medications given for ocular procedures required by the protocol, i.e. fluorescein, dilating drops, topical antibiotic, topical anesthetic) must be recorded on the Concomitant medications/Significant non-drug therapies CRF including start and stop dates and reason for use.
Laser photocoagulation for DME is permitted only as rescue treatment according to predefined criteria and needs to be
recorded on the Concomitant medications/Significant non-drug therapies CRF
Use of the following treatments is NOT allowed after the start of the study:

- Chronic concomitant therapy with topical ocular corticosteroids
- Other intravitreal medication in the study eye
- Systemic medications known to be toxic to the lens, retina or optic nerve, including Deferoxamine, Chloroquine/ hydroxychloroquine (Plaquenil), Tamoxifen, Phenothiazines and Ethambutol
- Treatment with glitazones during the study.
- Any other investigational drug

The below treatments will be prohibited 30 days before randomisation: verteporfin (Visudyne®), external beam radiation treatment, , submacular surgery or other surgical interventions for DME.

The below treatments will be prohibited 90 days before randomisation: focal laser photocoagulation treatment.

The below treatments will be prohibited 120 days before randomisation: macular laser photocoagulation treatment.

During the study, below treatment will be permitted: Retrobulber anesthesia to prevent eye movements, metochloropamide or other treatments for preventing the nausea due to fluorescein injection and other routine treatments for glaucoma. The patient will also be provided an additional topical antimicrobial medication to use 3 days after the injection which will be used 4 times a day.

If the investigator decided that the other eye (other that the study eye) has a DME lesion or has a new DME lesion occurred during the study which needs treatment, appropriate routine ranibizumab treatment will be applied by the investigator; however any data will not be collected for the other eye. The ranibizumab treatment applied to the other eye will be given by NOVARTIS.

If a patient needs cataract surgery, the surgery must not be performed at least 28 days after last study treatment. After that, the next injection of the study medication should at least be performed 28 days after the cataract surgery. The patients should give every effort to comply to their normal examinations even in the surgery period that they did not receive the medication. The study medication must not be started if post-operative complications such as uveitis, cyclitis are seen after the cataract surgery.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug and routine medications given for ocular procedures required by the protocol) and significant nondrug therapies (including physical therapy and blood transfusions) administered after enrollment into this study must be recorded on the Concomitant medications/Significant nondrug therapies page of the CRF.

5.5.9 Discontinuation of study treatment and premature patient withdrawal

Ranibizumab treatment must be discontinued if the investigator determines that continuing it would result in a significant safety risk for that patient. The following circumstances **require** study drug discontinuation:

- Withdrawal of informed consent
- 3 missed doses of the study medication
- Pregnancy
- Occurrence of the below adverse events: Any grade 3 target adverse event, Grade 3 retinal tear or detachment, Grade 3 vitreous hemorrhage that is not cured (decrease as 1+ or below level) until the next planned injection date
- Any other protocol deviation that results in a significant risk to the patient's safety.
- Use of prohibited medication

In addition to these requirements for study drug discontinuation, the investigator should discontinue study drug for a given patient if, on balance, he/she thinks that continuation would be detrimental to the patient's well-being.

Patients who discontinue study drug should NOT be considered withdrawn from the study. The investigator should encourage the patient to continue the scheduled assessments of the final visit.

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, or 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 determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF.

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.

5.5.10 Study completion and post-study treatment

The patient will be accepted to complete the study on Month 12 and in visit 14 for Labelled Regime Arm, the visit number may vary according the response of the patient for Wait and Extend Arm.

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.

5.5.11 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated 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 investigator will be responsible for informing HA and/or ECs of the early termination of the trial.

6 Visit schedule and assessments

In the below table, all the required study assessments are shown and the visits for those assessments are shown with an "X" sign. The patients must be seen during their planned visit days with a ±7 days visit window.

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 ranibizumab, including a final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documentation.

Assessment /Procedure	Phase	Screening		Main Treatment Visits / Control Visits											
	Visit for Labeled Regime Arm *	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
	Visit for Wait and Extend Arm*	**1**	**2**	**3**	**4**	**5**	**The visit numbers may vary according to the response of the patient.**								
	Month	0		1	2	3	4	5	5	7	8	9	10	11	12
	Day	-7 to -1	B (1)	30	60	90	120	150	180	210	240	270	300	330	360 EoT
Informed consent		X													
Incl/Exclusion criteria		X	X												
Randomisation			X												
Medical history		X													
Vital signs [a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab. Parameters (HbA1c and blood glucose)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Renal Function Parameters (Urea, Creatinin, Albumin, Total Protein, Uric Acid)		X				X									X
Pregnancy test [b]		X													
ECG (12-lead)		X													X
Concomitant Medication		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
Treatment (injections) [c]			X	X	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	
Rescue Laser Treatment						X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	
BCVA		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmologic examination [e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus photography		X													X
FFA		X		X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X
OCT		X		X	X	X	X	X	X	X	X	X	X	X	X
Tonometry [f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
VFQ-25		X[i]	X[i]												X
Study Completion															X

B=Baseline; EoT=End of the Trial; BCVA= Best Corrected Visual Acuity; VFQ-25=Visual Function Questionnaire

a) Blood pressure and pulse will be measured after the injection of the study medication (if applicable)

b) Urine pregnancy test will only be performed to WOCBP. Additional tests may be performed as a decision of the investigator.

c) Site staff will contact with the patient via phone 1-3 days after the study medication injection to inquire if there is any loss of vision, eye ache, unnormal redness or occurrence of any new ocular symptom. Patients will visit the site for an unscheduled visit if needed.

d) If the lesion is active, according to the Royal College of Ophthalmology

e) Ophthalmologic examination: slit lamp and fundus examination will be performed before injection (if applicable)

f) IOP measurement with tonomerty will be performed before injection and after 60 minutes of injection.

g) FFA is mandatory at month 0 and 12 and will be performed according to the investigators's desicion at the other visits.

h) Rescue laser treatment will be performed after the first three injection and according to the criteria described in the protocol.

i) VFQ-25 will be questioned in either of the first two screening visits.

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, 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 epoch of the study will have all adverse events **occurring after informed consent is signed** recorded on the Adverse Event CRF. Adverse events will be tracked in the baseline visit (visit 2) at day 0.

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 the informed consent signature.

6.2 Baseline characteristics

The below information will be recorded during screening/ visit 1

- Ocular medical history: primary diagnosis and all other ocular conditions

In addition below data will be collected during Screening/Visit 1 and Baseline/Visit 2 but if all the assessments/examinations are performed during Screening/Visit 1, they should not be repeated in Baseline/Visit 2. In this case, only the VFQ-25 and injection data should be completed in the CRF:

- Related medical history: significant medical conditions and surgeries start dates and current situation.
- Concomitant medication/significant non drug treatments: all applied medication/treatments

6.3 Treatment exposure and compliance

The patients will be accepted as full compliance if the injections are performed as planned.

6.4 Efficacy

Efficacy will be evaluated per visual acuity measurements, fundus photographs, fluorescein angiography and optical coherence tomography.

Visual Acuity

Visual acuity (VA) will be evaluated for both eyes in all study visits, as best corrected visual acuity according to the protocol. VA measurements will be performed in a sitting posture with a scale like ETDRS, 4 meters away from the baseline test distance..

Color Fundus Photography and Fluorescein Angiography

Fluorescein angiography and color fundus photography will be performed together in Screening/Visit 1 and month 12. Digital fluorescein angiograms will be used for evaluations and the investigators can use their standards while diagnosing the fluorescein angiography

results. Florescein Angiography can be performed in other visits according to the investigator's decision.

Optical Coherence Tomography

Optical Coherence Tomography (OCT), will be performed to both eyes during the control visits of all patients. OCT evaluations should be performed before the study injections. Those evaluations will be performed by the trained staff in each study site. The images should be recorded to the digital video discs.

6.4.1 Appropriateness of efficacy assessments

Those efficacy assessments were based on the previous studies performed with Ranibizumab. In addition the visual acuity assessments, as well as the optical coherence tomography that will be performed in this study are standard for this indication.

6.5 Safety

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), ophthalmic examinations, laboratory parameters and vital signs. Information on adverse events (AEs) and serious adverse events (SAEs) will be collected at every visit.

6.5.1 Vital signs

Vital signs include BP and pulse measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Vital signs will be evaluated at each visit and will be evaluated after the study injections if applicable.

6.5.2 Body Mass Index

Body Mass Index will be calculated using height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) and will only be measured only in Screening/Visit 1.

6.5.3 Laboratory evaluations

The routine laboratory assessments will be performed at all visits for clinical chemistry and for renal function parameters the assessments will be performed at Baseline/Visit 1, Month 3/Visit 5 and Month 12/Visit 14. The specimens will be obtained for the following assessments:

6.5.3.1 Clinical chemistry

HbA1c, fasting blood glucose

6.5.3.2 Renal Function Parameters

Urea, Creatinin, Albumin, Total Protein, Uric Acid

6.5.4 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at Screening/Visit 1 and at the end of study or premature discontinuation visit. Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the CRF. Each ECG tracing should be labeled with the study and subject number, date, and kept in the source documents at the study site. Clinically significant abnormalities should also be recorded on the Medical History/Adverse event CRF page. Clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study.

6.5.5 Pregnancy and assessments of fertility

A urine pregnancy testing will be performed only at screening for the WOCBP.

6.5.6 Appropriateness of safety measurements

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

6.6 Other assessments

Standard Ophthalmological Examination

In each study visit, a standard ophthalmological examination will be performed to both eyes by using a slit lamp for stereoscopic fundus biomicroscopy and indirect stereo ophthalmoscopy. If needed, the pupil will be dilated by eye drops (ex: tropicamide)

Tonometry

In each study visit, tonometry will be performed to measure the intraocular pressure. IOP will be measured before each injection and 60 minutes (±10 minutes). In any time during the study, if a significant increase in IOP (≥30 mm Hg) is seen in a patient, the patient should be followed closely according to the investigator's decision and additional IOP evaluations should be performed. The patient will leave the study site, after 60 minutes if any safety problems are not seen. If any safety problems or a sudden toxicity occurs, the patient will stay at the study site and will be followed according to the investigator's decision.

6.6.1 Resource utilization

Not applicable for this study.

6.6.2 Health-related Quality of Life

Visual Function Questionnaire – 25 (VFQ – 25), will be completed at the selected sites at visits Baseline/Visit 2, and 12. month. VFQ-25, is a questionnaire consists of 25 questions aiming to evaluate the general visual function of the patients. VFQ-25 will be applied by the

investigator. VFQ-25 scores will be calculated according to the related guidelines. (Mangione et al. 1998, 2001).

6.6.3 Pharmacokinetics

Not applicable for this study.

6.6.4 Pharmacogenetics/pharmacogenomics

Not applicable for this study.

6.6.5 Other biomarkers

Not applicable for this study.

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 providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The 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,
- 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 CTCAE grade

If CTCAE grading does not exist for an adverse event, use 1=mild, 2=moderate, 3=severe, and 4=life-threatening. CTCAE Grade 5 (death) is not used, but is collected in other CRFs (Study Completion, Death/Survival).

- its relationship to the study treatment (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, 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) 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 last study visit 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 is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department. The telephone and telefax number of the contact persons in the local department of Novartis Drug Safety are listed in the investigator folder provided to each site and is also listed below. 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 and sent by giving the original report date.

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 Novartis study drug, a Novartis 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 drug that this SAE has been reported.

SAE Reporting to Ministry of Health and Ethical Committee

Local Novartis Turkey Drug Safety Department will report all suspected unexpected serious adverse reactions (SUSARs) to Ministry of Health as per The Regulation on Clinical Trials and Guidance on the collection, verification and submission of Adverse Event/Reaction Reports Occurring During Clinical Trials of Medicinal Products and Biological Products.

7.3 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.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

Contact information for Novartis Drug Safety department:

[redacted]

Tel: [redacted]

Novartis Drug Safety Fax: [redacted]

Novartis Drug Safety Mailbox: [redacted]

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 study treatment is being

stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. *Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs.* 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 must enter the information required by the protocol onto the Novartis CRFs that are printed on 3-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to the Medical Documents Reception Center of Novartis *or CRO working on behalf of Novartis* by field monitors or by the investigational site, with one copy being retained at the investigational site. Once the CRFs are received by Novartis *or CRO working on behalf of Novartis*, their receipt is recorded, the original copy is placed in Central Files, and the non-carbon-required copy is forwarded to the responsible Data Management staff for processing.

8.3 Database management and quality control

Data from the CRFs are entered into the study database by Contract Research Organization (CRO) staff following their own internal standard operating procedures that have been reviewed and approved by Novartis.

Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the CRFs at the investigator site, and a copy is sent to Novartis so the resolutions can be entered into the database. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

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

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

9.1 Analysis sets

The Safety population will consist of all patients who received at least one intravitreal injection of ranibizumab.

All analyses will be performed using the Safety population

9.2 Patient demographics and other baseline characteristics

Descriptive statistics for continuous variables (i.e.: N, mean, standard deviation, median, maximum and minimum) and frequency and percent ranges for categorical variables will be given. Demographic data of the patients (including height and weight) and baseline visual acuity will be submitted as summary tables. Medical history and ocular medical history will be summarized per treatment arms.

9.3 Treatments

Descriptive statistics will be given for application of the study medication. To evaluate the dosage compliance, the percent range of the patient that accepted fully complied will be given. Concomitant medication/significant non-drug treatments will be summarized as numbers and per cents.

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

9.4.1 Variable(s)

Mean change in Best-corrected visual acuity (BCVA) with ETDRS-like chart at a starting distance of 4 meters, at 12th month from baseline

9.4.2 Statistical model, hypothesis, and method of analysis

There is no special hypothesis intended for this study.

9.4.3 Handling of missing values/censoring/discontinuations

Close monitoring of the study sites will be planned to prevent any missing data and any early drop outs due to lost to follow up of the patients.

9.4.4 Supportive analyses

Not applicable.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

- Mean change in CRT (μm) by Optical coherence tomography at 12th month from baseline
- Mean no. of injections over a 12-month treatment period
- Mean no. of visits over a 12-month treatment period
- Proportion of patients who gained ≥0, ≥5, ≥10 and ≥15 letters in BCVA at 12th month
- Incidence of adverse events (AEs) and serious AEs (SAEs), by ophthalmic examinations and IOP measurements, and by changes in vital signs and laboratory parameters over the 12-month assessment period.
- Mean change in VFQ25 scores at 12th month from baseline

9.5.2 Safety variables

All safety evaluations will be summarized and submitted for each visit per treatment arm.

All adverse events will be summarized per treatment arm, as patient numbers and per cents for any adverse event experience and adverse events for each system organ class will be summarized. All information collected (i.e.: severity or grade or causality assessment) will be summarized. Deaths and SAEs requiring early discontinuation will be summarized separately.

Laboratory details will be submitted as the descriptive statistics of the core data and for changes in the baseline data for each treatment arm (mean, median, standard deviation, interval) will be analyzed by highlighting the clinically notable changes.

Vital signs will be summarized and descriptive statistics will be given for heart rate and pulse in a sitting posture including the baseline changes.

9.5.3 Resource utilization

Not Applicable

9.5.4 Health-related Quality of Life

Quality of Life variables will include the total score and sub-scores of the Visual Function Questionnaire – 25 (VFQ – 25) Descriptive statistics will be given including the changes according to the baseline.

9.5.5 Pharmacokinetics

Not Applicable

9.5.6 Pharmacogenetics/pharmacogenomics

Not Applicable

9.5.7 Biomarkers

Not Applicable

9.5.8 PK/PD

Not Applicable

9.6 Interim analyses

NA

9.7 Sample size calculation

A sample size of 86 (43 for each treatment arm) can achieve 90% power to detect non-inferiority limit of 5 letter between treatment arm when significance level of the test is 0.025 and the mean (standard deviation) letter change of labeled regime arm will be around 7 (7). To eliminate the effects of incomplete data which are expected in 1 year follow-up period, a priori 20% of drop-out rate is accepted; therefore at least 104 patients (52 for each treatment arm) will be included to the study.

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), HA/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 a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is

considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the HA/IEC, and a copy of the approved version must be provided to the Novartis monitor after HA/IEC approval.

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

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (HA/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the HA/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, HA/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 HA/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 HA/IEC. Only amendments that are required for patient safety may be implemented prior to HA/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 HA/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

12 References

References are available upon request